Delayed Neointimalization on Sirolimus-Eluting Stents
— 6-Month and 12-Month Follow up by Optical Coherence Tomography —

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Background: Sirolimus-eluting stents (SES) have incomplete neointimal coverage at 6-month follow up as determined with optical coherence tomography (OCT). The long-term detailed changes of neointima in SES remains to be clarified.

Methods and Results: Serial changes in neointimal coverage of SES from 6 months to 12 months using OCT were examined. Of 21 SES in 13 patients, OCT was used to visualize 2,321 stent struts at 6 months and 2,285 stent struts at 12 months. The frequency of struts without neointimal coverage decreased from 6 months to 12 months (from 10.4 to 5.7%). The frequency of malapposed struts decreased from 6 months to 12 months (from 1.7 to 0.2%). The average thickness of the neointima increased (from 112±123 to 120±130 μm). The frequency of struts located at the side branch orifice without neointima decreased (from 4 out of 17 (24%) to 0 out of 17 (0%). Complete coverage with neointima was observed in 14% (3 of 21 SES) at 6 months, and 24% (5 of 21 SES) at 12 months.

Conclusions: Additional neointimal coverage was observed between 6 and 12 months, with a small increase in the neointimal thickness. The incidence of complete coverage, however, was still low at 12 months. These findings suggest delayed neointimalization on SES.

Key Words: Neointima; Optical coherence tomography; Sirolimus-eluting stents

Many studies have demonstrated that sirolimus-eluting stents (SES) inhibit neointimal proliferation and reduce in-stent restenosis. The inhibition of stent neointimalization, however, might increase susceptibility to late stent thrombosis. There are some reports state that thrombosis, which is relatively rare in bare metal stents, occurs on SES more than 1 year after SES implantation. Presently, one of the best morphologic predictors of stent thrombosis is thought to be the extent of uncovered stent strut surfaces in human autopsy studies. Therefore, the clinical assessment of neointimal coverage over stent struts has emerged as a potential avenue for assessing the risk of SES thrombosis. The long-term changes in neointimal coverage on SES, however, remain unknown, and the time required for full coverage remains to be clarified.

Optical coherence tomography (OCT) is a new intravascular imaging modality with a high resolution of approximately 10–20 μm, which is 10-fold higher than that of intravascular ultrasound (IVUS). OCT also enable us to visualize a small ruptured plaque and an eroded plaque with intraluminal thrombi, which cannot be visualized by IVUS. OCT can accurately measure the intima–media thickness and can be used to examine changes in neointimal thickness and stent apposition to the vessel wall in precise detail. In our previous study, OCT revealed that almost 90% of the SES region was covered with thin neointima at 6 months, but the frequency of SES full coverage was low (16%, 9 out of 57).

In the present study, we examined serial changes in SES strut conditions from 6 months to 12 months using OCT to elucidate the time-course of neointimal coverage of SES, and to determine whether the risk of thrombosis decreases with time.

Methods

Study Population

Thirteen patients were implanted with 21 SES (CYPHER™, Cordis Corp, Miami Lakes, FL, USA) under IVUS guidance at our hospital. All 21 SES were examined with binary angiography and OCT at 6 months and 12 months post-implantation. Patient exclusion criteria included acute myocardial infarction, contraindication for dual anti-platelet therapy, stenotic lesion of coronary bypass graft, left main coronary, or ostium of right coronary artery, and a lesion too tortuous or heavily calcified to be evaluated by OCT. All 13 patients took 100 mg aspirin/day at least 1 week prior to the intervention, and 200 mg ticlopidine immediately after SES deployment. After each successful intervention, ticlopidine was discontinued after 3 months, but aspirin therapy was maintained on a life-long basis. This study was approved by the Ethics Committee of Kobe University.
Hospital and all the patients enrolled in the study provided written informed consent for participation.

OCT Examination

OCT examination was performed as previously described. Briefly, an over-the-wire type occlusion balloon catheter (Helios™, LightLab Imaging Inc, Westford, MA, USA) and an OCT imaging probe (ImageWire™, LightLab Imaging Inc) were inserted into the stented coronary artery. The entire length of the stent was imaged using an automatic pullback device moving at 1 mm/s and the OCT image was clearly visualized the stent cross-section. OCT data were recorded on a CD-ROM for off-line analysis.

OCT Analysis

OCT images were analyzed by 2 independent observers, who were blinded to the clinical presentations and lesion characteristics, using proprietary off-line software provided by LightLab Imaging Inc. The SES strut condition was analyzed every 1 mm along the stented segment and classified into 6 categories: (1) well-apposed to vessel wall with neointima; (2) well-apposed without neointima; (3) malapposed with neointima; (4) malapposed without neointima; (5) side branch orifice with neointima; and (6) side branch orifice without neointima. Stent malapposition was defined as a distance between the center reflection of the strut and the vessel wall greater than 170 μm. This criterion was determined by adding the OCT axial resolution (20 μm) as a limit of error to the actual thickness of the SES strut (150 μm). If the 2 observers disagreed, a consensus diagnosis was obtained with repeated off-line readings. Representative images of the 6 strut categories are shown in Figure 1. If neointimal coverage of the strut was observed, its average thickness was measured on each cross-section image of the strut. These analyses were performed at both 6 months and 12 months post-implantation.

Statistical Analysis

Qualitative data are expressed as frequencies, and quantitative data are shown as mean values±SD or medians (25th, 75th percentiles). Comparison of the neointimal thickness between the 2 groups (6-month and 12-month) was performed with the Mann-Whitney U-test (for non-parametric variables). Comparisons of the frequencies of the strut conditions were performed using the chi-squared test. A two-tailed P-value of 0.05 was considered statistically significant.

Results

Clear OCT images of all 21 SES were obtained without any complications at both 6 months and 12 months. Table 1 shows the baseline characteristics of the study subjects comprising patients with angina pectoris (9 cases) and old myocardial infarction (4 cases). Of the 21 SES, 18 were implanted for de novo lesions, 2 for bare metal in-stent restenosis, and 1 for a chronic total occluded lesion. The average follow-up interval for the first SES was 205±33 days and that for the second SES was 407±27 days.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>13 cases</th>
<th>21 stents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(12 males; 1 female)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67±10</td>
<td>205±33</td>
</tr>
<tr>
<td>6 months (follow-up) (days)</td>
<td>407±27</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>9 (69%)</td>
<td>14 (66%)</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>4 (31%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (52%)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (86%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (43%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (43%)</td>
<td></td>
</tr>
<tr>
<td>Culprit coronary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>13 (62%)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>4 (19%)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>4 (19%)</td>
<td></td>
</tr>
<tr>
<td>Lesion type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>10 (77%)</td>
<td>18 (85%)</td>
</tr>
<tr>
<td>Restenosis</td>
<td>2 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>1 (8%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Figure 1. Sirolimus-eluting stent strut conditions were classified into 6 categories: (1) well-apposed to vessel wall with neointima; (2) well-apposed without neointima; (3) malapposed with neointima; (4) malapposed without neointima; (5) side branch orifice with neointima; and (6) side branch orifice without neointima.
SES sizes ranged from 2.5 to 3.5 mm (2.8±0.36 mm) in diameter and 13 to 28 mm (21±3.5 mm) in length. There was no angiographic restenosis among the studied SES.

### Classification of Stent Strut Condition in Relation to Neointimal Coverage

Of the 21 SES, images of 2,321 stent struts were obtained at 6 months and images of 2,285 stent struts were obtained at 12 months using OCT. The frequency of the 6 defined strut conditions is shown in Table 2. From 6 months to 12 months, the frequency of cross-sections showing well-apposed struts with neointima increased from 88.9% to 94.3% (P<0.0001), while the frequency of struts that were well-apposed without neointima decreased from 9.3% to 5.6% (P<0.0001). The frequency of malapposed struts decreased from 1.7% to 0.2% (P<0.0001). No late acquired malapposition and neointima regression was observed from 6 months to 12 months in this study population. Of the 17 struts located at a major side branch orifice at 6 months, 4 were not covered with neointima and the remaining 13 struts were covered with neointima; at 12 months, all 17 struts were covered with neointima. Thus, among all of the struts, most of the SES areas were covered with thin neo-intima, but only 14% (3 of 21 SES) had full coverage along

### Table 2. Classification of Stent Strut Condition

<table>
<thead>
<tr>
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<th>6 months</th>
<th>12 months</th>
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<tr>
<td>Numbers of Well-apposed with neo-intima</td>
<td>2,064 struts (88.9%)</td>
<td>2,154 struts (94.3%)</td>
</tr>
<tr>
<td>Numbers of Well-apposed without neo-intima</td>
<td>217 struts (9.3%)</td>
<td>127 struts (5.6%)</td>
</tr>
<tr>
<td>Numbers of Malapposed with neo-intima</td>
<td>15 struts (0.6%)</td>
<td>2 struts (0.1%)</td>
</tr>
<tr>
<td>Numbers of Malapposed without neo-intima</td>
<td>25 struts (1.1%)</td>
<td>2 struts (0.1%)</td>
</tr>
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</table>

**Main branch analysis**

| Numbers of Sidebranch orifice with neo-intima | n=17 struts (76%) | n=17 struts (100%) |
| Numbers of Sidebranch orifice without neo-intima | 4 struts (24%) | 0 struts (0%) |

![Figure 2.](image)
some malapposed struts and struts located at a side branch orifice. Stent thrombosis is a rare, but very serious and potentially fatal complication in the treatment of coronary atherosclerosis. It can cause myocardial infarction in 60–70% of patients and its estimated 30-day mortality rate ranges from 20 to 48%. An important question is whether the susceptibility of SES to late thrombosis is related to incomplete neointimalization of the stent struts. Following SES implantation, the duration of ticlopidine or clopidogrel administration is 3 months, 6 months, 12 months, or life-long based on an empirical protocol. We administered ticlopidine for 3 months according to the recommendation of the Japanese Ministry of Health, Labour, and Welfare. In the case of bare metal stents, Wilson et al. reported that discontinuation of antiplatelet therapy after 6 weeks for non-cardiac surgery is relatively safe. Based on angioscopy, Ueda et al. reported that neointimal coverage of bare metal stents was complete within 3 months after implantation. For SES, however, the time-course of neointimal coverage is unknown and the time-point at which complete neointimal coverage is achieved and dual-antiplatelet therapy can be safely discontinued remains to be clarified. Human autopsy studies indicate that implanted SES might be associated with incomplete endothelial coverage for as long as 4 years after intervention. The Randomized Study with SES and Velocity bare metal stent (RAVEL) reported 0% binary restenosis at 6 months in the SES group, and similar findings were found after 4 years of angiographic follow-up. This finding indicates that angiography is not adequate for assessing suppressed neointimal hyperplasia after SES implantation. IVUS is useful for quantifying neointima, but its resolution is not sufficient for measuring extremely thin neointima after SES implantation. Recent angioscopic studies demonstrated that 94% of SES had incomplete neointimal coverage after 2 years. Based on angioscopic results, Takano et al. reported that the minimal neointimal coverage scores of SES did not change between 6 months to 2 years after implantation, whereas maximal neointimal coverage scores increased serially. Angioscopy can visualize the luminal surface of vessels implanted with SES, but it might have a limitation for quantitative evaluation of thin neointima. Our findings suggest that OCT provides the most accurate measurements of strut condition and neointimal growth on SES.

In our study, OCT imaging disclosed that the frequency of stent struts without neointimal coverage decreased from 10.4% at 6 months to 5.7% at 12 months and malapposed struts decreased from 1.7% to 0.2%. In contrast, the thickness of neointima observed at 6 months showed a small but significant increase at 12 months. These results suggest delayed neointimalization of SES without obvious late catch-up restenosis. Although we previously reported a case with late acquired malapposition after stenting in the present study population, we did not observe late acquired incomplete apposition or neointimal regression. The frequency of full neointimal coverage of the SES at 12 months was only 24%. Thus, we speculate that complete cessation of dual anti-platelet therapy for SES might not be safe until after 12 months, and at least oral aspirin mono-therapy is necessary. Recent clinical reports suggested that endothelial dysfunction occurs after drug-eluting stent implantation, although no clinically-available imaging device can provide a morphologic delineation of re-endothelialization. Functionally competent endothelial regrowth is also crucial to

Discussion

The major findings of the present study are that between 6 months and 12 months post-implantation: (1) the distribution of uncovered SES struts decreased; (2) the thickness of neointima increased; (3) late tissue growth occurred in the entire stent length at 6 months and 24% (5 of 21 SES) had full coverage at 12 months. A representative case with serial changes in SES conditions implanted for a chronic total occlusion is shown in Figure 2. From 6 months to 12 months, further neointimal coverage was observed on malapposed struts and struts at the side branch orifices. At 12 months after SES implantation, the neointimal thickness and image intensity were increased, compared to those at 6 month. These findings might reflect neointimal maturation.

Neointimal Thickness on SES Struts Based on OCT Images

In previous reports, Bland-Altman analysis indicated that the mean difference in neointimal thickness for intra-observer measurements was 2.3 μm (upper 2SD: 29.6 μm and lower 2SD: −25.1 μm), and that for inter-observer measurements was 0.7 μm (upper 2SD: 31.5 μm and lower 2SD: −33.5 μm). The thickness of neointima observed at 6 months post SES implantation significantly increased from 6 months to 12 months (average ± SD: from 112±123 to 120±130 μm; P<0.05, median; from 70 μm (25th percentile: 40.0 μm, 75th percentile: 170.0 μm) to 80 μm (25th percentile: 40.0 μm, 75th percentile: 160.0 μm); P<0.05). Of the 17 struts at a side branch orifice, the thickness of neointima observed at 6 months did not change in 2 struts and the thickness increased in 11 struts (34±19 to 79±26 μm; P<0.001). The distributions of neointimal thickness on SES struts at 6 months and 12 months are shown in Figure 3. There was no remarkable shift in the thickness distribution between 6 months and 12 months, but the frequency of uncovered strut cross-sections was decreased and the frequency of neointimal thickness greater than 100 μm was increased.
anti-thrombotic homeostasis in the arterial wall. The pathologic mechanism of SES late thrombosis might be multi-factorial, such as stent malapposition, poor neointimalization, local hypersensitivity reaction, positive arterial remodeling, restenosis, stent under expansion, increased coagulability, and/or another plaque rupture adjacent to the stent.23,24 Thus, to more accurately predict the risk of stent thrombosis, a larger number of stents must be followed up with OCT.

**Study Limitations**

There were several limitations to our study. Our findings were based on observations in a relatively small number of patients and stented segments. Also, this study does not represent an unbiased sampling of all SES because OCT cannot be used to visualize coronary ostial lesions or very tortuous lesions. A non-occlusion image acquisition technique, which was introduced by Kataiwa et al.,25 might minimize OCT limitation. Because the resolution of OCT is 15–20 μm, tissue structures with dimensions less than 15 μm, such as the endothelium or thin smooth muscle cell layer, cannot be resolved with OCT. The possibility that SES struts that appear uncovered on OCT images are not completely devoid of tissue growth cannot be ruled out. To the best of our knowledge, however, there is no evidence that endothelium covers stent struts without neointimal growth. Thus, a certain proportion of SES struts is likely to be devoid of tissue coverage and would therefore have thrombogenic potential. OCT is limited in the differentiation between a thrombus and neointima, and some of the neointima observed on the strut after 12 months might in fact be a thin fibrin layer or thrombus. The results might have been different if ticlopidine had been administered prior to stent implantation and continued for 12 months.

**Conclusion**

Between 6 and 12 months post-implantation, the neointimal coverage of the struts increased, and the neointimal thickness on the struts observed at 6 months was further increased at 12 months. These findings suggest that neointimalization of SES continues for at least 12 months.

**Disclosure**

None.

**References**


24. Mintz GS, Shah VW, Weissman NJ. Regional remodeling, late incomplete stent apposition and continued for 12 months. These findings suggest that neointimalization of SES continues for at least 12 months.