Nonuniform Strut Distribution Correlates With More Neointimal Hyperplasia After Sirolimus-Eluting Stent Implantation

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Background—Little is known about causes of intimal hyperplasia (IH) after sirolimus-eluting stent (SES) implantation. Methods and Results—Intravascular ultrasound was performed in 24 lesions with intra-SES restenosis and a comparison group of 25 nonrestenotic SESs. To assess stent strut distribution, the maximum interstrut angle was measured with a protractor centered on the stent, and the visible struts were counted and normalized for the number of stent cells. In SES restenosis patients, minimum lumen site was compared with image slices 2.5, 5.0, 7.5, and 10.0 mm proximal and distal to this site. The minimum lumen site had a smaller IVUS lumen area at follow-up (2.7±0.9 versus 6.2±1.9 mm²; P<0.01), larger maximum interstrut angle (135±39° versus 72±23°; P<0.01), larger IH area (3.4±1.5 versus 0.6±1.1 mm²; P<0.01) and thickness (0.7±0.3 versus 0.1±0.2 mm; P<0.01) at maximum interstrut angle, and fewer stent struts (4.9±1.0 versus 6.0±0.5; P<0.01) even when normalized for the number of stent cells (0.78±0.15 versus 0.97±0.07; P<0.01). Compared with nonrestenotic SES, the restenosis lesions also had a smaller minimal lumen area, larger interstrut angle, thicker IH at maximum interstrut angle, fewer stent struts, and larger maximum interstrut angle. Multivariate analysis identified the number of visualized stent struts normalized for the number of stent cells and larger maximum interstrut angle as the only independent IVUS predictor of IH cross-sectional area (P<0.01 and P<0.01), minimum lumen area (P<0.01 and P<0.01), and IH thickness (P<0.01 and P<0.01).

Conclusions—The number and distribution of stent struts affect the amount of neointima after SES implantation.

Key Words: restenosis ■ stents ■ ultrasonics

Although sirolimus-eluting stents (SESs) strongly suppress neointimal hyperplasia (IH),1,2 in-stent restenosis after SES implantation still occurs.3–5 One in vitro study has shown that nonuniform circumferential stent strut distribution affects local drug concentration.6 It was our hypothesis that the number and distribution of the stent struts might also affect the magnitude of IH after SES implantation in human coronary arteries.

Methods

Study Patients

From the Lenox Hill Hospital clinical and core intravascular ultrasound (IVUS) laboratory databases, we identified 24 nonostial intrastent restenoses (>50% angiographic diameter stenosis) after de novo SES implantation. A consecutive series of 25 SES-treated lesions in asymptomatic patients without restenosis or late malapposition served as a comparison group. Prespecified clinical and laboratory data were obtained from hospital charts. This study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

Quantitative Coronary Angiography

Angiographic analysis was performed with a computer-assisted, automated edge-detection algorithm (CMS, MEDIS) by an independent observer unaware of the clinical and IVUS findings. Vessel angulation was measured in a nonforeshortened view at end diastole as the angle formed by the centerline through the lumen proximal to the stenosis and opposite a second centerline in the straight portion of the artery distal to the stenosis. The accuracy of this method has been reported in detail.7

IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.1 to 0.2 mg nitroglycerin with motorized transducer pullback and a commercially available scanner (Boston Scientific) incorporating a 40-MHz single-element beveled transducer rotating at 1800 rpm.

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The ultrasound catheter was advanced >10 mm beyond the stent into the distal vessel. The transducer was withdrawn at a pullback speed of 0.5 mm/s to a point >10 mm proximal to the stent. Images were recorded onto 0.5-in high-resolution super VHS for offline analysis.

Quantitative IVUS analysis was performed with computerized planimetry (TapeMeasure, Indec Systems) by an independent experienced observer who was unaware of the clinical data. Measurements were performed at 9 cross sections: the minimum lumen site and 8 remote sites 2.5, 5.0, 7.5, and 10.0 mm proximal and distal to the minimum lumen site. (The 2.5- and 5.0-mm slices and the 7.5- and 10.0-mm slices were combined for analysis.) For the nonrestenotic (comparison) group, measurements were performed only at the minimum lumen site because of the lack of neointima in these patients. At each cross section, the following were obtained: (1) maximum angle between adjacent stent struts; (2) number of stent struts; (3) stent, lumen, external elastic membrane (EEM), plaque and media (P&M) behind stent (peri-stent P&M equals EEM minus stent), and intimal hyperplasia cross-sectional area (CSA) (IH equals stent minus minimum lumen area (MLA)); (4) maximum IH and peri-stent P&M thickness; and (5) maximum IH and P&M thickness within the maximum interstrut angle (Figure 1). Stent eccentricity was calculated as minimum divided by maximum stent diameter. The number of visualized stent struts was normalized for (divided by) the number of stent cells: 2.5- and 3.0-mm SESs have 6 cells, and 3.5-mm SESs have 7 cells. To exclude strut fracture, the number of stent struts in 13 patients with postintervention and follow-up IVUS was counted millimeter by millimeter along the stent length at both time points.

Statistical Analysis
Statistical analysis was performed with StatView 5.0 (SAS Institute). Data are presented as frequencies or mean ± SD. Comparison was performed with χ² statistics, unpaired Student’s t test, and ANOVA with post hoc comparison using the Bonferroni correction. Values of P<0.05 were considered statistically significant. Univariate variables with P<0.2 were entered into the multivariate model to find independent predictors of IH CSA, MLA, and IH thickness.

Results
The interval from SES implantation to follow-up was 6.1±1.8 months (range, 2.0 to 10.6 months). In the restenosis

<table>
<thead>
<tr>
<th>TABLE 1. IVUS Data in 24 Patients With SES Restenosis Comparing the Minimum Lumen Site, Sites 2.5 and 5.0 mm Proximal and Distal to the Minimum Lumen Site, and Sites 7.5 and 10.0 mm Proximal and Distal to the Minimum Lumen Site</th>
<th>Minimum Lumen Site (n=24)</th>
<th>2.5/5.0-mm Sites (n=95)</th>
<th>7.5/10.0-mm Sites (n=72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLA, mm²</td>
<td>2.7±0.9</td>
<td>5.8±1.9</td>
<td>6.6±2.0</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>EEM area, mm²</td>
<td>12.6±4.5</td>
<td>13.5±4.6</td>
<td>14.0±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>P&amp;M area, mm²</td>
<td>6.5±2.9</td>
<td>6.8±3.2</td>
<td>7.2±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Stent area, mm²</td>
<td>6.2±1.9</td>
<td>6.6±1.8</td>
<td>6.7±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Stent eccentricity</td>
<td>0.88±0.04</td>
<td>0.89±0.05</td>
<td>0.89±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Stent struts, n</td>
<td>4.9±1.0</td>
<td>5.9±0.4</td>
<td>6.2±0.5</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Stent struts, n (%)</td>
<td>3 (13)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (21)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8 (33)</td>
<td>8 (8)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8 (33)</td>
<td>81 (85)</td>
<td>49 (68)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0 (0)</td>
<td>5 (5)</td>
<td>18 (25)</td>
<td></td>
</tr>
<tr>
<td>Normalized stent struts, n</td>
<td>0.78±0.15</td>
<td>0.95±0.08</td>
<td>0.99±0.05</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>IH area, mm²</td>
<td>3.4±1.5</td>
<td>0.8±1.3</td>
<td>0.2±0.5</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Maximum angle between stent struts, °</td>
<td>135±39</td>
<td>78±25</td>
<td>64±18</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>P&amp;M thickness at maximum interstrut angle, mm</td>
<td>0.8±0.4</td>
<td>0.8±0.4</td>
<td>0.7±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>IH thickness at maximum interstrut angle, mm</td>
<td>0.7±0.3</td>
<td>0.2±0.3</td>
<td>0.1±0.2</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

*n All P<0.01 minimum lumen site vs 2.5/5.0-mm sites, minimum lumen site vs 7.5/10.0-mm sites, and 2.5/5.0-mm sites vs 7.5/10.0-mm sites (post hoc analyses).
group, 19 of 24 patients had recurrent angina or a positive stress test, and 5 of 24 asymptomatic patients underwent scheduled follow-up. All 25 patients in the comparison group underwent scheduled follow-up.

SES Restenosis
SES restenosis was all focal (≤10 mm). There was no significant correlation between the follow-up interval and IH length ($r=0.206, P=0.3$), IH CSA ($r=0.049, P=0.7$), MLA ($r=0.044, P=0.8$), and IH thickness ($r=0.014, P=0.9$).

In the 24 SES restenosis lesions, the minimum lumen site was compared with sections 2.5/5.0 and 7.5/10.0 mm proximal and distal to the minimum lumen site (Table 1). The minimum lumen site had a smaller IVUS follow-up MLA, a larger maximum interstrut angle, and a larger follow-up IH CSA and thickness at the maximum interstrut angle.

To exclude strut fracture (defined as a decrease in number of stent struts between implantation and follow-up in a single cross section), we analyzed 13 SES restenosis patients with IVUS at implantation and follow-up. There was a decrease in the number of struts at the minimum lumen site in only 2 patients. In 1 patient, the number of stent struts decreased from 6 to 3, the maximum interstrut angle increased from 57° to 146°, but the stent CSA did not change (8.4 to 8.6 mm²) (Figure 2). In the second patient, the number of stent struts decreased from 6 to 3, the maximum interstrut angle increased from 62° to 157°, but there was also no change in stent CSA (8.6 mm² at implantation and follow-up). In the other 11 patients with SES restenosis and both postimplantation and follow-up IVUS studies, the minimum lumen site (compared with the 2.5/5.0- and 7.5/10.0-mm sites) had a smaller follow-up IVUS MLA and a larger IH CSA and thickness at the maximum interstrut angle.

Comparison With Non-SES Restenosis
Table 2 compares the 24 patients with SES restenosis and the group without SES restenosis. The SES restenosis group had longer SESs, higher maximum inflation pressures at implantation, smaller IVUS minimal lumen CSA at follow-up, smaller EEM CSA, less peri-stent P&M CSA, smaller minimal stent CSA, larger IH CSA, fewer visualized stent struts even when normalized for the number of stent cells, and a larger maximum interstrut angle at the minimum lumen site. We also compared implantation and follow-up IVUS studies in 15 non-SES restenosis patients; none had a decrease in the number of struts at the minimum lumen site suggestive of strut fracture.
Combining both the restenotic and nonrestenotic groups, we found no significant correlation between vessel angulation and normalized number of stent struts at the minimum lumen site ($r=0.219$, $P=NS$).

Of the 368 cross sections selected for analysis, detectable IH was present in 119. Maximum IH thickness was observed within the maximal interstrut angle in 98 of these 119 sections (82%), and the maximum peri-stent P&M thickness was observed within the maximal interstrut angle in 41 of these 119 sections (34%).

Univariate IVUS predictors of IH CSA, MLA, and IH thickness at follow-up are shown in Table 3. Multivariate analysis identified the number of visualized stent struts normalized for the number of stent cells and the maximum interstrut angle as the only independent predictor of IH CSA (coefficient, $4.154$, $P<0.01$; and coefficient, $0.013$, $P<0.01$) and thickness (coefficient, $0.642$, $P<0.01$; and coefficient, $0.003$, $P<0.01$). Stent CSA, number of visualized stent struts normalized for the number of stent cells, and maximum interstrut angle were the only independent IVUS predictors of MLA (coefficient, $0.788$, $P<0.05$; coefficient, $4.377$, $P<0.01$; and coefficient, $0.013$, $P<0.01$).

**Discussion**

IVUS analysis of SES restenoses demonstrated fewer stent struts, especially when normalized for the number of stent cells, and a larger maximum interstrut angle at the minimum lumen site compared with remote cross sections in restenotic SESs and with nonrestenotic SES lesions. This indicates that nonuniform strut distribution contributes to IH after SES implantation in de novo lesions.

In the Study of the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) and TAXUS-II trials, restenotic lesions frequently were located near the stent margins or at the site of a gap between stents (64.5% in...
TABLE 3. Univariate Predictors of IH Area and Thickness and MLA at Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>IH CSA</th>
<th></th>
<th>MLA</th>
<th></th>
<th>IH Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>EEM area</td>
<td>0.27</td>
<td>0.003</td>
<td>0.55</td>
<td>&lt;0.0001</td>
<td>0.18</td>
</tr>
<tr>
<td>Persistent P&amp;M area</td>
<td>0.23</td>
<td>0.012</td>
<td>0.38</td>
<td>&lt;0.0001</td>
<td>0.18</td>
</tr>
<tr>
<td>P&amp;M thickness at maximum interstrut angle</td>
<td>0.27</td>
<td>0.003</td>
<td>0.04</td>
<td>0.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Stent area</td>
<td>0.27</td>
<td>0.003</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td>0.14</td>
</tr>
<tr>
<td>Stent eccentricity</td>
<td>0.07</td>
<td>0.4</td>
<td>0.01</td>
<td>0.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Normalized number of stent struts</td>
<td>0.56</td>
<td>&lt;0.0001</td>
<td>0.43</td>
<td>&lt;0.0001</td>
<td>0.58</td>
</tr>
<tr>
<td>Maximum interstrut angle</td>
<td>0.47</td>
<td>&lt;0.0001</td>
<td>0.54</td>
<td>&lt;0.0001</td>
<td>0.53</td>
</tr>
</tbody>
</table>

SIRIUS, 50.0% in TAXUS-II).\(^3\,^8\) Recently, SES fractures have been reported in cases of very focal intrastent restenosis while there was complete abolition of IH in the rest of the stented segment.\(^9\,^10\) A gap between stents, stent strut fracture, or the stent edge may be associated with a decrease in local drug delivery that may then contribute to development of restenosis. Similarly, an in vitro study demonstrated that local drug underdosing occurred at sites of nonuniform circumferential stent strut distribution.\(^6\) The present report found that maximum IH thickness occurred at the site of the maximal interstrut angle in 82% of SESs, along with a significant positive correlation between IH CSA and IH thickness and the maximum interstrut angle. In addition, 16 of 24 intrastent restenoses occurred in segments with <6 struts; there was a negative correlation between IH CSA and IH thickness and number of struts (having fewer struts was associated with more IH); and the number of visualized struts normalized for the number of stent cells was an independent predictor of IH CSA and thickness. In 13 patients with IVUS at implantation and follow-up, there was a decrease in stent strut number in only 2 patients, suggesting stent strut fracture in these patients. (Evidence of strut fracture was not seen in any nonrestenotic lesion.) In the remaining 11 patients with IVUS at implantation and follow-up, the number of stent struts remained constant. This suggests that nonuniform stent strut distribution may more common than stent strut fracture. Because SES effectiveness depends on correct dosing, nonuniform stent strut distribution may be a more important cause of IH proliferation than stent strut fracture. It may be necessary to optimize stent expansion or to implant another drug-eluting stent to counteract underdosing from nonuniform stent strut distribution.

Study Limitations
The number of lesions was small. Longitudinal distribution of stent struts was not considered. The angle of the ultrasound beam relative to the stent may affect the number of struts visualized; however, there was no correlation between the number of struts visualized and the maximum vessel bend in the lesion (determined angiographically). Postimplantation and follow-up IVUS was performed in only 13 of 24 restenotic SESs; therefore, it is not possible to exclude strut fracture in the other 11 patients. However, when only the 11 patients with postimplantation and follow-up IVUS and no change in the number of stent struts were analyzed, the conclusions were unchanged. The correlation coefficients are not strong, indicating that other factors may be important.

Conclusions
Nonuniform stent strut distribution and fewer struts may result in more IH after SES.

References
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