In Vivo Comparison Between Optical Coherence Tomography and Intravascular Ultrasound for Detecting Small Degrees of In-Stent Neointima After Stent Implantation

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Objectives  The purpose of this study was to evaluate optical coherence tomography (OCT) for detecting small degrees of in-stent neointima (ISN) after stent implantation compared with intravascular ultrasound (IVUS).

Background  The importance of detecting neointimal coverage of stent struts has grown with the appreciation of the increased risk for late stent thrombosis after drug-eluting stent (DES) implantation. Intravascular ultrasound, the current standard for evaluating the status of DES, lacks the resolution to detect the initial neointimal coverage. Optical coherence tomography has greater resolution but has not yet been compared with IVUS in vivo with histological correlation for validation.

Methods  Intravascular ultrasound and OCT were performed with motorized pullback imaging in 6 pigs across 33 stents, 1 month after implantation. Each pig was euthanized, and histological measurements of vessel, stent, and lumen dimensions were performed in 3 sections of each stent. A small degree of ISN was defined as occupying < 30% of the stent area measured with histology. The IVUS, OCT, and histological assessment of ISN were compared in matched cross-sections of the stents with a small degree of ISN.

Results  Eleven stents had a small degree of ISN (average ISN area: 1.26 ± 0.46 mm², and percent area obstruction: 21.4 ± 5.2%). Compared with histology, the diagnostic accuracy of OCT (area under the receiver operating characteristic curve [AUC] = 0.967, 95% confidence interval [CI] 0.914 to 1.019) was higher than that of IVUS (AUC = 0.781, 95% CI 0.621 to 0.838).

Conclusions  Optical coherence tomography detects smaller degrees of ISN more accurately than IVUS and might be a useful method for identifying neointimal coverage of stent struts after DES implantation. (J Am Coll Cardiol Intv 2008;1:168–73) © 2008 by the American College of Cardiology Foundation
Polymer-based drug-eluting stents (DES) remain the primary device used for treating patients with symptomatic coronary artery disease undergoing percutaneous coronary intervention. Although this technology has reduced restenosis rates compared with bare-metal stents (BMS), late stent thrombosis, a life-threatening complication is emerging as a major concern (1–4). Autopsy studies have demonstrated heterogeneous healing in patients with DES dying from late stent thrombosis (5–8). Recently, Finn et al. (8) demonstrated that the best predictor of late stent thrombosis was the ratio of uncovered/total stent struts. The importance of detecting small degrees of in-stent neointima (ISN) covering stent struts has grown as the awareness of the risk of late stent thrombosis after DES implantation has grown.

Methods

Procedure. Animal protocols were approved by the Stanford University Administrative Panel on Laboratory Animal Care. Six juvenile Yorkshire swine (25 to 40 kg) were pre-treated with aspirin (ASA) (650 mg/day), clopidogrel (75 mg/day), and nifedipine (30 mg/day) at least 12 h before the procedure. After induction, vascular access was obtained with an 8-F vascular sheath in the carotid artery, and 300 IU/kg of heparin was administered systemically. The coronary arteries were then selectively cannulated, with a standard 8-F angioplasty system. Thirty-three stents (15 BMS [7 Bx Velocity (Cordis Corp., Miami Lakes, Florida), 8 Express (Boston Scientific, Natick, Massachusetts)], 18 DES [9 Cypher (Cordis Corp.), 9 TAXUS (Boston Scientific)]) were implanted in the left anterior descending artery, left circumflex artery, and right coronary artery to achieve a 1.2:1 to 1.4:1 stent:artery ratio. After stent implantation, animals were treated with ASA 650 mg and clopidogrel 75 mg daily until the end of the study. Quantitative coronary angiography was performed with a computer-assisted, automated, edge-detection algorithm by an isolated operator who was blinded to type of stent, IVUS, OCT, and histologic data. The lesion length, reference diameter, minimal lumen diameter, and diameter stenosis were calculated.

IVUS. The IVUS was performed with 2.9-F 40-MHz IVUS catheter (Boston Scientific) after administration of 200 μg of nitroglycerin with an auto-pullback at 0.5 mm/s.

All IVUS procedures were recorded on VHS videotapes, and images were digitized for analysis. Quantitative coronary ultrasound analysis (QCU) with the EchoPlaque imaging system (Indec Systems Inc., Mountain View, California) was performed by a reader blinded to the OCT and histologic analysis.

OCT. The OCT images were obtained with the M2 OCT imaging system (LightLab Imaging Inc., Westford, Massachusetts) (Figs. 1A to 1C). ImageWire (LightLab Imaging Inc.) is an imaging probe that delivers the light to the tissue and collects the signals. The ImageWire consists of 0.006-inch (0.15 mm) fiberoptic core inside a sheath with a maximum O.D. of 0.019-inch (0.48 mm). To image the vessel with OCT, blood must be replaced with saline with an occlusion balloon (Fig. 1D) with a thin-walled polyurethane 4.0-mm-diameter × 6.0-mm-length balloon designed for very-low-pressure inflation. A flush port located at the distal tip replaces blood with saline from the vessel segment being imaged. Motorized pull-back OCT imaging was performed at a pullback rate of 1.0 mm/s. Images were acquired at 15 frames/s, displayed with a color look-up table and digitally archived.

The OCT measurements were performed with the LightLab OCT imaging proprietary software with a mouse-based interface by a reader blinded to the IVUS and histologic results. The system was calibrated to the reflection of the OCT imaging wire, which is the standard calibration technique for this system; then, areas were manually traced.

Reproducibility. Interobserver and intraobserver variability were assessed for all images and all measurements. Interobserver variability was calculated as the SD of the difference between the measurements of the 2 independent observers and expressed as a percentage of the average value. Intraobserver variability was calculated as the SD of the difference between the first and second determinations (at a 1-week interval) for a single observer and expressed as a percentage of the average value.
Histology. The stented coronary arteries were dissected from the heart, and the rest of the heart was placed back in appropriately labeled containers without further examination. Serial cross-sections were obtained at 0.6-mm intervals from the proximal to the distal end. Multiple sections were polished and surface-stained with metachromatic stain to an equivalent of a 6-μm section before mounting in immersion oil for viewing under the microscope. Area measurements of the artery, stent/internal elastic lamina, and lumen were obtained with a Nikon Labophoto II compound microscope (Nikon, Melville, New York). We used the Sigma-Scan scientific measurement software from SPSS (SPSS Inc., Chicago, Illinois) for the area measurements and calculated the intimal area, average intimal thickness, and the percent area stenosis. In each stent, proximal, mid, and distal stented histologic segments were matched to the OCT and IVUS images with the percentile method on the basis of the total number of sections of the stent and the number of cuts by OCT and IVUS (Fig. 2). The IVUS, OCT, and histological cross-sections were matched by measuring the distance from the proximal end of the stent. These assessments of ISN were compared in matched cross-sections of the stents with a small degree of ISN. A small degree of ISN was defined as occupying <30% of the stent area on the basis of histology.

Statistical analysis. Statistical analysis was performed with SPSS 13.0 (SPSS Inc.). Data are presented as frequencies or mean ± SD. The correlation between OCT and histological measurements was analyzed by simple linear regression with 95% confidence intervals (CIs). Receiver-
operating characteristic (ROC) analysis was used to compare diagnostic accuracy of OCT and IVUS for detecting a small degree of ISN. Area under the ROC curve (AUC) was calculated to compare the accuracies of the different approaches. A p value $< 0.05$ was considered statistically significant.

**Results**

The occlusion catheter successfully provided motorized pullback OCT images in the stented coronary arteries without any complications. Representative matched images of OCT, IVUS, and histology are shown in Figure 3. Interobserver and intraobserver variabilities for the measurements were 3.7% and 4.3%, respectively.

The results of measurements by angiogram, IVUS, OCT, and pathology in all segments are shown in Tables 1 and 2. Compared with histology and OCT, IVUS tended to overestimate lumen area and underestimated percent area stenosis. The correlation between OCT and histology measurements ($r = 0.980$, $p < 0.001$, for lumen area; $r = 0.978$, $p < 0.001$, for stent area; and $r = 0.961$, $p < 0.001$, for neointimal area, shown in Fig. 4) was stronger than the correlation between IVUS and histology ($r = 0.803$, $p < 0.001$, for lumen area; $r = 0.817$, $p < 0.001$, for stent area; and $r = 0.776$, $p < 0.001$, for neointimal area).

In 11 of the 33 stents there was a small degree of ISN (3 Cypher, 3 Bx Velocity, 4 TAXUS, 1 Express), and as demonstrated in Table 3, IVUS again overestimated lumen area and underestimated percent area stenosis. The diagnostic accuracy for detecting a small degree of ISN by OCT (AUC = 0.967, 95% CI 0.914 to 1.019) was higher than that by IVUS (AUC = 0.781, 95% CI 0.621 to 0.838) (Fig. 5).

**Discussion**

Since the first studies of BMS were performed, stent thrombosis has been a major concern, owing to its significant morbidity and mortality. Dual antiplatelet therapy with aspirin and a thienopyridine as well as improved percutaneous coronary interventional techniques (13) have decreased measurements ($r = 0.980$, $p < 0.001$, for lumen area; $r = 0.978$, $p < 0.001$, for stent area; and $r = 0.961$, $p < 0.001$, for neointimal area, shown in Fig. 4) was stronger than the correlation between IVUS and histology ($r = 0.803$, $p < 0.001$, for lumen area; $r = 0.817$, $p < 0.001$, for stent area; and $r = 0.776$, $p < 0.001$, for neointimal area).

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**Table 1. Quantitative Coronary Angiogram Analysis in All Stents**

<table>
<thead>
<tr>
<th>Stents, n = 33</th>
<th>History</th>
<th>OCT</th>
<th>IVUS</th>
</tr>
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<tbody>
<tr>
<td>Lumen area</td>
<td>3.28 ± 1.36</td>
<td>3.47 ± 1.38</td>
<td>3.96 ± 1.51</td>
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<tr>
<td>Stent area</td>
<td>5.44 ± 1.26</td>
<td>5.63 ± 1.23</td>
<td>5.70 ± 1.48</td>
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<tr>
<td>ISN area</td>
<td>2.16 ± 1.08</td>
<td>2.17 ± 1.20</td>
<td>1.68 ± 1.48</td>
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<tr>
<td>% area stenosis</td>
<td>40.7 ± 19.2</td>
<td>38.9 ± 20.3</td>
<td>29.9 ± 20.1</td>
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ISN = in-stent neointima; IVUS = intravascular ultrasound; OCT = optical coherence tomography.
the risk of thrombosis to an acceptable level, although its incidence remains high when BMS are placed in complex patients and lesions. Drug-eluting stents have reduced restenosis rates dramatically; however, late stent thrombosis has emerged as a major concern. Histologic studies from human autopsies have reported that heterogeneity of healing is a common finding in DES with evidence of late stent thrombosis. Recently Finn et al. (8) demonstrated that the best predictor of late stent thrombosis was the ratio of incompletely endothelialized stent struts to total stent struts. Therefore, confirming neointimal coverage of stent struts after DES implantation might be critical in assessing the risk for late stent thrombosis.

Our data suggest a much stronger correlation between histological analysis and in vivo assessment of ISN with OCT as compared with IVUS imaging. This is likely explained by the fact that OCT provides enhanced resolution, on the order of 10 \( \mu \text{m} \), compared with a 150-\( \mu \text{m} \) resolution with IVUS. Both imaging technologies formulate images by detecting the intensity of back-reflected waves at varying depths in biological tissues. Owing to the difference in wavelength, the near-infrared light employed by OCT can be focused onto a much smaller cylinder at the lens focal point than the IVUS ultrasound waves and can therefore reveal smaller structures in the atherosclerotic tissue. However, the near-infrared light only penetrates 1 to 1.5 mm into the tissue, whereas the sound waves penetrate up to 4 mm. Several groups have reported comparisons between OCT and IVUS (9–11,14,15), in an ex vivo setting. To our knowledge, this is the first study comparing the diagnostic

<table>
<thead>
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<th>Stents, n = 11</th>
<th>Histology</th>
<th>OCT</th>
<th>IVUS</th>
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</thead>
<tbody>
<tr>
<td>Lumen area</td>
<td>4.52 ± 0.61</td>
<td>4.74 ± 0.69</td>
<td>5.21 ± 0.84</td>
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<tr>
<td>Stent area</td>
<td>5.78 ± 0.93</td>
<td>6.01 ± 1.01</td>
<td>6.19 ± 1.27</td>
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<tr>
<td>ISN area</td>
<td>1.26 ± 0.46</td>
<td>1.27 ± 0.57</td>
<td>0.98 ± 0.69</td>
</tr>
<tr>
<td>% area stenosis</td>
<td>21.4 ± 5.2</td>
<td>20.3 ± 7.0</td>
<td>14.7 ± 8.6</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
accuracy between OCT and IVUS for detecting small amounts of ISN after stent deployment in an in vivo setting, with histology as the reference standard.

The greater resolution provided by OCT is likely necessary in most clinical settings. The percent neointimal hyperplasia obstruction detected by IVUS analysis in the RAVEL (Randomized Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions) trial was 1 ± 3% (16), but Takano et al. (17) have reported that 3 months after DES implantation only 7% of stent struts achieve a neointimal hyperplasia ≤100 μm and that the percent neointimal hyperplasia area is 10 ± 4%. The current necessities for vessel occlusion and saline flushing as well as its invasive nature limit the broad application of OCT in the clinical setting. In addition, OCT lacks the penetration necessary to accurately image vessel dimensions.

**Study limitations.** There are a number of limitations to our study. Technical limitations include the difficulty in matching exactly the cross sections from histology, OCT, and IVUS. In addition, the preparation for histologic analysis can alter the morphology of the vessel. Histological samples might have the arterial cross-sectional artifacts can alter the morphology of the vessel. Histological specimens might have the cross sections from histology, OCT, and IVUS. In addition, the preparation for histologic analysis can alter the morphology of the vessel. Histological samples might have the arterial cross-sectional artifacts caused by pressure perfusion fixation-induced aldehyde cross-linking of tissue proteins and plastic resin polymerization-induced shrinkage.

Our findings are only applicable for stented segments; in nonstented vessels, balloon occlusion and saline flushing can result in vessel shrinkage. We investigated OCT and IVUS in a porcine model, and their accuracy might differ in the clinical setting. The study is also limited by the small sample size.

**Conclusions**

In this study, in vivo OCT measurements after coronary stenting correlated extremely well with histology. Optical coherence tomography can detect smaller degrees of ISN more accurately than IVUS, on the basis of histologic correlation. Optical coherence tomography might be a useful method for detecting adequate neointimal coverage of stent struts after DES implantation.

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**REFERENCES**