Tissue Characterization After Drug-Eluting Stent Implantation Using Optical Coherence Tomography

Caroline Malle, Tomohisa Tada, Kristin Steigerwald, Giovanni J. Ughi, Tibor Schuster, Masataka Nakano, Steffen Massberg, Johannes Jehle, Giulio Guagliumi, Adnan Kastrati, Renu Virmani, Robert A. Byrne, Michael Joner

Objective—To validate optical coherence tomography (OCT) imaging for assessment of vascular healing in a preclinical animal model and human autopsy cases and to translate the findings to the assessment of vascular healing after drug-eluting stent implantation in clinical practice.

Approach and Results—Drug-eluting and bare metal stents were imaged 28 and 42 days after implantation in atherosclerotic rabbits using OCT and simultaneously evaluated by histology. After coregistration with histology, gray-scale signal intensity (GSI) was measured for identified mature or immature neointimal tissue. Autopsy specimens were imaged with OCT and GSI values correlated with histology. Finally, prospective OCT imaging and GSI measurements were acquired in 10 patients undergoing follow-up 6 months after stenting with drug-eluting stents. Histopathologic and OCT morphometric analysis of implanted stents showed excellent correlation. Neointimal growth and vessel healing at 28 days in the animal model best correlated with human stented arteries at 6 months. In animal and human autopsy specimens, mature neointimal tissue consistently showed higher GSI values. Receiver operating characteristic curve analysis displayed high sensitivity and specificity for detection of mature neointima in animal (96% and 79%, respectively) and human autopsy (89% and 71%, respectively) data. In patients undergoing OCT follow-up 6 months after drug-eluting stent implantation, prospective GSI analysis revealed that a minimum of 27.7% of areas above stent struts represented mature neointima.


Key Words: atherosclerosis ■ drug-eluting stents ■ gray-scale ■ optical coherence tomography ■ signal intensity ■ vascular healing

Stent strut coverage is an important predictor of stent thrombosis in human autopsy studies particularly in patients treated with drug-eluting stents (DES). Optical coherence tomography (OCT) is a high-resolution imaging technology that permits a precise assessment of strut coverage in preclinical and clinical settings and may have an important role in the stratification of patients at risk for stent thrombosis. However, estimation of quantitative and qualitative strut tissue coverage requires fundamental validation in preclinical models, and currently available study data are associated with several important limitations, which hinder translation to human disease states.

First, fundamental differences in the temporal course of vascular healing between animal models and humans mean that the relevance of preclinical research data are limited by the inability to find chronological correlates in human disease. Second, although vascular healing after stenting is dependent on underlying disease morphology and plaque composition, existing OCT histopathology correlation studies have mostly been performed in healthy animal arteries. Third, lack of strut coverage by mature neointimal tissue, including smooth muscle and endothelial cells with interspersed extracellular matrix, has been reported to be an important risk factor for late stent thrombosis. However, although OCT imaging of stented coronary arteries has improved our capability to distinguish covered from uncovered stent struts, not all covered struts are covered by mature neointimal tissue, and OCT tissue characterization studies are lacking to date. Indeed, the development and validation of quantitative OCT tissue characterization methods to differentiate between mature and immature tissue coverage may have important implications for clinical practice.

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In the current study, we aimed to compare OCT morphometric parameters with preclinical histopathologic data at 2 different time points after stent implantation (28 and 42 days) in a rabbit iliac model of atherosclerotic disease. Furthermore, we sought to perform tissue characterization by gray-scale signal intensity (GSI) analysis to classify tissue areas overlying stent struts as either mature or immature. We then aimed to apply these findings to the assessment of human autopsy specimens and to a cohort of patients treated with DES undergoing OCT surveillance at 6 months after intervention.

Materials and Methods
Materials and Methods are available in the online-only Supplement.

Results
Histological Data After Stent Implantation in Atherosclerotic Rabbits and Correlation to OCT
Data from a total of 14 atherosclerotic rabbits treated with 2 types of DES or control bare metal stents (BMS) were available. Neointimal area increased between 28 and 42 days and was significantly higher in BMS at 28 days. A similar trend was observed for neointimal thickness above stent struts. In DES, a high degree of stent struts remained uncovered at 28 days, whereas almost complete coverage was observed at 42 days. In contrast, BMS showed almost complete strut coverage at 28 days (Table I in the online-only Data Supplement). With regard to vascular healing, BMS consistently showed lower fibrin deposition in the neointimal tissue and higher percent luminal reendothelialization (Table II in the online-only Data Supplement).

Comparison of OCT Data Between Animal and Humans
Lesion level–based percent volume obstruction showed comparable values for atherosclerotic rabbits at 28 days and humans (Table 2). Frame level–based analysis of neointimal area was 0.48 (0.26-0.71) and 0.98 (0.69-1.28) mm² in rabbits 28 and 42 days after stent implantation, respectively, whereas it was 0.60 (0.42-0.77) mm² in humans at 6-month follow-up (P=ns for humans versus 28-day rabbits; Table 3). Strut level analysis revealed 42.1% uncovered struts at 28 days versus 7.7% uncovered stent struts at 42 days in animals, whereas the

Figure 1. Correlation of representative histopathologic microscopy images of stented iliac arteries with optical coherence tomography (OCT) frames. Top, Histological cross-sections stained by Movat pentachrome (A, C) at magnification ×40. Bottom, The corresponding native OCT frames (B, D).
percentage of uncovered stent struts was 28.3% in humans at 6-month follow-up (P=ns for humans versus 28-day rabbits; Table 4; Figure 2).

Validation of Tissue Characterization in the Preclinical Setting

Histologically characterized regions of mature tissue showed significantly higher smooth muscle cell and, in turn, lower proteoglycan/collagen, fibrin, and inflammatory cell content as compared with immature tissue regions (Table 5; Figure 3). By immunohistochemistry, mature neointimal tissue was predominantly composed of α–actinin-positive smooth muscle cells with minimal presence of RAM-11–positive macrophages. In contrast, immature neointimal tissue was predominantly composed of RAM-11–positive macrophages with minimal interspersed smooth muscle cells (Figure 3). There was a significant statistical interaction between the presence of endothelialization above stent struts and mature tissue defined by histology (P=0.0005), whereas there was no statistically significant interaction for the presence of fibrin. Most regions of mature tissue were derived from vessels stented with BMS (118 of 136 mature areas).

GSI analysis of mature as compared with immature neointimal tissue above struts showed higher GSI values (115.6±14.6 versus 75.1±20.2 U) when retrieving data from converted OCT files normalized on the brightest strut. In line with these findings, GSI analysis of raw data obtained from the C7-XR imaging system showed consistent differences between mature and immature neointima (430.7±107.6 versus 205.2±87.8 U). Receiver operating characteristic curve analysis based on OCT image files revealed high sensitivity and specificity for detecting mature neointima (96% and 79%, respectively) at a GSI cutoff value of 91.6. GSI analysis of mature as compared with immature neointima resulted in a slight decrease of mature neointimal tissue areas (cutoff of 109.7 after normalization to the guide wire) revealed that 27.7% of the assessed tissue areas above stent struts represented mature neointima when a cutoff value of 91.6 after strut brightness normalization was used. Using a cutoff of 109.7 after normalization to the guide wire level resulted in a slight decrease of mature neointimal tissue areas with 22.9% showing GSI values for mature tissue.

Tissue Characterization at Autopsy

In receiver operating characteristic curve analysis, the corresponding cutoff value for human stented arteries at autopsy was 101.6. Sensitivity and specificity were 89% and 71%, respectively (Figure 4). Of 129 measured areas, 79 (61%) regions were identified as mature and 50 (39%) as immature. By histopathologic assessment, mature tissue revealed significantly higher smooth muscle cell content and lower proteoglycan/collagen, fibrin, and inflammatory cell content (Table 5). Both tissue types had a similar distribution of underlying plaque (Table IV in the online-only Data Supplement).

Prospective Assessment of Tissue Characterization in Patients

GSI of human OCT frames 6 months after DES implantation revealed that 27.7% of the assessed tissue areas above stent struts represented mature neointima when a cutoff value of 91.6 after strut brightness normalization was used. Using a cutoff of 109.7 after normalization to the guide wire level resulted in a slight increase of mature neointimal tissue areas with 22.9% showing GSI values for mature tissue.

Discussion

The current study aimed to characterize vascular healing after DES implantation in atherosclerotic rabbits, human autopsy specimens, and patients. As a first step, OCT-acquired morphometric data were validated against histopathology at 2 different time points in an atherosclerotic animal model. In a second step, morphometric OCT data were compared between animals and humans to find corresponding time points of vascular healing after implantation of DES. Next, we attempted

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**Table 1. Correlation of Corresponding Parameters Measured by Histology vs Optical Coherence Tomography**

<table>
<thead>
<tr>
<th></th>
<th>Stent Area, mm²</th>
<th>Area of Stenosis, %</th>
<th>Uncovered Struts, %</th>
<th>Mean Thickness Above Struts, mm</th>
<th>Neointimal Area, mm²</th>
<th>Lumen Area, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.93*</td>
<td>0.92*</td>
<td>0.88</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant correlation.

**Table 2. Comparison of Lesion Level–Based Optical Coherence Tomography Analysis Between Rabbits and Humans**

<table>
<thead>
<tr>
<th></th>
<th>Rabbit (28 d)</th>
<th>Rabbit (42 d)</th>
<th>Human (6 mo)</th>
<th>P Value (28 vs 42 d)</th>
<th>P Value (28 d vs Human)</th>
<th>P Value (42 d vs Human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Lesions</td>
<td>10 Lesions</td>
<td>10 Lesions</td>
<td>10 Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neointimal volume, mm³</td>
<td>0.45 (0.23–0.66)</td>
<td>0.97 (0.68–1.27)</td>
<td>0.60 (0.39–0.90)</td>
<td>0.004</td>
<td>ns</td>
<td>0.05</td>
</tr>
<tr>
<td>Volume obstruction, %</td>
<td>10.5 (6.3–14.7)</td>
<td>26.0 (18.9–33.1)</td>
<td>10.2 (5.2–15.2)</td>
<td>0.0005</td>
<td>ns</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;5% Uncovered struts</td>
<td>9/10 (90%)</td>
<td>7/10 (70%)</td>
<td>6/10 (60%)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>&gt;10% Uncovered struts</td>
<td>9/10 (90%)</td>
<td>5/10 (50%)</td>
<td>6/10 (60%)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>&gt;30% Uncovered struts</td>
<td>8/10 (80%)</td>
<td>0/10 (0%)</td>
<td>5/10 (50%)</td>
<td>0.0002</td>
<td>ns</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ns indicates not significant.
to validate a novel surrogate parameter of vascular healing after stent implantation to enable differentiation of mature and immature neointimal tissue using GSI analysis of OCT-acquired data. Finally, after verification and adjustment of this surrogate parameter in human autopsy samples, vascular healing was assessed during invasive imaging surveillance at 6-month follow-up in patients with DES.

In brief, the salient findings of the current study were as follows: (1) histopathologic morphometric parameters and OCT imaging analysis show excellent correlation in an atherosclerotic rabbit model of DES implantation. Although most of the morphometric area measurements showed slightly larger dimensions in OCT compared with histopathology, overall correlation was very high; (2) neointimal growth and vessel healing at 28 days after stent implantation in the animal model are close to what is seen in human stented arteries after 6 months, considering the expected variability of the underlying histopathologic plaque composition observed in patients. Against this, most parameters of healing assessed were further advanced in atherosclerotic rabbits at the time point of 42 days; (3) there is robust evidence that OCT-derived GSI analysis is capable of providing information on tissue characterization after stent implantation, which can reliably distinguish mature from immature neointimal tissue in atherosclerotic rabbits and human autopsy specimens and could be translated to routine assessment of vascular healing in clinical practice.

Validation of OCT Imaging Analysis With Preclinical Animal Models

One of the principal findings in our study was the fact that there is an excellent overall correlation between OCT-acquired morphometric data and their corresponding parameters assessed by histology. Despite the fact that the absolute numeric values were consistently lower for histology, the correlations remained statistically significant among the different parameters studied. Systematic differences in area measurements between OCT and histology have been reported previously and may be explained by tissue shrinkage during histopathologic processing. Nevertheless, correlations based on a stent strut level analysis of tissue coverage between OCT and histology were very high in our study.

A recent human autopsy study confirmed the excellent overall reliability of OCT in assessing both quality and quantity of tissue growth after stent implantation. However, in terms of detecting stent strut coverage with viable tissue, OCT-based analysis resulted in several false-positive counts owing to the limited ability of OCT to differentiate between neointimal tissue, fibrin, and inflammatory cell deposition. At the same time, the investigators found that OCT was unable to distinguish thin cellular layers above stent struts. Indeed, we also showed that the overall number of uncovered stent struts was higher with OCT-based analysis compared with histopathology, which was explained by the inability of OCT to identify small monolayers of nascent neointimal tissue. This clearly demonstrates the limitations of current technology in the range of cellular dimensions.

Temporal Differences in Vascular Healing Between Animal Models and Humans

It has been reported in the past that neointimal response after stent implantation is delayed, and the time course of healing is 5 to 6× longer in humans as compared with porcine and rabbit models. It has also been shown that vascular healing is accelerated in healthy porcine coronary arteries compared with healthy and atherosclerotic iliac arteries of the rabbit at similar time points. Moreover, in addition to differences in the

Table 3. Comparison of Frame Level–Based Optical Coherence Tomography Analysis Between Rabbits and Humans

<table>
<thead>
<tr>
<th></th>
<th>Rabbit (28 d)</th>
<th>Rabbit (42 d)</th>
<th>Human (6 mo)</th>
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<th>P Value (28 d vs Human)</th>
<th>P Value (42 d vs Human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Lesions</td>
<td>10 Lesions</td>
<td>10 Lesions</td>
<td>10 Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>582 Frames</td>
<td>208 Frames</td>
<td>192 Frames</td>
<td>182 Frames</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>3.7 (3.2–4.2)</td>
<td>2.7 (2.4–2.9)</td>
<td>6.8 (5.0–8.6)</td>
<td>0.0001</td>
<td>0.002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stent area, mm²</td>
<td>4.2 (3.6–4.8)</td>
<td>3.7 (3.6–3.8)</td>
<td>7.4 (5.6–9.1)</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Neointimal area, mm²</td>
<td>0.48 (0.26–0.71)</td>
<td>0.98 (0.69–1.28)</td>
<td>0.60 (0.42–0.77)</td>
<td>0.0001</td>
<td>ns</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ns indicates not significant.

*Estimation of probabilities of critical events (uncoverage/malapposition) was conducted by generalized linear mixed models.
life span of the species, there are 2 important factors that result in differences in the process of vascular healing after stenting in animals and humans: the underlying atherosclerotic process and technical differences in stent implantation. Advanced coronary atherosclerotic plaques cannot be reliably replicated in contemporary animal models. Indeed, important components of human coronary atherosclerotic lesions, such as calcification and presence of a necrotic core, have not been replicated to date in animal models. For this reason we chose as comparator relatively noncomplex atherosclerotic lesions (AHA type A/B1) in the clinical arm of our study. In addition, coronary stenting in humans is associated with extensive local trauma characterized by plaque splitting and medial disruption, and high-pressure balloon dilatations have been associated with increased neointimal growth. Pre- and high-pressure post dilatation are not routinely performed in animal models.

Impact of Tissue Characterization Using OCT Imaging Analysis

Despite its high resolution, one of the unresolved issues in OCT imaging is neointimal tissue characterization. Previous studies focused on the presence of fibrin as a predictor of delayed healing. Templin et al compared optical density measurements for stents which were covered with fibrin using morphological information gathered by scanning electron and light microscopy. They found a significant difference in optical density measurements pertaining to peristrut areas among struts covered with fibrin versus neointima. However, it should be acknowledged that because of limitations of scanning electron microscopy imaging, fibrin may not be readily distinguishable from other extracellular matrix proteins. To the best of our knowledge, in the current report, we have shown for the first time that smooth muscle cell-rich (mature) tissue can be reliably characterized using GSI measurements acquired by OCT imaging analysis. As the current study was aimed at proof-of-concept for the capability of OCT to distinguish between mature and immature neointimal tissue, further studies applying GSI analysis should be undertaken to validate this approach and to assess its relevance in clinical practice.

GSI Analysis Limitations and Future Perspectives

Because neointimal tissue immaturity has been shown to be an important predictor of late stent thrombosis in human autopsies, the ability to differentiate between mature and immature neointimal tissue in our study might have important implications for characterization of vascular healing after stent implantation in humans. As the accuracy of vascular imaging using OCT is limited by its resolution, we aimed to establish OCT-based tissue characterization on a histologically and clinically relevant level. In the current study, approximately 25% of tissue areas examined at 6-month follow-up in patients (depending on normalization methodology) represented mature neointima. These findings underscore that the presence of tissue coverage of stent struts is no indication of completeness of vascular healing. Completeness

Table 5. Characterization of Neointimal Tissue Above Struts Identified for Gray-Scale Signal Intensity Analysis

<table>
<thead>
<tr>
<th>Animal data (28 and 42 d)</th>
<th>Immature</th>
<th>Mature</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC content</td>
<td>0.99±0.67</td>
<td>3.21±0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteoglycan/collagen content</td>
<td>3.34±0.72</td>
<td>1.33±0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrin content</td>
<td>0.17±0.40</td>
<td>0.00±0.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inflammation cells/macrophage content</td>
<td>0.43±0.66</td>
<td>0.27±0.45</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human autopsy data</th>
<th>Immature</th>
<th>Mature</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC content</td>
<td>0.67±0.59</td>
<td>2.10±0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteoglycan/collagen content</td>
<td>2.91±0.91</td>
<td>1.85±0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrin content</td>
<td>0.65±0.89</td>
<td>0.21±0.61</td>
<td>0.002</td>
</tr>
<tr>
<td>Inflammation cells/macrophage content</td>
<td>1.23±0.92</td>
<td>0.16±0.42</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SMC indicates smooth muscle cell.
Scored according to the following: none=0; minimal (<25% area)=1; mild (25%–50% area)=2; moderate (51%–75% area)=3; and marked (>75% area)=4.
of vascular healing after DES implantation may be regarded as the presence of mature tissue coverage in the absence of fibrin deposition with complete and physiological endothelialization. An important limitation of OCT-based imaging analysis is that precise cellular composition of the tissue overlying stent struts cannot be distinguished because of spatial resolution constraints. Nevertheless, we believe that the characterization of tissue maturation after DES implantation may be an important step forward in the assessment of vascular healing. However, one of the important limitations in the current investigation of immature tissue areas after DES implantation is the lack of clinical studies examining the clinical impact of this novel surrogate end point at long-term follow-up. As OCT-acquired imaging analysis is now readily available in modern catheterization laboratories, dedicated clinical studies should be undertaken to delineate the causal relationship between immature tissue areas assessed by OCT and adverse clinical outcomes in humans.

**Study Limitations**

Preclinical data were derived from an atherosclerotic animal model. Despite its suitability for the assessment of vascular healing after stent implantation, this animal model remains hampered by the inability to reflect important patient comorbidities and other dependent parameters, such as the presence of diabetes mellitus and the influence of medications that may affect stent healing. As no OCT imaging was performed at the index procedure in patients, the exact morphology of atherosclerotic lesions at the time of stent implantation was not determined. As the nature of the underlying lesion has considerable impact on vascular healing after stent implantation, subsequent studies are warranted to address this question. Furthermore, the extent of positive vessel remodeling could not be assessed in the current study as a result of single-staged OCT analysis. Similarly, we did not attempt to correlate OCT findings in humans at 2 different time points, which may have simulated our animal model more closely.

This study aimed to establish evidence that OCT is capable of differentiating mature from immature neointima. In this regard, we proposed a simple GSI image analysis methodology. After quantification of mean image intensity values, it was possible to classify neointimal tissue as mature or immature with high sensitivity and specificity. However, it is important to recognize that the proposed methodology has some inherent limitations. The gray-scale analysis was performed on log-compressed OCT data, and gray-scale value normalization was performed by calibration based on values of either the brightest strut or the image wire. As a result the reported cutoff values
may be applicable only for the datasets used in the current study. However, comparable results were seen when the analysis was undertaken on raw data. Moreover, image intensity variations may not always be related to differences in tissue composition but also to other effects, such as blood clearance, flow dynamics, or, most importantly, to the use of different OCT systems. Complex image analysis methodologies, including optical properties of tissue quantification and textural image analysis, might theoretically overcome these limitations. Accordingly, the evidence created in this study may serve as a background for the development of more sophisticated OCT tissue characterization software. Furthermore, for logistical reasons different OCT systems were used for imaging of preclinical and autopsy samples. Nevertheless, both systems apply similar technical features, and images are of similar resolution.

Conclusions
The current study showed that data derived from histology and OCT imaging show excellent correlation in an atherosclerotic rabbit model of DES implantation. Moreover, neointimal growth and vessel healing at 28 days after stent implantation in the animal model is close to what is seen in human stented arteries after 6 months. Importantly, OCT-derived GSI analysis is capable of providing information on tissue characterization after stent implantation, which can reliably distinguish mature from immature neointimal tissue in atherosclerotic rabbits, human autopsy specimens, and routine clinical practice. These findings provide a basis for the conduct of further studies using OCT imaging and GSI analysis to assess extent and maturity of neointimal coverage after DES implantation in patients.

Acknowledgments
We thank Lila Adams, CVPath Institute Inc, for performing the immunohistochemistry.

Figure 4. Receiver operating characteristic curve analysis derived from animal and human autopsy data for the detection of mature neointimal tissue by gray-scale signal intensity (GSI) analysis using either raw or processed data sets. Regions of interest measured by GSI were coregistered with histology to identify mature and immature tissue. Frame data of the Lightlab/C7-XR and Terumo optical coherence tomography (OCT) systems were used in animals and human autopsy cases, respectively. Raw data sets were available for the C7-XR system. Distinction between mature and immature tissue was feasible with both OCT systems at high specificity and sensitivity using processed data sets. In a similar vein, using raw data from the Lightlab/C7-XR OCT system, mature tissue could reliably be distinguished from immature tissue. Values above the cutoff indicate mature tissue. AUC indicates area under the curve.

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Disclosures
None.

References
Optical coherence tomography (OCT) is a novel intravascular imaging technology that permits reliable assessment of tissue coverage after coronary stenting but fails to distinguish between tissue types indicating differential degrees of vascular healing. We were able to demonstrate that gray-scale intensity analysis of converted OCT frames facilitates detection of mature versus immature neointimal tissue, thus enabling tissue characterization after stent implantation. Validation of this novel technology was performed in atherosclerotic rabbits, human autopsy specimens, and patients undergoing invasive surveillance after coronary stenting. The results of the study provide basis for new algorithms to differentiate mature from immature neointimal tissue in patients undergoing OCT analysis after stent implantation. This may have important clinical impact for the identification of patients at risk for stent thrombosis and offers a new perspective for future clinical studies assessing long-term safety outcomes after stenting.
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## Supplemental tables

### Supplemental table I. Vessel morphometry based on OCT and histological analysis

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=4)</th>
<th>DES (n=10)</th>
<th>DES vs. BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCT</td>
<td>Histo</td>
<td>OCT</td>
</tr>
<tr>
<td><strong>28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neointimal area (mm²)</td>
<td>0.83±0.33</td>
<td>1.61±0.28</td>
<td>0.44±0.30</td>
</tr>
<tr>
<td>Neointimal Thickness (mm)</td>
<td>0.12±0.05</td>
<td>0.11±0.04</td>
<td>0.07±0.04</td>
</tr>
<tr>
<td>% uncovered struts</td>
<td>3.57±3.14</td>
<td>0.13±0.25</td>
<td>42.3±21.4</td>
</tr>
<tr>
<td><strong>42 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neointimal area (mm²)</td>
<td>0.94±0.48</td>
<td>1.67±0.83</td>
<td>0.97±0.41</td>
</tr>
<tr>
<td>Neointimal Thickness (mm)</td>
<td>0.16±0.09</td>
<td>0.16±0.14</td>
<td>0.16±0.08</td>
</tr>
<tr>
<td>% uncovered struts</td>
<td>4.89±6.32</td>
<td>4.24±6.08</td>
<td>7.68±6.21</td>
</tr>
</tbody>
</table>

*p <0.05, points out to significant differences between stent groups

Histo = Data derived from histological sections
**Supplemental table II.** Healing characteristics between BMS and DES at 28 and 42 days

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=4)</th>
<th>DES (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin score</td>
<td>0.04±0.08</td>
<td>1.17±0.87</td>
<td>0.03*</td>
</tr>
<tr>
<td>% Struts with fibrin</td>
<td>0.93±1.85</td>
<td>38.03±33.43</td>
<td>0.05</td>
</tr>
<tr>
<td>Inflammation score</td>
<td>0.84±0.23</td>
<td>0.50±0.19</td>
<td>0.02*</td>
</tr>
<tr>
<td>% Endothelialization</td>
<td>97.06±2.08</td>
<td>66.51±15.34</td>
<td>0.002*</td>
</tr>
<tr>
<td><strong>42 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin score</td>
<td>0.11±0.09</td>
<td>0.83±0.39</td>
<td>0.004*</td>
</tr>
<tr>
<td>% Struts with fibrin</td>
<td>2.35±1.99</td>
<td>19.07±14.88</td>
<td>0.05*</td>
</tr>
<tr>
<td>Inflammation score</td>
<td>1.10±0.31</td>
<td>0.79±0.32</td>
<td>0.14</td>
</tr>
<tr>
<td>% Endothelialization</td>
<td>83.23±5.39</td>
<td>70.75±11.33</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*p <0.05, points out to significant differences between stent groups
Supplemental table III. Baseline angiographic parameters

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Human 6 months n=10</th>
<th>Rabbit 28 days n=10</th>
<th>Rabbit 42 days n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean lesion length, mm</td>
<td>12.4 ± 6.9</td>
<td>19.3 ± 1.3</td>
<td>21.0 ± 1.0</td>
</tr>
<tr>
<td>Mean minimal lumen diameter, mm</td>
<td>0.9 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Mean reference diameter, mm</td>
<td>2.6 ± 1.1</td>
<td>2.5 ± 0.2</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>63.3 ± 10.9</td>
<td>38.0 ± 14.2</td>
<td>48.8 ± 18.8</td>
</tr>
</tbody>
</table>

Supplemental table IV. Grade and frequency of plaque underlying stented areas as ROI for GSI measurements, Human autopsy data

<table>
<thead>
<tr>
<th>Grade of atherosclerotic plaque*</th>
<th>Mature</th>
<th>Immature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (Intimal thickening)</td>
<td>45.07%</td>
<td>20.41%</td>
</tr>
<tr>
<td>Atheroma, type III and IV</td>
<td>14.09%</td>
<td>32.65%</td>
</tr>
<tr>
<td>Fibroatheroma, type Va</td>
<td>29.58%</td>
<td>34.69%</td>
</tr>
<tr>
<td>Fibrocalcific or fibroatheroma with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>large necrotic core, type Vb/c and VI</td>
<td>11.27%</td>
<td>12.25%</td>
</tr>
</tbody>
</table>

*defined according to methods of Virmani et al, 2001^1
Supplemental Figures

Supplemental figure I. Study flow chart

Reference

Methods and Materials

Preclinical evaluation of stent healing
The study protocol was approved by the responsible authority (Regierung von Oberbayern, AZ 55.2-1-54-2531-29-10) implementing the German Animal Welfare Act. Animal housing and care taking were in agreement with the directive 2010/63/EU, compliant with the US National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Rabbit model of experimental atherosclerosis and study endpoint
An atherosclerotic rabbit model of iliac artery stenting was applied for conducting the preclinical study at two different time points of follow-up. Atherosclerotic lesions were established by repeated vascular injury facilitated by diet-induced hypercholesterolemia as previously described.1 A total of 14 atherosclerotic New Zealand White rabbits received 2 types of DES (n=5 everolimus-eluting stents [EES, Xience®] and n=5 zotarolimus-eluting stents [ZES, Resolute®]) or control bare metal stents (Driver®, n=4) with assessment at 28 days and 42 days respectively. Commercially available EES (2.5 – 3 mm x 12 mm; n=10), ZES (2.5 – 3 mm x 12 mm; n=10) or Driver BMS (2.5 – 3 mm x 12 mm; n=8) stents were bilaterally implanted into the iliac arteries at nominal inflation pressure (8 to 9 atm, 30-second balloon inflation). Angiography was performed post-procedural to confirm vessel patency. To achieve adequate anticoagulation, 40 mg aspirin and 150 IU/kg heparin were administrated intravenously prior to catheterization procedures. In addition, all animals received aspirin 40 mg/d orally, until study termination at 28 or 42 days. Animals were euthanized with pentobarbital overdose. Subsequently, arteries were flushed with 500 ml of heparinized Ringer lactate. After performing OCT imaging the stents were harvested and processed for histological analysis.

Human autopsy samples
Fixed hearts or vessels with stents implanted in coronary arteries were acquired from medical examiners. Seven stented vessels with implant duration ranging from 5 to 120 months were included in the analysis. Stented arteries were fixed, dissected off the heart and submitted for embedding in methylmethacrylate for histopathological processing. The 7 vessels had previously been stented with 2 EES (Xience®), 2 paclitaxel-eluting stents (Taxus®), 2 bare metal stents and 1 sirolimus-eluting stent (Cypher®) with 1 bare metal stent overlapped. Arteries were sectioned 2 to 3 mm apart and stained with hematoxylin and eosin (H&E) and Movat pentachrome as previously described.2 Underlying plaque morphology was assessed to define the lesion type. Plaque morphology was categorized as intimal thickening type lesion, atheroma (Type III/IV), fibroatheroma (Type Va) or advanced atherosclerotic plaque with large necrotic core or calcified lesions (Type Vb/Vc/VI).3

Clinical study population and design
For the clinical assessment of OCT-acquired analysis of vascular healing patients were eligible for inclusion if they had stable coronary artery disease in the absence of acute coronary syndromes and received either a EES or a ZES (Clinical trial registration at www.clinicaltrials.gov, identifier NCT01230723). Ten patients (n=5 Resolute® RX and n=5 Xience V® stents) with simple coronary atherosclerotic lesions following index angiography were included for comparison with animal data. Angiography and OCT surveillance imaging was performed at 6 months. Offline
quantitative coronary angiography (QCA) analysis was performed using dedicated QCA analysis software (CMS Medis, The Netherlands) at the ISAR Research Center, Deutsches Herzzentrum, Munich, Germany. Clinical follow-up was done at baseline, 1 month and 6 months by phone or by office visit. All patients provided written informed consent for study participation.

**OCT imaging in rabbits and in humans**

In the animal model image acquisition was performed immediately after euthanasia followed by perfusion with Ringer’s solution to guarantee optimal image quality. OCT imaging of the stented vessel segments was achieved utilizing the Dragonfly DF-OCT-catheter combined with the C7-XR™ imaging system (LightLab Imaging Inc., Westford MA, USA). Imaging was performed at a pullback of 20 mm/sec (100 frames/sec) during flush with 20 ml contrast media (4 ml/s).

In human autopsy samples, image acquisition was performed using the Terumo OFDI system (Terumo Corporation, Tokyo, Japan) as previously described. Briefly, post-mortem angiography was performed using contrast media to locate the stented lesion. Then, a 0.014-inch guidewire was introduced into the vessel followed by an OCT catheter (2.4 Fr) with the entire stented segment imaged at a pull-back rate of 15 mm/s (120 frames/sec).

In patients with OCT follow-up, the OCT C7 Dragonfly™ catheter was advanced distally in the target vessel following administration of heparin. OCT imaging was performed after administration of 200 µg intracoronary nitrate at a pullback rate of 20 mm/s, during flush of 2–4 ml/s of contrast media to replace blood flow and permit visualization of the stented segment and intima–lumen interface.

**Data analysis**

**Histopathological assessment**

For histopathological processing, the stented vessel segments were embedded in methylmethacrylate plastic. Serial sections were cut at 1000 µm intervals starting from the proximal stent margin. A total of 9 sections (5-8 µm thickness) per stent were received and stained according to H&E and Movat pentachrome. Sections co-registered with OCT images were additionally stained for fibrin (Carstairs stain), smooth muscle cells (alpha-SM-actin immunostaining) and macrophages (RAM-11 immunostaining). Immunostaining for smooth muscle cells and macrophages was performed by utilizing anti alpha smooth muscle actin (alpha-SM-actin) and RAM-11 primary antibodies (Dako, Carpentaria, CA, USA), respectively. Epitope retrieval was conducted by steaming sections in citrate buffer. Sections were incubated over night at 4°C with the primary antibodies at 1:20 dilution. Biotin-conjugated anti-mouse IgG served as secondary antibody and was applied at a dilution of 1:200 for 1 hour at room temperature. Specific binding was visualized by the streptavidin-HRP (horseradish peroxidase) system utilizing diaminobenzidine as chromogen. Sections were counterstained with Gill’s hematoxylin, mounted and evaluated under x200 magnification. All sections were evaluated by computerized planimetry (Cell^F Software, Olympus, Hamburg, Germany). Measurements such as the external elastic lamina (EEL), internal elastic lamina (IEL), lumen area, neointimal thickness above struts, neointimal area and percent stenosis were assessed as previously described. Stent
area was additionally defined as the area within the contour of the inner strut surface. Neointimal volume was calculated by multiplying neointimal area of each consecutive frame with a frame thickness of 1 mm, while percent volume obstruction was calculated in relation to the total volume of all analysed frames. The number of uncovered struts was determined per section and expressed as percentage of uncovered struts relative to the total number of stent struts analysed.

Offline OCT Analysis
Offline OCT analysis was conducted as previously described.5 Strut malapposition was determined when the negative value of neointimal thickness above struts was higher than the strut including the thickness of the polymer coating, according to each stent manufacturer’s specifications, with addition of a compensation factor of 20 μm to correct for strut blooming.6 Geographical maps of strut coverage were created displaying struts using color codes. The resulting map represented the stented vessel cut longitudinally along the reference angle 0° (corresponding to the 12 o’clock position in the respective OCT cross section) and spread out on an area en face. Uncovered stent struts were defined as stent struts in the absence of minimal neointimal coverage ≥ 20μm owing to the limited spatial resolution of OCT and a compensation for strut blooming and the thickness of the DES polymer coating.

Co-registration and validation of stent healing parameters between histology and OCT
OCT frames were matched to comparative histological cross sections by using the proximal cut stent margin as the initial orientation point for matching the first OCT frame. Further frames were matched according to the cutting intervals (every 1000 μm). In some cases, orientation by the intervals was not feasible due to cutting loss and therefore frame correlates were acquired by optical resemblance at the approximate distance. Overall, a total of 155 frames could be directly matched to histological cross sections.

Validation of tissue characterization of OCT frames by grey-scale signal intensity measurements
OCT frames were further analyzed for differences in optical luminescence to acquire data relevant for tissue characterization. For that purpose, all available histological cross sections of the animal model at 28 and 42 days respectively were screened for clearly distinguishable smooth muscle cell-rich (SMC) and hypocellular matrix-rich areas within the neointimal layer above above stent struts. The neointimal tissue areas were further characterized on a score basis for tissue composition according to the following parameters: degree of SMC and proteglycan/collagen content, degree of fibrin deposition and degree of inflammation. A score of “0” represented none, 1 = <25% of tissue area, 2 = 25-50% tissue area, 3 = 51-75% tissue area, 4 = >75% tissue area. Furthermore, a total of 119 areas above stent struts categorized as either immature or mature by histology were assessed for the binary response of presence or absence of fibrin and/or endothelialisation. Presence was scored as 1 and absence as 0. Strut level analysis with appropriate statistical adjustment for clustering effects was performed to determine the statistical interaction of these parameters. The inner contour of each strut reflection (blooming) was delineated semi-automatically and its distance to the lumen contour was calculated automatically to determine strut-level neointimal thickness For the purpose of tissue characterization by OCT, the area above stent struts was defined as the area of neointimal tissue restricted by the width
of strut reflection and strut-level neointimal thickness from the luminal contour to a maximum of 400 μm. SMC-rich tissue areas were defined as red to pink stained areas in the presence of clearly spindle-shaped cellular formations with dark stained nuclei in H&E stained sections. In addition, there was absence of fibrin deposition, with minimally interspersed inflammatory cells and presence of proteoglycans. These areas were defined as mature neointima. On the other hand, hypocellular matrix-rich areas were defined as tissue areas devoid of SMC but rich in elastic fibers, including moderately interspersed inflammatory cells and macrophages as well as spotty fibrin deposition using H&E stained sections. Such areas were defined as immature neointima. These histological cross sections were matched with the corresponding OCT frames as mentioned above. A random of 45 well-matched OCT frames from 14 animals (28 stents) were manually transferred to an image editing software at a resolution of 1024 x 1024 pixel (Adobe Photoshop Extended CS4, Version 11.0, 2008) and converted to grey-scale signal in accordance with the software’s algorithm without loss of resolution. In addition, raw data captured from the individual pullbacks was also analyzed. Pixel intensity was extracted from raw data in the absence of any data processing such as log-compression and scan conversion to protect against loss of data during image transition. Two approaches were used for normalization of brightness levels among OCT frames. Grey scale values of the lumen and the brightest pixel of the stent strut (approach 1) or guide wire (approach 2) were delineated and set as reference in each analyzable frame (the brightest level of the stent strut or guide wire being set as a maximum and the darkest level of the lumen as minimum). A total of 320 above strut tissue areas were outlined and identified by histology as mature neointima (136 areas in 22 frames) or immature neointima (184 areas in 30 frames). Subsequently, the grey scale values of every pixel within the outlined areas were automatically detected by the software and expressed as maximum, minimum and mean data. All grey scale values were included in a final receiver-operating-characteristics (ROC) analysis. Mean values of mature neointima were used as true positive, other grey scale areas as true negatives in ROC analysis. As the spatial position of the OCT image wire largely influences luminescence of the arterial wall, final OCT pullbacks were analysed for eccentric versus concentric position of the imaging wire and split into two groups. Subsequently, ROC curve analysis was repeated for the two groups of eccentric versus concentric positioned image catheter analysis.

Tissue characterization in human stented coronary arteries at autopsy
Images from the Terumo OFDI system were co-registered with histological sections as previously reported.4 Exclusion criteria for GSI analysis were: presence of stent struts penetrating into a necrotic core, stent struts overlying areas of severe calcification, bifurcation stenting and malapposition as all these variables may influence signal intensity of grey scales. Fifteen well-matched OCT frames acquired from 7 human stented autopsy cases were used to perform GSI analysis after normalization on the brightest strut. As the absolute value of grey scales is dependent on many covariates, including the signal intensity of the OCT images, the underlying plaque morphology, the degree of luminal narrowing and the use of different OCT systems, all grey scale values derived from human autopsy samples were included in a separate receiver-operating-characteristics (ROC) analysis. The corresponding cut-off value for human stented arteries was derived to yield a maximum specificity and sensitivity.
Clinical evaluation of tissue characterization in human stented coronary arteries

170 selected tissue areas above stent struts were manually traced and GSI analyzed in 6 out of the 10 included patients with simple atherosclerotic lesions 6 months after DES implantation. The cut-off value derived from ROC curve analysis of log-compressed Lightlab/C7-XR™ OCT data co-registered with histology served to identify mature neointimal tissue areas. Exclusion criteria for GSI analysis were the same as mentioned in the autopsy samples and, additionally, when image quality was affected due to large vessel diameter or suboptimal blood clearance.

Statistics

Categorical data are reported as frequencies and proportions; continuous variables are summarized by mean ± standard deviation. The partial correlation coefficient was calculated to determine the strength of correlation between OCT and histology–based parameters within independent individuals. Nested generalized linear mixed models (GLMM) were employed in order to investigate group differences and associations of covariates in consideration of multiple measurements per individual. The Wilcoxon signed-rank test and Fisher exact test were used to compare distribution of ordinal and categorical data between independent groups of individuals. All statistical tests were two-sided and a p-value < 0.05 was considered to indicate statistical significance. In order to retain a maximum of power in consideration of the limited sample size, no correction of p-values was applied to adjust for potential inflation of type I error in the course of multiple statistical comparisons. However, results of all statistical tests being conducted were thoroughly reported so that an informal adjustment of p-values can be performed while reviewing the data. Statistical analyses were performed using JMP® Version 9.0.0 (SAS Institute Inc., Cary, NC, USA) and R software version 2.11.1 (R Development Core Team (2011), Vienna, Austria). An optimum cut-off value in the variable ratio of mature to immature neointimal tissue was derived by receiver-operating characteristic curve analysis, selecting a cut-off value that maximizes sum of sensitivity and specificity.
References


Optical Coherence Tomography (OCT)로 약물 방출 스텐트 신생내막의 조직학적 특성을 예측할 수 있다.

조상호 교수
한림대학교 성심병원 순환기내과

Summary

배경
약물 방출 스텐트 삽입 후의 OCT (Optical Coherence Tomography) 검사법을, 전임상의 동물 모델과 인간의 부검에서의 소견을 비교하여 혈관치유 평가 도구로서의 가능성을 검증하고 이 소견을 실제 임상에서 적용하고자 본 연구를 시행하였다.

방법 및 결과
죽상경화 토끼 모델에서 약물 방출 스텐트와 일반 금속 스텐트를 삽입한 후 28-42일째에 OCT로 혈관 내부 이미지를 살펴보고 동시에 조직 소견을 검사하였다. 성숙, 비성숙된 신생 내막을 구별하기 위해 서 조직 소견을 같이 합친 후에 gray scale의 신호 강도(gray-scale signal intensity, GSI)를 측정하였다. 부검 조직도 OCT로 영상화 하였고 GSI 수치를 조직 소견과 연관 지어 분석하였다. 최종적으로 10명의 환자에서 약물 방출 스텐트 삽입술 후 6개월 후에 전향적으로 OCT검사로 영상을 얻고 GSI를 측정하였다.

동물과 인간 부검 표본에서 성숙한(mature) 신생내막 조직은 일관되게 높은 GSI 값을 보였다. Receiver operating characteristic (ROC) curve 분석에서는 동물(민감도96%, 특이도79%)과 인간 부검(민감도89%, 특이도 71%)에서 성숙 신생내막을 발견하는 데에 높은 민감도와 특이도를 보였다. 약물 방출 스텐트 삽입 6개월 후 전향적 GSI 분석에서 스텐트 스트럿(strut) 상방 부위에서 최소 27.7% 이상 면적에서 성숙 신생내막이 관찰되었다.

결론
OCT의 새로운 GSI 분석 데이터는 동물, 부검 조직, 단순한 죽상경화증으로 침습적 치료를 받는 환자에서 성숙/비성숙 신생내막 조직 구별에 도움이 된다.
Commentary

DES (drug-eluting stents)를 관상동맥에 삽입하고 나서의 가장 큰 문제점은 혈류에 노출된 혈관 내강 쪽의 재상피화가 더디기 때문에 스텐트 혈전증의 위험이 높아진다는 것이다.

최근 새로운 세대의 DES들은 스텐트 재질과 두께, 디자인의 개선, 폴리머의 개선으로 이러한 위험성이 줄어들었다고는 하나 이는 아직도 주요 쟁점이다. 이를 피하기 위해서는 스텐트의 선택 이외에 충분한 기간 동안 이중(dual) 항혈소판제의 사용, 복잡한 스�tern 삽입술의 지양, 스텐트 혈전증의 고위험군(신부전, 당뇨병 등)의 인식 등이 필요하고, 최적화된(스텐트의 충분한 확장, 적절한 스텐트 길이) 스텐트 삽입술이 중요하다. 최근에는 영상 기술의 발전으로 스텐트 삽입의 최적화를 매우 정밀하게 판단할 수 있게 되었다.

OCT가 그 대표 주자로서 OCT는 매우 뛰어난 해상도로 스텐트 스트럿의 상피화 정도는 물론 미세한 박리, 혈전 생성 등의 확인에 도움을 준다. 최근 스텐트의 부적절한 확장(incomplete apposition)과 그에 따른 미세 혈전 등이 OCT로 확인되어 스텐트 삽입 후 스텐트 혈전증을 예측하는데 도움을 줄 가능성이 있다.

본 연구는 OCT로 스텐트의 신생내막을 관찰하여 그의 조직학적 평가까지 가능할 수 있다는 근거를 제시한 내용으로 안정화된 성숙 조직과 비성숙 조직을 구별할 수 있다는 내용이다. 성숙된 신생내막이란 기질외 matrix가 fiber가 내막의 주성분이 되고 smooth muscle cell이 주로 보이는 안정화된 내막을 지칭한다. 반면 비성숙 내막이란 내막 조직 사이에 염증 세포가 자리 잡고 있고 스텐트 스트럿 사이에 fibrin이 있어서 아직 완전히 치유(healing)가 안된 조직이다.

본 연구는 OCT로 살펴본 GSI 분석이 조직분석에 유용하다는 가능성을 보여주었다는 큰 의미가 있다. 향후 이를 활용하여 스텐트 혈전증의 위험도 평가, 항혈소판제의 사용기간 결정 등 임상 활용에 도움이 될 것으로 판단한다.

REFERENCE