Serial Assessment of Coronary Artery Response to Paclitaxel-Eluting Stents Using Optical Coherence Tomography

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Background—The paucity of longitudinal, serial high-resolution imaging studies has limited our understanding of in vivo arterial response to drug-eluting stents. We sought to investigate the human coronary response to paclitaxel-eluting stent implantation, using serial optical coherence tomography assessments.

Methods and Results—Thirty patients with at least 2 significant coronary lesions in different vessels were treated with a paclitaxel-eluting stent. The most severe stenosis (lesion A) was treated at the initial procedure, and the second target vessel (lesion B) was stented 3 months later. Optical coherence tomography was performed at baseline, 3-, and 9-month follow-up for lesions A and baseline and 6 months for lesions B. Prespecified end points were percent of uncovered and malapposed struts over time. In lesions A, uncovered struts were 3.77±4.94% and 3.02±4.35% at 3 versus 9 months (P=NS). Malapposed struts were 3.55±5.16% at post-procedure, 1.51±3.52% at 3 months, and 0.60±1.82% at 9 months (P<0.05, at 3 versus 9 months). Strut-level neointimal thickness was 0.19±0.09 mm and 0.20±0.11 mm (P=NS) over time. Newly acquired malapposition was detected in 10.4% and 3.3% of 2.5-mm segments at 3- and 9-month follow-up. In lesions B, uncovered struts were 2.91±5.47% at 6-months. Malapposed struts were 4.94±6.70% post-procedure and 1.01±3.11% at 6 months (P<0.01), with 0.19±0.09-mm neointimal thickness at follow-up.

Conclusions—Optical coherence tomography imaging suggested the first 3 months to be the period with most biological activity after paclitaxel-eluting stent implantation, when the proliferative reaction mainly occurs and malapposition resolves. A less active, yet continuous, dynamic arterial response, with resolution and development of malapposition, occurs through 9 months post-treatment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00704145.

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Key Words: percutaneous coronary intervention ■ drug-eluting stent ■ optical coherence tomography ■ malapposition ■ stent coverage

Late stent thrombosis after drug-eluting stent (DES) implantation remains a major clinical concern.1 Delayed arterial healing after DES implantation, revealed through incomplete strut coverage and malapposition, has been associated with late stent thrombosis.2-4 Early in the development of DES, serial imaging using angiography and intravascular ultrasound (IVUS) were performed to investigate vascular response over time.5 These studies were designed to evaluate the efficacy of DES to suppress neointimal proliferation and did not have sufficient imaging resolution to assess arterial wall response at the stent strut level. More recently, optical coherence tomography (OCT) has been established as an accurate and reproducible high-resolution imaging method to evaluate the in vivo vascular response to coronary stent implantation6-9; however, most OCT evaluations of stented vessels have been focused on single time-point imaging assessment.10-13 The lack of prospective longitudinal studies with sequential OCT image monitoring from the time of DES implantation has hampered our understanding of the arterial response to DES over time. We sought to investigate the in vivo coronary artery reaction to paclitaxel-eluting stent (PES) implantation using serial OCT evaluations.
WHAT IS KNOWN

- Delayed arterial healing after drug-eluting stent implantation, revealed through incomplete strut coverage and malapposition, has been linked with late stent thrombosis.
- Optical coherence tomography is an accurate and reproducible high-resolution imaging method to evaluate the in vivo vascular response to coronary stent implantation.
- Temporal evolution of in vivo human coronary artery response to paclitaxel-eluting stent implantation using serial optical coherence tomography imaging is poorly defined.

WHAT THE STUDY ADDS

- In paclitaxel eluting stents, >90% of the proliferative response occurs, and >85% of the post-procedure malapposition resolves in the first 3 months.
- Between 3 and 9 months, the proliferative response is less active, yet continuous, showing minimal changes in the proportion of strut coverage and resolution/development of new malapposition.

Methods

Study Design

This prospective, single-center study enrolled 30 consecutive patients with symptomatic multivessel coronary disease and at least 2 significant (≥75% by visual estimation) angiographic stenoses in different epicardial vessels suitable to stent implantation. All target stenoses were treated with the implantation of PES (Boston Scientific, Natick, Mass) in staged procedures. The initial target lesion (A) was selected and treated on the basis of stenosis severity and/or extent of myocardial area in jeopardy, whereas the second lesion (B) was stented 3 months after the initial intervention, when OCT imaging was repeated for lesion A. A final follow-up assessment (including coronary angiography, IVUS, and OCT of both treated vessels) was performed 6 months after the second intervention (ie, 9-month follow-up of lesion A). This study design was adopted (instead of imaging at consistent time-points [ie, 0, 3, 6, 9 months] for both lesion A and B) to avoid exposing patients to unnecessary procedures for mere investigational purposes. The study was conducted under Good Clinical Practice conditions and in compliance with the Medical Device Regulations for Italy. The Ethics Review Committee of Ospedali Riuniti di Bergamo approved the protocol (www.clinicaltrial.gov NCT 00704145); all patients provided written informed consent prior to enrollment.

Patient Selection, Procedure, and Follow-Up

Eligible subjects (≥18 years) had multivessel coronary artery disease (2- or 3-vessel disease) to be treated with percutaneous cardiac intervention stent procedures. The study only included lesions in native coronary arteries with diameter stenosis ≥75% and reference vessel diameter between 2.5 to 3.5 mm per visual estimation. Exclusion criteria were acute myocardial infarction; significant left main disease; lesions in coronary artery bypass grafts; poor cardiac function, as defined by left ventricular global ejection fraction ≤30%; renal failure with creatinine value >2.5 mg/dL; no suitable anatomy for OCT (ostial lesions and extreme vessel tortuosity); and inability to comply with dual antiplatelet therapy and follow-up requirements. Intracoronary nitroglycerin (200 mg) was administered before all imaging procedures. Aspirin (100 mg daily) was recommended indefinitely. All patients received clopidogrel (75 mg) daily for a minimum of 6 months; recommended for 12 months. Clinical follow-up (office visit or phone call) was planned at 1 month, 9 months (±2 weeks), 1 year, and 2 years.

Quantitative Coronary Angiography

Quantitative coronary angiography was performed at baseline, post-index percutaneous cardiac intervention, and at all follow-up time points. Angiographic measurements were made in the same 2 orthogonal projections at each time point. Offline analysis of digital coronary angiograms was performed by an independent core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio), using validated quantitative methods.

Intravascular Ultrasound

IVUS imaging was performed on both treated lesions at the completion of each stent implant and at final follow-up, using the Atlantis SR pro 40 MHz catheter and the iLab ultrasound console (Boston Scientific). Automated motorized pullback at 0.5 mm/s was used during all IVUS runs throughout the stent and at least 5 mm distal and proximal to the stent. All IVUS data were digitally stored for subsequent analysis. Quantitative volumetric IVUS analysis was performed using a validated semi-automated detection algorithm (Curad) and previously described methodology. The cross-sectional areas and associated volumes were determined for the stent, lumen, vessel, and neointimal area. Qualitative analysis included stent malapposition, defined as blood speckle behind the struts, categorized as persistent, resolved, and late acquired.

OCT Imaging Acquisition and Analyses

OCT images were obtained at all time points, according to a previously described procedure. In brief, a time-domain OCT system (LightLab Imaging) was used, and an occlusive technique was adopted. Images were acquired with an automated pullback at a rate of 1.0 mm/s, digitally stored, and submitted to the core laboratory for offline analysis. Imaging analyses were performed by an independent Core Laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio). Dedicated software (LightLab) was used for measurements. All cross-sectional images were initially screened for quality assessment and excluded from analysis if any portion of the stent was out of the screen; if a side branch occupied >45° of the cross-section; or if the image had poor quality caused by residual blood, artifact, or reverberation. Qualitative assessment was performed in every frame (ie, every 0.06 mm), whereas quantitative strut level analysis and morphometric analysis were performed at every 10 frames (ie, 0.6-mm interval) along the entire target segment. Strut-level intimal thickness (SIT) was determined based on automated measurements performed from the center of the luminal surface of each strut blooming and its distance to the lumen contour. Struts covered by tissue had positive SIT values, whereas uncovered or malapposed struts had negative SIT. Strut malapposition was defined when the negative value of SIT was higher than the sum of strut thickness plus abluminal polymer thickness, according to stent manufacturer specifications, plus a compensation factor of 20 μm to correct for strut blooming. Qualitative imaging assessment included detection of embedded struts at post-procedure, defined as struts covered by tissue and not otherwise interrupting the smooth luminal surface. Tissue protrusion was defined as a tissue prolapse between strut segments that directly correlates with the underlying plaque, without abrupt transition and different optical properties.

Serial OCT pullbacks were aligned based on fiducially points (end of stent, branches). A similar length of the lesion, determined by the shortest available common sequence, was analyzed at all time points. After alignment of the serial OCT pullbacks, the stented segment was automatically segmented in 2.5-mm intervals (subsegments), and the number of subsegments was matched at different time points. A subsegment with any malapposed struts was regarded as a malapposed subsegment. If no malapposition was detected, the
subsegment was counted as fully apposed. Newly acquired malaposition was defined as a fully apposed subsegment that developed any malapposition at follow-up. In order to determine longitudinal heterogeneity of uncovered or malapposed strut distribution, a coefficient of variation (CV) \(^{18}\) was assessed for each 2.5-mm subsegment and calculated dividing standard deviation by the mean % of uncovered or malapposed struts. A low CV denotes homogeneous longitudinal distribution within the stented segment, and a higher CV reveals heterogeneous distribution (clustering) of uncovered or malapposed struts, respectively.

**End Points and Data Management**

Primary imaging end points were the proportion of uncovered and malapposed struts as assessed at OCT at different time points. Secondary end points included neointimal hyperplasia (NIH) over time (3, 6, 9 months). We also investigated the impact of post-procedure OCT findings on the rate of uncovered struts and NIH at different time points. Data on clinical outcome, including major adverse cardiac events (a composite of cardiac death, myocardial infarction [MI], and target vessel revascularization, and stent thrombosis, as per the Academic Research Consortium definitions of definite/probable,\(^{19}\) were assessed at 30 days, 1 year, and 2 years.

**Statistical Methods**

Given the exploratory study design and lack of previous data using similar assessments, no formal sample size computation was performed. Given the exploratory study design and lack of previous data using similar assessments, no formal sample size computation was performed. Primary imaging end points were the proportion of uncovered and malapposed struts as assessed at OCT at different time points. Secondary end points included neointimal hyperplasia (NIH) over time (3, 6, 9 months). We also investigated the impact of post-procedure OCT findings on the rate of uncovered struts and NIH at different time points. Data on clinical outcome, including major adverse cardiac events (a composite of cardiac death, myocardial infarction [MI], and target vessel revascularization, and stent thrombosis, as per the Academic Research Consortium definitions of definite/probable,\(^{19}\) were assessed at 30 days, 1 year, and 2 years.

**Results**

**Patient, Procedural, and Angiographic Characteristics**

Baseline clinical characteristics are reported in Table 1. All patients underwent planned angiography, OCT, and IVUS imaging without clinical complications. Procedural and angiographic data are shown in Tables 2 and 3. There were no differences in procedural characteristics between lesions A and B, with the exception of a trend for larger stents used to treat lesion B. This is probably because of the numerically, albeit nonsignificantly larger reference vessel diameter in lesions B compared with lesions A (2.49±0.48 versus 2.55±0.35, \(P=0.61\)).

**Optical Coherence Tomography**

The incidences of tissue protrusion and embedded struts at post-procedure, as detected by OCT, were 26.40±5.0% and 18.93% respectively. These OCT findings were not correlated with degree of NIH or uncovered struts over time.

**Table 1. Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>Patients (n=30)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.8±9.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (76.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (56.6)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (56.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft surgery</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14 (46.7)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%).

**Lumen and Neointimal Hyperplasia**

Lumen volume and mean lumen area showed a slight, yet statistically significant, decrease over time both in lesions A and B (Table 4); however, neointimal proliferation only partially explains the observed changes in lumen dimensions, as there were no significant differences in mean NIH area, NIH thickness, or % volume obstruction by OCT between 3 and 9 months. Malapposition resolution accounts for the remaining lumen loss observed over time (Table 4).

**Strut Coverage**

At 3 months, 96.23±4.94% of PES struts were covered. The rate of uncovered struts remained unchanged between 3 and 9 months (3.77±4.94% versus 3.02±4.35%, respectively, \(P=0.35\), Table 4). Similarly, the proportion of lesions with complete stent coverage did not change significantly between 3- and 9-month follow-up (13.8% versus 18.5%, \(P=0.53\)). Figure 1 shows strut coverage for individual PES implanted in lesions A and B at different time points. The CV for % of uncovered struts was high and not significantly different between time points: 184.0±96.3% at 3 months, 162.0±107.4% at 9 months in lesions A, and 171.8±110.3% at 6 months in lesions B, suggesting clustering of uncovered struts, which remained unchanged over time.

**Table 2. Procedural Characteristics**

<table>
<thead>
<tr>
<th>Procedural Characteristics</th>
<th>Lesion A (n=30)</th>
<th>Lesion B (n=30)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>16 (53.3)</td>
<td>8 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>13 (43.3)</td>
<td>12 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>1 (3.3)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>21.8±14.4</td>
<td>28.4±16.3</td>
<td>0.13</td>
</tr>
<tr>
<td>No. of stents implanted</td>
<td>1.6±0.83</td>
<td>1.4±0.72</td>
<td>0.08</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>2.77±0.25</td>
<td>2.93±0.24</td>
<td>0.052</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>28.1±14.0</td>
<td>33.1±16.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Pre-dilation, n (%)</td>
<td>22 (73)</td>
<td>21 (70)</td>
<td>0.77</td>
</tr>
<tr>
<td>Post-dilation, n (%)</td>
<td>15 (50)</td>
<td>18 (60)</td>
<td>0.44</td>
</tr>
<tr>
<td>Max inflation pressure (atm)</td>
<td>18.7±2.6</td>
<td>19.0±2.6</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%).
Table 4. OCT Findings at Different Time Points After PES Implantation

<table>
<thead>
<tr>
<th>Lesion A (n = 30)</th>
<th></th>
<th>Lesion B (n = 30)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Procedure</td>
<td>Pre-Procedure</td>
<td>Post-Procedure</td>
<td>Pre-Procedure</td>
</tr>
<tr>
<td></td>
<td>3 Mo</td>
<td>9 Mo††</td>
<td>6 mo‡‡</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.49±0.48</td>
<td>2.50±0.37</td>
<td>2.44±0.39</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.80±0.37†</td>
<td>2.22±0.34††</td>
<td>1.87±0.54*†</td>
</tr>
<tr>
<td>% DS</td>
<td>67.9±12.3§</td>
<td>11.0±6.9*</td>
<td>24.2±16.1*</td>
</tr>
<tr>
<td>LL (mm)</td>
<td>. . . .</td>
<td>0.36±0.40</td>
<td>0.39±0.49</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.
RVD indicates reference vessel diameter; MLD, minimum lumen diameter; DS, diameter stenosis; LL, lumen loss.

Table 3. Quantitative Coronary Angiography Over Time

<table>
<thead>
<tr>
<th>Lesion A (n = 30)</th>
<th>Lesion B (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Procedure</td>
<td>Post-Procedure</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.49±0.48</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.80±0.37†</td>
</tr>
<tr>
<td>% DS</td>
<td>67.9±12.3§</td>
</tr>
</tbody>
</table>

Strut Malapposition

The number and frequency of malapposed struts decreased over time, with its peak observed immediately post-procedure. Nevertheless, early acquired focal malapposition with aneurismal formation led to increased volume of malapposition at 3-month follow-up (Table 4). Interestingly, resolution of aneurysms and associated malapposition were observed at 9-month follow-up (Figure 2).

Strut malapposition was also evaluated using a subsegmental analysis in order to better appreciate its temporal evolution (Figure 3). Post-stent implantation, strut malapposition was observed in 32.7% (89/272) of subsegments in lesions A and in 41.4% (137/331) in lesions B. Malapposition was resolved in 85.4% (76/89) of these subsegments at 3 months in lesions A. Similarly, 87.6% (120/137) of malapposed subsegments post-stent implantation.
in lesions B showed resolution at 6 months. Among subsegments with fully apposed struts at post-procedure (183 subsegments in lesions A and 194 in lesions B), new malapposition appeared in 19 (10.4%) at 3-month (lesion A) and 14 (7.2%) at 6-month follow-up (lesion B). Among subsegments with fully apposed struts at 3 months (240 subsegments in Lesion A), newly acquired malapposition developed at 9 months in 8 (3.3%).

Intravascular Ultrasound and Clinical Outcomes

IVUS results are reported in Table 5. Clinical follow-up at 1 and 2 years was 96.7% (29/30 patients), because of 1 death (sudden death, probably cardiac in origin) that occurred at 204 days after enrollment. Overall target lesion revascularization rate per target vessel was 15.5% (9/58 lesions) through 1 year, including 5 lesions A and 4 lesions B. One year major adverse cardiac events rate was 26.7% (8/30

Figure 1. Time course of uncovered and malapposed struts after paclitaxel-eluting stent (PES) implantation. Percentage of uncovered and malapposed struts at post-procedure, 3-, and 9-month follow-up in (A, B) lesions A, and implant and 6 months in (C, D) lesions B. Red dashed lines represent mean±standard deviation of uncovered and malapposed struts percentage at each time point for lesions A and B.

Figure 2. Serial optical coherence tomography (OCT) images, illustrating the dynamic nature of the vascular response after paclitaxel-eluting stent (PES) implantation over time (upper panels indicate post-procedure; middle panels, 3-month follow-up; lower panels, 9-month follow-up). The target segment is shown in longitudinal views (left panels), which are divided in 2.5-mm subsegments (white dashed lines and numbers). The right panels show corresponding cross-sectional OCT images at various subsegments. OCT image post-procedure showed good stent expansion with a few malapposed struts in the proximal subsegment (arrowhead, subsegment 9). At 3-month follow-up, almost all the struts were covered, and the malapposition in subsegment 9 was resolved. Interestingly, a newly acquired malapposition area was observed, involving subsegments 5, 6, and 7 (asterisks in the longitudinal view). At 9-month follow-up, similar amount of coverage through the entire stent was measured, with complete resolution of the acquired malapposition observed at 3 months.
At 2 years follow-up, there was 1 additional acute myocardial infarction because of definite very late stent thrombosis (Figure 4).

**Discussion**

In the present study, we investigated the temporal evolution of in vivo human coronary artery response to PES implantation, using serial OCT imaging. Sequential assessments of the arterial reaction to PES from the time of stent implantation through 9-month follow-up provided the following observations: (1) $\geq90\%$ of the proliferative response, depicted through the magnitude of neointimal proliferation and strut coverage occurs in the first 3 months after PES implantation; (2) thereafter, the proliferative response subsides, showing minimal changes in the proportion of strut coverage and amount of neointimal hyperplasia between 3 and 9 months; (3) $\geq85\%$ of the post-procedure malapposition resolves by 3-month follow-up; and (4) newly acquired malapposition is a dynamic and bidirectional biological phenomenon, illustrated by concomitant resolution and development of strut malapposition throughout the first 9 months post-stenting.

![Figure 3. Subsegmental optical coherence tomography (OCT) analysis of the temporal evolution of strut malapposition. Bar graphs depict (left) number of subsegments with malapposition and (right) volumes of malapposition at different time points (white bars indicate post-procedural strut malapposition; dashed bars, newly developed malapposition at 3-month follow-up; and solid black bars, new malappositions developed at 9-month follow-up). A, B, Lesion A; (C, D), Lesion B. Both resolution and development of new strut malapposition were observed at different periods.](image)

**Table 5. Intravascular Ultrasound Analysis at Implant and Final Follow-Up**

<table>
<thead>
<tr>
<th></th>
<th>Lesion A (n=28)</th>
<th>Lesion B (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-Procedure</td>
<td>9 Mo Follow-Up</td>
</tr>
<tr>
<td>Mean EEM CSA, mm²</td>
<td>11.50±2.52&quot;</td>
<td>12.53±3.36&quot;</td>
</tr>
<tr>
<td>Mean lumen CSA, mm²</td>
<td>6.58±1.44$\dagger$</td>
<td>6.06±1.94$\dagger$</td>
</tr>
<tr>
<td>Mean stent CSA, mm²</td>
<td>6.56±1.44</td>
<td>6.69±1.71</td>
</tr>
<tr>
<td>Malapposition volume, mm³</td>
<td>0.62±1.38</td>
<td>4.67±19.43</td>
</tr>
<tr>
<td>Percent net volume obstruction, %</td>
<td>...</td>
<td>11.58±11.27</td>
</tr>
<tr>
<td>Stent malapposition per lesion, n (%)</td>
<td>7 (25.0)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Persistent malapposition, n (%)</td>
<td>...</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Late acquired malapposition, n (%)</td>
<td>...</td>
<td>3 (10.7)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). EEM indicates external elastic membrane; CSA, cross-sectional area.

*P<0.01 between post-procedure vs 9 mo follow-up for lesion A.
†P<0.01 between post-procedure vs 6 mo follow-up for lesion B.
‡P<0.05 between post-procedure vs 9 mo follow-up for lesion A.
§P<0.05 between post-procedure vs 6 mo follow-up for lesion B.
The biological process that follows coronary artery stent deployment is a response to vascular injury and has been characterized by smooth muscle cell migration and proliferation. Intramural delivery of potent cell-cycle inhibitors via DES was developed to block this proliferative process. Human pathology studies have observed the presence of uncovered and malapposed stent struts in patients who died of ST. Others using IVUS and, more recently, OCT have also found malapposed and uncovered struts months after deployment of DES, although the frequency of these imaging findings in vivo was much lower than those observed in necropsy specimens. These findings led to the notion of a delayed vascular response, also referred to as “healing,” after DES implantation. Our recent OCT trials confirmed lower degree of strut coverage and higher rate of malapposition in PES compared with bare-metal stents at 6- and 13-month follow-up. The present study provides unprecedented detailed analysis of the temporal evolution of the arterial reaction to PES. This study revealed that the proliferative response after PES is an early process and follows the same pattern as that observed with bare metal stents, with >90% of tissue response taking place within the first 3 months post-vascular injury. The magnitude of the neointimal response is inhibited after PES deployment but not significantly delayed.

The time period between DES deployment and early follow-up has been largely unexplored by in vivo studies. This OCT study revealed that strut penetration and tissue protrusion through the stent struts had no relevant impact on early vascular response after PES implantation. These results are in line with recent OCT studies, showing that small imaging findings at implant, such as tissue prolapse and intrastent dissections after stenting, were not associated with adverse outcomes.

The very first clinical investigation to assess the vascular response to DES implantation in humans over time used serial IVUS imaging. These early studies were essentially focused on overall neointimal proliferation and did not address strut-level tissue coverage or malapposition. Recent serial OCT imaging investigations have suggested a late increase in neointimal proliferation in sirolimus-eluting stent between 6 and 12 months. Whether these early observations also apply to PES, which deliver a drug with different properties and kinetics, remains to be determined. In the present study, we could not detect significant growth in neointimal proliferation or improvement in strut coverage between 3 and 9 months in lesions A, and the degree of NIH and uncovered struts at 6 months in lesion B was similarly low. Indeed, in vivo vascular response to different DES varies substantially. Whether our results can be applied to different DES requires further investigations.

The temporal evolution of strut malapposition development and resolution after PES seems complex. Our data suggest that both formation of new malapposition and resolution of “old” ones occur simultaneously in the same stented vessel and that these opposing biological phenomena are observed throughout the 9-month follow-up period. The time frame from implantation to 3 months was the most active period in the malapposition process (Figures 1 and 3), when the largest number of malapposed struts resolved at the same time that new malappositions and aneurysms were observed. Interestingly, the subsequent period (3- to 9-month follow-up) was marked by an almost complete resolution of the early acquired malapposition and appearance of late malapposition at completely new sites. The overall rate and volume of malapposition showed reduction beyond the 3-month follow-up period in spite of a lower proliferative response observed during the same time period. Apparently, malapposition and aneurysm resolution were important contributors of...
lumen loss over time. Whether strut malapposition will continue to develop or completely resolve beyond 9-month follow-up cannot be determined in the present study. Nevertheless, it is important to notice that new strut malappositions observed at 9 months were less frequent than in previous assessments and limited in size (Table 4).

Study Limitations
The design of this study imposes several limitations on the conclusions. Performing OCT imaging at consistent time points (ie, 0, 3, 6, or 9 months) for both lesions A and B would have been ideal. A less-than-ideal design was adopted in the present study in keeping with clinical, technical, and ethical considerations and recommendations from the Institutional Review Board, in order to limit patients’ exposure to unnecessary procedures for mere investigational purposes. Although serial OCT imaging demonstrated detailed repeatable arterial wall features inside PES, these imaging findings were based on observations in a relatively small number of patients. Small discrepancies between baseline and follow-up OCT pullback lengths may affect comparative volumetric analyses, whereas presence of artifacts necessitating rejection of consecutive frames can introduce biases in comparative segment evaluation. Current OCT cannot differentiate between different tissue types (whether cellular or not cellular in nature) and, of course, cannot determine the endothelial function. Moreover, the study was not designed and not powered to investigate the clinical implications of OCT end points. Future evaluations linking observed OCT findings to clinical outcomes are needed.

Conclusions
The present study provides unique and potentially important insights to understand the in vivo temporal evolution of vascular response in patients undergoing PES implantation. Serial OCT imaging revealed the first 3 months to be the period with most biological activity after PES implantation, when the proliferative reaction mainly occurs and malapposition resolves. The study also revealed a less active, yet continuous, dynamic arterial response beyond 3 months, with resolution and development of new malapposition and minimal changes in the proportion of strut coverage through 9 months post-treatment. Serial intravascular OCT is valuable to characterize the in vivo vascular response to DES implantation.

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