High Incidence of Intramural Thrombus After Overlapping Paclitaxel-Eluting Stent Implantation

Angioscopic and Histopathologic Analysis in Porcine Coronary Arteries

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Background—Systematic analysis of in vivo angioscopy and postmortem histopathology for paclitaxel-eluting stents (PES) has not been previously reported. We assessed 1-month angioscopic and histopathologic sequelae of overlapping PES in pig coronary arteries.

Methods and Results—Overlapping PES and bare-metal stents (BMS; n = 9, one pair per pig) were implanted, and animals were euthanized at 1 month. Late lumen loss was reduced in PES compared with BMS (0.46 ± 0.63 mm versus 1.30 ± 0.50 mm; P = 0.01). Angioscopically, PES stent struts were clearly visible and accompanied by substantial red material indicating mural thrombi. In contrast, stent struts and mural thrombi were barely visible in BMS (P < 0.001 versus PES). Macroscopically, mural thrombi were abundant but distributed irregularly throughout the PES, with greater concentration in overlapping segments. Only occasional mural thrombi were noted for BMS. Microscopically, neointima of BMS was fibrocellular and mature, whereas only a thin layer of immature neointima was seen in PES. Neointimal thickness was less in PES than BMS (0.11 ± 0.07 mm versus 0.33 ± 0.12 mm; P = 0.018). Additionally, extensive para-strut and intramural thrombi, red blood cell debris, and minute luminal thrombi were observed in PES. Despite normal angioscopic appearance of both proximal and distal nonstented reference segments, endothelium-dependent relaxation to substance P was notably diminished (PES, 0 ± 7% versus BMS, 10 ± 6%; P = 0.007), whereas nitroglycerin response was preserved (PES, 9 ± 5% versus BMS, 12 ± 7%; P = 0.34).

Conclusions—In the porcine coronary model, overlapping PES is associated with marked intramural thrombi, which was accurately detected on angioscopy at 1 month. Moreover, despite normal luminal angioscopic appearance, adjacent nonstented reference segments demonstrated impaired endothelium-dependent vasoreactivity. (Circ Cardiovasc Intervent. 2008;1:28-35.)

Key Words: stents, drug-eluting ■ angioscopes ■ histology ■ endothelium ■ thrombus

Drug-eluting stents (DES) have become the predominant interventional modality for treatment of patients with coronary artery disease. Although multiple DES clinical trials have demonstrated significant reductions in target lesion revascularization,1–3 late stent thrombosis (LST), with the attendant risks of vessel closure, myocardial infarction, and death, has emerged as a major concern.4–7 Human autopsy studies have implicated delayed arterial healing and poor reendothelialization as potential mechanisms in the pathogenesis of LST.8–10 Recently, the latest meta-analysis of randomized trials showed no difference between bare-metal stents (BMS) and DES for the cumulative 4-year incidences of death or myocardial infarction using Academic Research Consortium definitions.11 However, a numeric increase in the incidence of LST after DES still has been observed.2 Therefore, additional research into the vascular pathophysiological response to DES as it potentially relates to LST is warranted.

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Angioscopy allows for direct visualization of the vascular lumen, as well as stent strut (SS) surfaces. It has been used for thrombus assessment in vivo, with ample clinical data supporting its superiority over angiography for this purpose.12 Several clinical angioscopic studies have demonstrated DES-associated delayed vessel healing, as well as sustained (intramural thrombus (MT) formation. However, there have been no published studies evaluating angioscopic appearance of coronary arteries with DES conducted in parallel with assessment of arterial wall histological characteristics. To date,

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most of the existing angioscopic DES literature involves single de novo sirolimus-eluting stents.13–15 The angioscopic appearance and histological findings after overlapping paclitaxel-eluting stent (PES) implantation are still largely unknown.

Clinically, overlapping DES are at times required for diffuse, long coronary lesions to assure full coverage. Indeed, the incidence of multiple stent placement is up to 28% in diffuse, long coronary lesions to assure full coverage. Indeed, unknown.

Thrombus formation and development after overlapping PES implantation are still largely unknown.18–20 Even more than single stents, overlapping PES might be expected to elicit delayed healing responses, including increased MT as well as reduced neointimal coverage (NC). Furthermore, vasomotor dysfunction in coronary segments adjacent to DES has been reported18–20 and may be associated with delayed healing in either a causative fashion or as a bystander phenomenon. Therefore, in the present study, we aimed to evaluate 1-month angioscopic, macroscopic, and histopathological features in overlapping PES versus BMS in a coronary artery experimental animal model. We also measured the vasomotor function in proximal and distal adjacent nonstented reference segments (NSRS).

Methods

Animals and Experimental Protocol

Animal handling and care followed the recommendations of the National Institutes of Health guide for the care and use of laboratory animals and was consistent with guidelines of the American Heart Association. All protocols were approved by the Animal Care and Use Committee and were consistent with Association for Assessment and Accreditation of Laboratory Animal Care guidelines. Nine juvenile female or castrated male Yorkshire farm pigs (weight, 31.2 ± 2.4 kg) were enrolled onto this study.

All animals received a combination of 81 mg of aspirin and 75 mg of clopidogrel by mouth daily for 3 days before stent implantation, continued until termination, and were fasted overnight before the procedure. The animals were sedated by intramuscular injection of ketamine 20 mg/kg, xylazine 2 mg/kg, and atropine 0.05 mg/kg. After intubation, general anesthesia was induced and maintained with isoflurane (2.5%). The ECG and blood pressure were continuously monitored.

Cardiac catheterization was performed with full heparinization (200 U/kg), and stents were implanted with quantitative coronary angiography guidance to obtain a stent-to-arterial diameter ratio of 0.1:1 to 1.2:1. Activated clotting time measurements were performed. Overlapping PES (TAXUS, Express 2; Boston Scientific Corp, Natick, Mass) or BMS (Express 2, Boston Scientific Corp, or Multi-Link Penta, Abbott Vascular, Abbott Park, Ill) were implanted into the coronary arteries by a scheme of constrained randomization (2 pairs of overlapping stents/animal). There were no between-group differences for the total stent length (BMS, 26.0 ± 1.7 mm versus PES, 26.8 ± 1.2 mm; P = 0.28) or stent overlap length (BMS, 5.1 ± 1.3 mm versus PES, 5.2 ± 1.2 mm; P = 0.85). Angiographic target-vessel diameter, stent-to-arterial diameter ratio, poststenominal luminal diameter, and late lumen loss were measured in all animals either at implantation or at 1-month follow-up.

Angioscopic Analysis

All stents were assessed by angioscopy during the terminal procedure. The system consisted of a 4.5F rapid-exchange catheter (Vecmova Neo; FiberTech, Tokyo, Japan) and a light source (3 charge-coupled device Imaging System Flt-203; FiberTech). The angioscope catheter was advanced into the distal segment of the coronary artery, followed by infusion of room temperature lactated Ringer’s solution through the outer catheter at a rate of 0.5 to 1.0 mL/s. The occlusion balloon was then hand-inflated at the proximal portion of the stented segment; after clearance of blood from the field of view, the angioscope catheter was then manually retracted through the stented segment.21

Angioscopic images for proximal single-strut, overlap, and distal single-strut areas were analyzed for degrees of NC over SS, MT, and luminal thrombi according to a modified grading system.22 The arterial segments 1.5 cm proximal and distal to the stent were also analyzed. NC score was classified into 4 semiquantitative grading categories: grade 0, fully visible SS (similar to immediate postimplantation); grade 1, SS covered but protruding into lumen and transparently visible; grade 2, SS embedded by neointima but still translucent; and grade 3, SS fully embedded and invisible. MT score was likewise classified into 4 grades: grade 0, no visible red spot; grade 1, focal red or pink spots along the SS; grade 2, red spot partially extending to interstrut space; and grade 3, red spot spanning across interstrut space. The presence or absence of luminal thrombi (a coalescent, red or pink, or white protruding mass adhering to the vessel surface but clearly a separate structure) was also evaluated.

All angioscopic imaging was evaluated and scored in an independent fashion by 2 experienced investigators, who were unaware of treatment group assignments. There was no interobserver variability, as the angioscopic scorings were identical between the 2 observers.

Macroscopic Evaluation

At 1 month after interventional procedures, all animals were euthanized. The hearts were explanted and perfusion-rinsed with 0.9% NaCl solution. The stented coronary vessels were quickly but carefully excised and trimmed free of adherent adjacent myocardium and adipose tissue. Each artery was longitudinally incised, and the coronary luminal surface was exposed. Digital images were obtained under uniform exposure conditions. The proximal and distal single-stent regions and overlap sites were analyzed separately. NC was scored and classified into 4 semiquantitative grades similar to those used in angioscopic analysis. For MT assessment, the overall red spots on the luminal surfaces were measured by planimetry and expressed as a percentage of the stented area.

Microscopic Analysis

Samples for histopathological analysis were fixed with a mixture of buffered 1.25% glutaraldehyde and 5% formalin and then immersed in formalin overnight. After dehydration in graded ethanol series to 100%, the vessels were finally embedded in methyl methacrylate. Sections from the proximal, overlap, and distal stent regions were cut using a heavy-duty microtome and collected on glass slides; they were stained with hematoxylin-eosin and Movat pentachrome. Morphometric analysis for neointimal thickness at each SS site was performed by computerized planimetry using Image Pro Plus software (Image Pro-Plus, Silver Spring, Md) on proximal, overlapping, and distal sections. Sections from each stented vessel were scored for intramural thrombus (a mixture of fibrin, para-strut amorphous material, and red blood cell debris) deposition on the basis of the following semiquantitative grading scale: grade 0, not present; grade 1, mild (scattered); grade 2, moderate (encapsulating <50% of a strut in at least 25% to 50% of the circumference length); and grade 3, severe (surrounding a strut in at least 50% of the circumference length) according to previously published methods.23 Reendothelialization was also scored by the circumferential extent of luminal surface coverage in each section with flattened, confluent endothelial or endothelial-like cells as follows: 0, 0% to 25% coverage of circumference length; 1, 25% to 50% coverage; 2, 50% to 75% coverage; and 3, 75% to 100% coverage.

Evaluation of Endothelial Function

At follow-up, endothelium-dependent and -independent coronary vasorelaxation capacities were assessed after intracoronary infusion of the endothelium-dependent receptor-mediated dilator substance P (sP, 2 ng/kg) followed by the endothelium-independent vasodilator nitroglycerin (200 µg) administered via the guide catheter. sP was infused over a period of 30 seconds.24 After a 10-minute interval, nitroglycerin was administered as a bolus. Coronary angiography
Table 1. Angiographic Analysis at 1 Month

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Proximal</th>
<th>Overlap</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Target-vessel diameter, mm</td>
<td>2.76±0.21</td>
<td>. . .</td>
<td>2.67±0.24</td>
</tr>
<tr>
<td>Stent/artery ratio</td>
<td>1.14±0.22</td>
<td>. . .</td>
<td>1.14±0.04</td>
</tr>
<tr>
<td>Poststenting MLD, mm</td>
<td>3.10±0.24</td>
<td>3.04±0.27</td>
<td>2.97±0.31</td>
</tr>
<tr>
<td>Follow-up MLD, mm</td>
<td>2.22±0.42</td>
<td>1.74±0.57</td>
<td>2.07±0.48</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.86±0.35</td>
<td>1.30±0.50</td>
<td>0.90±0.45</td>
</tr>
<tr>
<td>PES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target-vessel diameter, mm</td>
<td>3.02±0.25*</td>
<td>. . .</td>
<td>2.93±0.30</td>
</tr>
<tr>
<td>Stent/artery ratio</td>
<td>1.14±0.05</td>
<td>. . .</td>
<td>1.12±0.05</td>
</tr>
<tr>
<td>Poststenting MLD, mm</td>
<td>3.41±0.38</td>
<td>3.29±0.36</td>
<td>3.24±0.42</td>
</tr>
<tr>
<td>Follow-up MLD, mm</td>
<td>3.11±0.40†</td>
<td>2.83±0.85‡</td>
<td>2.98±0.45§</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.30±0.13†</td>
<td>0.46±0.63‡</td>
<td>0.27±0.13§</td>
</tr>
</tbody>
</table>

Values are mean±SD. MLD indicates minimal lumen diameter.

*P<0.05 vs BMS proximal; †P<0.05 vs BMS proximal; ‡P<0.05 vs BMS overlap; and §P<0.05 vs BMS distal. There were no differences among proximal, overlap, and distal in each group.

Results

All animals tolerated the stent implantation and angioscopic procedures well, without any adverse cardiac or systemic events. There were no complications of morbidity or mortality until final euthanasia of the animals.

Angiographic Analysis

The angiographic data comparing PES with BMS are presented in Table 1. A representative coronary angiogram at 1 month after overlapping PES and BMS implantation is shown in (Figure 1A). At baseline, the target-vessel diameter was significantly greater in proximal NSRS of PES (3.02±0.25 mm) than of BMS (2.76±0.21 mm; P=0.029); a trend toward higher baseline diameter was evident in the distal NSRS also (PES 2.93±0.30 mm versus BMS 2.67±0.24 mm; P=0.053). Neither stent–to–arterial diameter ratio nor poststent minimal lumen diameter at proximal, overlap, and distal segments was different. Immediately after implantation, all vessels demonstrated full patency, with brisk antegrade flow. At follow-up, no luminal thrombus was identified angiographically in any animal. Late lumen loss was significantly reduced in PES as compared with BMS at proximal, overlap, and distal segments (Figure 1B). Although there was a trend toward greater late lumen loss at overlap versus nonoverlap segments for both groups, no statistically significant results were detected within segments.

Angioscopic Findings

At 1-month angiographic evaluation, the NSRS in all arteries, both proximal and distal, were free of detectable injury; luminal surfaces were smooth and uniformly white, without protruding intraluminal material.

Scoring of angioscopic appearance by segments is shown in Table 2. In stented segments, angioscopic NC grade was lower for PES than BMS (P<0.001; Figure 2A). For the majority of PES (74% grade 1), SS bulged into the lumen and were visible angioscopically through the transparency of

![Image](http://circinterventions.ahajournals.org/)

**Figure 1.** One-month angiographic follow-up and late lumen diameter loss (LL) after overlapping PES and BMS implantation. A, The BMS showed mild diffuse narrowing, especially in overlapped area. Dotted lines indicate proximal and distal reference segment measurement sites. B, LL was lower in PES than in BMS at proximal, overlap, and distal segments of overlapping stents, and there were no differences across segments for both PES and BMS. LCx indicates left circumflex coronary artery; RCA, right coronary artery.
overlying neointimal tissue. The remainder of PES SS (26%) were translucent in appearance (grade 2), and no grade 3 SS were observed. In contrast, 93% of BMS NCs were angiographic grade 3, with invisible SS and overlying coverage of white, opaque neointima. A total of 7% and 0% of BMS met criteria for grades 2 and 1, respectively. Additionally, proximal, overlap, and distal segments in BMS group all demonstrated similar NC scores.

Although angioscopy revealed no luminal thrombus in any sample, MTs were identified in all PES to varying degrees, with the highest incidence in the overlap region. The majority of PES (96%) were categorized as MT grade 1. Angioscopic grade 1 was present for 11/100 of macroscopic red spot area, grade 2 was present in 27/100 of these areas, and grade 3 was present in 45/100. The frequency of MT-free luminal surfaces in the PES group was low (3%). In contrast, we detected no angioscopic evidence of MT in any BMS.

Macroscopic Findings
To assess gross NC and overall red spot distribution, stents were longitudinally transected and examined (Figure 2B). The SS were readily visible in all PES specimens. Conversely, for BMS, no SS were visible through the intimal tissue. The respective distribution of angioscopic and macroscopic NC gradings were thus consistent for both PES and BMS segments.

No luminal surface red spots were observed for BMS segments. Only 2 BMS overlapping segments showed scarce pink-colored appearance. Consistent with angioscopic findings, the PES luminal surfaces demonstrated widespread, unevenly distributed red spots, with higher densities concentrated in the overlap segments; red spots comprised 31±15% of PES coverage areas.

Table 2. Angioscopic Analysis of Neointimal Coverage and Mural Thrombi

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
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<tbody>
<tr>
<td><strong>BMS (n=9)</strong></td>
<td></td>
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<td></td>
<td><strong>Mural Thrombi</strong></td>
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<tr>
<td>Proximal</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>9 (100)</td>
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<tr>
<td>Overlap</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>8 (89)</td>
<td></td>
<td>9 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Distal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (11)</td>
<td>8 (89)</td>
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<td>9 (100)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td><strong>PES (n=9)</strong></td>
<td></td>
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<td></td>
<td><strong>Mural Thrombi</strong></td>
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<tr>
<td>Proximal</td>
<td>0 (0)</td>
<td>8 (89)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td></td>
<td>1 (11)</td>
<td>2 (22)</td>
<td>6 (67)</td>
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<tr>
<td>Overlap</td>
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<td>5 (56)</td>
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<tr>
<td>Distal</td>
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<td>0 (0)</td>
<td>4 (44)</td>
<td>2 (22)</td>
<td>3 (33)</td>
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</table>

Values are expressed as n (%). The distributions of angioscopic neointimal coverage and mural thrombi scores among proximal, overlap and distal segments were no different.

Microscopic Histological Findings
Neointimal thickness was markedly decreased for PES versus BMS (0.11±0.07 mm versus 0.33±0.12 mm; P=0.018; Figure 3A). The endothelial coverage was equivalent between stent types and scored 3 for all sections. Notably, PES exhibited higher intramural thrombus than BMS at both overlap and distal sections (P<0.05). The MT score was similar across section levels within BMS. However, the overlap section in PES demonstrated higher MT than did the proximal section (Figure 3B).

Low-magnification light microscopic images of Movat pentachrome–stained sections (Figure 4A) illustrate overall vessel wall morphologies. The neointima formation was clearly suppressed in PES as compared with BMS. All stents displayed full stent apposition to the tunica media. With the
rare exception of widely isolated gaps, luminal stented surfaces were covered with a layer of flattened endothelial or endothelial-like cells.

Evaluation of hematoxylin-eosin–stained sections from PES samples consistently revealed parastrut thrombus, occasional luminal microthrombi, intramural fibrin, and red blood cell debris (Figure 4B and 4C). In particular, these morphological findings were markedly enhanced in overlapped regions of PES, often involving most of the arterial cross-sectional circumference. In contradistinction, these observations were rare for BMS samples (Figure 4D), in which only diffuse, small, and patchy para-strut amorphous materials were seen.

Endothelium-Dependent and -Independent Vasorelaxation

There were no between-group differences in lumen diameters in either proximal (PES, 3.07±0.34 mm versus BMS, 3.12±0.20 mm; \( P=0.678 \)) or distal (PES, 2.98±0.37 mm versus BMS, 2.83±0.33 mm; \( P=0.392 \)) NSRS at 1-month follow-up. No notable heart rate or mean blood pressure changes were detected after injection of either sP or nitroglycerin.

Although vasodilatation occurred with both sP and nitroglycerin, endothelium-dependent diameter change in response to the former was diminished for PES-stented arteries compared with BMS. Diameter change was 0±6% for PES
Awata et al.13 found fully visible or protruding into the lumen and was contrasted stent implantation. This was furthermore accompanied by SS of MT, which persisted for 6 months after sirolimus-eluting angioscopically and histopathologically, that a high incidence thoroughly covered by neointima, there is clear evidence, both morphologically and quantitatively analyze the in vivo angiographic luminal patency. Moreover, our observed PES-induced delay in vessel healing, detected both histologically and angioscopically, further supports the need for long-term dual-antiplatelet therapy.

Discussion

To the best of our knowledge, this is the first study to both systematically and quantitatively analyze the in vivo angioscopic findings in concert with postmortem macroscopic and microscopic histology and, in parallel, to assess vasoreactivity after overlapping PES implantation in pig coronary arteries. The present study verified significant neointimal inhibition with PES in this laboratory animal model at the 1-month time period. Although both stent types were thor-oughly covered by neointima, there is clear evidence, both angioscopically and histopathologically, that a high incidence and extent of intramural thrombus occurred primarily in overlapping PES segments.

Consistent with our in vivo findings, recent angioscopic observations in human subjects also reported high frequency of MT, which persisted for 6 months after sirolimus-eluting stent implantation. This was furthermore accompanied by SS fully visible or protruding into the lumen and was contrasted with BMS that were well covered.13–15 Awata et al.13 found that MT correlated inversely with neointimal grade (P=0.002) >2 years after sirolimus-eluting stent implantation, whereas MT was nondetectable angioscopically in BMS. Currently, from human autopsy studies, the best morphological predictor of LST seems to be the extent of uncovered and nonendothelialized SS surfaces.9 Therefore, clinical assessment of SS neointimal coverage has emerged as a potential avenue for evaluation of LST risk in patients with DES.

The endoluminal fiberoptic angioscope may become a valuable tool for such evaluation because it provides direct visualization of the coronary luminal surface and, therefore, assessment of both neointimal stent coverage and MT. So far, there have been no published angioscopic studies after PES placement. The present report provides information in a clinically relevant animal model from angioscopic examination of the chronic effects of PES implantation, concordant with macroscopic and histological data.

In concordance with our findings, Finn et al.25 demonstrated that PES overlap was prone to fibrin deposition in a rabbit model. More recently, both sustained para-strut amorphous fibrinoid material and similar neointimal growth patterns were also evidenced histopathologically in a porcine coronary model after overlapping PES implantation, with persistence of MT for up to 1.5 years.26 The mechanism of favorable MT deposition after overlapping PES implantation is still not fully understood. Beyond the potential sequelae of longer stent length, doubling of SS, and elevated local drug levels, one possible explanation for diminished MT reabsorption may involve paclitaxel suppression of cell-mediated fibrino-lytic and phagocytic pathways.27 The histopathologic confirmation of angioscopic findings at 1 month in our animal model suggests a potential clinical role of the angioscope in detection of the high-risk/thrombosis-prone PES patient. The persistent MT/fibrin deposition observed in the present study is also a sobering reminder of the necessity of careful clinical follow-up after PES implantation, despite sufficient angiographic luminal patency. Moreover, our observed PES-induced delay in vessel healing, detected both histologically and angioscopically, further supports the need for long-term dual-antiplatelet therapy.

Large animal models play an instrumental role in the assessment of tissue response to DES.28 The stages of healing after swine coronary interventional procedures follow a similar, but accelerated, pattern when compared with those of humans. The chronologic equivalency between 1-month and 6-month follow-ups in porcine and human models, respectively, has been validated.29 Although in our study, all PES struts appeared covered and therefore not exposed to the arterial lumen flowing blood (a finding somewhat discrepant from histopathologic studies of human autopsy samples), the overgrown tissue was characterized as poorly healed. Even when the luminal surface was covered or mostly covered with a confluent layer of flattened cells, the presence of adherent leukocytes and even microthrombi suggested an unhealthy endothelium (or pseudoendothelium).

The healthy endothelium plays an integral secretory role in the maintenance of vascular homeostasis and regulation of vascular tone.30 Recently, a growing body of evidence has shown that endothelial dysfunction is more likely to occur after DES implantation than after BMS implantation.18–20 In these studies, coronary vasomotion was assessed at baseline and at 6 months’ follow-up. Togni et al.19 observed that, in contrast with BMS, PES implantation led to significantly attenuated vasodilatory response to exercise-induced shear stress at proximal and distal adjacent segments to the stent. Similarly, Kim et al.20 reported the presence of abnormal coronary vasoconstriction to the endothelium-dependent va-
sodiotator acetylcholine more significantly in the distal epicardial segments of coronaries with PES than in those with BMS. This paradoxical pathophysiological vasoreactivity may augment the vulnerability of DES-stented arteries to LST via exacerbation of flow stasis and turbulence and reduction of laminar flow and flow velocity.9,10 Such conditions would be expected to create a prothrombotic as well as proinflammatory vascular environment.

Our study is the first to evaluate endothelium-dependent and -independent vasorelaxation in combination with angiographic observation after overlapping PES implantation. Interestingly, despite normal luminal morphology of all targeted NSRS 1.5 cm proximal and distal to the SS, luminal diameter change was significantly diminished in PES vessels as compared with BMS vessels. Although the exact mechanism for such vasomotor dysfunction in adjacent angioscopically normal NSRS remains unclear, earlier studies have implicated a direct drug effect on endothelial repair.18–20 Drug diffusion into the vessel wall may result in elution into the vasa vasorum, thereby eventually reaching the adjacent arterial vessel wall, including the endothelium, beyond the stented segment. Further studies are needed to elucidate the mechanism of this mismatch phenomenon (normal angioscopic and histological appearance with abnormal vasomotor function) in detail. Vasomotor function, as evaluated angiographically in response to vasodilator administration, may serve as an important surrogate benchmark for vessel healing and functional recovery after DES in the clinical setting.

Limitations
First, the relatively small number of animal subjects should be considered and the statistical data analysis interpreted accordingly. Second, the current angioscope technology provides a forward-viewing system only; complete circumferential luminal surface visualization is limited. Conversely, optical coherence tomography provides high-resolution cross-sectional imaging (at 10- to 20-μm pixel resolution) of the entire vasculature and may offer superior quantitative evaluation of vascular responses to DES.31 However, differentiating thin neointimal growth from fibrin/thrombus deposition is not possible with optical coherence tomography at the present time.

Biological results in normal porcine coronary arteries after PES implantation may be not be representative of those in the diseased human coronary system, as the latter consists of lipid-rich atherosclerotic, and potentially thrombotic, stenotic lesions. In contrast to human postmortem findings, full neointimal coverage was seen for both stent varieties in the porcine coronary model. Finally, serial long-term studies, with varying durations of angiographic and histological follow-up to evaluate neointimal coverage, thrombus burden, and vasomotor function, were not performed in the present study; therefore, the latter stages of structural and functional recovery after PES in this model remain unknown.

Conclusions
Our study demonstrated persistent MT and attenuated NC by fiberoptic angiography in porcine coronary arteries at sites of overlapping PES at 1 month after implantation. These in vivo observations corresponded to macroscopic examination of excised, longitudinally transected stented coronary samples and were furthermore related to histological findings of persistent MT and fibrinoid deposits in various layers of the vessel wall, including neointima and media. Furthermore, endothelium-dependent vasorelaxation was found to be impaired in adjacent, angioscopically normal, proximal, and distal NSRS. Our findings support the notion that toxic effects of PES on the coronary endothelium and neointimal tissue exist, which may contribute to intractable vasospasm and, potentially by means of blood flow disturbance, to LST clinically. The potential implications of these findings in the pathophysiology of human DES LST may be further elucidated in longer-term animal studies as well as in vivo human angiographic evaluation.

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Disclosures
None.

References


In the current era of drug-eluting stent (DES) use for interventional cardiology, the importance of accurate and appropriate intravascular imaging for optimal patient monitoring, prognosis, and management has gained special prominence. Intravascular ultrasound is accepted as a standard clinical imaging modality, whereas optical coherence tomography and fiberoptic angioscopy are still considered research tools in many countries, including the United States. Although DES are highly effective for in-stent restenosis suppression, they carry a small but real risk of late stent thrombosis (LST). Certain patient and lesion characteristics appear to be associated with sirolimus-eluting stent versus paclitaxel-eluting stents. Angioscopy allows direct visualization of the arterial luminal surface and thereby supplies image information that cannot be provided by intravascular ultrasound or optical coherence tomography. In this study, we have demonstrated that the angiographic changes in infra- and inter-observer agreement: European Working Group on Coronary Angiography. Eur Heart J. 1994;15:815–822.

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High Incidence of Intramural Thrombus After Overlapping Paclitaxel-Eluting Stent Implantation: Angioscopic and Histopathologic Analysis in Porcine Coronary Arteries

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