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. 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,
most of the existing angioscopic DES literature involves single de novo sirolimus-eluting stents. 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 paclitaxel-eluting stent (TAXUS) trials. 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 reported 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 nonstent 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 1:1:1 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, poststent minimal lumen 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 Ft-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.

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. 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 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 (encompassing <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. 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. After a 10-minute interval, nitroglycerin was administered as a bolus. Coronary angiography
was performed with identical angiographic projections before and after vasoactive drug administration. The percent diameter change from baseline to after infusion at 1.5 cm proximal and distal to the stented segment (NSRS) was considered to reflect vasorelaxation capacity.

Statistical Analysis

All numeric data were expressed as mean ± SD. Statistical analysis was performed by Sigma Stat version 3.5 (Systat Software, Erkrath, Germany). Angiographic percent diameter change in the reference segments were evaluated between the groups by the Student unpaired 2-tailed t test. Differences among the segments (proximal, overlap, and distal) for both BMS and PES groups were evaluated by 2-way ANOVA, followed by the Fisher least-squares temporal-difference post hoc test. For nonnumeric data (scoring data), Kruskal-Wallis ANOVA on Ranks was used for comparison among the segments for both groups. A critical value of P < 0.05 was considered to indicate significant treatment effect or between-groups difference.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

All animals tolerated the stent implantation and angiographic 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 poststenotic 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.

Table 1. Angiographic Analysis at 1 Month

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<tr>
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<th>BMS</th>
<th>PES</th>
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<tbody>
<tr>
<td></td>
<td>Proximal</td>
<td>Overlap</td>
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<tr>
<td>Target-vessel diameter, mm</td>
<td>2.76±0.21</td>
<td>2.67±0.24</td>
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<tr>
<td>Stent/artery ratio</td>
<td>1.14±0.22</td>
<td>1.14±0.04</td>
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<tr>
<td>Poststenting MLD, mm</td>
<td>3.10±0.24</td>
<td>3.04±0.27</td>
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<tr>
<td>Follow-up MLD, mm</td>
<td>2.24±0.42</td>
<td>1.74±0.57</td>
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<tr>
<td>Late loss, mm</td>
<td>0.86±0.35</td>
<td>1.30±0.50</td>
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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 across proximal, overlap, and distal in each group.

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 angiographic appearance by segments is shown in Table 2. In stented segments, angiographic 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 the stent struts.

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. Angiographic grade 1 was present for 44% of macroscopic red spot area, grade 2 was present in 27% of these areas, and grade 3 was present in 45%. 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.

**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...
versus 10±7% for BMS at proximal NSRS (P=0.007), with a similar pattern seen at distal NSRS (0±9% for PES versus 10±7% for BMS; P=0.019). Conversely, nitroglycerin-induced endothelium-independent vasorelaxation was comparable between BMS and PES at both proximal (PES, 8±6% versus BMS, 12±7%; P=0.15) and distal (PES, 10±5% versus BMS, 14±7%; P=0.29) NSRS. The unit change for nitroglycerin was similar between groups (proximal, P=0.19; distal, P=0.39). Figure 5 shows diameter changes in response to sP or nitroglycerin at proximal and distal NSRS in all individual animals.

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`us, doubling of SS, and elevated local drug levels, one possible explanation for diminished MT reabsorption may involve paclitaxel suppression of cell-mediated fibrinolytic and phagocytic pathways. The histopathologic confirmation of angioscopic findings at 1 month in our animal model suggests a potential clinical role of the angiographic detection of the high-risk/thrombosis-prone PES patient. The persistent MT/fibrin deposition observed in the present study may involve paclitaxel suppression of cell-mediated fibrinolytic and phagocytic pathways. Consistently with our findings, Finn et al 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. 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. Additionally, the histopathologic confirmation of angioscopic findings at 1 month in our animal model suggests a potential clinical role of the angiographic detection of the high-risk/thrombosis-prone PES patient. The persistent MT/fibrin deposition observed in the present study may involve paclitaxel suppression of cell-mediated fibrinolytic and phagocytic pathways. Moreover, our observed PES-induced delay in vessel healing, detected both histologically and angioscopically, further supports the need for long-term antiplatelet therapy.

Large animal models play an instrumental role in the assessment of tissue response to DES. 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. 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. Recently, a growing body of evidence has shown that endothelial dysfunction is more likely to occur after DES implantation than after BMS implantation. In these studies, coronary vasomotion was assessed at baseline and at 6 months’ follow-up. Togni et al 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 reported the presence of abnormal coronary vasoconstriction to the endothelium-dependent va-
sodilator 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 paradoxical pathophysiological vasoreactivity overlying 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
CLINICAL PERSPECTIVE

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 angiography 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 increased risk of LST for DES, yet there are currently no consensus methods by which specific DES implantation sites may be identified as having high LST potential. An additional tool that 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 appearance of DES 1 month after implantation in porcine coronary arteries is distinct from the appearance of bare metal stents. In parallel, we have shown that DES are histologically identified as having less complete healing, with persistent appearance of DES 1 month after implantation in porcine coronary arteries is distinct from the appearance of bare metal stents.
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