Interference of Drug-Eluting Stents With Endothelium-Dependent Coronary Vasomotion Evidence for Device-Specific Responses

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Background—There is evidence that endothelial coverage of drug-eluting stents might be delayed or absent, a risk factor for late thrombotic events. We studied the effects of different drug-polymer-device iterations on endothelium-dependent coronary vasomotion. Systemic markers of endothelial inflammation were correlated with coronary vasomotor changes.

Methods and Results—Patients with paclitaxel-eluting stents (n = 11), sirolimus-eluting stents (n = 21), biolimus A9-eluting stents (n = 28), zotarolimus-eluting stents (n = 10), and bare-metal stents (n = 13) were studied 10, 9, 9, 9, and 12 months after implantation, respectively. Endothelium-dependent coronary vasomotion was tested proximally and distally to the stent and at a reference vessel segment during atrial pacing at increasing heart rates by quantitative coronary angiography. Indexes of platelet-monocyte binding and other biomarkers were studied in a subgroup of 19 patients. The baseline characteristics and hemodynamics of the patients in the different stent groups were comparable. Significant differences were observed across the 5 stent groups, concerning the vasomotion of segments proximal (P = 0.006) and distal (P = 0.003) to the stent. Normal vasomotion (vasodilatation) was maintained in the biolimus A9-eluting stent, zotarolimus-eluting stent, and bare-metal stent groups, whereas vasoconstriction was observed in the sirolimus-eluting stent and paclitaxel-eluting stent groups. Platelet-monocyte binding in whole blood showed a significant inverse correlation with vasomotion in reference but not in segments adjacent to the stent (r = −0.57; P = 0.01).

Conclusions—Paclitaxel-eluting stents and sirolimus-eluting stents seem to cause endothelial dysfunction of the implanted vessel, whereas biolimus A9-eluting stents and zotarolimus-eluting stents behave more closely to bare-metal stents, with preserved endothelial vasomotor response. Coronary vasoconstriction was not associated with detectable systemic endothelial activation. (Circ Cardiovasc Intervent. 2008;1:193-200.)

Key Words: endothelium ■ stents ■ coronary vasomotion ■ platelet-monocyte binding

Drug-eluting stent (DES) implantation portends a significant reduction in restenosis and target vessel revascularization rates compared with bare-metal stents (BMS). Although all DES approved for clinical use were shown to reduce restenosis, marked differences exist between various drug-polymer-device combinations that may translate into different biological responses and eventually impact on net clinical outcome. For instance, implantation of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) has been associated with a small but incremental risk for late stent thrombosis, a potentially lethal complication. Human in vivo studies and autopsy studies in patients suffering from stent thrombosis revealed poor stent strut endothelialization, fibrin deposition, and local inflammatory or hypersensitivity reaction at the site of SES and PES implantation. Recent in vivo studies have shown that both SES and PES cause paradoxical coronary vasoconstriction distal to the stented segments 6 to 9 months after implantation, whereas a study from our group showed relatively preserved endothelium-dependent coronary vasomotion 9 months after biolimus-eluting stent (BES) implantation. To which extent these vasoconstrictive changes are device specific and whether they represent a local or a systemic phenomenon remain unknown. We sought to study the effects of different DES on endothelium-dependent coronary vasomotion compared with BMS. Systemic markers of endothelial inflammation were studied in a subgroup of patients.
Specifically, index of platelet-monocyte binding (PMB) as a marker of systemic endothelial activation was correlated with observed local vasomotor changes.

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Methods

Patients previously implanted with 5 types of coronary stents who consented to the study protocol were included prospectively: PES (n=11), SES (n=21), BES (n=28), zotarolimus-eluting stents (ZES; n=10), and BMS (n=13). Most of the patients with SES (n=19) and BES (n=21) underwent mandated follow-up angiography 9 months after stent implantation in the context of the NOBORI CORE study,15 and part of the data were previously reported.14 In the remaining patients, repeat coronary angiography was justified on the basis of routine clinical follow-up. Median time from stent implantation was 10 months for PES, 9 for SES, 9 for BES, 9 for ZES, and 12 for BMS. All patients consented to undergo the study protocol, which was approved by the local ethics committee.

All stents had been implanted in de novo lesions. Patients presenting with angiographically significant in-stent restenosis were not considered for this study. The quality of angiography was not sufficient to allow accurate measurement of vessel diameter changes in 4 cases (2 BES, 2 SES) and those patients were excluded, as well as 3 patients with in-stent restenosis (1 PES, 1 SES, 1 BES).

Study Protocol

All vasoactive drugs were discontinued at least 24 hours before catheterization except for sublingual nitroglycerin, which was withheld for at least 1 hour. Long-acting β-blockers were stopped 48 hours before study. Diagnostic left heart catheterization and coronary arteriography were performed by a standard percutaneous femoral approach. Diagnostic catheters (6F) were introduced into the left main or right coronary artery, depending on the vessel under study. A 5F bipolar pacing wire (St Jude Medical) was placed against the high lateral right atrial wall. The pacing study was then performed. After control conditions were established, rapid atrial pacing was conducted at 20 bpm above baseline heart rate for 2 minutes, followed by increments in the pacing rate of 20 bpm for 2 minutes each until a final pacing rate of 150 bpm was reached, angina was produced, or atrioventricular Wenckebach block developed. After rapid atrial pacing, a 2-minute recovery period was allowed. Intracoronary isosorbide dinitrate (1 to 2 mg total dose) was administered. Atrioventricular Wenckebach block was not treated with intravenous atropine so as to not influence coronary vasomotion and blood flow responses. Pacing from the right ventricle was performed up to 150 bpm in the patients who developed atrioventricular Wenckebach block at rates below 110 bpm.

Serial contrast injections of the study vessel were performed at baseline, at the end of a 2-minute period at each pacing rate, within beats after ending the highest pacing step and after intracoronary nitrates administration. Heart rate and blood pressure were digitally recorded during the entire study protocol. Rate-pressure product at baseline and at maximal pacing rate was calculated as heart rate × systolic blood pressure.

Quantitative Coronary Angiography

Coronary angiography was performed on a digital x-ray system (Siemens Axiomatis dSC) at 25 frames/s. An appropriate view that permitted clear visualization of both the target artery and the reference vessel segment was selected. The angle of view, the distance from the x-ray focus to the object, and the distance from the object to the image intensifier were kept constant throughout the entire study. The computer-based analysis system Siemens Quant-Cor.QCA based on CAAS II system (Pie Medical Imaging) was used for off-line quantitative coronary angiography analysis. All measurements were done by an independent observer who was blinded to the study protocol and type of stent implanted. Using an Acom.PC 5.01 system,14 interobserver variability for coronary arterial dimensions was 0.11 mm, and intraobserver variability was 0.08 mm (mean lumen diameter on repeated analysis of the same frame). Percent changes were calculated in all patients using the baseline values as reference. In all groups, measurements were performed at 3 selected sites: a reference angiographically normal segment in noninstrumented vessel, and proximal and distal coronary segments adjacent to the stented segment (at least 10 mm from proximal and distal stent edges). If the intervened vessel was the right coronary artery, an angiographically normal segment as far as possible from the stented vessel segment was taken as reference, usually in the distal postero-lateral branches. Because of ostial stent location, the proximal vessel segment could not be evaluated in 11 patients (2 PES, 2 SES, 4 BES, 1 ZES, and 2 BMS). All measurements were done exactly at the same location, at baseline, at every pacing step, immediately after stopping pacing and after intracoronary nitrates. During pacing stress, a progressive, rate-dependent reduction in vessel diameter was coined as vasoconstruction and an increase as vasodilatation. Patients with vasoconstruction in the reference segment were not included in the comparative analysis because they seem to have a generalized endothelial disorder.

Indirect Immunofluorescence Analysis of Platelets and Leukocytes

Whole blood was drawn from the femoral sheath at the beginning of the procedure before the administration of heparin. Blood samples were anticoagulated in PPACK tubes, before immediate immunolabeling using a cocktail of preconjugated monoclonal antibodies directed against platelet and monocyte surface markers at saturating concentrations. Specific antibodies (sourced from Becton Dickinson Inc) included CD14-PE, CD14 fluorescein isothiocyanate (FITC), CD40 PE, CD11b PEcy5, CD62P FITC, and CD40L FITC. Samples were incubated with antibodies at room temperature for 20 minutes in a light-proof container. Samples were then treated with a commercial fixative and erythrocyte lysis reagent (BD FacsLyse, Becton Dickinson Inc) before immediate analysis on a flow cytometer (BD FacsCanto, Becton Dickinson Inc). In samples labeled with CD14 and CD42a, PMB was calculated as a percentage of double-labeled events above that displayed by relevant isotype control antibodies, as previously described.16 The same technique was applied to assess monocyte surface CD40 and platelet surface CD62P and CD154. Monocyte surface CD11b was calculated from mean fluorescence intensity above isotype control fluorescence.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 15.0, SPSS Inc). Continuous data are summarized as mean±SD. One-way ANOVA was used to test differences between the stent groups and posttest Bonferroni multiple comparison for pairs. χ² test or Monte Carlo exact test was used to test the differences in the categorical variables between groups. Unpaired t test was used to compare values of biological markers between patients with vasodilatation and vasoconstruction of the segment distally to the stent. Correlation among variables was determined by Spearman correlation tests or nonlinear best fit routines accordingly. A probability value of <0.05 was considered significant.

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

Results

Flow chart of the study is shown in Figure 1. The baseline clinical (Table 1) and angiographic (Table 2) characteristics of the patients are comparable.

Hemodynamic Data

Baseline and maximal pacing rate mean arterial pressure at baseline and at maximal pacing rate and rate-pressure product both at baseline and at maximal pacing rate were similar in...
the 5 groups (Table 3). Changes in mean arterial pressure from baseline to peak pacing were not significantly different between the 5 groups. Seven patients (2 PES, 1 SES, 1 BES, 1 ZES, and 2 BMS) required right ventricular pacing because of atrioventricular block at heart rate below 110 bpm. No significant complications resulted from the pacing test or the study protocol. One patient developed paroxysmal atrial fibrillation that converted shortly after β-blocker administration.

Coronary Vasomotor Response to Pacing and Nitrates

Abnormal constrictor response of the reference vessel segment (−9.9 ± 3.6%) was seen in 5 segments (1 SES, 2 BES, 1 ZES, and 1 BMS), significantly different (P < 0.001) from the 11.2 ± 7.4% dilator response seen in all other reference segments (n = 71). All data obtained in these 5 patients have been excluded from further comparative analysis. Mean data for the mean vessel diameter of the proximal and distal coronary segments are shown in Table 4.

As expected, the stented vessel segments in all 5 groups showed no diameter change (Table 4). The reference segment not related to the stented vessel showed pacing-induced vasodilatation in all groups (PES, 9.25 ± 9.1%; SES, 12.65 ± 6.7%; BES, 12.4 ± 6.4%; ZES, 12.06 ± 7.2%; and BMS, 12.1 ± 11.9%; P = 0.11; Figure 2A). Significant difference was observed within the 5 groups concerning the vasomotion of the proximal and the distal to the stent segments (P = 0.006 and P = 0.003, respectively). More specifically, for the segment proximal to the stent, normal vasomotion (vasodilatation) was maintained in the BES, ZES, and BMS group, whereas vasoconstriction was observed in the SES and PES group (Table 4; Figure 2B). For the segment distal to the stent, normal vasomotion (vasodilatation) was maintained in the BES, ZES, and BMS group, whereas vasoconstriction was observed in the SES and PES group (Table 4; Figure 2C). In the SES and PES group, the

![Figure 1](image_url)

**Figure 1.** Flow chart of the study. Patients were excluded from the analysis because of in-stent restenosis (n = 3), insufficient quality of the angiogram (n = 4), or constriction of the reference segment (n = 5).

<table>
<thead>
<tr>
<th>Table 1. Patient Clinical Characteristics</th>
<th>Group A (n = 43)</th>
<th>Group B (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>61±10</td>
<td></td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>32/11</td>
<td>23/5</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (74)</td>
<td>18 (64)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (21)</td>
<td>7 (25)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36 (84)</td>
<td>24 (86)</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (47)</td>
<td>14 (50)</td>
<td>0.81</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>22 (51)</td>
<td>12 (43)</td>
<td>0.63</td>
</tr>
<tr>
<td>Statins</td>
<td>38 (88)</td>
<td>26 (93)</td>
<td>0.47</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25 (57)</td>
<td>17 (61)</td>
<td>0.81</td>
</tr>
<tr>
<td>β-blockers</td>
<td>30 (70)</td>
<td>19 (68)</td>
<td>1</td>
</tr>
<tr>
<td>Nitrates, %</td>
<td>16 (37)</td>
<td>7 (25)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD. Group A consists of patients who showed pacing-induced vasoconstriction, and Group B consists of patients who showed vasodilatation in the distal segment. M indicates male; F, female; ACE, angiotensin-converting enzyme.

<table>
<thead>
<tr>
<th>Table 2. Angiographic and Lesion Characteristics</th>
<th>Group A (n = 43)</th>
<th>Group B (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA lesion class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>8 (19)</td>
<td>4 (14)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>11 (26)</td>
<td>8 (29)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>15 (35)</td>
<td>9 (32)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>9 (20)</td>
<td>7 (25)</td>
<td></td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>21.8 ± 10</td>
<td>25 ± 9</td>
<td>0.19</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.15 ± 0.3</td>
<td>3.17 ± 0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Stent deployment pressure, mm Hg</td>
<td>12 ± 5</td>
<td>14 ± 3</td>
<td>0.1</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>16.4 ± 7.9</td>
<td>18.4 ± 7</td>
<td>0.3</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD. Group A consists of patients who showed pacing-induced vasoconstriction, and Group B consists of patients who showed vasodilatation in the distal segment. ACC indicates American College of Cardiology; AHA, American Heart Association.
vasomotor response in the reference segment was better in both the proximal and distal segments (P=0.003 and P<0.001, respectively).

Intracoronary nitrates were associated with vasodilatation of all the evaluated vessel segments (proximal, distal, and reference) in all groups (Table 4). The maximal vasodilatation observed after nitroglycerin administration was not statistically significantly different for any of the segments between the 5 groups.

Systemic Biomarkers and Cell Surface Indices of Platelet and Monocyte Activation and Adhesion
PMB in the whole blood seemed to show a significant inverse square root correlation with pacing-induced flow-mediated coronary vasodilatation in reference vessels (Figure 3). No statistically significant correlation was observed with the expression of monocyte surface CD40 (P=0.78; r=−0.07), and with platelet surface P-selectin (P=0.42; r=−0.19) and CD154 (P=0.76; r=−0.07).

No significant differences in systemic levels of cellular activation indices as well as other systemic biomarkers were noted in the coronary vasoconstrictor group in comparison to the vasodilator group (Table 5). Specifically, PMB was not significantly altered in patients with local vasoconstrictor responses in comparison to those with vasodilator responses (P=0.12). Similar findings emerged for assessments of platelet surface P selectin (P=0.15), monocyte surface CD40 (P=0.95), and CD11b (P=0.83).

Late Lumen Loss and Vasomotion
Angiographic in-stent and in-segment late lumen loss was available in 62 patients (9 PES, 15 SES, 22 BES, 8 ZES, and 8 BMS). In the remainder, either the baseline angiogram was not available or the angiographic views were not identical, precluding accurate calculation of late loss. The mean values for in-stent late loss (mm) were 0.31±0.19 for PES, 0.04±0.43 for SES, 0.15±0.28 for BES, 0.26±0.38 for ZES, and 0.56±0.47 for BMS. The mean values for in-segment late loss were 0.15±0.06, 0.19±0.36, 0.21±0.30, 0.25±0.24, and 0.38±0.31 mm for PES, SES, BES, ZES, and BMS, respectively. The in-stent or in-segment late loss values did not correlate with the vasomotor pattern in the proximal or in the distal stented segments (Figure 4A and 4B).

Discussion
The present study shows that endothelium-dependent coronary vasomotion is significantly different at coronary segments proximal and distal to the different stent brands studied. These differences do not seem to be related to a systemic inflammatory process but rather to local-regional device-specific responses.

Vasomotor Response to Pacing-Induced Tachycardia
Coronary segments adjacent to BMS show relatively preserved coronary endothelial function, consistent with previous reports. On the contrary, local endothelial-dependent vasomotor responses varied with different DES brands. Vessels previously implanted with SES and PES showed coronary vasoconstriction, more pronounced in the distal but also present in the proximal segment. BES and ZES showed coronary vasodilatation in both segments. The explanation for

Table 3. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>PES (n=10)</th>
<th>SES (n=17)</th>
<th>BES (n=23)</th>
<th>ZES (n=9)</th>
<th>BMS (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure baseline, mm Hg</td>
<td>95.8±10.5</td>
<td>96.9±13.9</td>
<td>95.1±11.9</td>
<td>103.8±9.2</td>
<td>97.9±13.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean arterial blood pressure peak pacing, mm Hg</td>
<td>95±11</td>
<td>101±17</td>
<td>95.5±16</td>
<td>97.9±8.7</td>
<td>104.1±15</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart rate baseline, bpm</td>
<td>70±14.2</td>
<td>79.1±20.3</td>
<td>77.5±13.9</td>
<td>61±7.8</td>
<td>70.8±9.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Maximal pacing rate, bpm</td>
<td>137.5±8.7</td>
<td>133.1±19.7</td>
<td>133.7±14.2</td>
<td>138.9±11.7</td>
<td>133.0±12.3</td>
<td>0.78</td>
</tr>
<tr>
<td>Rate-pressure product baseline, mm Hg×bpm</td>
<td>9812±2571</td>
<td>10202±4174</td>
<td>10039±2436</td>
<td>9257±1890</td>
<td>9987±1683</td>
<td>0.77</td>
</tr>
<tr>
<td>Rate-pressure product peak pacing, mm Hg×bpm</td>
<td>17171±1984</td>
<td>15703±3913</td>
<td>15258±3123</td>
<td>17771±1343</td>
<td>18023±2160</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.

Table 4. QCA Measurements in All Groups at Baseline, Maximal Pacing, and After Nitroglycerin Administration

<table>
<thead>
<tr>
<th></th>
<th>Proximal</th>
<th>Distal</th>
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<tr>
<td></td>
<td>PES (n=8)</td>
<td>SES (n=15)</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.43±0.3</td>
<td>3.1±0.7</td>
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<tr>
<td>Max Pacing</td>
<td>2.31±0.18</td>
<td>3.09±0.8</td>
</tr>
<tr>
<td>Change, %‡</td>
<td>−4.3±7.7</td>
<td>−0.9±9.1</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>2.62±0.19</td>
<td>3.42±0.9</td>
</tr>
</tbody>
</table>

Data are presented in mm as mean±SD.

‡Changes in diameter from baseline.

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the observed differences may be related to any of the following, alone or in combination: the different drug, the different polymer, or the pharmacokinetics and bioavailability of the drug.

Of 4 DES studied, 3 contain a drug belonging to the limus family. Similar to sirolimus, which was the first drug used in a DES platform, biological effects of biolimus and zotarolimus are mediated by the intracellular receptor FK506-binding protein 12. The FK506-binding protein 12-drug complex blocks progression from phase G1 to S in the cell cycle, inhibiting smooth muscle cell progression and proliferation. Despite the existing similarities in the drug action, release kinetics are different for those 3 stent platforms. Zotarolimus and Biolimus A9 are more lipophilic drugs than sirolimus and would quickly bind to the target, lipid rich, tissue on release.\(^18,19\) This results in a more localized effect and reduced systemic drug exposure. Moreover biolimus is present only on the vessel side (abluminally) and as such enters into peripheral circulation in only minimal quantities, whereas total drug content is released as a small initial burst followed by sustained simultaneous drug release and polymer degradation \(>6\) months, exposing the surrounding tissue at any given time to a lower amount of drug.\(^18\) Finally, although the polymer used in SES platform has been associated with fibrin deposition and late hypersensitivity reactions, ZES uses a biocompatible phosphorylcholine coating, which has been shown in vitro to resist fibrinogen adsorption and cause less platelet and monocyte activation.\(^20\) Similarly, the polymer used with BES is expected to be absorbed in a few months, and because durable polymers have been held responsible for some of the late adverse events related to SES it is anticipated that the degradation of polymer will improve arterial healing and long-term safety of BES.

Paclitaxel has a different mechanism of action. It is a lipophilic diterpenoid that promotes cell cycle arrest and, eventually, inhibition of vascular smooth muscle cell migration and proliferation. In addition, paclitaxel also enhances tissue factor expression and activity in endothelial cells.\(^21\) PESs have a biphasic drug release profile in vitro with an initial burst during the first 48 hours after implantation followed by a sustained low-level release for at least 2 weeks.\(^22\) In vitro, paclitaxel not only inhibits proliferation and migration of vascular smooth muscle cells but equally suppresses endothelial cells, thereby potentially impeding endothelialization.\(^23\) Those differences may explain the somewhat different clinical performance in terms of restenosis of those 4 stents as well as the findings of our study showing different degrees of endothelial functional recovery following their implantation.

Finally, it is obvious from our study that the response to pacing stress is not homogenous in all stent groups; indeed, some patients show vasodilatation whereas some others show vasoconstriction. This variability indicates that local endothelial function is not restored in a certain subset of patients. There is compelling evidence that healing process varies from patient to patient; the response to drug also varies, with some patients requiring a lower drug dose for equivalent benefit.

Figure 2. Percent changes in mean diameter from baseline (mean±SEM) in all stent groups, at reference (A), proximal (B), and distal (C) segment.

Figure 3. Relationship between vasomotion in the reference segment and PMB. Nonlinear fit with the square root of the reference vasomotion (%) shows a significant inverse correlation \((r=-0.57; P=0.01)\).

Table 4. Continued

<table>
<thead>
<tr>
<th>Stent</th>
<th>PES ((n=10))</th>
<th>SES ((n=17))</th>
<th>BES ((n=23))</th>
<th>ZES ((n=9))</th>
<th>BMS ((n=12))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.73±0.5</td>
<td>2.097±0.5</td>
<td>3.18±0.4</td>
<td>3.07±0.4</td>
<td>2.19±0.4</td>
</tr>
<tr>
<td></td>
<td>2.74±0.5</td>
<td>2.98±0.5</td>
<td>3.18±0.4</td>
<td>3.07±0.4</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td></td>
<td>2.74±0.5</td>
<td>3.0±0.5</td>
<td>3.2±0.4</td>
<td>3.06±0.4</td>
<td>2.21±0.4</td>
</tr>
</tbody>
</table>
Late Loss and Abnormal Vasomotor Response

As already known from previous studies, BMS and the 4 different DES studied have a completely different clinical performance in terms of angiographic restenosis. It was hypothesized that first generation DES that significantly decrease neointimal formation by preventing smooth muscle cell migration and proliferation may cause delayed endothelialization by preventing endothelial cell migration and proliferation as well. In our study, late lumen loss, a marker of neointima formation, did not seem to be related to the local endothelial response in any of the stent groups studied. This observation indicates that the neointima reduction caused by the drug does not necessarily imply that endothelialization is also encumbered. Drugs interact with smooth muscle and endothelial cells in many ways, and several factors related to the other components of the DES devices (stent, polymer) may be important as well, including drug release kinetics. Angiographic in-stent late loss has been shown to have a significant impact on the clinical outcome of patients treated either with BMS or DES. A recently published study showed that the incidence of stent thrombosis (definite or probable) was not related to antiproliferative efficacy of DES, as measured by in-stent late loss. As a result, it is conceivably that new drug-device combinations could be designed that retain the impressive effects of first generation DES on neointima formation while at the same time, prohealing properties may favor endothelialization. The goal of research in DES technology should be to preserve the benefits of restenosis prevention without the risks of delayed healing and late stent thrombosis. The present study suggests that measurements of endothelial vasomotor responses could be used as an intermediate end point in the early evaluation of new drug-device combinations.

Systemic Inflammation and Abnormal Vasomotor Response

In a subgroup of patients, we used flow cytometry analysis to explore cellular activation levels in circulating platelet and monocyte populations. Atherosclerotic plaque progression is characterized by low-grade inflammation locally acting on the coronary endothelium but reflected by an increase in systemically detectable markers of inflammation. Activated platelets in the circulation bind avidly and dynamically to leukocytes. These platelet-leukocyte complexes are mostly considered markers of platelet-activating conditions and vessel wall disease, such as unstable atherosclerosis, stable coronary disease, and hypercholesterolemia, and they have been related to endothelial function as well.

Thus, many factors influence the healing process and vary with individual risk factors.

Study Limitations

In the present study, time from implantation varies to some extent between the different DES. However, this could not have influenced our conclusions because the stents with the longer time from implantation (SES and PES) showed the worst behavior in terms of endothelial function. At the same time, time course of vasomotor changes could not be studied.
for each stent type because of an insufficient number of observations at various time points. Another potential study limitation is that patients did not have baseline endothelial function measurements before stent implantation. Pacing stress is not useful for that purpose because of the presence of significant coronary lesions at baseline, requiring antianginal medication and the need for intracoronary nitrates use during the intervention. In addition, pacing-induced ischemia in the presence of significant stenosis will affect vasomotor response. This limitation is further compensated for by the analysis of a reference vessel segment, used as an internal, patient-specific control. Another possible limitation of the study is that the blood samples drawn from the femoral artery are representative of changes detectable in the systemic circulation. Blood samples harvested from the coronary sinus could have been more representative of the local coronary changes in the indices studied. Finally, the clinical relevance of our findings remains unknown. Local coronary vasoconstriction is only an indirect sign of endothelial dysfunction probably attributable to delayed endothelialization in the segments proximally and distally to the stent. Lack of stent strut coverage has been closely related to several adverse events, the most severe being thrombus generation. Accordingly, this finding raises the hypothesis that the increased rate of late thrombotic events that was observed with the use of first generation DES could relate to a more extensive disorder of vessel healing than was initially anticipated from invasive imaging using intravascular ultrasound or optical coherence tomography and autopsy studies. 

Conclusions

First-generation DES seem to cause endothelial dysfunction of the implanted coronary vessel, whereas newer generation DES, such as BES and ZES, show preserved endothelial-dependent vasomotion at comparable time points, similar to BMS. Such endothelial dysfunction represents a local-regional effect related to the implantation of specific DES brand types rather than the result of a systemic process.

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Disclosures

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References


CLINICAL PERSPECTIVE

Increased risk for (very) late stent thrombosis has been associated with delayed or absent endothelial coverage of drug-eluting stent (DES) struts. The present study examined endothelium-dependent vasomotion using pacing-induced tachycardia in coronary segments proximal and distal to different DES, when compared with vessels implanted with bare-metal stents. The normal response to pacing-induced tachycardia is epicardial vasodilation. In-stent late lumen loss by quantitative angiography and systemic markers of endothelial inflammation were correlated with coronary vasomotor changes. Sirolimus and paclitaxel DES caused blunted or absent vasodilatation, respectively, in response to increased flow in the implanted vessel, whereas biolimus and zotarolimus DES showed vasomotor responses similar to BMS. Endothelium-dependent coronary vasoconstriction was not associated with abnormal systemic markers of endothelial inflammation and showed no relation to in-stent late lumen loss. Indirect evidence of endothelial dysfunction at segments distant from some DES could be another manifestation of delayed or incomplete healing that is specific for one brand versus others. Dissociation between antiproliferative power of DES and vasomotor response indicates options for optimizing the balance between high antirestenosis efficacy and retained safety with newer generation drug-polymer-device combinations.
Interference of Drug-Eluting Stents With Endothelium-Dependent Coronary Vasomotion: Evidence for Device-Specific Responses
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