The Long-Term Effect of Coronary Stenting on Epicardial and Microvascular Endothelial Function

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Background—Coronary stents, drug-eluting stents in particular, have been linked to coronary epicardial endothelial dysfunction after implantation. However, less is known about their impact on coronary microvascular function and their long-term effects on the vasculature.

Methods and Results—We evaluated 71 patients (mean age, 53.0±10.1 years) with chest pain and angiographically nonsignificant coronary artery disease 17.1±17.1 months after left anterior descending coronary artery stenting. Seventy-one age- and sex-matched patients (mean age, 53.0±10.3 years) with chest pain but no prior coronary intervention served as controls. Coronary blood flow in response to the endothelium-dependent vasodilator acetylcholine as well as the microvascular (endothelium-independent) coronary flow reserve in response to intracoronary adenosine were evaluated. Quantitative coronary angiography was used to study epicardial diameter changes to acetylcholine. Microcirculatory function was not significantly different between the stenting and control groups (median [interquartile range] coronary flow reserve, 2.9 [2.5–3.4] versus 3.0 [2.4–3.4] mL/min, P=0.24; change of coronary blood flow, 34.9% [−34.4% to 90.0%] versus 54.7% [−5.6% to 104.6%], P=0.18). Both groups exhibited epicardial endothelial dysfunction (−23.0% [−47.4% to −7.6%] versus −20.0% [−40.0% to 0.0%], P=0.4). Results did not differ between patients with drug-eluting stents (n=46) and patients with bare-metal stents (n=24).

Conclusions—This study demonstrates that in patients with coronary arteries in which a stent has been placed, coronary microcirculatory and epicardial vascular function are not significantly different from that of an age- and sex-matched population with similar symptoms but nonsignificant coronary artery disease. (Circ Cardiovasc Interv. 2012;5:523-529.)

Key Words: endothelium ■ stents ■ microcirculation ■ coronary disease

Percutaneous coronary intervention with balloon angioplasty and adjuvant coronary stenting is an efficacious treatment in patients with obstructive coronary artery disease (CAD). However, catheter-based coronary interventions are associated with arterial injury, resulting in endothelial dysfunction. Several studies have reported the presence of focal endothelium-dependent vasomotor dysfunction in both proximal and distal nonstented reference segments of coronary arteries 6 to 12 months after stent implantation in patients with sirolimus-eluting and paclitaxel-eluting stents. This might raise concerns that these segments are at higher risk for future events. Furthermore, recent studies pointed out that endothelial dysfunction after stent implantation could be linked to a long-term clinical outcome such as stent thrombosis. In addition to the well-recognized effect of stents on epicardial endothelial function in the shorter term, little is known about vascular function after >1 year. Additionally, the effect of stents on coronary microvascular function, an important measure of the integrity of the microvasculature and a prognosticator for future coronary events, is not known.

Interestingly, a substantial number of patients after stent implantation continue to have recurrent symptoms and need further angiograms, although in many, no residual obstructive lesion can be detected. Thus, microvascular dysfunction could contribute to recurrent symptoms. However, the association between coronary microvascular function and coronary artery stenting in patients with chest pain in the absence of obstructive CAD is uncertain.

The aim of this study was to evaluate microvascular and epicardial vascular function in patients with recurrent chest pain after stenting and compare them to an age- and sex-matched control group with chest pain but a normal coronary angiogram. Additionally, we were interested in any differences between patients receiving drug-eluting stents (DES) and patients receiving bare-metal stents (BMS).
Coronary stenting has been linked to epicardial endothelial dysfunction, with a consecutive risk for future events. Although no residual obstructive lesion can be found, a substantial number of patients after stent implantation continue to have recurrent symptoms, which might be attributed to microvascular dysfunction.

**WHAT THE STUDY ADDS**

- The study adds knowledge about microcirculatory and epicardial vascular function in patients with stents presenting with chest pain.
- A long-term worsening of vascular function by drug-eluting stent implantation is not supported.

**Methods**

**Patient Population**

This retrospective analysis followed patients in the Mayo Clinic Rochester Catheterization Laboratory Registry from March 1998 to December 2011. In the stent group, 71 consecutive patients referred for evaluation of chest pain (Canadian Cardiovascular Society class III angina or less) in the absence of obstructive CAD (>30%) on coronary angiogram were included. Of these, 24 originally received BMS and 46 DES into the left anterior descending coronary artery (LAD). Seventy-one age- and sex-matched patients with chest pain and normal coronary angiogram (absence of obstructive CAD) and no prior coronary intervention served as controls.

Exclusion criteria were as follows: history of coronary artery bypass graft surgery; ejection fraction of ≤50%; valvular heart disease; peripheral vascular disease; uncontrolled hypertension; significant endocrine, hepatic, renal, or inflammatory disease; and no informed consent from the patient. Patient demographics and laboratory data, including fasting lipid profile and serum glucose level, were obtained. The study was approved by the Mayo Clinic Institutional Review Board.

**Measurement of Coronary Microvascular Function**

Diagnostic coronary angiography was performed by a standard percutaneous femoral approach. The methodology for coronary endothelial function analysis has been described previously. In brief, heparin 5000 U was given intravenously, and a Doppler guidewire (FloWire; Volcano Corp) was positioned within a coronary infarction catheter (Ultrafuse; SciMed Life Systems) in the mid portion of the LAD. Velocity signals were instantaneously obtained from the Doppler guidewire and average peak velocities (APVs) were determined. Intracoronary bolus injections of incremental doses (18–60 μg) of adenosine were administered until maximal hyperemia was achieved (or the highest dose was given) to evaluate endothelium-independent microvascular function. CFR was calculated by dividing peak APV after adenosine by APV at baseline. Subsequently, to assess coronary blood flow (CBF), the endothelium-dependent vasodilator acetylcholine (Ach) was selectively infused at increasing concentrations (10⁻⁶, 10⁻⁴, and 10⁻² mol/L) for 3 minutes at each concentration into the LAD. Coronary artery diameter and APV were measured, and CBF was calculated after each infusion of Ach (the maximal tolerable dose of Ach used). CBF was calculated from the Doppler-derived time-velocity integral, and vessel diameter was determined at baseline and after both Ach and nitroglycerin administration. The reference segment was not exposed to Ach and, thus, served as a control segment. Coronary diameter was analyzed from digital images using a modification of a previously described technique from this institution. In brief, the changes in LAD diameter were measured in 2 segments distal to the stent. The distal segment was defined as the segment 5 mm distal to the tip of the Doppler guidewire (which translates to ≤5–10 mm distal to the distal stent margin) and as the far distal segment beginning >10 mm distal from the first segment. An end-diastolic cine frame at each infusion (baseline, Ach, and nitroglycerin) was selected, and calibration of the video and cine images was accomplished with the diameter of the guide catheter identified. All offline measurements of coronary artery diameter were performed by an experienced operator who was unaware of the results of the coronary reactivity data and the type of stent.

**Statistical Analysis**

Continuous data are summarized as the mean±SD if approximately normally distributed; otherwise, medians and interquartile ranges (25th–75th percentile) are stated. To compare the matched control group with the stented group, conditional logistic regression was used. Unpaired t test or Wilcoxon rank sum test was used to compare the continuous distributions between the BMS and the DES groups; Pearson χ² was used to test categorical variables between the BMS and the DES groups. P<0.05 (2-tailed) was considered to indicate statistical significance.

**Results**

**Patient Characteristics**

The total study population comprised 142 patients, 71 in each group. In the 71 patients of the stent group (mean age, 53.0±10.1 years; 36 men), the mean time between percutaneous coronary intervention of the LAD and the actual measurement was 17.1±17.1 months. Among them, 24 patients received BMS and 46 DES (17 sirolimus-, 15 paclitaxel-, and 4 everolimus-eluted stents; 10 remained unidentified) on average age 19.8±15.9 and 15.3±17.6 months, respectively (P=0.31) before endothelial function measurement. Baseline characteristics are presented in Table 1. In general, patients in the stent group had a higher prevalence in traditional cardiovascular risk factors (all patients had stents originally placed because of significant CAD) and were taking more cardiovascular medications than those in the matched control group. However, most hemodynamic and laboratory characteristics were not significantly different between the 2 groups (Table 2).

In patients who received DES compared with BMS, there were no significant differences between groups with regard to age, sex, body mass index, and cardiovascular risk factors. The frequency of cardiovascular medications did not differ.
Data for hemodynamics, including biochemical parameters, are also shown in Table 2.

Endothelium-Dependent Microvascular Endothelial Function

Baseline CBF was lower in the stent group than in the matched control group (37.7 [25.3–48.6] versus 50.6 [39.7–72.7] mL/min, \( P < 0.05 \)). However, endothelial microvascular function (change in CBF after Ach infusion) was not different between groups (34.9% [−34.4% to 90.0%] versus 54.7% [−5.6% to 104.6%], \( P = 0.18 \)) (Figure, Table 3). Abnormal coronary endothelium-dependent microvascular function was present in 38 patients in the stent group (57%) and 33 patients in the control group (47%) (\( P = 0.25 \)).

Endothelium-Independent Microvascular Endothelial Function

Mean CFR, as measured with adenosine, was not different between the stent and control groups (2.9 [2.6–3.5] versus 2.7 [2.4–3.3] mL/min, \( P = 0.39 \)). Both groups had a similar number of patients with impaired CFR (15 [21%] and 19 [27%], \( P = 0.27 \)) (Table 3).

Coronary Microvascular Endothelial Function Between DES and BMS

There was no significant difference between the DES and BMS groups with respect to change in CBF (35.9% [−35.1% to −90.0%] versus 8.6% [−34.4% to 91.0%], \( P = 0.78 \)) and CFR (2.9 [2.6–3.5] versus 2.7 [2.4–3.3] mL/min, \( P = 0.39 \)) in the stent group compared to the control group.
The frequency of abnormal microvascular function was not significantly different between the DES and BMS groups (CFR <2.5%; 8 [17%] versus 7 [29%], P=0.25; change of CBF <50%; 23 [53%] versus 14 [61%], P=0.56). There was also no significant difference in microvascular function by follow-up duration (Table 4).

Epicardial Vascular Function
Quantitative coronary angiography data for both groups are shown in Table 5. Resting baseline distal epicardial diameters were larger in the control group than in the stent group (2.3±0.6 versus 2.0±0.5 mm, P<0.05). However, Ach-induced percent changes in coronary artery diameter revealed no significant difference between the stent group and the control group (−9.5% [−23.1% to 0.0%] versus −19.8% [−33.3% to 0.0%], P=0.33). In both groups, endothelial dysfunction was present, as shown by vasoconstriction to Ach. Furthermore, there was no difference between patients treated with DES or BMS (21.0% [34.2% to 0.0%] versus 14.0% [31.5% to 4.3%], P=0.37). Intracoronary nitroglycerin induced an endothelial-independent vasodilation of all evaluated vessel segments, without differences between groups (Table 5).

CIs and Statistical Power
Given the negative findings, we calculated CIs for the median difference between matched cases and controls (Table 6). The CI for maximum CFR shows that the data are consistent under the possibility that CFR is typically 0.20 higher in controls as well as the possibility that CFR is 0.37 lower in controls. This range is fairly narrow given the interquartile ranges of 1.0 and 0.9 in controls and stented patients, respectively. Additionally, 71 paired responses should provide 80% power to detect a standardized effect size of 0.34 (ie, one third of the SD) with a paired t test. In general, these results indicate that we are not likely missing any large group differences.

Discussion
The current study demonstrates nonsignificant differences in coronary microvascular function after >1 year following stent implantation compared with age- and sex-matched patients without stents and only minimally diseased vessels. Remarkably, microvascular function did not differ based on whether DES or BMS were used. Furthermore, epicardial coronary endothelial function, although dysfunction was present in both groups and irrespective of stent type, was not different between the groups.

Although the effect of stents, DES in particular, on epicardial endothelial function has recently been studied, the effect of stent implantation on the downstream microvasculature has not been evaluated thoroughly, despite the fact that the coronary microcirculation is crucial for myocardial blood flow and myocardial perfusion regulation.17,19 In the current study, we found nonsignificantly different microvascular function in patients with significant CAD compared with a control population with similar symptoms but nonsignificant CAD. Thus, one can argue that microvascular coronary function in patients with chest pain is irrespective of prior stent implantation. Remarkably, microvascular function did not differ in those patients who received DES compared with those with who received BMS.
There are several possible explanations for the current findings. Importantly, the evaluation of endothelial function has been performed on average >1 year after stent implantation; thus, the microvascular endothelium may have recovered from periprocedural injury and after the potentially deleterious effects of drugs released by DES subsided. It has been shown that 30 days after DES placement, drug release from the stent is only minimal. However, we cannot exclude that a potential persistent negative effect of stent implantation on the endothelium was abrogated by the statins or other cardiovascular medications more often used in the stent group and which have been shown to have a positive effect on the vasculature. However, statin use was not different between the DES and BMS groups.

A recent study reported a deterioration of the coronary microvascular endothelial dysfunction between 6 and 12 months after DES implantation, and another study in porcine coronary vasculature pointed out a differential effect of DES on microvascular function, given that sirolimus-eluting stents did not affect vascular function but paclitaxel-eluting stents did. In the current study, we did not find any difference in microvascular function between the BMS and the DES groups after an average of >12 months, and there was no difference between the different types of stents used. At least in the current study population, which was characterized by epicardial endothelial dysfunction as demonstrated by vasoconstriction after Ach infusion, a condition typical for atherosclerotic vessels. It may be speculated that the presence of endothelial function during this period (again after an average of >12 months after stent implantation) is related to the presence of CAD and not the effect of stenting, particularly with DES.

The other important finding of the current study is that we did not find any difference in epicardial endothelial function in patients with chest pain and stents compared with similar patients with chest pain but no stents. Furthermore, despite the recent demonstration of endothelial dysfunction after DES implantation, epicardial vascular function was not significantly different between patients with BMS and DES. In the current population, however, most patients were characterized by epicardial endothelial dysfunction as demonstrated by vasoconstriction after Ach infusion, a condition typical for atherosclerotic vessels. It may be speculated that the presence of endothelial function during this period (again after an average of >12 months after stent implantation) is related to the presence of CAD and not the effect of stenting, particularly with DES.

Previous studies have demonstrated an association between coronary stenting, irrespective of BMS or DES, and epicardial endothelial function and raised concerns of continuous vascular injury following percutaneous coronary intervention and the potential effect on thrombosis and the potential for myocardial ischemia. Moreover, mechanisms of endothelial dysfunction after stent implantation remain incompletely defined, but recent work has suggested several possible mechanisms, including direct toxic effect from the entrapped drug, acute or delayed hypersensitivity reaction to the polymer of the stent or the drug, and delayed reendothelialization with inadequate endothelial coverage. Additionally, stent placement frequently produces dissection of the media and adventitia. These events induce focal inflammation in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤6 Months (n=22)</th>
<th>6–12 Months (n=14)</th>
<th>&gt;12 Months (n=33)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum CFR</td>
<td>3.3 (2.7 to 3.7)</td>
<td>2.7 (2.4 to 3.1)</td>
<td>2.8 (2.5 to 3.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>CFR&lt;2.5</td>
<td>2 (9)</td>
<td>5 (36)</td>
<td>8 (24)</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline CBF</td>
<td>39.5 (25.5 to 48.2)</td>
<td>33.6 (25.4 to 45.7)</td>
<td>38.5 (27.5 to 55.4)</td>
<td>0.70</td>
</tr>
<tr>
<td>CBF (Hyperemia)</td>
<td>47.5 (19.7 to 97.9)</td>
<td>38.2 (27.1 to 76.8)</td>
<td>48.5 (16.8 to 94.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Percent change CBF (Ach)</td>
<td>17.0 (−51.2 to 78.3)</td>
<td>68.2 (20.0 to 90.0)</td>
<td>−4.1 (−37.9 to 101.8)</td>
<td>0.42</td>
</tr>
<tr>
<td>Percent change CBF&lt;50%</td>
<td>14 (67)</td>
<td>4 (31)</td>
<td>19 (61)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or n (%). CFR indicate coronary flow reserve; CBF, coronary blood flow; Ach, acetylcholine. *P values based on rank sum and χ² tests.
injured vessel, which may cause endothelial dysfunction. Furthermore, several recent studies implicated a differential effect of DES on endothelial function, the mechanism of which is not clear but may be secondary to the specific drug or the polymer of the stent. In the current study, although we found epicardial dysfunction, no difference between the different stent groups were found in the long term (>1 year after stent implantation).

Study Limitations

This is a retrospective study, and the limitations of potential selection bias have to be taken into account. Although we tried to match the control population as closely as possible, there are some differences between the control and stent groups that potentially affected the results. All patients were referred because of chest pain and had undergone coronary angiography based on clinical indications. However, patients in the stent group all had recently received a stent because of significant CAD, thus potentially representing a sicker population with more cardiovascular risk factors than the control, non-stent group. However, in light of these differences, the nonsignificant findings in the difference in endothelial microvascular and macrovascular function are especially intriguing because the combination of atherosclerosis and previous stent implantation would argue worse vascular function compared with the control group. On the other hand, as outlined previously, the higher frequency of statin use and other cardioprotective medications in the stent group could have an opposite effect. Importantly, there were no differences between the DES and the BMS groups with respect to medications and risk factor distribution.

To overcome the limitation of a matched control group, it would have been elegant to compare the effect of stent implantation on microvascular function with nonstented vessels in the same patient. However, to assess the effect on the microcirculation in the current study, the administration of Ach was directly into the LAD, and thus, other arteries were not exposed. Another potential limitation is that baseline endothelial function before stent implantation was not assessed. However, the assessment of endothelial function in patients with significant coronary lesions is not practical.

Conclusions

We demonstrated that in patients with a stent in the coronary arteries that coronary microcirculatory and epicardial vascular function were not significantly different from that of an age- and sex-matched population with similar symptoms but non-significant CAD, a finding that was irrespective of the stent type implanted. Thus, the study does not support a long-term worsening of vascular function by DES implantation.

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Disclosures

None.

References


Table 6. Median Differences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum CFR</td>
<td>−0.10 (−0.37 to 0.20)</td>
</tr>
<tr>
<td>Percent change CBF (Ach)</td>
<td>−0.97 (−26.4 to 39.9)</td>
</tr>
<tr>
<td>Percent change diameter distal to stent</td>
<td>5.88 (−4.7 to 16.7)</td>
</tr>
<tr>
<td>Percent change diameter (NTG) distal to stent</td>
<td>0.00 (−11.3 to 7.7)</td>
</tr>
<tr>
<td>Percent change diameter far distal</td>
<td>7.82 (−10.2 to 16.0)</td>
</tr>
<tr>
<td>Percent change diameter (NTG)</td>
<td>−1.68 (−5.4 to 7.1)</td>
</tr>
</tbody>
</table>

* Differences are calculated within matched pairs as control patient response-stent patient response.


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