Exercise-Induced Coronary Artery Vasodilation Is Not Impaired by Stent Placement

Willibald Maier, MD; Stephan Windecker, MD; Adrian Küng, BA; Roland Lütolf, MD; Franz R. Eberli, MD; Bernhard Meier, MD; Otto M. Hess, MD

Background—Stenting has proved beneficial for treating threatened closure and reducing restenosis after balloon angioplasty. However, the implantation of a coronary metallic prosthesis has been related to impaired vasomotion distal to the stent as assessed by acetylcholine infusion. Thus, the purpose of the present study was to determine the vasomotion of stented coronary arteries and to assess its influence on the vasomotion of adjacent vessel segments during bicycle exercise.

Methods and Results—Biplane quantitative coronary angiography was performed at rest and during bicycle exercise in 26 patients with coronary artery disease. Twelve patients had single vessel disease with stable angina pectoris (controls; group 1). Fourteen patients underwent coronary stenting for therapeutic reasons and were studied 10±3 months after the intervention (group 2). Minimal luminal area, stent area, and proximal and distal vessel areas were determined. In controls (group 1), vasoconstriction of the stenotic artery (−29±4%; P<0.001) was observed during exercise, whereas the normal segment showed vasodilation (15±4%; P<0.05). In group 2, vasomotion of the stented segment was eliminated (0±1%), whereas the proximal and distal segments showed exercise-induced vasodilation (8±2% and 11±3%, respectively; P<0.005), which was not different from control segments (10±2%). Sublingual nitroglycerin was associated with maximal vasodilation of the proximal and distal vessel segments (30±8% and 38±13%, respectively; P<0.005).

Conclusions—In contrast to the vasoconstriction of vessels in control patients, normal vasodilation of proximal and distal segments occurred during the physiological stress of exercise in patients with coronary stent placement. As expected, vasomotion was abolished in the stented region. (Circulation. 2002;105:2373-2377.)

Key Words: stents ■ exercise ■ vasodilation ■ vasoconstriction ■ stenosis

Coronary artery stenting has become a standard procedure in patients undergoing percutaneous coronary intervention for mechanical stabilization of the dilated segment, prevention of abrupt vessel closure,1 and improvement of long-term patency.2 Recently, the British National Institute for Clinical Excellence recommended that “for patients with either stable or unstable angina or acute myocardial infarction and where percutaneous coronary intervention is the clinically appropriate procedure, stents should be used routinely.”3 These guidelines imply that almost all patients with percutaneous coronary intervention should receive a stent, despite of the potential risk for stent thrombosis, in-stent restenosis, or endothelial dysfunction of the vessel segment distal to the stent.

Enhanced endothelial dysfunction distal to the implanted stent has been reported by Caramori et al4 using acetylcholine testing late after the intervention. In contrast, partial normalization of coronary vasomotion of the treated vessel segment was found late after conventional balloon angioplasty.5 Stenting mechanically stabilizes the dilated segment, which might convert a formerly dynamic artery into a rigid tube. Furthermore, the implantation of a metallic prosthesis induces considerable injury to the arterial wall, with prolonged inflammatory, prothrombotic, and proliferative reactions6,7 that are likely to extend beyond the stented segment. The purpose of the present study was, therefore, to evaluate coronary vasomotor response of the proximal and distal vessel segment several months after stenting using bicycle exercise as a physiological stress test.

Methods

Of the 26 patients presented, 12 had coronary artery disease with stable angina pectoris and served as controls (group 1), and 14 patients were studied 10±3 months after successful balloon angioplasty with stent implantation (group 2). Patients with restenosis were excluded.

Mean age and distribution of cardiovascular risk factors were similar in the 2 groups, as were the number of diseased vessels (Table 1). Balloon angioplasty and stent implantation were performed according to standard techniques. About half of the stents were premounted (AVE Microstent and Johnson & Johnson Cross-
Results

A representative coronary angiogram in a patient after coronary stenting of the proximal left anterior descending artery is shown at rest and during bicycle exercise in Figure 1. The stent in the left anterior descending (LAD) coronary artery does not show any vasomotion during exercise, whereas the proximal (prox) segment dilates by 12.5% and the distal (dist) segment by 8%. After sublingual nitroglycerin, the proximal segment dilates by 25% and the distal segment by 23%.

0.11 mm, and interobserver variability of 0.10 mm. The tip of the diagnostic catheter (SF) was used for calibration purposes. At our center, intraobserver variability was ≤0.15 mm for minimal luminal diameter and ≤7% for stenosis severity. The measurements were taken by an independent observer who was blinded to the protocol. The diameter of defined vessel segments was determined at baseline and at the various steps of the protocol. Care was taken to select reference vessel segments between 2 branching points and not to include side branches. The same segments, identified by the anatomical landmarks, were assessed at all steps of the protocol. Mean cross-sectional lumen area was calculated from the 2 projections using an elliptical model. For monoplane projections, a circular shape was assumed. To optimize accuracy of the measurements, 3 measurements for each vessel segment were carried out and averaged. Percent changes were calculated in all patients using the baseline angiogram as reference.

In the control group, a vessel segment of a normal coronary artery, as well as thestenotic segment, were evaluated. In group 2, a normal vessel segment not related to the stented lesion, as well as the stented segment and its adjacent segments (between 5 and 15 mm proximal and distal to the stent edges) were assessed (Figure 1).

Statistics

Patient data are given as mean±1SD and cross-sectional lumen area measurements as mean±1SEM. Statistical analysis was performed by ANOVA for repeated measurements. When the test was significant, post hoc (Student-Newman-Keuls) tests for paired comparisons were applied. For intergroup comparisons, an unpaired Student’s t test was used. P<0.05 was considered significant.

Results

A representative coronary angiogram in a patient after coronary stenting of the proximal left anterior descending artery is shown at rest and during bicycle exercise in Figure 1. The proximal and distal vessel segments, as well as the reference

Study Protocol

The local ethics committee approved the protocol, and informed consent was obtained from all patients. Vasoactive medication was discontinued 24 hours before catheterization. Only short-acting nitrates were allowed for angina relief, if necessary. Diagnostic catheterization was performed with standard techniques using SF Judkins coronary catheters (Cordis). At the end of diagnostic catheterization, biplane coronary angiography was performed at rest with the patient’s feet attached to the supine bicycle ergometer. Exercise was begun at 50 or 75 W, and workload was increased every 2 minutes in increments of 25 W. The catheter was left in place during exercise. Coronary angiography was performed at the end of the maximal exercise level in deep inspiration. Average workload was slightly higher in the control group with stable angina pectoris (81±34 W) than in group 2 (63±13 W; P<0.05). This difference was attributable to several factors, such as smaller body size, higher age, and more exercise-limiting symptoms such as fatigue and leg weakness in group 2. The exercise test was terminated because of fatigue, angina pectoris, or ST-segment depression >0.2 mV. At the end of the exercise test, all patients received 1.6 mg of nitroglycerin sublingually and 5 minutes later, coronary angiography was repeated. Nitroglycerin was administered routinely to assess endothelium-independent vasodilation. There were no complications related to the study protocol.

Quantitative Coronary Angiography

Coronary angiography was performed on a digital x-ray system (Philips DCI-SX and Philips Integris) at 12.5 frames/s. Simultaneous biplane projections were acquired in all patients, and rotation and angulation were adapted to minimize foreshortening of the target vessel.

Quantitative evaluation (Figure 1) was carried out in monoplane projection. Two orthogonal views were averaged for biplane assessment. Because of vessel overlap, analysis had to be restricted to a single plane in 50% of group 1 and 43% of group 2 segments, respectively. Data analysis was performed with the ACA package on Philips DCI/Integris systems with a documented accuracy of <0.01 mm, precision of <0.10 mm, intraobserver variability of

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
<th>Group 1 (Control)</th>
<th>Group 2 (Stent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±7</td>
<td>58±11</td>
</tr>
<tr>
<td>Male/female sex</td>
<td>12/0</td>
<td>12/2</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>2.6±0.7</td>
<td>1.8±0.9</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>58</td>
<td>71</td>
</tr>
<tr>
<td>Family history, %</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.0±0.6</td>
<td>5.7±0.7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage of patients.
segment, show coronary vasodilatation during dynamic exercise, whereas the stented segment remains unchanged.

**Hemodynamic Data**
Heart rate, left ventricular end-diastolic pressure, left ventricular ejection fraction, and mean aortic pressure were similar in the 2 groups (Table 2). During exercise, heart rate increased in both groups significantly, as did mean aortic pressure. Exercise workload was significantly lower in group 2, and the rate-pressure-product tended to be smaller, although this difference did not reach statistical significance.

**Quantitative Coronary Angiography**
In the control group, the percent diameter stenosis of the stenotic vessel segment was 59 ± 4%. This segment showed exercise-induced vasodilatation (−29 ± 4%), whereas the control segment elicited vasodilatation of 15 ± 4% (P ≤ 0.005 versus rest; Figure 2). Sublingual nitroglycerin induced maximal vasodilatation (34 ± 6%; P < 0.005) in normal segments and mild vasodilatation in stenoses (10 ± 8%; P = NS).

In group 2, 5 of the 14 patients showed mild in-stent restenosis (23 ± 10%). Vasomotion was completely abolished in the stented segment during exercise and after nitroglycerin, but it was maintained in the proximal and distal segment adjacent to the stent (proximal, 8 ± 2%; distal, 11 ± 3%; P < 0.005 versus rest; Figure 3). Exercise-induced vasodilatation of the control vessel in group 2 amounted to 10 ± 2% and was not significantly different from that in the control vessel of group 1 (15 ± 4%). Sublingual nitroglycerin was associated with significant vasodilatation of the proximal, distal, and control vessel segment (proximal, 30 ± 8%; distal, 38 ± 13%; and control, 49 ± 7%).

In the subgroup of patients with mild restenosis (n = 5), the behavior of the proximal and distal vessel segment during exercise was similar to the whole group (proximal, 9 ± 3%; distal, 8 ± 4% vasodilatation).

**Discussion**
Coronary vasomotion after stenting has been shown to be abnormal distal to the stented segment, which has been attributed to diffuse endothelial dysfunction with reduced nitric oxide bioavailability. In contrast, balloon angioplasty has been found to improve exercise-induced coronary vasomotion after intervention, although normalization was not achieved (exercise-induced vasodilatation, 5%). Thus, vasomotor response is maintained after balloon angioplasty, whereas stenting eliminates exercise-induced vasomotion at the site of the lesion. The recommendation of the British National Institute of Clinical Excellence to stent all vessels >3.5 mm and <3.5 mm on a routine basis may have important consequences, with loss of vasomotion at the site of stent implantation and propagation of endothelial dysfunction to the distal part of the artery. Thus, we performed the present study to examine the effect of exercise as a more physiological stimulus on coronary artery vasomotion compared with pharmacological examination by acetycholine infusion. The findings of the present study indicate that (1) paradoxical vasoconstriction of the stenotic vessel during exercise is abolished after stent placement and (2) normal vasodilatation of proximal and distal segments occurred during exercise.
the physiological stress of exercise in patients with coronary stent placement.

Coronary Vasomotion During Exercise

Coronary artery disease is associated with exercise-induced vasoconstriction at the site of the stenotic lesion; normal coronary arteries dilate. The paradoxical response of the stenotic arteries during exercise has been attributed to (1) reduced nitric oxide bioavailability at the site of the stenosis (endothelial dysfunction); (2) enhanced vasoconstrictor response due to an increase in circulating catecholamines (enhanced sympathetic stimulation); (3) enhanced platelet aggregation due to turbulent blood flow through the stenotic lesion with release of thromboxane A2 and serotonin; and (4) flow-induced (passive) collapse of the normal vessel segment within the stenosis (Venturi effect).

These mechanisms alone or in combination may be responsible for exercise-induced vasoconstriction of stenotic lesions, and they may aggravate myocardial ischemia by a reduced flow increase during exercise, whereas normal vessel segments dilate as a result of the exercise-induced nitric oxide release. These mechanisms are stenosis related and do not necessarily apply to the proximal and distal vessel segments. However, a drop in distal perfusion pressure beyond a paradoxical response of the lesion, rather than diffuse endothelial dysfunction alone, might contribute to reduced distal vasomotor response.

A diminished vasomotor response to exercise has also been reported in patients with hypercholesterolemia or hypertension; this was thought to be due to endothelial dysfunction. Endothelial dysfunction has been assessed by intracoronary acetylcholine infusion showing vasodilation in normal coronary vessels but vasoconstriction in diseased arteries. In the present study, the normal, although slightly reduced, vasodilation of the vessel segments adjacent to the stent during exercise (proximal, 8±2%; distal, 11±3%) can be explained by the presence of an increased serum cholesterol level (Table 1). Nevertheless, maximal vasodilation after nitroglycerin indicated preserved vasodilatory capacity. Mechanical stabilization of the treated vessel segment by coronary stenting abolishes vasoreactivity, but the loss is limited to the length of the implanted stent and does not extend to the adjacent vessel segments, as suggested by Caramori et al.

The difference between the 2 studies may be related to the different techniques for measuring coronary vasomotor response (ie, pharmacological assessment of endothelial function by acetylcholine infusion versus flow-mediated [physiological] changes induced by bicycle exercise), although one earlier comparative study has shown a similar response in diseased coronary arteries during acetylcholine infusion and physiological exercise.

Because testing endothelial function in human coronary arteries is a technically difficult procedure both with intracoronary acetylcholine infusion or supine bicycle exercise, almost no comparative data exist in the literature. However, even in the study of Gordon et al., the comparison between the 2 methods is limited to 6 patients. In 5 of these 6 patients, all vessel segments showed the same directional response to acetylcholine and exercise: 3 irregular and 2 stenotic segments constricted, whereas 4 smooth segments dilated to both acetylcholine and exercise. In accordance with our previously published data, Gordon et al. showed vasoconstriction of stenotic and vasodilation of normal vessel segments in response to exercise. The order of magnitude of normal vessel vasodilation was similar to that in the present study (14.0±1.8%). Caramori et al. reported vasoconstriction in the vessel segments distal to the stent and, to a lesser degree, after balloon angioplasty and even in normal control vessels. This is in contrast to our long-term data after balloon angioplasty.

In line with the results of Gordon and coworkers, the discrepancy between the 2 studies could be explained by a more diffuse morphological disease in the cohort of Caramori et al. The response of angiographically normal vessel segments to intracoronary acetylcholine has been shown to be dependent not only on structural changes, but also on cardiovascular risk factors such as hypercholesterolemia or hypertension. Thus, a varying degree of coronary artery disease might provide an explanation for the differences.

Clinical Implications

Healing an injured vessel segment after percutaneous transluminal coronary angiography is associated with re-endothelialization and improvement of endothelial function. Although the cells of the neoendothelium are smaller and have a different shape compared with normal cells, the mechanical stabilization prevents vasodilation and, thus, may indirectly reduce nitric oxide bioavailability and diminish flow-mediated vascular changes. Therefore, the interruption of the continuity of the endothelial layering may lead to a propagation of arteriosclerosis distal to the stented vessel and impair the long-term outcome of coronary interventions. However, the present study indicates that the vasomotor response to exercise is maintained at the proximal and distal vessel sites and, thus, seems not to jeopardize the long-term results of coronary artery stenting.

It is of interest that even in those patients who developed some degree of in-stent restenosis (n=5), proximal and distal vasomotion was preserved. Apparently, mild in-stent restenosis does not affect the vasomotor response of the distal vessel segment.

Study Limitations

The following limitations may have influenced the data of the current study. (1) The differences in workload between the 2 groups may be explained by differences in body size, age, and exercise-limiting symptoms. Despite the lower workload in group 2, the reaction to exercise was similar to that in group 1. (2) Cardiovascular risk factors were slightly different between the 2 study groups. However, these differences were not statistically significant, although the stent group showed more risk factors than the control group. Nevertheless, the stent group elicited a nearly normal reaction of the vessels adjacent to the stented segment, indicating that there is no diffuse endothelial dysfunction after stent placement.

Conclusions

Coronary artery stenoses show exercise-induced vasoconstriction, whereas normal arteries dilate. This paradoxical
response of stenotic arteries has been attributed to endothelial dysfunction with reduced nitric oxide bioavailability, enhanced sympathetic stimulation during exercise, platelet activation due to turbulent blood flow, or a passive vessel collapse of the normal vessel segment within the stenosis. In the present study, we showed that stent placement abolishes paradoxical vasoconstriction of the coronary stenosis but does not adversely affect vasomotion of the adjacent vessel segments. Thus, paradoxical vasoconstriction is a local, stenosis-related problem and does not extend to the proximal and distal vessel segments during the physiological stress of exercise.

References
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