Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 2, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.01.062

CLINICAL RESEARCH **Interventional Cardiology**

Sirolimus-Eluting Stents Associated With Paradoxic Coronary Vasoconstriction

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OBJECTIVES The purpose of the present study was to assess coronary vasomotor response to exercise after sirolimus-eluting stent (SES) implantation.

BACKGROUND Sirolimus-eluting stents have been shown to markedly reduce the incidence of angiographic and clinical restenosis. However, long-term effects of sirolimus on endothelial function are unknown.

METHODS Coronary vasomotion was evaluated with biplane quantitative coronary angiography at rest and during supine bicycle exercise in 25 patients with coronary artery disease. Eleven patients were treated with a bare-metal stent (BMS) (control group) and 14 patients underwent SES implantation (sirolimus group) for de novo coronary artery lesions. Both groups were studied 6 ± 1 month after the intervention. Minimal luminal diameter; stent diameter; and proximal, distal, and reference vessel diameter were determined.

RESULTS The reference vessel showed exercise-induced vasodilation (+13 ± 4%) in both groups. Vasomotion within the stented vessel segments was abolished. In controls, the adjacent segments proximal and distal to the stent showed exercise-induced vasodilation (+15 ± 3% and +17 ± 4%, respectively). In contrast, there was exercise-induced vasoconstriction of the proximal and distal vessel segments adjacent to SESs (−12 ± 4% and −15 ± 6%, respectively; $p < 0.001$ vs. corresponding segments of controls). Sublingual nitroglycerin was associated with maximal vasodilation of the proximal and distal vessel segments in both groups.

CONCLUSIONS Implantation of a BMS does not affect physiologic response to exercise proximal and distal to the stent. However, SESs are associated with exercise-induced paradoxic coronary vasoconstriction of the adjacent vessel segments, although vasodilatory response to nitroglycerin is maintained. These observations suggest (drug-induced) endothelial dysfunction as the underlying mechanism. (J Am Coll Cardiol 2005;46:231–6) © 2005 by the American College of Cardiology Foundation

Sirolimus-eluting stents (SES) are widely used for percutaneous coronary interventions because of their excellent long-term results with regard to clinical and angiographic outcome. Several investigations have shown an impressive reduction in the rates of angiographic restenosis and associated clinical events (1–6). However, long-term results of

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SES implantation with regard to vascular integrity and coronary endothelial function are largely unknown. In vitro investigations indicate that apart from suppressing smooth muscle cell proliferation (7), sirolimus also reduces the replication of human endothelial cells (8). Recently, concern has been raised that SES could be associated with increased rates of stent thrombosis owing to delayed or absent endothelialization (9,10). Furthermore, restenosis after SES implantation has been observed predominantly at the stent margins (peri-stent region), indicating that this region might be affected by the drug or intervention (1). Thus, the purpose of the present study was to assess coronary endothelial function six months after SES implantation, with bicycle exercise used as a physiologic stimulus to evaluate vasomotor response.

METHODS

Twenty-five patients were included in the present analysis. Eleven patients were studied 6 ± 2 months after successful bare-metal stent (BMS) implantation and served as control patients (control group), and 14 patients were studied 6 ± 1 month after SES (CYPHER, Cordis Corp., Miami Lakes, Florida) implantation for de novo coronary lesions. Mean age, distribution of cardiovascular risk factors, and medication were similar in the two groups (Table 1). Procedural data were also comparable with regard to stented vessel and stent length and diameter (Table 2). Stent implantation was carried out according to standard guidelines. In the control group nine patients received a BX-SONIC stent (Cordis Corp.) and two patients an AVE stent (Medtronic Inc., Minneapolis, Minnesota).

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Manuscript received October 11, 2004; revised manuscript received December 27, 2004, accepted January 11, 2005.

Abbreviations and Acronyms
BMS = bare-metal stent
NO = nitric oxide
NTG = nitroglycerin
SES = sirolimus-eluting stent

Inclusion criteria were willingness and physical ability to perform supine bicycle exercise and successful coronary stent implantation without angiographic restenosis at the time of re-angiography. Exclusion criteria were unstable angina, recent myocardial infarction, coronary revascularization after stent placement, coronary radiotherapy, history of coronary spasm, severe left ventricular dysfunction, and clinically significant extracardiac disease.

Study protocol. The local ethics committee approved the protocol, and informed consent was obtained from all patients. Vasoactive medication was discontinued at least 48 h before catheterization. Diagnostic catheterization was performed with standard techniques. At the end of diagnostic catheterization, biplane coronary angiography was carried out 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 min in increments of 25 or 50 W. The catheter was left in place during exercise. Coronary angiography was carried out at the end of each exercise level and at maximal exercise in deep inspiration. Average workload was slightly higher in the sirolimus group (102 ± 23 W) than in the control group (86 ± 13 W, p = 0.07). The exercise test was terminated because of fatigue, angina pectoris, or ST-segment depression of more than 0.2 mV. At the end of the exercise test, all patients received 1.6 mg nitroglycerin (NTG) sublingually, and 5 min later, coronary angiography was repeated. Nitroglycerin was administered routinely to assess endothelium-independent vasodilation. There were no complications related to the study protocol.

Table 1. Patient Characteristics

	Control Group (Bare Stent) (n = 11)	Sirolimus Group (n = 14)
Age, yrs	57 ± 12	54 ± 13
Gender, male/female	9/2	12/2
No. of diseased vessels	1.7 ± 0.9	1.7 ± 0.7
Hypertension, %	55	43
Cigarette smoking, %	64	50
Family history, %	45	71
Total cholesterol, mmol/l	5.7 ± 0.7	5.6 ± 0.6
Diabetes, %	9	7
Beta-blockers, %	73	57
Nitrates, %	27	29
ACE inhibitors, %	55	57
Calcium channel blockers, %	9	21
Statins, %	82	86

Values are mean ± SD or percentage of patients.
ACE = angiotensin-converting enzyme.

Table 2. Angiographic Data

	Control Group (n = 11)	Sirolimus Group (n = 14)
Location of lesion		
LAD	6/11 (55)	9/14 (64)
LCX	1/11 (9)	2/14 (14)
RCA	4/11 (36)	3/14 (21)
Mean stent length, mm	16 ± 6	18 ± 5
Stent deployment pressure, bar	13 ± 3	14 ± 3
Nominal stent diameter, mm		
3.5	2/11 (18)	4/14 (29)
3.0	7/11 (64)	8/14 (57)
2.5	2/11 (18)	2/14 (14)

Values are no. of patients (%) or mean ± SD.
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

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 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 27% of control group and 36% of sirolimus group segments, respectively. Data analysis was performed with the quantitative coronary analysis package on Philips DCI/Integris systems and has been described in detail previously (11–13). Percent changes were calculated in all patients using the baseline angiogram as reference. In both groups, a reference vessel not related to the stented lesion, as well as the stented segment and its adjacent segments proximal and distal (5 to 10 mm proximal and distal to the stent edges), were assessed. In addition, vessel segments between 10 and 20 mm proximal and distal to the stent edges were investigated (proximal reference and distal reference). This measurement was performed to determine the response to exercise within and outside the zone where sirolimus might be effective. The intra- and interobserver variability was low for minimal luminal diameter (<0.10 mm for intraobserver and <0.11 for interobserver variability) (11–13). All measurements were done by an independent observer who was blinded to the protocol.

Statistics. Patient data are given as mean ± 1 SD. Vessel diameters as well as cross-sectional lumen area calculations are reported as mean ± 1 SEM unless otherwise specified. Comparison of hemodynamic (heart rate, aortic blood pressure) and angiographic data (including minimal luminal diameter of the stented segment, the proximal and distal segments to the stent, and the proximal and distal reference segments) was performed by an analysis of variance for repeated measurements, specifying stent assignment (BMS/SES) as a between-subjects factor. Data were analyzed at baseline, after exercise, and after NTG administration. For intergroup comparisons we used an unpaired Student *t* test