Sirolimus-Eluting Stents Associated With Paradoxic Coronary Vasoconstriction

Mario Togni, Stephan Windecker, Rosangela Cocchia, Peter Wenaweser, Stephane Cook, Michael Billinger, Bernhard Meier, and Otto M. Hess

J. Am. Coll. Cardiol. 2005;46;231-236; originally published online Jul 5, 2005;
doi:10.1016/j.jacc.2005.01.062

Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
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

Mario Togni, MD, Stephan Windecker, MD, Rosangela Cocchia, MD, Peter Wenaweser, MD, Stephane Cook, MD, Michael Billinger, MD, Bernhard Meier, MD, FACC, Otto M. Hess, MD, FACC
Bern, Switzerland

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 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.

See page 237

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).

From the Swiss Cardiovascular Center Bern, Bern, Switzerland.
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

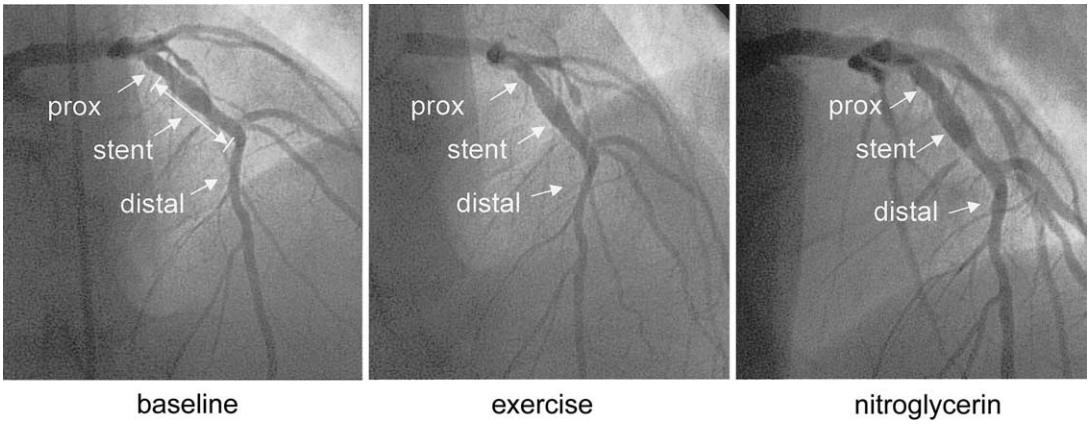

Figure 1. Original recording of the left coronary artery at baseline **(left)**, during exercise with 75 W **(middle)**, and after 1.6 mg of sublingual nitroglycerin **(right)**. The proximal (prox) and the distal segment adjacent to the sirolimus-eluting stent show vasoconstriction by 8% and 14%, respectively, during exercise. After sublingual nitroglycerin, the proximal and distal segment dilate by 26% and 28%, respectively.

and for within-group comparisons we used a paired Student *t* test. A p value <0.05 was considered significant.

RESULTS

A representative coronary angiogram in a patient after SES implantation of the proximal left anterior descending artery is shown at rest and during bicycle exercise in Figure 1. The proximal and distal vessel segments adjacent to the stent (peri-stent region) show coronary vasoconstriction during dynamic exercise.

Hemodynamic data. Heart rate, left ventricular end-diastolic pressure, left ventricular ejection fraction, and mean aortic pressure were similar in the two groups (Table 3). During exercise, heart rate increased in both groups significantly, as did mean aortic pressure. Exercise workload was significantly lower in the control group.

Quantitative coronary angiography. Individual and mean data for the two patient groups with regard to vessel diameter of the proximal and distal as well as the stent segments are shown in Table 4 and Figure 2. In the control group, normal vasomotion (vasodilation) was maintained in the proximal and distal segment adjacent to the stent, as well as in the proximal and distal reference segments (proximal 15 ± 3%; distal 17 ± 4%; proximal reference 11 ± 3%; distal reference 15 ± 4%; all p = NS) (Fig. 3).

Table 3. Exercise Hemodynamics

	Rest		Exercise	
	Control Group	Sirolimus Group	Control Group	Sirolimus Group
LVEDP, mm Hg	12 ± 5	9 ± 5	NA	NA
EF, %	68 ± 8	63 ± 8	NA	NA
HR, beats/min	64 ± 5	69 ± 10	106 ± 13	108 ± 14
MAP, mm Hg	97 ± 19	88 ± 14	113 ± 11	117 ± 19
RPP, 10^3 mm Hg/min	6.3 ± 1.5	6.1 ± 1.2	11.9 ± 1.1	12.6 ± 2.5
Workload, W	0	0	86 ± 13	102 ± 23

Values are mean ± SD.

EF = ejection fraction; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; NA = not available; RPP = rate-pressure product.

Sublingual NTG was associated with significant vasodilation of all vessel segments (proximal 28 ± 4%; distal 31 ± 7%; proximal reference 23 ± 4%; distal reference 32 ± 11%; all p = NS). In the sirolimus group, there was exercise-induced vasoconstriction of the proximal and distal vessel segments adjacent to the stent (proximal −12 ± 4%; distal −15 ± 6%; $p < 0.001$ vs. corresponding segments of the control group). However, the proximal and distal reference vessel segments showed vasodilation during exercise (proximal reference 9 ± 3%; distal reference 13 ± 5%; p = NS vs. corresponding segments of the control group). Sublingual NTG was associated with maximal vasodilation of all the evaluated vessel segments (proximal 22 ± 5%; distal 22 ± 6%; proximal reference 28 ± 13%; and distal reference 48 ± 9%; p = NS vs. corresponding segments of the control group). The stented vessel segments in both groups showed no vasomotion. The control vessel not related to the stented vessel showed exercise-induced vasodilation in both groups (13 ± 4%), and maximal vasodilation after sublingual NTG (26 ± 4%).

DISCUSSION

Sirolimus-eluting stents have been associated with a significant reduction in the incidence of in-stent restenosis and have led to a breakthrough in the percutaneous treatment of coronary artery disease (1–6). Sirolimus inhibits smooth muscle cell as well as endothelial cell proliferation via cell cycle arrest in the late G1 phase (7,8). Preliminary data suggest that SES are associated with endothelial dysfunction (14). The extent and duration of endothelial recovery after drug-eluting stent implantation as well as its long-term sequelae, however, remain to be determined. Impairment of endothelial recovery may have adverse long-term effects such as stent thrombosis, reoccurrence of coronary lesions, and negative vascular remodeling (15,16).

The findings of the present study are as follows: dynamic exercise is associated with paradoxic vasoconstriction of coronary artery segments adjacent to the SES (endothelial

JACC Vol. 46, No. 2, 2005
July 19, 2005:231–6

Table 4. Quantitative Coronary Angiography

	Proximal Reference			Proximal			Stent			Distal			Distal Reference		
	Control	Sirolimus	p	Control	Sirolimus	p	Control	Sirolimus	p	Control	Sirolimus	p	Control	Sirolimus	p
B	2.92 ± 0.49	2.87 ± 0.45	NS	2.80 ± 0.60	2.69 ± 0.36	NS	2.98 ± 0.25	3.02 ± 0.42	NS	2.59 ± 0.36	2.37 ± 0.48	NS	2.57 ± 0.61	2.30 ± 0.46	NS
E	3.07 ± 0.42	2.96 ± 0.52	NS	2.99 ± 0.56	2.51 ± 0.31	0.043	2.99 ± 0.26	2.99 ± 0.43	NS	2.79 ± 0.72	2.15 ± 0.39	0.011	2.73 ± 0.59	2.47 ± 0.65	NS
NTG	3.23 ± 0.53	3.44 ± 0.49	NS	3.27 ± 0.70	2.96 ± 0.39	NS	3.01 ± 0.27	3.00 ± 0.42	NS	2.92 ± 0.78	2.66 ± 0.79	NS	2.92 ± 0.63	2.7 ± 0.47	NS
p B *vs.* E	0.008	0.034		0.001	0.017		0.88	0.11		0.001	0.016		0.002	0.023	
p E *vs.* NTG	0.001	0.052		0.007	0.003		0.89	0.44		0.005	0.001		0.005	0.014	
p B *vs.* NTG	0.001	0.02		0.001	0.002		0.53	0.20		0.001	0.004		0.002	0.009	

Values are mean of diameters in mm (± SD), sirolimus and control indicate sirolimus-eluting stent and control groups. Student *t* test used for paired and unpaired observations.
B = baseline; E = exercise; NTG = nitroglycerin; NS = not significant; p = p value.

dysfunction) and vasodilatory response of the peristent region to NTG is maintained (preserved vasodilatory capacity). This does not, however, imply structural integrity of the endothelium, because NTG is a non–endothelium-dependent vasodilator.

Normal coronary arteries dilate during dynamic exercise because of the enhanced release of nitric oxide (NO) by the endothelium (17,18). In contrast, coronary vasomotion is impaired in patients with coronary artery disease, resulting in exercise-induced vasoconstriction at the site of the stenotic lesions (19). This paradoxic response of the stenotic arteries during exercise has been attributed to the following four mechanisms (12): 1) reduced nitric oxide bioavailability (endothelial dysfunction); 2) enhanced vasoconstrictor response due to enhanced sympathetic stimulation during exercise; 3) enhanced platelet aggregation due to turbulent blood flow; and 4) flow-induced collapse (Venturi effect). Percutaneous transluminal coronary angioplasty normalizes or improves coronary vasomotion (20). Recently, stent implantation has been shown to abolish paradoxic vasoconstriction of coronary stenoses and to render a previously vasoresponsive vessel into a rigid tube (12).

Endothelial recovery after SES implantation. Suzuki et al. (21) have described in the porcine overstretch model that vascular healing after SES and BMS implantation are comparable at 28 days with regard to endothelialization and smooth-muscle cell proliferation. However, fibrin deposits adjacent to SES struts have been observed, representing delayed healing. With paclitaxel, direct inhibition of reendothelialization has been described by Farb et al. (22). Moreover, atherectomy specimens from late in-stent restenotic lesions after implantation of a paclitaxel derivate-eluting stent system have demonstrated delayed endothelial healing and chronic inflammation (23).

Coronary vasomotion after stent implantation. Previously, we have reported (12) that vessel segments adjacent to BMS show physiologic vasodilation during exercise. The present study revealed exercise-induced vasoconstriction of coronary artery segments adjacent to SES (i.e., within a range of 5 to 10 mm proximal and distal to the stent edges [peristent region]). Outside this region (i.e., 10 to 20 mm proximal and distal to the stent edges) exercise-induced vasomotion was normal, comparable to patients with BMS, suggesting that sirolimus may induce vascular damage with endothelial dysfunction, thereby reducing NO availability in the peristent region. Angiographic and intravascular ultrasound data indicate normal structural appearance of the target vessel after SES (24,25). This observation, however, does not exclude functional abnormalities of the peri-stent and in-stent segments after SES implantation. Together with the findings of incomplete endothelial coverage within the stented segment (21,26) and the dysfunctional endothelium proximal and distal to the stent, SES may be vulnerable for late stent thrombosis and peristent restenosis. However, the link between adverse clinical events and abnormal peristent vasomotion is speculative and has yet to be

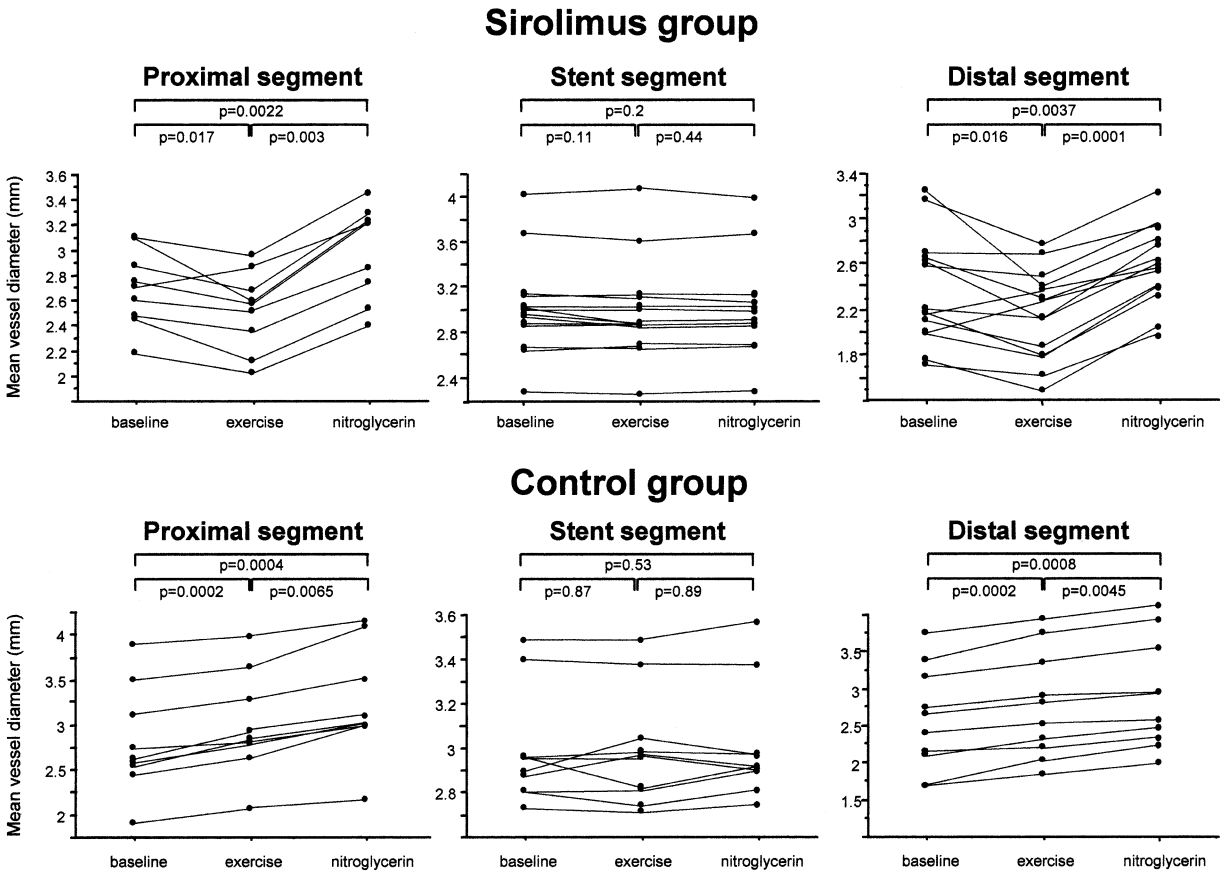

Figure 2. Line chart with individual values for vessel diameter (mm) in the proximal, distal, and stent segment at baseline, during exercise, and after nitroglycerin. The p values for paired comparison are indicated.

established. The fate of the endothelium after SES implantation remains uncertain, and endothelial recovery may be perturbed.

Study limitations. Testing endothelial function in human arteries is a technically difficult procedure, both with intracoronary acetylcholine infusion and supine bicycle exercise. Therefore, little comparative data are available in the literature, and sample sizes are usually small. Nevertheless, our data provide important insights into vascular physiology of SES-treated coronaries.

Patients with restenosis were excluded for practical and theoretical reasons. First, it is difficult to find patients with in-stent restenosis, because with the introduction of SES it has almost disappeared. Second, in-stent restenosis influences flow pattern with reduced (limited) blood flow and thus decreases in NO release and, therefore, is associated with limited or absent exercise-induced vasomotion.

In our protocol, vasomotion was tested six months after stent implantation. Endothelial healing after SES implantation may be delayed. Therefore, testing endothelial function six months after the intervention may miss long-term functional recovery. Furthermore, the vasomotor response

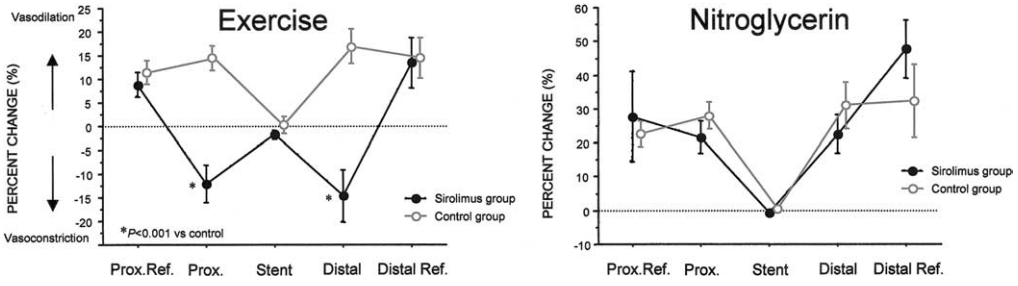

Figure 3. Line chart with percent changes of the mean cross-sectional lumen area in the sirolimus and control groups during exercise **(left panel)** and after nitroglycerin application **(right panel)**. Mean values ± SEM are shown for the proximal reference segment (Prox.Ref.), the proximal segment (Prox.), the stent segment (Stent), the distal segment (Distal), and the distal reference segment (Distal ref.). The stent segment does not elicit any vasomotion. The sirolimus group shows exercise-induced vasoconstriction of the proximal (−12 ± 4%) and distal (−15 ± 6%) segment to the stent, whereas the control group demonstrates exercise-induced vasodilation of the respective segments (15 ± 3% and 17 ± 4%) ($p < 0.001$). The proximal and distal reference segments dilate during exercise in both groups. After nitroglycerin application, all the segments (except for the stent) show maximal vasodilation.

of the peristent region probably reflects a dose-dependent effect of sirolimus on the endothelium. With the advent of stents with different pharmacokinetic properties of sirolimus release, we may observe other responses to exercise.

There was no randomization with regard to stent assignment. Patients were included on a consecutive basis. During a first phase of the study only BMS were used, followed by a later phase during which only SES were implanted. The selection of the individual patient was at random, including those patients who were willing to undergo a second angiogram and to participate in an exercise protocol. Because the assignment of stent type was dependent only on the time point of study inclusion, bias with regard to stent-type decision was minimal and has probably not influenced the result.

Sousa et al. (26) have recently reported lack of complete endothelial coverage in a patient four years after SES implantation without clinical consequence.

The results of this study cannot be directly applied to other drug-eluting stents, particularly those coated with paclitaxel or derivatives thereof.

Conclusions. Coronary artery stenoses show exercise-induced vasoconstriction, whereas normal arteries dilate. Previously, it was reported that stent placement abolishes paradoxic vasoconstriction of the coronary arteries and does not adversely affect vasomotion of the adjacent vessel segments. In the present study, we observed paradoxic exercise-induced vasoconstriction of vessel segments adjacent to SES, although dilatory response to NTG was maintained. Paradoxic vasoconstriction in a vessel segment not subjected to percutaneous transluminal coronary angioplasty barotrauma may be due to diffusion of the antiproliferative drug from the stent to the peri-stent region, inducing endothelial dysfunction.

Reprint requests and correspondence: Dr. Otto M. Hess, Professor of Cardiology, Swiss Cardiovascular Center, Inselspital, CH-3010 Bern, Switzerland. E-mail: otto.hess@insel.ch.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
2. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
3. Regar E, Serruys PW, Bode C, et al. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106: 1949–56.
4. Serruys PW, Degertekin M, Tanabe K, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002;106:798–803.
5. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001;103:192–5.
6. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–5.
7. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277–83.
8. Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128–35.
9. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004;109:1930–2.
10. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.
11. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 2001;345:1593–600.
12. Maier W, Windecker S, Kung A, et al. Exercise-induced coronary artery vasodilation is not impaired by stent placement. Circulation 2002;105:2373–7.
13. Togni M, Windecker S, Wenaweser P, et al. Deleterious effect of coronary brachytherapy on vasomotor response to exercise. Circulation 2004;110:135–40.
14. Hofma SH, Van der Giessen WJ, Van Dalen B, Lemos PA, Serruys PW. Prolonged endothelial dysfunction late after stenting with sirolimus-eluting stent compared to bare metal stent (abstr). Eur Heart J 2004;25 Suppl:525.
15. Schwartz RS, Chronos NA, Virmani R. Preclinical restenosis models and drug-eluting stents: still important, still much to learn. J Am Coll Cardiol 2004;44:1373–85.
16. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
17. Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehl HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. Circulation 1986;73:865–76.
18. Hess OM, Bortone A, Eid K, et al. Coronary vasomotor tone during static and dynamic exercise. Eur Heart J 1989;10:105–10.
19. Gordon JB, Ganz P, Nabel EG, et al. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. J Clin Invest 1989;83:1946–52.
20. Suter TM, Hess OM, Bortone A, Nonogi H, Grimm J, Krayenbuehl HP. Coronary stenosis vasomotion during dynamic exercise before and after PTCA. Eur Heart J 1989;10:58–63.
21. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188–93.
22. Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001;104:473–9.
23. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation 2002;106:2649–51.
24. Sousa JE, Costa MA, Sousa AGMR, et al. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003;107:381–3.
25. Holmes DR, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial. A randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109:634–40.
26. Sousa JE, Costa MA, Farb A, et al. Images in cardiovascular medicine. Vascular healing 4 years after the implantation of sirolimus-eluting stent in humans: a histopathological examination. Circulation 2004; 110:e5–6.

Sirolimus-Eluting Stents Associated With Paradoxic Coronary Vasoconstriction

Mario Togni, Stephan Windecker, Rosangela Cocchia, Peter Wenaweser, Stephane Cook, Michael Billinger, Bernhard Meier, and Otto M. Hess

J. Am. Coll. Cardiol. 2005;46;231-236; originally published online Jul 5, 2005;
doi:10.1016/j.jacc.2005.01.062