Deleterious Effect of Coronary Brachytherapy on Vasomotor Response to Exercise

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Background—Intracoronary radiotherapy (brachytherapy) has been proposed as treatment option for in-stent restenosis. Long-term results of brachytherapy with regard to vascular integrity and vasomotor responsiveness are unknown. The purpose of the present study was to determine the vasomotor response after brachytherapy and to assess its influence on vasomotion during exercise.

Methods and Results—Biplane quantitative coronary angiography was performed at rest and during bicycle exercise in 27 patients with coronary artery disease. Fourteen patients underwent coronary stenting and were studied 10±3 months after intervention (control group). Thirteen patients were treated with brachytherapy (Guidant Galileo System) for in-stent restenosis with a mean dosis of 20 Gy at 1 mm into the vessel wall and were studied 9±1 months after radiation (brachytherapy group). Minimal luminal area, stent area, and proximal, distal, and a reference vessel area were determined. The reference vessel showed exercise-induced vasodilation (26±4%, $P<0.001$) in both groups. Vasomotion within the stented vessel segments was abolished. In control subjects, the proximal and distal segments showed exercise-induced vasodilation (17±2% and 22±7%, respectively; $P<0.005$). In contrast, there was exercise-induced vasoconstriction in the proximal and distal vessel segments of the brachytherapy group (−14±3% and −16±4%, respectively; $P<0.01$). Sublingual nitroglycerin was associated with maximal vasodilation of the proximal and distal vessel segments in both groups.

Conclusions—Normal vessel segments elicit flow-mediated vasodilation during exercise. Stent implantation does not affect physiological response to exercise proximal and distal to the stent. Brachytherapy eliminates exercise-induced vasodilation, although dilatory response to nitroglycerin is maintained, suggesting endothelial dysfunction as the underlying mechanism. **(*Circulation*. 2004;110:135-140.)**

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

Intracoronary radiotherapy is effective in reducing excessive neointimal proliferation after balloon angioplasty or stent placement.[1–6] Before the advent of drug-eluting stents, brachytherapy was considered the most promising treatment option for in-stent restenosis, reducing the chance for repeat restenosis from 50% to 60% to 25% to 35%.[7] However, radiation has been associated with late (>30 days) stent thrombosis caused by delayed or missing reendothelialization.[8,9] The reported rates range between 6% and 15%, especially in those patients who received a new stent. Late stent thrombosis is accompanied by a high risk of cardiovascular morbidity and mortality. The occurrence of late stent thrombosis is enhanced through a malfunctioning endothelium proximal and distal to the stent. Previous studies in human carotid arteries have shown that external radiation leads to a reduction in nitric oxide production,[10] which could promote platelet aggregation and thrombus formation of the not endothelialized stent.[11,12] Thus, the purpose of the present study was to assess coronary endothelial function late after radiation therapy (>6 months), with bicycle exercise used as a physiological stimulus to evaluate vasomotor response.

Methods

Of the 27 patients presented, 14 were studied 10±3 months after successful balloon angioplasty with stent implantation and served as control subjects (control group), and 13 patients were studied 9±1 months after treatment with balloon angioplasty and intracoronary radiotherapy for in-stent restenosis (brachytherapy group). Twenty-two of the 27 patients had a history of restenosis. Nine of 14 patients in the control group had been treated by stent implantation for restenosis after balloon angioplasty. Thus, the restenosis potential in the brachytherapy group was slightly higher.

Mean age, distribution of cardiovascular risk factors, and medication are shown in Table 1. Although the cardiovascular risk score was similar (NS) in the two groups, patients in the brachytherapy group were slightly sicker with regard to the number of diseased vessels, incidence of diabetes, and cholesterol levels. Procedural data were comparable in the two groups with regard to stented vessel, stent length, and diameter (Table 2). Balloon angioplasty and stent implantation were carried out according to standard techniques.

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TABLE 1. Patient Characteristics

	Control Group (n=14)	Brachytherapy Group (n=13)
Age, y	58±11	65±8
Gender, male/female	12/2	12/1
Number of diseased vessels	1.8±0.9	2.1±0.9
Hypertension, %	71	77
Cigarette smoking, %	71	62
Family history, %	21	23
Total cholesterol, mmol/L	5.7±0.7	6±1.2
Diabetes, %	0	23
Cardiovascular risk score	8.2±2.4	8.6±2.2
β-Blockers, %	79	85
Nitrates, %	14	8
ACE inhibitors, %	43	54
Ca^{2+} channel blockers, %	14	8
Statins, %	86	85

Values are mean±SD or percentage of patients. Cardiovascular risk score is based on Framingham experience.[27]

Brachytherapy

The system used for intracoronary β-radiation has been described previously (Galileo Centering Catheter, Guidant Vascular Interventions).[13] Briefly, the system consists of 3 components. The source wire is a 0.018-inch flexible Nitinol wire, with the active 32P source encapsulated in the distal 27 mm of the wire. The centering balloon catheter is a double-lumen catheter with a short monorail distal tip for a rapid exchange method of delivery and a 34-mm or 52-mm-long spiral balloon, with nominal diameters of 2.5, 3.0, and 3.5 mm, which centers the source within the lumen while allowing perfusion of side branches and distal vessel. The source delivery unit provides safe storage of the active wire and automated delivery and retrieval. Patients received a dosis of 20 Gy at 1-mm vessel depth. For in-stent restenosis lesions >30 mm in length (n=2), the 52-mm-long spiral balloon was applied with "stepping" of the source. For the rest (n=11), the 34-mm-long spiral balloon was used. The irradiated segment always included the injured segment after angioplasty and a safety margin >10 mm (ie, >5 mm per proximal and distal edge).

Inclusion criteria were (in addition to willingness and physical ability to participate in the study protocol with bicycle exercise) for the control group, successful coronary stent implantation without angiographic restenosis, and for the brachytherapy group, successful coronary radiotherapy with delivery of 20 Gy at 1 mm into the vessel wall without restenosis at the time of repeat angiography.

Exclusion criteria were unstable angina, recent myocardial infarction, coronary revascularization after stent placement and radiotherapy, history of coronary spasm, severe left ventricular dysfunction, and clinically significant extracardiac disease.

TABLE 2. Angiographic Data

	Control Group (n=14)	Brachytherapy Group (n=13)
Location of lesion		
LAD	7/14 (50)	6/13 (46)
LCX	2/14 (14)	4/13 (31)
RCA	5/14 (36)	3/13 (23)
Mean stent length, mm	15±4	15±5
Stent deployment pressure, bar	11±1	11±2
Nominal stent diameter		
3.5 mm	7/14 (50)	3/13 (23)
3.0 mm	7/14 (50)	8/13 (62)
2.5 mm	0/14 (0)	2/13 (15)

Values are number of patients (%) or mean±SD. LM indicates left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery.

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 by means of standard techniques, with 5F Judkins coronary catheters (Cordis). 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 minutes 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 brachytherapy group (81±34 W) than in the control group (63±13, $P<0.05$). This difference was due to several reasons such as smaller body size and more exercise-limiting symptoms such as fatigue and leg weakness in the control group. The exercise test was terminated because of fatigue, angina pectoris, or ST-segment depression of >0.2 mV. At the end of the exercise test, all patients received 1.6 mg 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 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 43% of control group and 31% of brachytherapy group 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 0.11 mm, and interobserver variability of 0.10 mm.[14,15] The contrast-filled tip of the diagnostic catheter was used for calibration purposes. At our center, intraobserver variability is ≤0.15 mm for minimal luminal diameter and ≤7% for stenosis severity.[16,17] An independent observer blinded to the study protocol performed the measurements. 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 two branching points and not to include side branches. The same segments, identified by anatomical landmarks, were assessed at all steps of the protocol. Mean cross-sectional lumen area was calculated from the two projections, with the use of an elliptical model. For monoplane projections, a circular shape was assumed. To optimize accuracy of the measurements, for each vessel segment, 3 measurements were carried out and averaged. Percent changes were calculated in all patients, with the baseline angiogram used as reference. In both groups, a reference 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. In addition, a peripheral vessel segment of the radiated artery outside the radiation zone and a corresponding segment in the control group were evaluated. This was performed to determine whether the response to exercise was similar or different in and outside the radiation zone.

Normalization of vessel diameters for the maximally vasodilated state was performed by dividing resting and exercise data by the

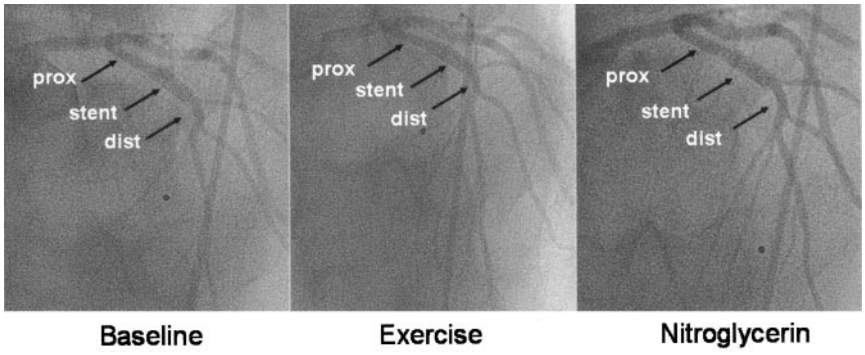

Figure 1. Original recording of the left coronary artery at baseline (left), during exercise with 75 W (middle), and after 1.6 mg of sublingual nitroglycerin (right). Proximal (prox) and distal (dist) segments to the stent show vasoconstriction by 10% and 12%, respectively, during exercise. After sublingual nitroglycerin, proximal and distal segments dilate by 23% and 25%, respectively.

vessel diameter after nitroglycerin administration. This normalization method ("ceiling") was used to account for variations in baseline vasomotor tone.

Statistics

Patient data are given as mean±1 SD and cross-sectional lumen area measurements as mean±1 SEM. 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. A value of $P<0.05$ was considered significant.

Results

A representative coronary angiogram in a patient after brachytherapy for in-stent restenosis of the proximal left anterior descending artery is shown at rest and during bicycle exercise in Figure 1. The proximal and distal vessel segments show mild coronary vasoconstriction during dynamic exercise.

Hemodynamic Data

Heart rate, left ventricular end-diastolic, left ventricular ejection fraction, and mean aortic pressure were similar in the 2 groups (Table 3). During exercise, heart rate increased in both groups significantly, as did mean aortic pressure. Exercise workload and rate-pressure product were 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 Figure 2 and Table 4.

TABLE 3. Exercise Hemodynamics

	Rest		Exercise	
	Control Group	Brachytherapy Group	Control Group	Brachytherapy Group
LVEDP, mm Hg	12±5	16±5	NA	NA
EF, %	70±8	60±10	NA	NA
HR, bpm	65±6	69±11	90±11	102±16
MAP, mm Hg	104±15	105±11	110±12	126±16
RPP, 10^3 mm Hg/min	6.8±1.1	7.2±1.4	9.8±1.3	12.0±4.6
Workload, W	0	0	63±13	88±17

Values are mean±SD. LVEDP indicates left ventricular end-diastolic pressure; EF, ejection fraction; HR, heart rate; MAP, mean arterial pressure; RPP, rate pressure product; and NA, not available.

Coronary vessels in the radiation group were slightly smaller compared with the control vessel segments at baseline, but only the peripheral segments were significantly different between the two groups ($P<0.05$). In the control group, vasomotion was maintained in the proximal and distal segment adjacent to the stent as well as in the peripheral segment (proximal, 17±2%; distal 22±7%; peripheral 18±4%; $P<0.005$ versus rest). Exercise-induced vasomotion of the reference vessel amounted to 24±4%. Sublingual nitroglycerin was associated with significant vasodilation of the proximal, distal, peripheral, and reference vessel segment (proximal, 30±8%; distal, 38±13%; peripheral, 35±7% and reference, 49±7%). In the brachytherapy group, one of the 13 patients had in-stent occlusion after brachytherapy and was excluded from further analysis. The other 12 showed no angiographic restenosis. Some minor neointimal proliferation compared with the angiogram immediately after the intervention (brachytherapy) was found in most patients (n=10). In contrast to the control group, there was exercise-induced vasoconstriction of the proximal and distal vessel segment of the irradiated artery (proximal, −14±3%, distal, −16±4%, respectively; $P<0.01$) (Figures 2 and 3). The peripheral vessel segment as well as the reference vessel in the brachytherapy group showed, however, marked dilation during exercise (peripheral 18±4%; reference vessel, 27±5%, $P<0.001$). Sublingual nitroglycerin was associated with maximal vasodilation of all evaluated vessel segments (proximal, 25±6%; distal, 20±6%; peripheral, 34±6%; and reference, 48±7%). The stented vessel segments in both groups showed no vasomotion.

Normalization of vessel diameter to maximal vasodilation with nitroglycerin is depicted in Figure 4. The brachytherapy group showed slightly lower basal vasomotor tone in the segment distal to the stent (NS). However, basal tone was similar in the segment proximal to the stent and the peripheral vessel segment. During exercise, tone increased in the brachytherapy group for both proximal and distal vessel segments (vasoconstrictory response) but decreased in the control group (vasodilatory response).

Discussion

Intracoronary radiotherapy has been regarded as the most promising therapeutic option for in-stent restenosis before the advent of drug-eluting stents.[7] Late vessel occlusion and stent thrombosis are the most serious complications associated with coronary brachytherapy.[8] Both phenomenons have been

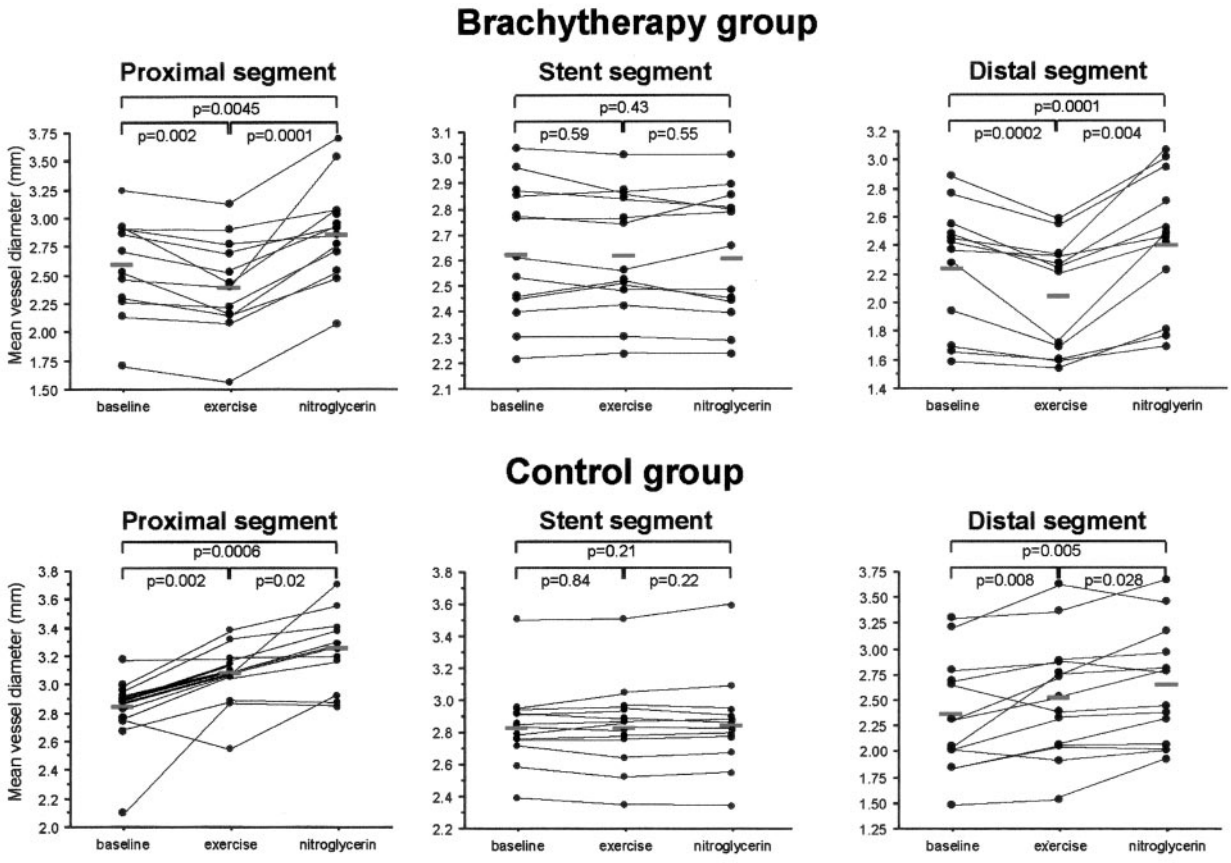

Figure 2. Line chart with individual values for vessel diameter (mm) in proximal, distal, and stent segments at baseline, during exercise, and after nitroglycerin. Red bars show mean values. Probability values for paired comparison are indicated.

attributed to the lack of endothelialization after radiation.[18] Conflicting data exist regarding the short- and long-term effects after radiation to the vessel and specifically to the endothelium. Sabate et al[19] have described preserved endothelium-dependent vasodilation in coronary segments 6 months after brachytherapy assessed by selective infusion of acetylcholine proximally to the treated vessel. In contrast, Scheinert and coworkers[20] reported induction of coronary artery spasm immediately after β-radiation. Thus, the purpose if the present study was to examine the effect of exercise-induced flow increases as a physiological stimulus for coronary artery dilatation compared with pharmacological vasodilation by acetylcholine infusion.

The findings of the present study indicate that (1) dynamic exercise is associated with a paradoxical vasoconstriction of irradiated coronary artery segments, and (2) vasodilatory response to nitroglycerin is maintained.

Pathophysiological Considerations

Coronary vasomotion is impaired in coronary artery disease with exercise-induced vasoconstriction at the site of the stenotic lesions and an increase in vasomotor tone. Normal coronary arteries dilate during dynamic exercise.[21] Percutaneous transluminal coronary angioplasty of stenotic lesions normalizes or improves coronary vasomotion.[22] Stent implantation abolishes paradoxical vasoconstriction of coronary stenosis and renders a previous vasoresponsive vessel into a rigid tube.[17]

A diminished vasomotor response to exercise has also been reported in patients with hypercholesterolemia,[23] hypertension, or left ventricular hypertrophy.[24] The mechanisms of abnormal coronary vasomotion is different in various disease entities, namely, endothelial dysfunction induced by hypercholesterolemia, media hypertrophy followed by endothelial dysfunction in hypertension, and increased oxygen demand with reduced vasodilatory capacity in patients with LV hypertrophy.

TABLE 4. Quantitative Coronary Angiography

	Proximal		Stent		Distal		Peripheral		Reference	
	Brachy	Control	Brachy	Control	Brachy	Control	Brachy	Control	Brachy	Control
Baseline	2.58±0.43	2.85±0.31	2.63±0.26	2.83±0.25	2.25±0.44	2.37±0.69	1.74±0.36	2.31±0.75‡	3.05±0.73	3.33±0.71
Exercise	2.41±0.42†	3.09±0.25†§	2.62±0.24	2.83±0.27	2.05±0.4*	2.53±0.66*‡	1.87±0.38†	2.50±0.81†‡	3.41±0.77†	3.65±0.89†
NTG	2.87±0.44	3.26±0.33	2.61±0.25	2.85±0.29	2.39±0.47	2.68±0.65	1.95±0.37	2.66±0.79‡	3.68±0.93	3.83±1.14

Values are mean of diameters in mm (±SD). Brachy and Control indicate brachytherapy and control groups; NTG, nitroglycerin.
*$P<0.05$, †$P<0.005$ vs baseline; ‡$P<0.05$, §$P<0.005$ vs brachytherapy group. Student's t test used for paired and unpaired observations.

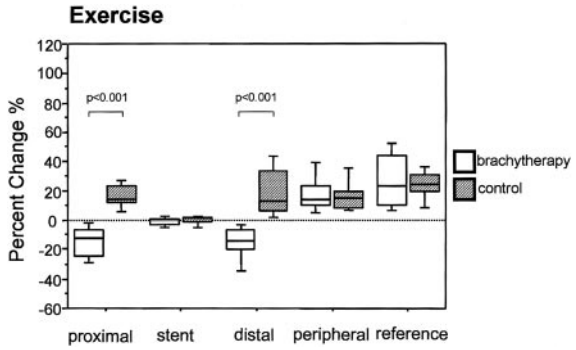

Figure 3. Box plot of exercise-induced changes of mean cross-sectional lumen area in brachytherapy and control groups. Brachytherapy group shows exercise-induced vasoconstriction of proximal (−14±3%) and distal (−16±4%) segments to the stent, whereas the control group demonstrates exercise-induced vasodilation of the respective segments (17±2% and 22±7%). Stent segment does not elicit vasomotion; vessel diameter remains unchanged with exercise. Peripheral segment and reference vessel dilate in both groups during exercise. Median values and quartiles are shown.

In the present study, irradiated vessel segments show exercise-induced vasoconstriction proximal and distal to the stented vessel segment. Parallel to the decrease in vessel diameter an increase in vasomotor tone was observed (Figure 4) in the brachytherapy group, whereas in the control group, both segments (proximal and distal to the stent) showed a decrease in vasomotor tone during exercise, similar to that in the peripheral segments for both groups. This paradoxical response of the irradiated vessel segments may be attributed to (1) reduced nitric oxide bioavailability at the site of irradiation (endothelial dysfunction); (2) enhanced platelet aggregation with release of thromboxane A_2 and serotonin; and (3) lack of endothelialization after irradiation.

Reduced Nitric Oxide Bioavailability

Impairment of nitric oxide–mediated endothelium-dependent relaxation after irradiation has been described in human carotid arteries.[10] Attenuated relaxation resulted from impaired production of nitric oxide and prostacyclin. Immunohistochemical staining for endothelial nitric oxide synthase indicated no expression of endothelial nitric oxide synthase in the endothelium of irradiated arteries.

Enhanced Platelet Aggregation With Release of Thromboxane A_2 and Serotonin

A recently published study reported enhanced vasoreactivity with nitroglycerin-resistant coronary artery spasms after high-dose endovascular β-radiation.[20] These findings suggest severe impairment of endothelium-dependent smooth muscle cell relaxation. Animal studies have demonstrated incomplete endothelial recovery, with a dose-dependent increase in platelet recruitment after balloon angioplasty followed by endovascular irradiation.[18] Enhanced release of thromboxane A_2 and serotonin may play an important role in the occurrence of coronary artery spasms and paradoxical reaction of the coronaries to exercise.

Lack of Endothelial Coverage or Incomplete Endothelialization

Incomplete endothelial coverage may explain the abnormal response to dynamic exercise. This phenomenon has been proposed as explanation for late stent thrombosis (>6 months after irradiation).[8,9]

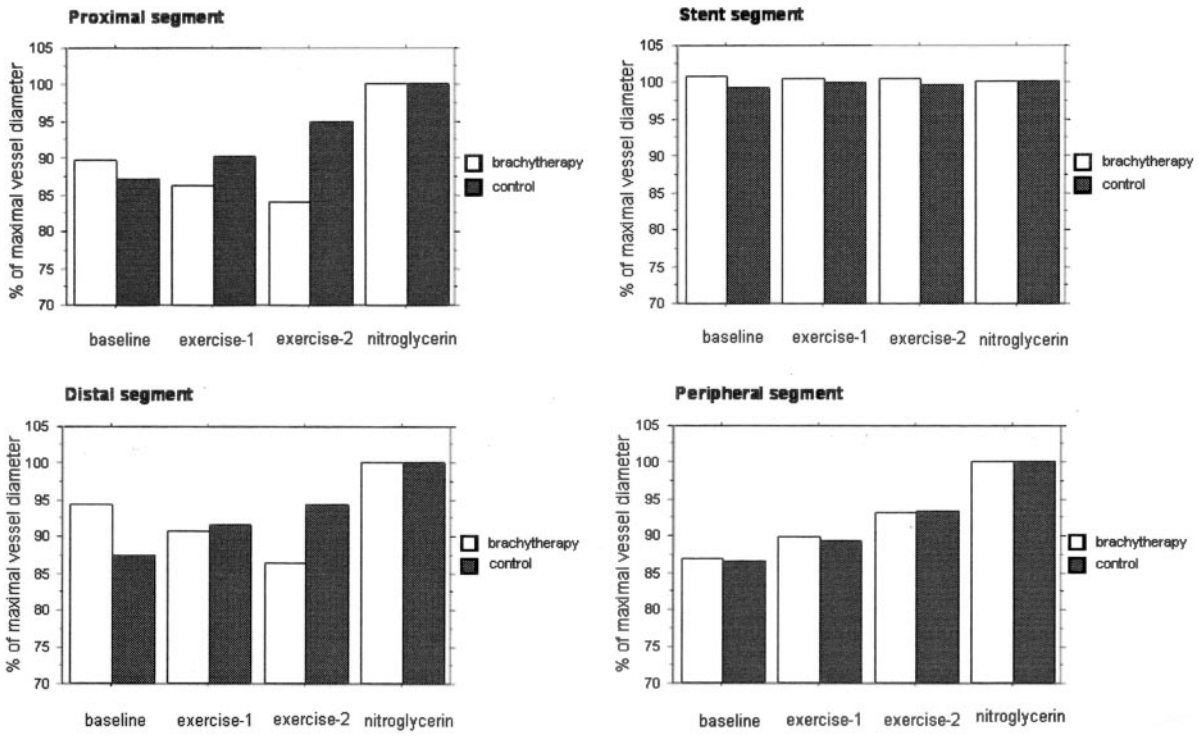

Figure 4. Vessel diameters in the proximal, distal, peripheral, and stent segments expressed as percentage of maximal vessel diameter after administration of nitroglycerin. Values at baseline, at two levels of exercise, and after sublingual nitroglycerin in both patient groups. Brachytherapy group shows slightly lower basal vessel tone in the distal segment compared with the control group (NS).

Limitations

Testing endothelial function in human arteries is a technically difficult procedure, both with intracoronary acetylcholine infusion or supine bicycle exercise. Therefore, almost no comparative data exist in the literature and sample sizes are small, as is the case with our study population. Gage et al[21] and Gordon et al[25] have shown vasoconstriction of stenotic but vasodilation of normal coronary vessel segments in response to exercise. Recently, we reported that stent implantation does not impair exercise-induced coronary artery vasodilation proximal and distal to the stented vessel,[17] as it was reported by Caramori et al.[26] Sabate et al[19] have reported preserved endothelium-dependent vasodilation 6 months after brachytherapy, assessed by the vasomotor response to acetylcholine infusion. The contrary findings may be related to (1) the different techniques for measuring coronary vasomotor response (ie, pharmacological assessment of endothelial function by acetylcholine infusion versus flow-mediated changes induced by bicycle exercise) and (2) the different radiation dose (our brachytherapy group received 20 Gy, the brachytherapy group studied by Sabate et al,[19] 14 Gy).

Our control group included 9 patients who had development of restenosis after balloon angioplasty, which was treated by stent implantation. Thus, this population compares well with the brachytherapy group, which had development of restenosis after stent placement. We admit that the brachytherapy patients may have a slightly higher restenosis potential than the control group. Nevertheless, the analysis of an additional peripheral segment distal to the irradiated zone showed a vasodilatory response indicating normal vessel behavior, despite a slightly different restenosis potential.

Patients in the brachytherapy group were older and slightly sicker than those in the control group with regard the number of diseased vessels, cholesterol levels, and incidence of diabetes. In particular, the irradiated vessels were slightly smaller than those in the control group, which is associated with a higher risk of restenosis.[27]

Conclusions

Coronary artery stenoses show exercise-induced vasoconstriction, whereas normal arteries dilate. We have previously reported that stent placement abolishes paradoxical vasoconstriction of the coronary stenosis but does not adversely affect vasomotion of the adjacent vessel segments. In the present study, we have shown that brachytherapy eliminates exercise-induced vasodilation in the vessel segments adjacent to the stent, although dilatory response to nitroglycerin is maintained. Paradoxical coronary artery vasoconstriction after brachytherapy is a radiation-related problem that may be attributed to endothelial dysfunction caused by incomplete endothelial coverage or lack of reendothelialization. Lack or delay of reendothelialization puts the patient at risk for late stent-thrombosis.

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