Deleterious Effect of Brachytherapy on Vasomotor Response to Exercise

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Abstract

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 largely unknown. Thus, the purpose of the present study was to determine the vasomotor response following brachytherapy and to assess its influence on vasomotion during exercise.

Patients 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 (controls; group 1). Thirteen patients were treated with brachytherapy (Guidant Galileo System) for in-stent restenosis with a mean dosis of 20 Gy and were studied 9±1 months after radiation (group 2). Minimal luminal area, stent area, proximal, distal and a reference vessel area were determined. The reference vessel showed exercise-induced vasodilatation (15±4%,$p<0.05$) in both groups. Vasomotion within the stented vessel segments was abolished. In controls (group 1), the proximal and distal segments showed exercise-induced vasodilatation (8±2% and 11±3%, respectively; $p<0.005$). In contrast, there was exercise-induced vasoconstriction in the proximal and distal vessel segments of the irradiated artery (-14±3% and -16±4%, respectively; $p<0.01$). Sublingual nitroglycerin was associated with maximal vasodilatation of the proximal and distal vessel segments in both groups.

Conclusions: Normal vessel segments elicit flow-mediated vasodilatation during exercise. Stent implantation does not affect physiologic response to exercise proximal and distal to the stent. Brachytherapy eliminates exercise-induced vasodilation although dilatatory response to nitroglycerin is maintained suggesting endothelial dysfunction as the underlying mechanism.

Condensed abstract

Long-term effects of brachytherapy on endothelial function, apart from the occurrence of late stent thrombosis due to delayed endothelialization, are unknown. Thus, the purpose of the present study was to determine vasomotor function of stented coronary arteries after brachytherapy and to assess its influence on vasomotion during bicycle exercise. Luminal area of stented and adjacent vessel segments were determined by quantitative coronary angiography. Stented vessel segment showed no vasomotion, whereas the proximal and distal vessel segment elicited exercise-induced vasoconstriction. The response to nitroglycerin was maintained. These observations suggest a deleterious effect of brachytherapy on endothelial function of the irradiated vessel.

Key words: stents, restenosis, radiotherapy, exercise, vasodilation, vasoconstriction.

Introduction

Intracoronary radiotherapy is effective in reducing excessive neointimal proliferation after balloon angioplasty or stent placement[1-9]. Prior to 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 50-60% to 25-35%[10]. However, radiation has been associated with late (> 30 days) stent thrombosis due to delayed or missing re-endothelialization [11,12]. The reported rates ranged 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 compared to subacute stent thrombosis (<30 days). 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[13] which could enhance platelet aggregation and thrombus formation of the not endothelialized stent[14,15]. Thus, the purpose of the present study was to assess coronary endothelial function late after radiation therapy (> 6months) using bicycle exercise as a physiological stimulus to evaluate vasomotor response.

Methods

Of the 27 patients presented, 14 patients were studied 10±3 months after successful balloon angioplasty with stent implantation and served as controls (group 1), and 13 patients were studied 9±1 months after treatment with balloon angioplasty and intracoronary radiotherapy for in-stent restenosis (group 2).

Mean age and distribution of cardiovascular risk factors were similar in the two groups (table 1). Procedural data were comparable in the 2 groups with regard stented vessel, stent length and diameter (table2). Balloon angioplasty and stent implantation were carried out according to standard techniques.

Brach therapy

The system used for intracoronary beta-radiation has been described previously (Galileo Centering Catheter, Guidant Vascular Interventions, Houston, TX) [16]. 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 27mm 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 > 10mm (i.e., >5mm 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 group 1 successful coronary stent implantation without angiographic restenosis, and for group 2 successful coronary radiotherapy with delivery of 20 Gy at 1 mm into vessel wall without restenosis at the time of reangiography.

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.

Study protocol

The local ethics committee approved the protocol, and informed consent was obtained from all patients. Vasoactive medication was discontinued 24 hours before catheterisation. Only short –acting nitrates were allowed for angina relief, if necessary. Diagnostic catheterization was performed with standard techniques using 5 F Judkins coronary catheters (Cordis). At the end of diagnostic catheterisation, 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 Watt) 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 group 1. 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 sublingually and 5 minutes later coronary angiography was repeated. Nitroglycerin was administered routinely to assess endothelium-independent vasodilatation. 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/sec. 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 43% of group 1 and 31% 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[17], intraobserver variability of 0.11 mm, and interobserver variability of 0.10 mm[18]. The tip of the diagnostic catheter (5 F) was used for calibration purposes. At our center, intraobserver variability is ≤0.15 mm for minimal luminal diameter and 7±% for stenosis severity[19]. 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 (CSA) was calculated from the two projections using an elliptical model. For monoplane projections, a circular shape was assumed. To optimize accuracy of the measurements, for each vessel segment three measurements were carried out and averaged. Percent changes were calculated in all patients using the baseline angiogram as reference. In both groups, 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.

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 inter-group comparisons, an unpaired Student t-test was used. $P < 0.05$ 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 in figure 1 at rest and during bicycle exercise. The proximal and distal vessel segments show mild coronary vasoconstriction during dynamic exercise as opposed to the reference vessel segment in the left circumflex artery which dilates during 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 group 1.

Quantitative Coronary Angiography

In the control group, vasomotion was maintained in the proximal and distal segment adjacent to the stent (proximal, 8±2%; distal 11±3%; $p<0.005$ versus rest). Exercise- induced vasomotion of the reference vessel amounted to 10±2%. Sublingual nitroglycerin was associated with significant vasodilation of the proximal, distal, and reference vessel segment (proximal, 30±8%; distal, 38±13%; and control, 49±7%). In group 2, one of the 13 patients developed in-stent occlusion after brachytherapy and was excluded from further analysis. The other twelve 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 (-14±3% and -16±4%, respectively; $p<0.01$) (figure 2). The reference vessel in group 2 showed, however, marked dilatation during exercise (27±5%). Sublingual NTG was associated with maximal vasodilatation of the proximal, distal, and control vessel segment (proximal 25±6%; distal 20±6%; and control, 48± 7%). The stented vessel segments in both groups showed no vasomotion.

Discussion

Intracoronary radiotherapy has been regarded as most promising therapeutic option for in-stent restenosis prior to the advent of drug eluting stents[10]. Late vessel occlusion and stent thrombosis are the most serious complications associated with coronary brachytherapy[12]. Both phenomenons have been attributed to the lack of endothelialization following radiation[20]. Conflicting data exist regarding the short and long-term effect after radiation to the vessel and specifically to the endothelium. Sabate et al have described preserved endothelium-dependent vasodilation in coronary segments six months after brachytherapy assessed by selective infusion of acetylcholine proximally to the treated vessel[21]. In contrast, Scheinert and coworkers reported induction of coronary artery spasm immediately after β-radiation[22]. Thus, the purpose if the present study was to examine the effect of exercise-induced flow increases as a physiologic stimulus for coronary artery dilatation compared to pharmacologic vasodilatation 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) vasodilatatory response to nitroglycerin is maintained.

Pathophysiologic Considerations

Coronary vasomotion is impaired in coronary artery disease with exercise-induced vasoconstriction at the site of the stenotic lesions. Normal coronary arteries dilate during dynamic exercise[23]. Percutaneous transluminal coronary angioplasty of stenotic lesions normalizes or improves coronary vasomotion [24]. Stent implantation abolishes paradoxical vasoconstriction of coronary stenosis and renders a previous vasoresponsive vessel into a rigid tube[25].

A diminished vasomotor response to exercise has also been reported in patients with hypercholesterolemia[26], hypertension or left ventricular hypertrophy[27]. The mechanisms of abnormal coronary vasomotion is different in the various disease entities, namely endothelial dysfunction induced by hypercholesterolemia, media hypertrophy followed by endothelial dysfunction in hypertension and increased oxygen demand with reduced vasodilatatory capacity in patients with LV hypertrophy.

In the present study, irradiated vessel segments show exercise-induced vasoconstriction proximal and distal to the stented vessel segment. 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 A2 and serotonin; and (3) enhanced sympathetic stimulation during exercise with reduced flow-mediated vasodilatation.

Reduced nitric oxide bioavailability: Impairment of nitric oxide-mediated endothelium-dependent relaxation after irradiation has been described in human carotid arteries[13]. Attenuated relaxation resulted from impaired production of nitric oxide and prostacyclin. Immunhistochemical staining for endothelial nitric oxide synthase indicated no expression of eNOS in the endothelium of irradiated arteries.

Enhanced platelet aggregation with releases of thromboxane A2 and serotonin: A recently published study reported enhanced vasoreactivity with nitroglycerin resistant coronary artery spasms after high dose endovascular β-radiation[22]. These findings suggest severe impairment of the endothelium-dependent smooth muscle cell relaxation. Animal studies have demonstrated incomplete endothelial recovery with a dose-dependent increase in platelet recruitment after ballon angioplasty followed by endovascular irradiation[20]. Enhanced release of thromboxane A2 and serotonin may play an important role in the occurrence of coronary artery spasms and paradoxical reaction of the coronaries to exercise. Thus, incomplete endothelial coverage or lack of endothelializaiton may explain the abnormal response to dynamic exercise.

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 and Gordon et al have shown vasoconstriction of stenotic but vasodilation of normal coronary vessel segments in response to exercise[23,28]. Recently we reported that stent implantation does not impair exercise-induced coronary artery vasodilation proximal and distal to the stented vessel as it was reported by Caramori et al[25,29]. Sabate et al has reported preserved endothelium-dependent vasodilation 6 months after brachytherapy, assessed by the vasomotor response to acetylcholine infusion[21]. 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, physiological, changes induced by bicycle exercise) and to (2) the different radiation dose (our brachytherapy group received 20 Gy, the brachytherapy group studied by Sabate et al 14 Gy).

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 dilatatory response to nitroglycerin is maintained. Paradoxical coronary artery vasoconstriction after brachytherapy is a radiation-related problem which may be attributed to endothelial dysfunction due to incomplete endothelial coverage or lack of reendothelialization.

Legend to Figures

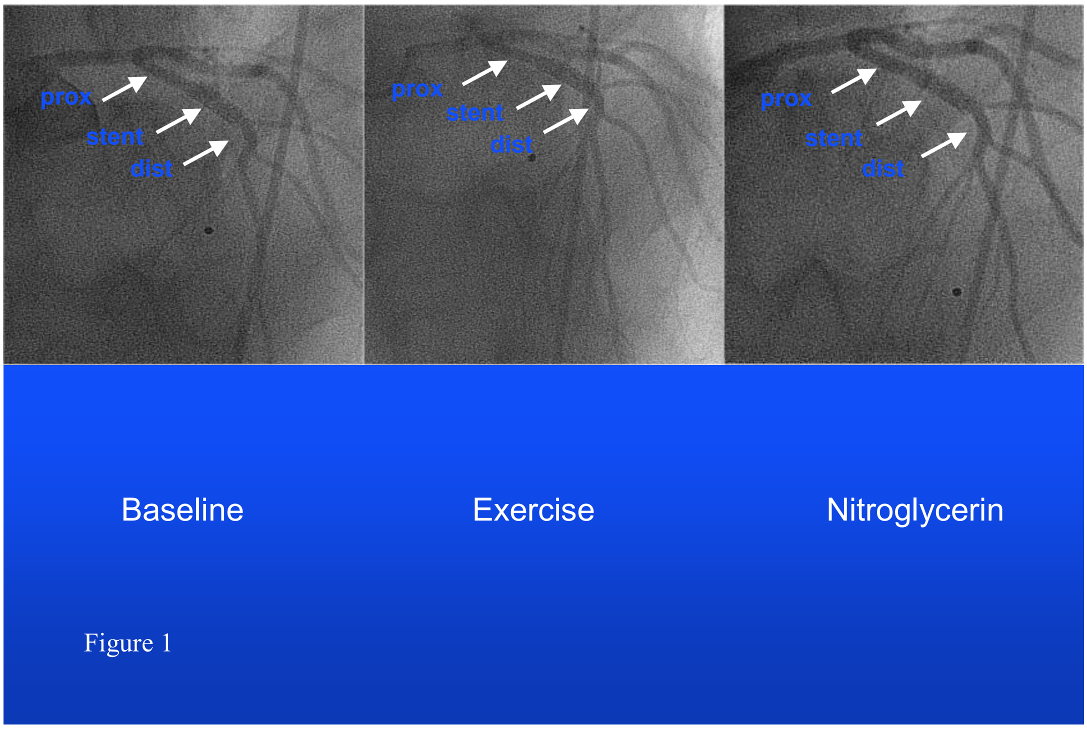

Figure 1. Original recording of the left coronary artery at baseline (top), during exercise with 75 W (middle), and after 1.6 mg of sublingual nitroglycerin (bottom). The proximal (prox) and the distal (dist) segment to the stent show vasoconstriction by 10% and 12 %, respectively, during exercise. After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

Coronary Vasomotion During Exercise

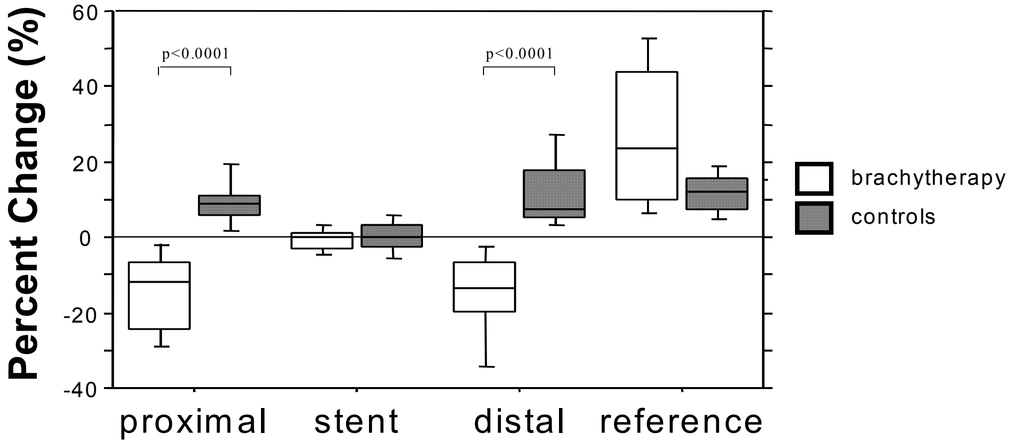

Figure 2

Figure 2. Box plot of the exercise-induced changes of the mean cross-sectional lumen area in the brachytherapy and control group. The brachytherapy group shows exercise-induced vasoconstriction of the proximal (-14±3%) and distal (-16±4%) segment to the stent, whereas the control group demonstrates exercise-induced vasodilatation of the respective segments (8±2% and 11±3%). The stent segment does not elicit any vasomotion, and the vessel diameter remains unchanged with exercise. The reference vessel dilate in both groups during exercise. Median values and quartiles are shown.

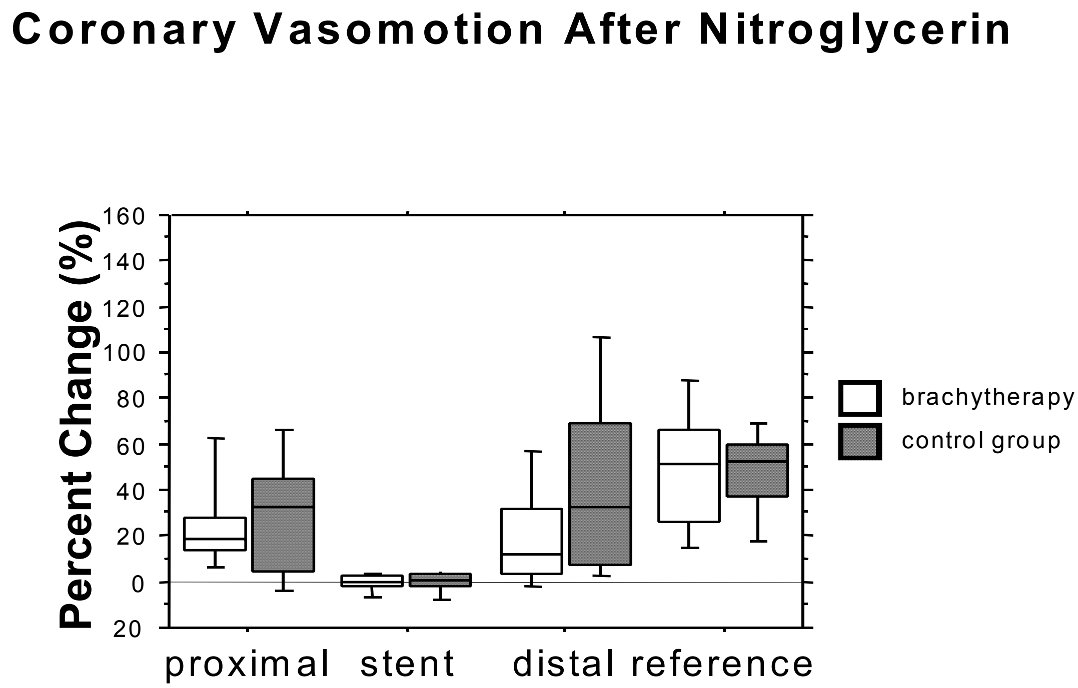

Figure 3

Figure 3. Box plot of nitroglycerin-induced changes of the mean cross-sectional lumen area in the brachytherapy and control group. Both groups show similar vasodilation of the proximal and distal segment to the stent as well as the reference vessel. The stented vessel segment did not show any vasomotion after nitroglycerin application in both groups. Values are median and ±1 quartile.

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