High-Dose Intravascular $\beta$-Radiation After De Novo Stent Implantation Induces Coronary Artery Spasm

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**Background**—Intracoronary brachytherapy is effective in preventing restenosis after coronary interventions. However, in vitro and animal studies have shown that irradiation produces immediate and sustained endothelial dysfunction. This study assesses the clinical relevance of impaired vasomotoric function induced by brachytherapy.

**Methods and Results**—We analyzed the occurrence of postradiation coronary artery spasms in 1 animal study and 2 clinical trials investigating the effects of high-dose intracoronary $\beta$-radiation after de novo coronary artery stenting. Irradiated segments (IRSs) proximal and distal to the stent were studied by quantitative coronary angiography after stenting, after radiation, and at the end of the procedure. There was an 67% overall incidence of coronary artery spasm in the IRSs immediately after $\beta$-radiation compared with 9% after sham treatment ($P<0.001$). Whereas in most cases this phenomenon was only minor or moderate, in 12 cases, 4 (22%) animals and 8 (28%) patients, severe coronary spasm (>90% diameter stenosis) with significant ECG-changes or hemodynamic instability was observed. Relief of spasms was protracted (mean time until complete relief of spasm 423±122 seconds) and required repetitive intracoronary administration of nitroglycerin (mean dose: 1.2±0.6 mg).

**Conclusions**—Vasoconstriction is a frequent reaction of coronary arteries after high-dose intracoronary $\beta$-radiation, necessitating repetitive administration of vasodilators. (*Circulation.* 2002;105:1420-1423.)

**Key Words:** stents • restenosis • radioisotopes • vasoconstriction

Intracoronary irradiation effectively reduces neointimal proliferation after coronary interventions.1–2 Although the technique is generally considered safe, angina associated with significant ECG changes occurs in a considerable number of patients during radiation treatment, and in some cases interruption of radiotherapy becomes necessary. The phenomenon of symptomatic coronary spasm during irradiation has been attributed to the mechanical irritation by the brachytherapy delivery devices and the long treatment time.

The present report details our observations regarding occurrence of coronary spasm in 3 different animal and clinical studies with high-dose intravascular $\beta$-radiation after de novo coronary stenting.

**Methods**

**Preclinical Study in the Porcine Model**

All animal treatment and care conformed to the National Institute of Health’s *Guidelines for Care and Use of Laboratory Animals*. The protocol was approved by the Animal Protocol Review Committee at the Montreal Heart Institute.

Eighteen domestic juvenile swine were studied in the double balloon injury model.3 Animals were subjected to oversized balloon dilatation (Balloon to artery ratio 1.2 to 1.3 by online QCA) in the left anterior descending (n=8) or circumflex coronary artery (n=10).

Four weeks after balloon injury, stent implantation (stent diameter to artery ratio 1.2 to 1.3; stent length 13 mm) was performed followed by high-dose endovascular $\beta$-radiation treatment. Animals underwent follow-up angiography 6 weeks after the procedure.

**Randomized Prospective Study**

Fifteen patients were enrolled in a nonrandomized prospective registry with high-dose endovascular $\beta$-irradiation after de novo coronary stenting. Patients with symptomatic type A and B1 stenoses, a reference vessel diameter of 3.0 to 3.5 mm, and a maximum lesion length of 15 mm were eligible for enrollment. Patients with acute myocardial infarction or troponine I-positive unstable angina were excluded. Intravascular ultrasound (IVUS)–guided direct stent implantation (ACS MultiLink RX Tristar; diameter 3.0 to 3.5 mm; length 18 mm) was performed followed by high-dose endovascular $\beta$-irradiation (Figure).

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Radiation Procedural Details
The medical ethics committee of our institution approved the investigational use of β-radiation, and informed consent was obtained from all patients. Endovascular β-irradiation or sham treatment was applied using the Beta-Cath system (Novoste Inc), which is a catheter based noncentered radiation delivery system described previously. The 40-mm radiation source train consists of a series of cylindrical seeds containing the radioisotope 90 Sr/90 Y sources and is bordered by 2 gold radiopaque markers. In all cases, IVUS was performed after stenting prior to radiation. By quantitative analysis of the motorized IVUS pull-back, the distances from the center of the catheter (representing the center of the radiation source) to the external elastic lamina were measured in the 4 major directions (every 90°) in multiple tomographic cross-sections throughout the stent and the adjacent vessel (cross-sections every 3 mm throughout the stent as well as 2 reference cross-sections proximal and distal to the stent, respectively). From these individual measurements, a mean reference radius was calculated. In all actively treated cases of the animal and the human studies, the effective dose of 24 Gy was applied at the depth of the calculated mean reference radius, which corresponds to an average dose of 28.7±0.7 Gy (range 21.7 to 35.8 Gy) at 2 mm from the center of the radiation source. For sham treatment an inactive, placebo source was delivered through the Beta-Cath system.

Angiographic Analysis
For the present report, the coronary angiograms after stent implantation, immediately after radiation, and at the end of the procedure were quantitatively assessed offline by an independent operator using the QuanCor software (Siemens, Erlangen, Germany). Nitroglycerin (0.3 mg) was given prior to all angiographic images. Minimal luminal diameter (MLD) and degree of stenosis (as a percentage of the diameter) were measured in the irradiated segments (IRSs) proximal and distal to the stent. The IRS was defined as the area encompassed by the 2 gold markers of the radiation source train. It was identified on angiography by contrast injection with the source in place.

Coronary artery spasms were quantified (using diameter stenosis) as severe (>90%), moderate (50% to 89%), mild (10% to 49%), or none (<10%).

Statistical Analysis
Data are expressed as counts and percentages, or mean±standard deviation. Continuous data measured before and after radiation treatment were compared using a 2-tailed paired Student’s t test. A value of P<0.05 was considered significant.

Results
In the animal series, 18 irradiated coronary arteries with 36 separate IRSs (proximal and distal to the stent) were analyzed. Accordingly, 30 IRSs from 15 patients of the clinical pilot study and 50 IRSs from 25 patients in the randomized study were investigated.
In the animal study, coronary spasms were observed in 24 of 36 (67%) IRSs. Similarly, in the radiation treated patients of the pilot study and the treatment arm of the randomized trial, in total, 39 of 58 (67%) IRSs showed a severe or moderate vasoconstriction after brachytherapy. In contrast, only mild spasm was evident in 2 of 22 (9%) vessel segments undergoing sham treatment (Table 1). Clearly, the distal IRSs was more affected by major or moderate coronary spasm. Accordingly, postradiation MLD was significantly smaller in the distal IRSs as compared with the proximal IRSs (Table 2).

In the human trials, all coronary spasms could be reversed by intracoronary administration of nitroglycerin (mean dose 1.2 ± 0.6 mg; mean time until complete relief of spasm 423 ± 22 seconds). All cases were completed successfully without in-hospital major adverse cardiac event. In the animal study, 2 animals with severe nitroglycerin refractory spasm died within 2 hours after the procedure due to stent thrombosis.

Discussion
The results of the present study show that high-dose endovascular β-irradiation can often cause sudden, sometimes profound, coronary artery spasm. The frequency of coronary vasoconstriction was significantly higher after active radiation as compared with sham treatment, implicating that this phenomenon is caused by the irradiation rather than by catheter irritation of the vessel.

### TABLE 1. Coronary Artery Spasm in the IRSs Proximal and Distal to the Stent

<table>
<thead>
<tr>
<th>Diameter Stenosis</th>
<th>Severe Spasm ≥90%</th>
<th>Moderate Spasm 50% to 89%</th>
<th>Mild Spasm 10% to 49%</th>
<th>No Spasm &lt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal IRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal study (n=18)</td>
<td>4 (22)</td>
<td>8 (44)</td>
<td>3 (17)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Pilot study (n=15)</td>
<td>4 (27)</td>
<td>5 (33)</td>
<td>4 (27)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Radiation treatment</td>
<td>4 (29)</td>
<td>5 (36)</td>
<td>2 (14)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Sham treatment (n=11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (18)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Proximal IRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal study (n=18)</td>
<td>2 (11)</td>
<td>5 (28)</td>
<td>2 (11)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Pilot study (n=15)</td>
<td>2 (13)</td>
<td>3 (20)</td>
<td>3 (20)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Radiation treatment</td>
<td>1 (7)</td>
<td>3 (21)</td>
<td>3 (21)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Sham treatment (n=11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

Values are n (%).

### TABLE 2. Quantitative Angiographic Analysis of Proximal and Distal IRSs

<table>
<thead>
<tr>
<th>Minimal Lumen Diameter, mm</th>
<th>After Stenting</th>
<th>After Radiation</th>
<th>End of Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal IRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal study (n=18)</td>
<td>2.94 ± 0.11</td>
<td>0.88 ± 0.66*</td>
<td>2.90 ± 0.13†</td>
</tr>
<tr>
<td>Pilot study (n=15)</td>
<td>3.01 ± 0.17</td>
<td>0.99 ± 0.87*</td>
<td>2.98 ± 0.19†</td>
</tr>
<tr>
<td>Randomized study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation treatment (n=14)</td>
<td>3.18 ± 0.16</td>
<td>0.94 ± 0.94*</td>
<td>3.14 ± 0.17†</td>
</tr>
<tr>
<td>Sham treatment (n=11)</td>
<td>3.20 ± 0.16</td>
<td>3.01 ± 0.31†</td>
<td>3.19 ± 0.14†</td>
</tr>
<tr>
<td>Proximal IRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal study (n=18)</td>
<td>3.21 ± 0.15</td>
<td>1.61 ± 0.54*</td>
<td>3.16 ± 0.15†</td>
</tr>
<tr>
<td>Pilot study (n=15)</td>
<td>3.31 ± 0.14</td>
<td>1.64 ± 0.77*</td>
<td>3.25 ± 0.17†</td>
</tr>
<tr>
<td>Randomized study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation treatment (n=14)</td>
<td>3.33 ± 0.12</td>
<td>1.77 ± 0.81*</td>
<td>3.30 ± 0.16†</td>
</tr>
<tr>
<td>Sham treatment (n=11)</td>
<td>3.35 ± 0.13</td>
<td>3.31 ± 0.14†</td>
<td>3.34 ± 0.11†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Minimal lumen diameter values after radiation and at the end of the procedure were compared with the value after stent implantation, *P<0.001; †P=NS.
According to animal experiments, irradiation can produce endothelial damage with severe impairment of vasomotor function. Local administration of the vasodilator acetylcholine to irradiated coronary arteries induced vasoconstriction, with loss of smooth muscle response to nitroglycerin. Furthermore, isometric tension measurements of rat aortic rings in an organ bath showed an immediate increase in vascular tone, which reached a plateau about 5 minutes after the beginning of the radiation.

In our clinical studies, an almost uniform vasoconstrictive response of the coronary artery after β-irradiation was observed. However, considering the potential shielding effect after stenting, a very high dose was applied, which is over the upper limit of what has previously been used in large clinical trials where no or few cases with coronary spasms were reported. ST-segment analysis demonstrated similarly to the in vitro findings that in most cases the vasoconstriction developed during the first minutes of radiation and reached a maximum 4 to 6 minutes later. Intracoronary administration of nitroglycerin had insufficient effect; repetitive doses were necessary to achieve complete relief of spasm. These findings support a severe impairment of the endothelium-dependent smooth muscle cell relaxation induced by high-dose radiation.

Moreover, it has recently been reported that endovascular radiation contributes to a dose-dependent increase in platelet recruitment at the angioplasty site. The release of vasoconstrictive mediators from activated platelets may also be a mechanism that could contribute to the development of arterial spasm.

Clinically, the phenomenon of nitroglycerin-resistant coronary artery spasm may provoke mechanical attempts for treatment of this condition including balloon dilatation and stent implantation. In many cases, the additional trauma of these manipulations will extend beyond the effectively radiated area causing a so-called edge effect due to Geographic Miss (injury not covered by prescribed dose of radiation). Recently, Sabaté et al demonstrated a Geographic Miss in 31.9% of the IRSs resulting in significantly higher restenosis rates as compared with uninjured but effectively radiated edges (40.9% versus 1.9%; P<0.001).

In summary, vasoconstriction is a frequent reaction of coronary arteries to high-dose intracoronary β-irradiation with more than 28 Gy on average, which may be due to acute radiation-induced endothelial dysfunction and/or platelet adhesion. Recognition of this phenomenon is important and may result in improved interventional results, if vasoconstrictions are treated by preventive and repetitive administration of vasodilators rather than by additional mechanical interventions.

References
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