Intracoronary Radiation for Prevention of Restenosis
Dose Perturbations Caused by Stents

H.I. Amols, PhD; F. Trichter, DSc; J. Weinberger, MD, PhD

**Background**—Intravascular irradiation with β-emitters has been proposed for inhibition of restenosis in coronary arteries after balloon angioplasty or stent implantation. Previous studies have shown the effectiveness of γ-radiation to prevent recurrent restenosis, even in the presence of an implanted stent. The limited range of β-particles compared with γ-radiation, however, opens the question of whether absorption and scattering of β-particles by stent struts will cause significant perturbations in the uniformity and magnitude of the radiation dose, which may in turn compromise treatment.

**Methods and Results**—Nine different stents were deployed with a balloon filled with a β-emitting radioactive liquid. Dose distributions were measured with Gafchromic film. Stents varied significantly in their absorption of β-particles. Some stents, constructed of fine meshed wires, produced minimal dose perturbations. Others, with thicker, high-atomic-number struts, induced cold spots in the dose distribution adjacent to the wires of ≤35%. Average dose reduction varied from 4% to 14% in the presence of various stents.

**Conclusions**—Radiation strategy may have to be tailored to stent design. Stents that minimally perturb the dose distribution may be deployed before irradiation. Those that significantly alter the radiation dose might be better deployed after irradiation. Dose prescriptions may require modification if such perturbations prove clinically significant. Observed dose perturbations, however, decreased rapidly with increasing distance from the stent, which may mitigate the clinical impact of these findings. This, as well as the effects of stents on γ-dose distributions, requires further investigation.

**Key Words:** angioplasty ■ restenosis ■ brachytherapy ■ stents ■ beta rays

Percutaneous transluminal coronary angioplasty has an angiographic restenosis rate of ≈32%,1 which can be reduced to 22%2 when accompanied by stent implantation. It has been demonstrated in animal models3–7 and more recently in clinical studies that intracoronary irradiation significantly reduces restenosis, presumably by inhibiting smooth muscle cell proliferation and neointima formation. Irradiation of human femoral arteries appears to confirm these findings.8 A recent report9 of a clinical trial of intravascular γ-irradiation of restenotic lesions (60% of which had been previously stented) in human coronary arteries showed 6-month restenosis rates of 17% in irradiated arteries versus 54% in controls. Large-scale randomized human trials and longer-term follow-up studies are currently in progress.

Several irradiation techniques have been proposed, including temporary insertion of high-activity γ- or β-emitting seeds or wires; temporary filling of the dilatation balloon catheter with a high-activity β-emitting solution; implantation of radioactive β-emitting stents; and external beam irradiation. The dosimetric characteristics of each technique have been presented.10–12 To date, most trials have been performed with 192Ir (a γ-emitter), 32P, 90Sr, 90Y, or 188Re (all β-emitters).

The major dosimetric difference between β- and γ-radiations is that the former have a finite range in tissue (typically a few millimeters), whereas the latter are exponentially attenuated. Most β-emitters proposed for intraluminal brachytherapy have transition energies <2.4 MeV, with mean ranges in tissue of only a few millimeters. Such ranges are sufficient for treating smaller arteries, but scattering and absorption of the β-particles by stent wires could limit the dose to sections of the arterial wall. In particular, stent struts are often made of high-density, high-atomic-number metals in which the range of β-particles is only a fraction of a millimeter. Stents also perturb the dose for γ-radiation sources, but to a lesser extent because γ-particles lack a finite range. Short-ranged β-particles, however, offer radiation safety advantages and yield lower whole-body doses to patients and staff than γ-sources. Thus, many ongoing clinical trials now use β-sources.

We explore herein the perturbations in β-dose distribution induced by 9 different stents from 7 manufacturers. Implantation of radioactive stents, irradiation by external beam, and intraluminal irradiation from β- or γ-sources entail different geometries and require separate study.
Methods

The stents tested are listed in Table 1, along with the wire composition as given by the manufacturers. Some data on stent design are proprietary information. All stents were nominally rated for 3-mm-diameter arteries and were deployed by filling a 3- or 4-mm-diameter dilatation balloon catheter with a radioactive $^{188}$Re solution to nominal pressures. $^{188}$Re is a $\beta$-minus emitter with 2.2 MeV of maximum $\beta$-energy. Its production and radioactive properties have been described.\textsuperscript{12,13} A $^{188}$Re-filled balloon provides a homogeneous, cylindrically symmetrical radiation source, which in the absence of perturbing factors yields a uniform dose distribution to the inner lumen wall, as shown in Figure 1A (see Results), which was obtained by placing a radioactive filled balloon in direct contact with a piece of Gafchromic film (Nuclear Associates).

The film is a 0.25-mm-thick transparent polymer containing a 20-$\mu$m-thick radiosensitive emulsion that changes from clear to translucent blue after irradiation. The radiosensitive emulsion is sandwiched in the center of the film, meaning that dose distributions cannot be measured at distances $<0.125$ mm. The transmission of red light (the color complement of blue) through the film is a function of the radiation dose received by the film. The utility of the film derives from its tissue equivalence, capability for direct readout (no processing required), insensitivity to visible light, high spatial resolution, and independence of response to radiation energy or dose rate.\textsuperscript{14,15}

Each of the 9 stents tested was deployed with a separate angioplasty balloon and placed on top of a stack of 4 slices of Gafchromic film (see Figure 2). Doses were measured at distances of 0.125, 0.375, 0.625, and 0.875 mm from the surface of the balloon. A slab of tissue-equivalent material was placed on top of and around each balloon to ensure solid contact between the balloon/stent and the film and to simulate a homogeneous unit density geometry. Stents were inspected visually to ensure full deployment and good film contact.

A relatively low-specific-activity $^{188}$Re solution was used (5 to 10 mCi/mL, versus a therapeutic activity of 50 to 100 mCi/mL) to reduce the dose to which the experimenters were exposed. Film exposures lasted several hours each.

Exposed films were optically scanned with a computer-controlled red-light transmission scanner, converted to a digital image with 23.6 pixel/mm resolution and 8-bit gray scale. These were converted to dose by use of calibration values obtained by exposing film to known doses of $^{60}$Co radiation.

To better quantify the dose distributions, various parameters were extracted from the central 5-mm-axial by 0.5-mm-radial section of each film (where the balloon and stent were tangent to the Gafchromic film). The dose within this region was normalized to unity, and dose histograms were determined. The minimum, mean, and SD of each dose distribution were tabulated.

Next, stents were cut along their axial lengths, flattened, placed in direct contact with a piece of radiographic film, and irradiated with parallel, monoenergetic, 1-MeV electrons from a linear accelerator.

<table>
<thead>
<tr>
<th>Type</th>
<th>Manufacturer</th>
<th>Composition (Atomic Number)</th>
<th>Wire Thickness (mm) and Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordis Coil</td>
<td>Johnson &amp; Johnson</td>
<td>Tantalum (73)</td>
<td>0.127 round</td>
</tr>
<tr>
<td>CardioCoil</td>
<td>Medtronic</td>
<td>Nitinol (22, 28)</td>
<td>0.15 round</td>
</tr>
<tr>
<td>Multilink</td>
<td>Guidant/ACS</td>
<td>Steel (26)</td>
<td>0.05×0.1 rectangle</td>
</tr>
<tr>
<td>NIR</td>
<td>Medinol</td>
<td>Steel (26)</td>
<td>0.11 square</td>
</tr>
<tr>
<td>Radius</td>
<td>Boston-Sci</td>
<td>Nitinol (22, 28)</td>
<td>0.13 round</td>
</tr>
<tr>
<td>Palmaz-Schatz</td>
<td>Johnson &amp; Johnson</td>
<td>Steel (26)</td>
<td>0.06×0.13 rectangle</td>
</tr>
<tr>
<td>Wallstent (E)</td>
<td>Schneider</td>
<td>Elgiloy (24, 27, 28)</td>
<td>0.09 round</td>
</tr>
<tr>
<td>Wallstent (D)</td>
<td>Schneider</td>
<td>Platinum + elgiloy (24, 27, 28)</td>
<td>0.09 round</td>
</tr>
<tr>
<td>Wiktor</td>
<td>Medtronic</td>
<td>Tantalum (73)</td>
<td>0.13 round</td>
</tr>
</tbody>
</table>

**Figure 1.** A, Dose distribution measured with Gafchromic film for unstented 3-mm-diameter×20-mm-long dilatation balloon filled with liquid $^{188}$Re radioactive $\beta$-particle emitter at a distance of 0.125 mm from the balloon surface. Doses are represented in color, with maximum dose shown in red and minimum in purple. B, Dose distribution at 0.125 mm radial distance from the Wallstent(D). C, Dose distribution at 0.125 mm radial distance from the Wiktor stent. D, Dose distribution at 0.125 mm radial distance from the Radius stent.

**Figure 2.** Experimental setup showing cylindrical balloon catheter filled with radioactive $^{188}$Re used to deploy a stent. The balloon and deployed stent are placed in contact with Gafchromic film and covered with tissue equivalent bolus (not shown) to ensure good contact.
Results

Stents induce 2 primary effects on β-dose distributions. The first is an overall reduction in average dose rate due to absorption of some β-particles by the stent struts. This dose reduction (see Table 2) was found to be <14% for all stents tested and <5% for 4 of the stents. Figure 3 plots the results of depth-dose measurements for a 4-mm-diameter open balloon and for the same balloon with a Palmaz-Schatz (model 153) stent in place. Curves are plotted on an absolute scale of cGy/min per mCi/mL versus distance from the balloon surface. Although the absolute dose is reduced in the presence of the stent, the shape of the depth-dose curve is not significantly changed. Thus, corrections can be made for these dose reductions when doses are prescribed.

The second perturbation induced by stents is dose shadowing, shown in Figure 1. Figure 1A shows a dose distribution measured with Gafchromic film in direct contact with a balloon. For clarity, the dose is displayed by use of a color scale, with the maximum dose represented by red and the minimum by purple. The nominal dimensions of the balloon are 2 cm in length by 3 mm in diameter. There is a central region of uniform high dose (red) where the balloon is tangent to the film. Dose decreases with increasing radial and axial distance from the center of the balloon (yellow, green, and blue regions).

Figures 1B, 1C, and 1D show similar dose distributions for the Wallstent(D), Wiktor, and Radius stents, respectively. A separate balloon deployed each stent, with stents interposed between balloons and film. The Wallstent(E) is a fine elgiloy (an alloy of chromium, cobalt, and nickel) mesh of ~25 rows of thin strut wire along the axial length of the stent. The thin, relatively low-atomic-number wires (Cr=24, Co=27, and Ni=28) produced only a shallow ripple of cold spots in the dose distribution, seen as yellow in the central high-dose zone (red) of Figure 1B. The maximum dose measured in the red zone of Figure 1B for the Wallstent(E) was equal to the maximum dose measured with an unstented balloon (Figure 1A), but the average and minimum doses were decreased by the stent. For the Wallstent(E), the dose decrease was 3% to 4%, although other stents produced larger perturbations (see Table 2).

The Wiktor stent (Figure 1C) has fewer wires than the Wallstent(E), but they are thicker and are made of tantalum (atomic number 73, specific gravity 16.7). The high-atomic-number, high-density wires absorb and scatter more electrons and produce a larger zone of low dose (yellow) than the Wallstent(E). Yellow waves or low-dose shadows within the central red zone are clearly seen in Figure 1C for the Wiktor stent. Figure 1D shows the dose distribution for the Radius stent, which also has yellow and even green shadow patterns from the stent wires. The Radius stent is constructed of nitinol, an alloy of nickel and titanium. These struts are less dense than the Wiktor tantalum struts but are thicker and more massive.

Figures 1B through 1D graphically depict β-dose distributions very close (0.125 mm) to the stent surface, where the most severe effects are seen. Beyond a distance of ~0.5 mm, multiple coulomb scattering of the electrons washes out the shadowing effects of the stent struts, although the reduction in average dose remains. Other radioactive sources, such as solid wires and seeds, may produce different electron scattering patterns from the liquid balloon shown here.

Table 2 and Figures 3 through 7 present various parameters of the central 5 × 0.5-mm² area of each radiochromic film. Table 2 lists the minimum, mean, and SD of the dose distributions for each stent (all distributions normalized to unity), plus the relative linear accelerator beam absorption. Stents are listed in approximate order of increasing dose perturbation, as defined by a decrease in the mean dose. The maximum dose measured on the surface of the balloon always occurred between struts and was measured to be equal to the maximum dose for the unstented balloon. Only the mean and minimum doses were decreased by the stent.

The ordering of stents in Table 2 changes slightly when ranked by minimum dose, SD, or accelerator beam transmission, respectively. By any of these criteria, however, all stents

### Table 2. β-Dose Perturbations Caused by Stents

<table>
<thead>
<tr>
<th>Stent</th>
<th>Minimum Dose (cGy/min/mCi/mL)</th>
<th>Mean Dose (cGy/min/mCi/mL)</th>
<th>SD</th>
<th>Accelerator Beam Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>0.92</td>
<td>0.89</td>
<td>0.018</td>
<td>0</td>
</tr>
<tr>
<td>Wallstent (E)</td>
<td>0.90</td>
<td>0.96</td>
<td>0.021</td>
<td>1</td>
</tr>
<tr>
<td>Wallstent (D)</td>
<td>0.87</td>
<td>0.96</td>
<td>0.028</td>
<td>1</td>
</tr>
<tr>
<td>NIR</td>
<td>0.86</td>
<td>0.95</td>
<td>0.027</td>
<td>2</td>
</tr>
<tr>
<td>CardioCoil</td>
<td>0.84</td>
<td>0.95</td>
<td>0.036</td>
<td>3</td>
</tr>
<tr>
<td>Multilink</td>
<td>0.82</td>
<td>0.92</td>
<td>0.026</td>
<td>2</td>
</tr>
<tr>
<td>Cordis Coil</td>
<td>0.70</td>
<td>0.89</td>
<td>0.058</td>
<td>3</td>
</tr>
<tr>
<td>Palmaz-Schatz</td>
<td>0.65</td>
<td>0.89</td>
<td>0.060</td>
<td>2</td>
</tr>
<tr>
<td>Radius</td>
<td>0.68</td>
<td>0.86</td>
<td>0.069</td>
<td>2</td>
</tr>
<tr>
<td>Wiktor</td>
<td>0.67</td>
<td>0.86</td>
<td>0.062</td>
<td>3</td>
</tr>
</tbody>
</table>

All measurements were made at 0.125-mm radial distance from stent surface.

This permitted measurements of electron beam absorption for a less-complicated geometry. We estimated the relative value of absorption for each stent by measuring the average optical density over a 1-mm-diameter circle of the irradiated film in the vicinity of the stent struts. A qualitative score of 0 (least absorption) to 3 (most absorption) was assigned to each stent on the basis of its optical density.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Measured depth-dose-curve comparison between a 4-mm-diameter unstented balloon (×) and a Palmaz-Schatz stent (○). Open circles represent calculated doses. All data are plotted on an absolute scale of cGy · min⁻¹ · mCi⁻¹ · mL⁻¹ versus distance.
tested fell roughly into 2 categories. Both Wallstents, NIR, CardioCoil, and Multilink stents produced relatively small dose perturbations, with ratios of mean dose to maximum dose within 4% of the unstented balloon and the ratio of minimum to maximum dose within 10%. The Cordis tantalum, Palmaz-Schatz (PS-153), Radius, and Wiktor stents all produced larger dose perturbations, with mean doses up to 14% lower than the unstented balloon and minimum doses up to 35% lower. These dose inhomogeneities applied only at the closest distance measured (0.125 mm from the balloon surface) and decreased significantly with increasing distance, as discussed below.

In Figure 4, we plot dose surface histograms (DSH) for the central 5×0.5-mm² regions of an unstented balloon and for the Wallstent(E), Wiktor, and Radius stents. In a DSH plot, the abscissa represents dose (normalized to 1.0) and the ordinate represents the fraction of lumen surface receiving a dose greater than or equal to a given value of dose. For example, for an unstented balloon, 80% of the lumen wall receives a dose >95% of the maximum (see dashed lines in Figure 4), indicating a very uniform dose distribution. For the Radius stent, that same surface fraction (of 80%) receives only >73% of the maximum dose. In other words, for the Radius stent, 20% of the lumen surface (ie, 100%−80%) receives a dose 27% (ie, 100%−73%) lower than prescribed.

Another way to compare DSH plots is to recognize that large surface fractions and large dose values (ie, the upper right corner of the graph) represent uniform dose distributions [unstented balloon or Wallstent(E)], whereas curves in the lower left (Wiktor or Radius stents) represent inhomogeneous distributions. This can also be seen in Figure 5, which plots the differential dose distributions. In this graph, the abscissa again represents dose (normalized to 1.0), but the ordinate represents the fraction of the lumen surface receiving a dose equal to a given value of dose. Again we see a decrease in mean dose (the peak in the distribution shifts toward lower doses) and an increase in SD (or full width, half maximum of the distribution) for the Wallstent(E), Wiktor, and Radius stents compared with the unstented balloon.

For clarity, only 3 of the 9 stents are plotted in Figures 4 and 5. Dose inhomogeneities depicted were measured 0.125 mm from the surface of the stents. Figures 6 and 7 depict the relative dose inhomogeneity for all stents tested, as measured by the SD of the dose distribution (Figure 6), and the mean dose (Figure 7). All doses in Figures 1, 4, 5, 6, and 7 and Table 2 have been normalized for comparative purposes. Figures 6 and 7 indicate the relatively large dose perturbations induced by the Cordis tantalum, Palmaz-Schatz, Radius, and Wiktor stents compared with the other 5 stents. This ranking is not a reflection of the clinical efficacy of the stent but merely indicates effects on β-dose distributions.

Dose perturbations induced by stents were most evident at the stent-lumen interface. Scattering of electrons by stent struts and tissue rapidly filled in the pattern of cold spots seen...
Discussion

Intravascular irradiation with a radioactive liquid β-source delivers a uniform dose to the arterial wall. The dose uniformity can be compromised by many factors, including vessel asymmetry and curvature, nonuniform wall thickness, and presence of plaque. Stent struts introduce yet another perturbing factor, which may or may not prove to be clinically significant. It has, however, been reported that equal doses of β-radiation delivered before implantation of a tantalum stent are superior to poststenting radiation for prevention of restenosis in an animal model.

In that study, however, the vessels irradiated after stenting may have had larger diameters and hence lower doses, and the results do not definitively demonstrate a clinical significance of dose shielding by stent struts.

We also do not know which structures in the vessel wall need be irradiated, or the minimum or maximum acceptable doses. Large dose inhomogeneities, however, may limit the ability to deliver adequate doses to the entire circumference of the vessel wall without overdosing other tissues. This would be particularly true if target cells were close to (i.e., <0.5 mm from) the stent surface, where inhomogeneities are large, but less important if target cells were further into the lumen wall or adventitia. In either case, other factors such as vessel asymmetry, noncentered sources, and plaque could conceivably introduce larger dose inhomogeneities than stents.

In any case, each stent tested in the present study produced a unique signature on the dose distribution. The degree of dose inhomogeneity induced by a stent is a complicated function of stent mass, geometry, strut thickness, and composition. Thicker, denser struts absorb more β-particles than thinner wires. It is notable, however, that large variations were seen among the various stents tested.

Wallstent(E), Wallstent(D), and NIR stents are constructed of fine meshes of thin wires that minimally alter the absolute dose rate or degree of inhomogeneity. The Palmaz-Schatz, Wiktor, Cordis tantalum, and Radius stents, which have thick and/or high-density wires, produce larger inhomogeneities. With the Radius, Wiktor, or Palmaz-Schatz stents, for example, the minimum dose to the lumen wall is only 65% to 68% of the maximum dose.

No single parameter, however, uniquely correlates with either the measured dose distributions or electron beam absorption. For example, the mass of the Cordis tantalum stent per millimeter of length is nearly twice that of the Wiktor stent (23.75 versus 14.0 mg/mm), although both significantly absorb the linear accelerator beam, and the latter induces slightly larger dose inhomogeneities. The Radius stent is constructed of a nickel-titanium alloy with a lower atomic number than either stainless steel or tantalum, yet it induces large dose inhomogeneities.

Nonetheless, some general observations can be made. The Wallstent(E) and Wallstent(D) induce the least dose heterogeneity and are also the most transparent to the linear accelerator beam. This is a result of their relatively low mass and thin wire design. The Wiktor stent induces the most dose heterogeneity and the most absorption of the 1 MeV linear accelerator beam despite its lower mass (14.0 mg/cm) because it is constructed of a small number of relatively thick tantalum wires with an atomic number of 73. Similarly, the Cordis tantalum stent induces large dose perturbations and absorbs the 1-MeV accelerator beam because of its relatively large mass (23.8 mg/cm) and high atomic number. Stents exhibiting intermediate degrees of dose perturbation and accelerator beam absorption, such as the NIR and Multilink, have various combinations of either low mass, low atomic number, or intermediate strut thickness.

Thus, one can qualitatively understand the observed dosimetric properties of stents on the basis of composition and geometry, although no single parameter correlates with the observed dose distributions. It appears that only dosimetric measurements or theoretical calculations can accurately predict reductions in average dose and increased inhomogeneities introduced by stents. Average reduction in dose rate can be measured, as shown in the present study, and compensated for in dose prescription. Dose inhomogeneity, on the other hand, cannot be compensated for and may be clinically significant if the target tissues for restenosis are <0.5 mm from the lumen wall.

Thus, radiation absorption properties, as well as the usual considerations of strength, flexibility, and “trackability”, need be considered when a stent is being selected for use with radiation. Dose adjustments may be required to effectively use β-sources when one is treating restenotic lesions that have previously been stented, particularly when there are multiple or overlapping stents. Overlapping stents would be expected to approximately double the magnitude of the effects reported here, although this was not measured in the present study.

We also did not measure dose perturbations for γ-sources, which should be less affected by stents than are β-particles because of their increased range. Because it will be necessary in some cases to irradiate patients who have previously been stented, a study of γ-dose perturbations appears to be in order. Results from the SCRIPPS trial, however, show no significant clinical difference between stented and unstented patients after irradiation with 192Ir γ-rays. This could be the result of much lower (insignificant) dose perturbation induced by stents when γ-radiation is used. Alternatively, in-stent restenosis may involve the irradiation of cells that are inside rather than outside the stent and thus not affected, at least dosimetrically, by the presence of the stent.
Conclusions
The dose uniformity for intravascular irradiation with $\beta$-sources can be compromised by the presence of stents as well as vessel asymmetry and curvature, nonuniform wall thickness, and the presence of plaque. The degree of dose perturbation varied significantly between the stents tested, although no single parameter (such as mass, atomic number, or geometry) uniquely correlated with the measured doses or beam absorption. It appears that only direct measurements or perhaps Monte Carlo calculations can accurately predict in vivo patient doses. Large dose homogeneities were measured close to stent surfaces, but the degree of inhomogeneity decreased rapidly at larger distances (>0.5 mm). The clinical significance of these findings will depend on whether the target cells are close to the stent or further into the lumen wall or adventitia and also on whether or not vessel asymmetry or variable wall thickness mitigates the inhomogeneity introduced by the stent. Answers will come only from clinical trials.

Limitations
Several experimental conditions limit the accuracy of our results. Incomplete contact between the balloon and the radiochromic film can reduce measured doses, although specific measures to minimize this possibility were used. The thickness of stent struts also introduces some uncertainty as to the true distance between the balloon and film surface, although balloons tend to bulge out and maintain good contact with the film between struts.

Radiochromic film has small inhomogeneities in emulsion thickness, which in turn affect dose accuracy, and film scanner resolution introduces some spatial averaging in the dose readings. In addition, in vivo stent wires may become twisted owing to resistance from vessel walls, and a deployed stent may have a varying diameter along the axial extent of the lesion. These factors could not be duplicated in our experiments, nor could anatomic factors such as vessel asymmetry and curvature, nonuniform wall thickness, and the presence of plaque.

Finally, the clinical significance of our reported dose inhomogeneities can only be determined from clinical trials.

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References
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