Failure of a Novel Balloon-Expandable $\gamma$-Emitting ($^{103}$Pd) Stent to Prevent Edge Effects

Christoph Hehrlein, MD; Jennifer J. DeVries, LATG; Amina Arab, MD; Scott D. Haller, BS; Klaus Schloesser, PhD; Ferman O. Tio, MD; Tim A. Fischell, MD

Background—Balloon-expandable $\beta$-particle–emitting ($^{32}$P) stents inhibit within-stent neointimal hyperplasia but induce lumen narrowing beyond the stent margins, ie, the so-called “edge effects.”

Methods and Results—We prospectively investigated the performance of novel stents impregnated with the $\gamma$-emitting isotope $^{103}$Pd, designed to reduce edge effects, in 24 rabbits. The stents had a length of 18 mm and were mounted on 20-mm-long delivery balloons for deployment. Angiograms were obtained immediately and 1 month after direct implantation of control and 1-, 2-, and 4-mCi $^{103}$Pd stents into the iliac arteries without predilatation or postdilatation. Late lumen loss was measured with quantitative angiography. Neointimal hyperplasia and vascular remodeling were evaluated by histomorphometry. Late lumen loss was inhibited within $^{103}$Pd stents (control 0.18 mm, 1 mCi 0.08 mm, 2 mCi 0.05 mm, and 4 mCi −0.03 mm, $P<0.05$ all activities versus control). Conversely, late lumen loss occurred at the edges of $^{103}$Pd stents, correlating with areas of high balloon/artery ratios and vessel overstretch injury. Edge effects were primarily due to neointimal hyperplasia but were also caused by negative vessel remodeling at high stent activities.

Conclusions—Edge effects after implantation of radioisotope stents can occur independently of the isotope chosen for stent impregnation. (Circulation. 2001;104:2358-2362.)

Key Words: radioisotopes ■ remodeling ■ restenosis ■ stents

It was previously demonstrated that smooth muscle cell proliferation and neointima formation are markedly inhibited within $\beta$-particle–emitting stents in vitro and in a rabbit restenosis model.1–3 Clinical studies have shown an effective inhibition of late loss due to neo-intima formation within balloon-expandable $\beta$-particle–emitting stents ($^{32}$P) after treatment of patients with coronary artery disease.4–6 These studies also showed, however, that $\beta$-particle–emitting stents can induce “edge effects” (restenosis at the stent ends). A number of factors have been suggested to be responsible for edge effects: balloon injury beyond the irradiation zone (geographic miss), radiation doses too low to prevent restenosis (dose falloff at stent ends), inhibition of cell migration within the stents resulting in accumulation of neointimal cells at the stent ends, rheological or inflammatory stimuli, etc. Early studies with coronary $^{32}$P stents suggested that edge effects may be caused by the dose falloff at the stent margins.5 $^{32}$P stents with higher activities, however, even increased the incidence of edge restenosis.6

$\gamma$-Emitting isotopes provide a shallower dose gradient in tissue than $\beta$-particle emitters and are therefore thought to be more effective in overcoming edge effects caused by a rapid dose falloff at the stent margins. The purpose of this study was to evaluate the performance of a novel balloon-expandable stent impregnated with $^{103}$Pd, a weak $\gamma$-radiation–emitting isotope, in a rabbit iliac artery overstretch model.

Methods

Radioisotope Characteristics, Stent Manufacture, Shielding, and Dosimetry

$^{103}$Pd (half-life 17 days) decays by electron capture and emits low-energy x-rays (21 keV) and Auger electrons. The dose rate constant for $^{103}$Pd is 23 mrem/h per mCi at 10 cm. Homogeneous $^{103}$Pd coating of BX stents (Cordis) and activity measurements were performed by MDS Nordion in Kanada, Ontario. Dosimetry calculations comparing dose rates at the stent ends of $^{103}$Pd stents with those of $^{32}$P stents were performed in Karlsruhe, Germany (K.S.). In all coated stents, the measured activity was ±10% of true activity, axial dose uniformity was ±15%, and the environmental isotope retention value was >98% (<2% activity washoff in ultrasonic bath). The $^{103}$Pd stents were shielded with a lead-impregnated acrylic cylinder. Radiation protection for manipulating the stents was achieved with lead-impregnated surgical gloves. Reading of the skin radiation dose of the animals after stent implantation indicated no significant radiation dose outside the body.

Animal Care and Surgical Procedure

All experiments were performed in accordance with the guidelines for animal research established by the American Heart Association.
Zealand White rabbits (n = 24) weighing 2.7 to 3.2 kg were used for the study. Anesthesia was performed with acepromazine (0.1 mg/kg), ketamine (35 mg/kg), and xylazine (3 mg/kg) SC. Both femoral arteries were exposed, and a 4F pediatric sheath was inserted into each artery. Heparin 500 U IA was given via the sheath, and retrograde angiograms were obtained. Fifteen nonradioactive control BX stents (length 18 mm) and 33 BX stents impregnated with 1.1 (n = 11), 2.2 (n = 12), and 4.04 (n = 10) mCi of 103Pd premounted on a balloon delivery system (balloon length 20 mm) were implanted into both iliac arteries. The 3.0-mm stent delivery balloon was inflated to 8 atm under fluoroscopic control. Control stents and radioactive stents were deployed opposite to each other in the common iliac artery without predilatation or postdilatation of the artery. All rabbits received aspirin 40 mg PO every 3 days for 1 month.

**Quantitative Angiography**

The angiographic films were analyzed with a quantitative coronary analysis program (Medis). Reference diameters and lumen diameters (proximal to, within, and distal to stents) of the iliac arteries were measured before and after stent implantation and at the 1-month follow-up. Balloon-to-artery (B/A) ratios were measured proximal to, within, and distal to the stents. Late lumen loss was calculated as minimal lumen diameter of the artery poststent minus minimal lumen diameter follow-up. To compare the edge effects of the proximal with those of the distal stent ends, the data were corrected for vessel tapering of the proximal to the distal end of the iliac artery.

**Tissue Collection and Fixation**

The rabbits were killed by a lethal dose of KCl and sodium pentobarbital (120 mg/kg) after 1 month. The abdominal aorta was cannulated, and the iliac arteries were flushed with physiological saline solution for 3 minutes. For in situ pressure fixation, the iliac arteries were infused with 10% formalin at 100 mm Hg for 10 minutes. The arterial specimens were dehydrated in graded alcohol solutions and were then embedded in methylmethacrylate and serially sectioned from the proximal to the distal end. The stented cross sections were stained with metachromatic stains, and the proximal and distal edges with hematoxylin-eosin and elastin stains.

**Histomorphometry**

The neointimal cross-sectional areas were measured with computer assistance with a compound microscope integrated to a digitizing tablet through a drawing tube attachment for histomorphometric analysis. Sections were graded semiquantitatively for arterial wall injury (score 0 to 3), inflammation, intimal fibrin deposition, density of intimal smooth muscle cells, and adventitial fibrosis. Neointimal area was expressed as percentage of lumen area. Vessel area was defined as the cross-sectional area encompassed by the adventitia.

**Statistics**

The data are expressed as mean ± SD and were compared by use of the StatView software package. The paired t test was applied for comparisons of the stents. Univariate regression analysis was performed to compare B/A ratios with angiographic late lumen loss.

**Results**

**Quantitative Angiography**

In-stent lumen loss was inhibited in a dose-dependent fashion within 103Pd stents compared with nonradioactive control stents. The results for each stent activity are summarized in Figure 1. The lumen diameter at the distal stent edge was significantly decreased with radioisotope stents (control 1.5 ± 0.3 mm, 1 mCi 1.1 ± 0.3 mm, 2 mCi 1.0 ± 0.2 mm, and 4 mCi 0.8 ± 0.3 mm; P = 0.002, 4 mCi versus control). B/A ratio, however, was also higher at the distal stent edge (1.3 ± 0.1) than at the proximal stent edge (1.0 ± 0.1, P < 0.001). Figures 2 and 3 depict the correlation between B/A ratios and late lumen loss after 1 month (control and 103Pd stents). Figure 4 shows the angiogram of the iliac arteries at 1-month follow-up with edge effects after the implantation of the 103Pd stents.

**Histological Assessment and Morphometry**

Arteries with nonradioactive control stents showed healing responses different from those with 103Pd stents at 1, 2, and 4 mCi after 1 month. The control stents were covered with mature neointima, whereas the 103Pd stents with activities of 2 and 4 mCi were covered only with fibrin-platelet deposits without significant endothelialization. Medial necrosis was present after implantation of 2- and 4-mCi stents, but rarely after use of 1-mCi 103Pd stents or control stents. Injury and inflammation scores were generally higher in arteries after implantation of 2- and 4-mCi 103Pd stents compared with 1-mCi 103Pd or control stents. Injury scores and lumen areas of the vessels beyond the stent edges are summarized in the Table. All vessels tapered from the proximal to the distal stent end (vessel area in mm2: control 1.4 ± 0.5, 1 mCi 1.44 ± 0.4, 2 mCi 1.3 ± 0.1) than at the proximal stent edge (1.0 ± 0.1, P < 0.001). Figures 2 and 3 depict the correlation between B/A ratios and late lumen loss after 1 month (control and 103Pd stents). Figure 4 shows the angiogram of the iliac arteries at 1-month follow-up with edge effects after the implantation of the 103Pd stents.

**Figure 1.** Lumen loss within stented arteries (nonradioactive control, 1-mCi, 2-mCi, and 4-mCi 103Pd stents) determined by quantitative angiography (QCA).

**Figure 2.** Late loss ratio at 1 month in arteries with nonradioactive control stents (late lumen loss control, LLC) vs B/A ratio during stent implantation as determined by quantitative angiography. Note significant correlation between late loss and B/A ratios during stent implantation (P = 0.034).
Elsewhere in intracoronary radiation therapy to prevent restenosis. With catheter-based radiation therapy, however, it is difficult to differentiate whether vessel injury alone outside the irradiation zone, radiation injury alone, or a combination of radiation dose falloff and vessel injury causes edge effects. This distinction can be made by investigating a "direct-stenting" procedure using radioactive stents in a controlled experimental setting. Our study shows that direct stenting without predilatation or postdilatation does not appear to be a sufficient strategy to prevent edge effects with balloon-expandable radioactive stents.

Interestingly, lumen narrowing beyond the stent edge increased with stent activity, ie, with radiation dose, in our study. The 2 highest stent activities induced negative vessel remodeling, indicating that there may be a threshold dose for the occurrence of vessel shrinkage after radiation therapy. Previous animal studies of radioactive 90Y stents producing high dose rates showed that these implants cause delayed healing within the stented lumen and atherosclerotic lesion formation. The clinical evaluation of β-particle–emitting stents indicated that only low to moderate radiation doses are

### Injury Scores and Edge Effects 1 Month After Stent Implantation Evaluated by Histomorphometry at 1 mm Proximal and Distal to the Stent Edge

<table>
<thead>
<tr>
<th></th>
<th>IS (P)</th>
<th>IS (D)</th>
<th>LA (P), mm²</th>
<th>LA (D), mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS</td>
<td>0.1±0.1</td>
<td>0.6±0.1*</td>
<td>2.6±0.5</td>
<td>0.9±0.6</td>
</tr>
<tr>
<td>1-mCi 103Pd RS</td>
<td>0.1±0.1</td>
<td>0.5±0.2*</td>
<td>2.2±0.6</td>
<td>0.9±0.7</td>
</tr>
<tr>
<td>2-mCi 103Pd RS</td>
<td>0.1±0.1</td>
<td>0.5±0.2*</td>
<td>2.0±0.5†</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>4-mCi 103Pd RS</td>
<td>0.1±0.1</td>
<td>0.4±0.2</td>
<td>2.0±0.6†</td>
<td>0.5±0.4</td>
</tr>
</tbody>
</table>

NRS indicates nonradioisotope stent (control); RS, radioisotope stent; IS, injury score; LA, lumen area; P, proximal to stent; and D, distal to stent.

*P<0.001 (P) vs (D); †P<0.001 NRS vs RS.
needed to markedly reduce late loss within the stent body and that higher doses may not bring a benefit for patients.6 Radioisotope stents emitting low dose rates have already been reported to reduce neointimal hyperplasia without apparent edge effects.2 Several years ago, we did not observe edge effects from stainless steel stents bombarded with protons yielding mixed β-particle and γ-radiation (55Co, 56Co, 57Co, 57Ni, 52Mn, etc). Those Co stents delivered lower dose rates than 32P stents but remained active over a longer period.2,3 γ-Emitting isotopes appear to be as suitable as β-particle–emitting isotopes to prevent within-stent restenosis. Another γ-emitting isotope (133Xe), ion-implanted into metallic stents, was reported to reduce neointimal hyperplasia in a similar rabbit restenosis model.11 Despite the shallower dose gradient, however, γ-emitters may not be superior to β-particle emitters with respect to the prevention of edge effects. In addition, γ-emitters have the disadvantage of requiring more radiation protection than β-particle emitters.12,13

An approach to reduce barotrauma beyond the stent ends caused by a stent delivery balloon and possibly reduce edge effects may be a self-expanding design for a radioisotope stent. This strategy should be investigated further.

Limitations of the Study
Only 71% of the total dose was delivered after 30 days; thus, the 103Pd stents were still radioactive after removal for histopathological analysis. In general, novel coronary brachytherapy devices should be studied in animals for a period of...
≥6 months to fully understand the potential therapeutic benefit or recognize side effects if the early follow-up results, ie, after 4 weeks, are promising. Further studies are needed to fully understand the causes of edge effects.

Acknowledgments
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References
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