Basic Science Reports

Dose-Response Effects of $^{32}$P Radioactive Stents in an Atherosclerotic Porcine Coronary Model

Andrew J. Carter, DO; Douglas Scott, MD; Lynn Bailey, AA; Timothy Hoopes, MD; Russ Jones; Renu Virmani, MD

**Background**—Experimental studies have demonstrated that $^{32}$P radioactive stents reduce neointimal formation at 28 days in porcine iliac and coronary arteries. Our objective was to determine the long-term dose-response effects of 1.0- to 12.0-$\mu$Ci $^{32}$P radioactive stents in a porcine atherosclerotic coronary model.

**Methods and Results**—Control (n=19) and 1.0- to 12.0-$\mu$Ci $^{32}$P radioactive (n=43) stents (total, n=62) were implanted in the coronary arteries of 31 miniature swine at 28 days after creation of a fibrocellular plaque by overstretch balloon injury and cholesterol feeding. Angiography and histomorphometry were performed at 6 months. Stent thrombosis occurred in 3 radioactive (7.7%) and no control stents ($P=0.54$). On histology, the mean neointimal area and the percent in-stent stenosis correlated positively with increasing stent activity ($r=0.64$, $P<0.001$). The mean neointimal area (mm$^2$) for the stents with $\geq3.0$ $\mu$Ci $^{32}$P (3.57±1.21) was significantly greater than that for the nonradioactive stents (1.78±0.68, $P<0.0001$). The neointima of the stents with $\geq3.0$ $\mu$Ci $^{32}$P was composed of smooth muscle cells, matrix proteoglycans, calcification, foam cells, and cholesterol clefts.

**Conclusions**—Continuous low-dose-rate irradiation delivered by high-activity $^{32}$P radioactive stents promotes the formation of an “atheromatous” neointima after 6 months in this experimental model. These data may be useful for predicting late tissue responses to radioactive stents in human coronary arteries. *(Circulation. 1999;100:1548-1554.)*

**Key Words:** stents ■ restenosis ■ radioisotopes

Radioactive stents have been proposed as a means to reduce in-stent restenosis by inhibiting neointimal formation. Presumably, continuous low-dose rate irradiation delivered by a radioactive stent may be sufficient to impair the ability of smooth muscle cells (SMCs) to proliferate after delivery to the arterial wall by a radioactive stent. Wehrlein et al. however, reported a reduction in neointima after 12 weeks in rabbit iliac arteries after placement of radioactive stents with only 13 $\mu$Ci of $^{32}$P. Stents with a $\mu$Ci of $^{32}$P were histologically similar to nonradioactive stents. In the porcine coronary restenosis model, we observed an unusual biphasic biological response to low- (0.5 $\mu$Ci), intermediate- (1.0 $\mu$Ci), and high- ($\geq3.0$ $\mu$Ci) activity 7-mm-long $^{32}$P Palmaz-Schatz stents at 28 days. The low-activity $^{32}$P radioactive stents reduced neointimal formation to a degree similar to that reported in the porcine iliac model with 0.14-$\mu$Ci $^{32}$P radioactive stents. The intermediate-activity stents, however, promoted the formation of a matrix proteoglycan-rich neointima, whereas the high-activity stents reduced neointimal formation but with histological evidence of delayed vascular repair. Thus, the present experimental data suggest important dose-, time-, species-, and model-dependent variations in the vascular response to $^{32}$P radioactive stents.

The purpose of this study was to determine the long-term dose-response effects of $^{32}$P $\beta$-particle-emitting radioactive stents in a porcine atherosclerotic coronary model. A double-injury model of accelerated atherosclerosis was selected to mimic the geometric effects of plaque mass on radiation delivery to the arterial wall by a radioactive stent.

**Methods**

**Stent Preparation and Dosimetry**

Commercially available 15-mm-long balloon-expandable stainless steel stents (Palmaz-Schatz, Cordis, a Johnson & Johnson Co) were rendered radioactive by direct ion implantation of $^{32}$P. The activity of the stent was determined, and stents were allowed to decay to desired $^{32}$P activities before the time of implantation. The dosimetry of $^{32}$P radioactive Palmaz-Schatz stents has previously been reported by...
TABLE 1. Estimated 28-Day Cumulative Dose and Initial Dose Rate at Implantation at a Distance of 0.5 mm From the Surface of the 32P Stents

<table>
<thead>
<tr>
<th>Activity, μCi 32P</th>
<th>Cumulative Dose, cGy</th>
<th>Initial Dose Rate, cGy/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1000</td>
<td>3</td>
</tr>
<tr>
<td>3.0</td>
<td>3000</td>
<td>10</td>
</tr>
<tr>
<td>6.0</td>
<td>6000</td>
<td>20</td>
</tr>
<tr>
<td>12.0</td>
<td>12,500</td>
<td>60</td>
</tr>
</tbody>
</table>

Janicki et al. The estimated 1-month cumulative dose and initial dose rate at implantation for the 32P radioactive stents are shown in Table 1.

Animal Preparation

The animal work was completed after approval by the institutional scientific review committee and conformed to the position of the American Heart Association on animal research. Sixty-two stents 3.0 to 4.0 mm in diameter (19 control and 43 radioactive) were implanted in the coronary arteries of 31 miniature swine at 28 days after creation of a fibrocellular plaque by overstretch injury with a 10-mm-long angioplasty balloon and cholesterol feeding. Animals were medicated with aspirin 650 mg, ticlopidine 250 mg, and nifedipine extended release 30 mg by mouth the evening before stent placement. Under general anesthesia, an 8F sheath was placed retrogradely in the right carotid artery, and heparin (150 U/kg) was administered intra-arterially to achieve an activated clotting time >300 seconds (Hemochron, International Technidyne). After completion of angiography, the stent was implanted at a site of balloon injury that was identified by an anatomic landmark (such as a side branch) or the presence of luminal narrowing. The stents were implanted with the guiding catheter used as a reference to obtain a 1:1 stent-to-artery ratio compared with the normal reference vessel diameter. Placement of the stent was completed with a single balloon inflation at 10 to 14 atm for 30 seconds. Angiography was completed after implantation to confirm patency of the stent. Animals were allowed to recover and then returned to care facilities, where they received a normal diet and were treated with ticlopidine 250 mg/d for 28 days and aspirin 325 mg/d. After 6 months, the animals were returned to the laboratory for coronary angiography and were euthanized with a lethal dose of barbiturate.

Pathological Evaluation

The methods for tissue and stent processing have been described in detail. Four sections from each stent were evaluated for the presence of cholesterol clefts, foam cells, calcification, and necrotic core within the intima. The coronary artery area (area of whole vessel) proximal, distal body, and distal edge stent sections were measured with digital morphometry to determine the areas within the adventitia (area of dense fibrous tissue outside the external elastic lamina [EEL]), EEL, internal elastic lamina (IEL), stent, and lumen. The area within the stent or IEL was considered the normal reference lumen area. The percent area stenosis was then defined as [(stent or IEL area − lumen area)/(stent or IEL area)]×100. Neointimal area was determined by subtracting the area of the lumen from the area within the stent or IEL. The area of the plaque + media was determined by subtracting the area of the stent or IEL from the area of the EEL. Neointimal thickness extending perpendicularly from the stent to the lumen surface was measured at each strut. The extent of vessel wall injury induced by the stent was determined by the methods of Schwartz et al. The morphometry parameters and injury score were measured for each of the 4 sections, and an average for each stent was then calculated.

Quantitative Angiography

The baseline, postimplantation, and 6-month minimal lumen diameter within the stent were measured from nonoverlapped and nonforeshortened views, with the guiding catheter used as a standard (CMS, Medis, Inc). The poststenot percent diameter stenosis, short-term stent-to-artery ratio (minimal stent balloon-inflated diameter/referen lumen diameter), and 6-month percent diameter stenosis were calculated from these data for each vessel.

Statistical Analysis

The angiographic parameters were compared by paired t test. The mean morphological data for each stent were compared by ANOVA with Scheffé’s F tests for multiple comparisons. Angiographic late lumen loss, injury score, neointimal area, percent in-stent stenosis, and stent activity were analyzed with linear regression to determine relations. Significance was established by a value of P<0.05. Data are expressed as mean±SD. All statistics were calculated by use of Statview 4.5 (Abacus).

Results

General

Sixty of 62 stents (96.8%) were successfully implanted into the coronary arteries of 31 swine. Two stent implantations were complicated by ventricular fibrillation that was refractory to medical therapy and DC cardioversion. Twenty-five of 29 animals (86.2%) survived after stent implantation for the duration of the study. One animal was euthanized 2 months after stent implantation because of an inner ear infection refractory to antibiotic therapy. This animal received a 1.0-μCi 32P stent and a nonradioactive stent. The histological data from this animal were excluded from analysis, although each stent was patent on microscopic analysis, with similar cellular appearance and degree of neointimal formation.

Subacute Stent Thrombosis

Three of 29 animals (10.3%) with successful stent placement had sudden death secondary to subacute thrombosis of a stent. Subacute stent thrombosis occurred in 3 of 39 radioactive stents (7.7%) and none of the nonradioactive stents (P=0.54). Stent thrombosis occurred on days 4, 27, and 28 after implantation. The radioactive stents with subacute thrombosis were in the 6.0-μCi 32P activity group at the time of implantation.

Quantitative Angiography

Quantitative angiography of the coronary angiograms at implantation and at 6 months is summarized in Table 2. The stent-to-artery ratio (1.04±0.02) was similar for the radioactive and nonradioactive stents (P=0.48). Linear regression analysis demonstrated a dose-dependent increase in the late lumen loss (r=0.72, P<0.001).

Pathology

Morphology of In-Stent Lesions After Sudden Death

Histology of the coronary arteries from the animal with sudden death on day 4 revealed an occlusive thrombus distal to a 6.0-μCi 32P stent implanted in the left anterior descending coronary artery. Focal compression of the plaque and media was present without deep vessel wall injury within the stent. Analysis of the proximal and distal reference sections failed to identify a cause for stent thrombosis, such as a medial dissection. The nonradioactive stent in the left circumflex coronary artery was patent and had a thin neointima consisting of an organized fibrin thrombus with inflammatory cells and SMCs. Focal necrosis of the plaque and media underneath the struts was more prominent for the radioactive than the nonradioactive stent. The histology of the stents from the animals with sudden death on days 27 and 28 revealed a large organizing thrombus...
The neointima of the radioactive stents with 6.0 \( \mu \text{Ci} \) \( ^{32} \text{P} \) (3.57±1.21) was significantly greater than the nonradioactive stents (1.78±0.68, \( P<0.0001 \)), resulting in greater in-stent stenosis (53±14 versus 28±9, \( P<0.0001 \)). The mean neointimal area and the percent in-stent stenosis correlated positively with increasing stent activity \( (r=0.64, P<0.001) \). The neointimal area correlated with the injury score for the control stents \( (r=0.33, P=0.009) \) but not the radioactive stents \( (r=0.02, P=0.86) \).

The neointima of the nonradioactive stents consisted of well-organized SMCs within a collagen matrix. Neovascularization was present adjacent to the strut wires. The adventitia contained collagen, fibroblasts, and neovascular capillaries. The neointima of the radioactive stents with \( \leq 1 \mu \text{Ci} \) of \( ^{32} \text{P} \) appeared similar to that of the nonradioactive stents (Figure 2). Occasional regions of cholesterol-rich macrophages were identified adjacent to the stent struts. Neovascularization of the neointima and adventitia was also similar to that in the nonradioactive stents.

The morphology of the high-activity stents was somewhat variable. The neointima contained areas of SMCs in a proteoglycan-collagenous matrix localized primarily in the

<table>
<thead>
<tr>
<th>TABLE 2. Summary of Angiographic Data at Baseline and 6 Months After Placement of Nonradioactive and Radioactive ( ^{32} \text{P} ) Stents in Atherosclerotic Porcine Coronary Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Activity</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Control (( n=16 ))</td>
</tr>
<tr>
<td>0.5–1.0 ( \mu \text{Ci} ) (( n=8 ))</td>
</tr>
<tr>
<td>3.0 ( \mu \text{Ci} ) (( n=9 ))</td>
</tr>
<tr>
<td>6.0 ( \mu \text{Ci} ) (( n=8 ))</td>
</tr>
<tr>
<td>12.0 ( \mu \text{Ci} ) (( n=10 ))</td>
</tr>
</tbody>
</table>

| **Stent Placement**                                      | **Follow-up** |
|---------------------------------------------------------------|
| **Reference** | **Lesion** | **%** | **Stenosis** |
|---------------------------------------------------------------|
| Control (\( n=16 \))                                    | \( 3.18\pm0.36 \) | \( 2.76\pm0.40 \) | 13±7  |
| 0.5–1.0 \( \mu \text{Ci} \) (\( n=8 \))                 | \( 3.21\pm0.97 \) | \( 2.79\pm0.55 \) | 18±8  |
| 3.0 \( \mu \text{Ci} \) (\( n=9 \))                     | \( 3.15\pm0.41 \) | \( 2.14\pm0.71 \) | 33±19§|
| 6.0 \( \mu \text{Ci} \) (\( n=8 \))                     | \( 2.97\pm0.27 \) | \( 1.83\pm0.38 \) | 38±14§|
| 12.0 \( \mu \text{Ci} \) (\( n=10 \))                    | \( 3.28\pm0.25 \) | \( 1.96\pm0.31 \) | 35±16§|

MLD indicates minimal lumen diameter.

\( ^{32} \text{P} \) stents in Atherosclerotic Porcine Coronary Arteries

The neointima of the nonradioactive stents consisted of a proteoglycan-rich matrix with occasional SMCs and fibrin adjacent to the struts resulting in >75% luminal narrowing. A mural thrombus was present in this case, but without evidence of complete occlusion of the lumen. A nonradioactive stent implanted in the left anterior descending coronary artery was patent, with mild neointimal thickening and evidence of surface endothelialization on light microscopy.

**Dose-Response Effects on Arterial Morphology**

The results of vessel morphometry are summarized in Table 3. The area of the plaque plus media (mm\(^2\)) was similar for the control (1.88±0.52) and radioactive (1.73±0.53, \( P=0.12 \)) stents. The mean neointimal area (mm\(^2\)) for the stents with \( \geq 3.0 \) \( \mu \text{Ci} \) \( ^{32} \text{P} \) was 500 \( \mu \text{m} \) in A and 50 \( \mu \text{m} \) in B.
region of the struts, with other areas rich in macrophages, necrotic debris, cholesterol clefts, and giant cells (Figures 3 and 4). Calcification was observed in some cases. Neovascularization was more prominent in the neointima than in the control and 1.0-μCi 32P stents. The media was compressed beneath the stent struts, and in other locations the media was of normal thickness and appearance. Only rare areas of severe medial disruption were observed. At other sites near the stent struts, the neointima was markedly hypocellular and consisted of a loose proteoglycan matrix with occasional SMCs.

TABLE 3. Summary of Vessel Morphometry 6 Months After 32P Radioactive Stent Placement in Atherosclerotic Porcine Coronary Arteries and Comparison With Control Stent Vessels

<table>
<thead>
<tr>
<th>Stent Activity</th>
<th>Adventitia</th>
<th>Stent/IEL</th>
<th>Neointima</th>
<th>Lumen</th>
<th>Stenosis (%)</th>
<th>Injury Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=16)</td>
<td>1.43±0.54</td>
<td>6.40±1.27</td>
<td>1.78±0.68</td>
<td>4.62±1.07</td>
<td>28±9</td>
<td>0.57±0.54</td>
</tr>
<tr>
<td>0.5–1.0 μCi (n=8)</td>
<td>1.33±0.43</td>
<td>6.52±1.17</td>
<td>2.23±0.66</td>
<td>4.30±1.04</td>
<td>34±10</td>
<td>0.94±0.89*</td>
</tr>
<tr>
<td>3.0 μCi (n=9)</td>
<td>1.56±0.56</td>
<td>6.58±1.08</td>
<td>3.39±1.10</td>
<td>3.24±1.02†</td>
<td>51±14‡</td>
<td>0.83±0.36</td>
</tr>
<tr>
<td>6.0 μCi (n=8)</td>
<td>2.02±1.06†</td>
<td>6.12±1.08</td>
<td>3.37±1.02‡</td>
<td>2.85±0.92‡</td>
<td>53±16§</td>
<td>0.94±0.46</td>
</tr>
<tr>
<td>12.0 μCi (n=10)</td>
<td>2.52±1.09‖</td>
<td>7.14±1.04</td>
<td>3.94±1.21†</td>
<td>3.23±0.82‡</td>
<td>54±13§</td>
<td>0.81±0.41</td>
</tr>
</tbody>
</table>

Data expressed as mean area (mm²) ± SD.
*P<0.045 for 0.5–1.0 μCi vs control.
†P<0.002 for 3.0, 6.0, and 12.0 μCi vs control and =1.0 μCi.
‡P<0.0001 for 3.0, 6.0, and 12.0 μCi vs control and =1.0 μCi.
§P<0.001 for 3.0, 6.0, and 12.0 μCi vs control and =1.0 μCi.
∥P<0.03 for 6.0 and 12.0 μCi vs control and =1.0 μCi.

Figure 2. Composite low- and high-power photomicrographs of 0.5-μCi 32P (A and B) and nonradioactive (C and D) stents at 6 months after placement in atherosclerotic porcine coronary arteries. Neointima of nonradioactive stents consists of well-organized SMCs within a collagen matrix. Neointima of 0.5-μCi 32P radioactive stent is similar to nonradioactive stent. *Strut void. Bars=500 μm in A and C, 100 μm in B and D.
and some condensation of SMCs near the lumen. The adventitia was significantly thickened, without any inflammatory infiltrate in the stents with $6.0 \text{ mCi}$ of 32P (Table 3).

**Discussion**

Radioactive stents have been proposed as a means to reduce in-stent restenosis by inhibiting neointimal formation. We evaluated the long-term dose-response effects of radioactive stents ion-implanted with activities of 1.0 to 12.0 $\mu$Ci of 32P in a porcine atherosclerotic coronary model. A double-injury model of accelerated atherosclerosis was selected to more closely mimic the geometric effects of plaque mass on radiation delivery to the arterial wall by a radioactive stent. Histological analysis demonstrated a dose-dependent increase in neointimal area and the percent in-stent stenosis with increasing stent 32P activity. The neointima of the stents with $\geq 3.0 \mu$Ci 32P was composed of SMCs and a proteoglycan matrix with calcification, foam cells, and cholesterol clefts. Therefore, the main finding of the present study is that continuous low-dose rate irradiation delivered by $\geq 3.0- \mu$Ci 32P radioactive stents promotes the formation of an atheromatous neointima in this experimental model.

**Long-Term Effects of Continuous Low-Dose-Rate Endovascular Irradiation**

The present study, unlike previous 28-day studies in the porcine coronary model of restenosis, failed to demonstrate a significant reduction in neointimal formation for low-activity (0.5 to 1.0 $\mu$Ci 32P) radioactive stents at 6 months in atherosclerotic pig coronary arteries. The lack of efficacy at 6 months in this model for the low-activity 32P stents suggests inadequate cumulative radiation dose, dose rate, or delayed neointimal growth after 28 days, although the higher injury score observed in the 0.5- to 1.0-$\mu$Ci 32P group suggests that stent-induced arterial trauma may have contributed to the failure at this activity. Importantly, a dose-dependent increase in neointimal formation was observed with increasing activity of 32P on the stent at the time of implantation.

The histological features of the 3.0- to 12.0-$\mu$Ci 32P radioactive stents observed in the present study are consistent with radiation-induced arteriopathy. Experimental studies in canine and rabbit models indicate that external-beam irradiation of the aorta or vascular grafts causes intimal hyperplasia and accelerated atherosclerosis after 6 months.

**Figure 3.** Low- and high-power photomicrographs of coronary arteries at 6 months after placement of 3.0- $\mu$Ci 32P radioactive stents in separate animals. A and B are from same animal. Note marked neointimal formation with abundant proteoglycan-rich matrix (arrowheads) adjacent to strut (*strut void*). Neointima contains organized SMCs with minimal matrix at luminal surface (arrow). C and D are from a separate animal with a 3.0-$\mu$Ci 32P stent demonstrating variability in response to irradiation. C, Cellular neointima is present with large focal area of calcification (large void area with arrowhead). Box shows area of D. D, Higher-power photomicrograph shows necrotic lesion close to strut (*). Macrophage infiltration is present around cholesterol clefts (arrowheads) with calcification (arrow) above strut (*). Bars $= 500 \mu$m in A and C, 100 $\mu$m in B, and 50 $\mu$m in D.
with single doses $\geq 30$ Gy. \cite{9,10,11,12} Hoopes et al\cite{12} reported that large single intraoperative doses of radiation (60 Gy) delivered to the canine aorta resulted in decreased or delayed intimal proliferation and lumen narrowing compared with lower fractionated doses. Our data suggest that the cumulative dose delivered by a \$3.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stent exceeds vascular tissue tolerance in this model. The estimated lifetime cumulative tissue dose at a distance of 0.5 mm from the surface of a \(3.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stent is $20$ to $125$ Gy. Importantly, the lifetime cumulative near-field (0.1 mm from the stent surface) dose for a \(3.0-\text{mCi}\) \(\text{P}^{32}\) stent is $>125$ Gy. Therefore, the arterial tissue immediately adjacent to the struts of a permanently implanted \(3.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stent receives a lifetime cumulative dose nearly 5-fold greater than a single dose of irradiation known to induce an arteriopathy.

Several experimental and initial clinical trials have demonstrated efficacy in preventing restenosis after stenting by treatment with 8 to 30 Gy irradiation given in a single dose via a high-dose-rate (1200 to 5000 cGy/h) \(\text{Ir}^{192}\) catheter-based system.\cite{13,14} In the present study, the 28-day cumulative dose (10 Gy) or initial dose rate (3 cGy/h at implantation) delivered by a \(1.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stent was insufficient to reduce neointimal formation and in-stent stenosis at 6 months. The arterial morphology of the \(1.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stents did not exhibit the pathological features identified in the \(3.0-\text{to}\ 12.0-\text{mCi}\) \(\text{P}^{32}\) radioactive stents consistent with a radiation-induced arteriopathy. Together, these preliminary data suggest that dose rate may be a critical factor in predicting efficacy for the prevention of restenosis with endovascular irradiation, whereas the cumulative dose predicts toxic radiation–induced late tissue responses.

**Comparison With Previous Studies of Radioactive Stents**

Hehrlein et al\cite{5} also reported a series of experiments with similar activities of \(\text{P}^{32}\) stents in rabbit iliac arteries. In contrast to the porcine experiments, these authors reported a dose-dependent reduction in neointimal formation, with the maximal effect evident at 3 months after placement of a \(13.0-\text{mCi} 7\text{-mm-long stent.}\) The contrasting results with the doses of continuous \(\beta\)-particle irradiation used in these experimental studies suggest a species- or model-dependent response to endovascular irradiation delivered via a stent. Others have demonstrated species differences in response to nonradioactive stent implantation that may be related to endothelial cell regeneration or the intrinsic fibrinolytic capacity of the animal.\cite{15,16} Studies are currently under way to examine species differences in the response to stent-based irradiation that may have important implications for the selection of animal models used to evaluate radioactive stents.

The clinical phase 1 Isostent for Restenosis Intervention Study (IRIS) demonstrated similar target-lesion revascularization and angiographic restenosis after 6 months for 0.5- to 1.5-\(\text{mCi}\) \(\text{P}^{32}\) Palmaz-Schatz stents compared with expected late outcomes for a nonradioactive Palmaz-Schatz stent in patients with focal native coronary arterial lesions.\cite{17} Cur-
rently, dose-escalation trials are in progress with stent activities of \( \approx 3.0 \) to 24 \( \mu \)Ci \( ^{32} \)P to determine safe and potentially effective irradiation doses delivered via a \( \beta \)-particle–emitting stent to reduce restenosis.

**Limitations of the Study**

Interpretation of the data obtained in the present study must be made with caution, because the study involves the dose-response effects of a radioactive stent in vessels with focal experimentally induced atherosclerotic lesions. The atherosclerotic pig coronary lesions created by balloon injury and high-cholesterol diet differ from the complex atherosclerotic lesions in humans in which focal plaque rupture, necrosis, and calcification are often observed. The diet- and injury-induced lesions in the porcine atherosclerotic coronary model consist primarily of SMCs. The extent of atherosclerotic plaque is substantially less in this model than that encountered when stents are implanted in diseased human coronary arteries. These factors will have significant effects on radiation dose distribution to the vessel wall because of variations in tissue density and plaque mass as well as uniformity of stent expansion. The present study, however, clearly defines the late tissue responses to continuous low-dose-rate irradiation delivered by a 0.5- to 12-\( \mu \)Ci \( ^{32} \)P radioactive stent in an experimental model of restenosis. Therefore, these data may be useful for predicting dose-dependent long-term effects of \( ^{32} \)P radioactive stents in human coronary arteries.

**Acknowledgments**

This study was funded by a grant from Isostent, Inc, Belmont, Calif, through the Henry M. Jackson Foundation, Rockville, Md.

**References**


