Vascular Stenting in Normal and Atherosclerotic Rabbits

Studies of the Intravascular Endoprosthesis of Titanium-Nickel–Alloy

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Percutaneous transluminal balloon angioplasty would be more effective if the rate of recurrent stenosis were reduced. To evaluate the prevention of restenosis after percutaneous transluminal angioplasty, intravascular endoprosthetic stents of titanium-nickel–alloy were implanted transluminally in seven normal and 21 atherosclerotic rabbits. In normal rabbits, a 3.5-mm diameter stent was implanted in the aorta and a 2.5-mm diameter stent in the right iliac artery, which were followed with serial angiograms from 6 weeks (n=7) to 8 months (n=4). There was a mean stenosis of 13.1% in the 2.5-mm and 13.6% in the 3.5-mm stent. There was no significant narrowing compared with the adjacent control segments of artery; histopathology showed a thin, fibrous neointima with smooth muscle cells. Each atherosclerotic rabbit was balloon dilated at two separate stenotic sites; each site was 2.0 cm in length. The aortic site (with 28.8±13.8% mean stenosis [±SD]) was dilated with a 3.5-mm balloon, and the iliac site (with 36.5±14.2% stenosis) was dilated with a 2.5-mm balloon. In each site, an intravascular stent of corresponding diameter and 7-mm length was implanted in one half of the dilated segment, assigned randomly, and the other half served as the angioplasty control. Angiographically observed restenosis rates and the corresponding histopathology were similar in the atherosclerotic segments that had angioplasty alone versus the atherosclerotic segments that had angioplasty plus stenting. The mean neointimal thickness in the aortas and iliac arteries, respectively, measured 247±181 μm (±SD) and 218±77 μm after 6 weeks (n=8) versus 321±168 and 308±189 μm after 20 weeks (n=5, p=NS). At 20 weeks follow-up, there was 29.1±29.8% (median, 16.4%) stenosis in the aortic stent versus 38.9±24.1% (median, 34.0%) stenosis in the percutaneous transluminal angioplasty control segment of aorta (n=5, p=NS) and 81.4±25.5% stenosis in the iliac artery stent versus 89.3±15.3% stenosis in the PTA control segment of the right iliac artery (n=5, p=NS). Comparing stenotic arterial segments treated with angioplasty alone with angioplasty plus intravascular stenting in the atherosclerotic rabbits showed that there was no significant difference in either the histopathologic changes or the restenosis rates. (Circulation 1990;81:667–683)

There is a need for an endovascular prosthetic stent for the treatment of symptomatic arterial dissection and acute occlusion resulting from percutaneous transluminal angioplasty (PTA).

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A stent would be applicable to more clinical situations if it prevented recurrent atherosclerotic stenosis after PTA. To determine the feasibility of a titanium-nickel–alloy 5-mm diameter intravascular stent for these purposes, we performed preliminary studies in dogs and found that the prosthesis had a patency rate of 92% for as long as 2 years.1,2 We now report the results of implanting the endovascular prosthesis in normal and atherosclerotic rabbits. The endoprostheses were miniaturized to a 2.5- or 3.5-mm outer diameter and 7-mm length and were transluminally implanted via catheter into normal rabbits. The endoprostheses were implanted after angioplasty in
atherosclerotic rabbits to evaluate the prevention of recurrent atherosclerotic stenosis, the reduction of pressure gradients across the stenotic lesion, the patency of side branches, and the cellular response to angioplasty plus implantation of the endovascular prosthesis. Using each rabbit as its own control, the sites with angioplasty alone were compared with the sites with angioplasty plus endoprosthetic stenting. These sites were evaluated by sequential angiography, gross pathology, histopathology, and scanning electron microscopy (SEM).

Methods

Titanium-Nickel-Alloy Endoprosthesis

The intravascular endoprosthesis is a coiled wire tube composed of titanium-nickel-alloy. This alloy has two crystalline structures that can be switched back and forth by small changes in temperature, resulting in a visible change in configuration, due to the thermal shape memory effect. The titanium-nickel-alloy (Special Metals, New Hartford, New York), consisting of 45% titanium and 55% nickel, was obtained in the form of a flat wire with a rectangular cross section of 0.15 x 0.33 mm. A coiled tube of any diameter and length could be fabricated; 2.5- and 3.5-mm external diameters were selected to match the rabbit right iliac artery and aorta, respectively. The surface of the wire was finished by abrading manually with Scotchbrite (3M, St. Paul, Minnesota) and then wiping with 1,1,1-trichloroethane. The thermal shape memory was set by annealing the wire, coiled in the shape of a tube, at 500°C for 60-120 minutes. On cooling to room temperature, the wire became ductile and was readily wound on the delivery catheter. The alloy’s memory was activated on warming. Starting at 40°C and finishing at 50°C, the stent firmly expanded to the 2.5- or 3.5-mm external diameter and 7-mm length coiled tubular configura-
Implantation was and the water, for 30 by acetone, absolute ethanol, and distilled deionized water, for 30 minutes in each solvent.

**Catheter Delivery System**

The delivery catheter was a modified 4.3F PTCA catheter (USCI-Bard, Billerica, Massachusetts). The endoprosthesis was wound tightly around the catheter, between a silk stay suture and the distal balloon, reducing the stent's external diameter to 1.6 mm (Figure 2). The catheter plus stent readily passed through a 5F introducer sheath (i.d., 1.93 mm), so it could be inserted percutaneously or via an arteriotomy in a peripheral artery and delivered transluminally to the desired vascular site under fluoroscopic guidance. Five to 10 milliliters of warm normal saline was injected rapidly by hand into the catheter's infusion port, exiting at the slot adjacent to the endoprosthesis. In a mock circulatory loop, 10 ml 70°C normal saline warmed the stent up to 55°C for less than 1 second, causing immediate conversion of the stent to a coiled tube of the original diameter at annealing, either 2.5 or 3.5 mm.

**Implantation in Normal Rabbits**

Fourteen endoprosthetic stents were implanted into seven normal New Zealand male rabbits (3.2–4.9 kg) in the aorta and right iliac arteries. The handling and experimentation of the rabbits was conducted in a gentle manner to minimize the discomfort and stress of the rabbits; all protocols followed Federal Department of Agriculture guidelines for laboratory animal care and the guiding principles of the American Physiological Society and were approved by the Cleveland Clinic Foundation's Institutional Animal Care and Use Committee. The rabbits were administered aspirin 90 mg by mouth each day from 2 days before implantation until 30 days after implantation, benzathine penicillin G and procaine penicillin G (150,000 units each) i.m. before implantation, 35 mg ketamine and 5 mg/kg xylazine i.m. for anesthesia, and heparin 1,000 units i.v. before catheterization. A 5F introducer sheath (Cordis, Miami, Florida) was inserted via a right femoral arteriotomy. The arteriotomy was preferred to percutaneous insertion because of the combination of aspirin with heparin, the small caliber of the rabbit vessels, and the difficulty in maintaining effective compression to prevent hematoma formation. A 2-mm grid lead rule was placed at the level of the lumbar spine. Arteriography showed that the normal aortas measured a mean of 3.30 mm (range, 3.0–3.6 mm), and the iliac arteries were a mean of 2.25 mm (range, 2.1–2.4 mm). The 3.5-mm diameter endoprosthesis, wound tightly to 1.6-mm diameter and mounted on the catheter, was introduced into the infrarenal aorta by fluoroscopic guidance. Warm saline injection (70–80°C in the syringe) converted the stent from 1.6- to 3.5-mm e.d., slightly larger than the native vessel, pressing firmly against the wall to secure itself in place. A second endoprosthesis, 2.5-mm diameter, was implanted in the right iliac artery in a similar manner, followed by angiography.

Intravenous digital subtraction angiograms (DSA) were obtained in the anteroposterior plane at 6 weeks and 3, 6, and 8 months. The rabbits were killed using the established American Veterinary Medical Association (AVMA) guidelines on euthanasia at 6 weeks (n=3) or 8 months (n=4). Five minutes after general anesthesia using ketamine, xylazine, and 2,000 units heparin i.v., 250 mg pentobarbital was injected i.v.; then the aorta and superficial femoral arteries were cannulated. The arteries underwent perfusion followed by pressure fixation at 80 mm Hg for 2 hours using 2.0% glutaraldehyde and 3.0% sucrose in 0.1 M phosphate buffer. The vascular implantation sites were dissected from the tissues and bisected lengthwise in a coronal plate. One longitudinal half of each arterial site was dehydrated, critical-point dried, and then sputter-coated with gold and observed with SEM using a JSM-U3 (JEOL, Tokyo, Japan). After the prostheses were carefully dissected out of the other half of the arterial site, it was embedded in paraffin, sectioned longitudinally, and stained using hematoxylin and eosin, elastin Van Gieson, Masson’s trichrome, and Von Kossa’s stains. Microscopic pigment foci were evaluated for trace materials by energy dispersive radiographic microanalysis with an EDAX-9100 system (EDAX International, Prairie View, Illinois). The thickness of the neointimal layer was measured in the histologic longitudinal sections from the outer surface of each coil of wire to the luminal surface with an ocular micrometer of a light microscope.

**Induction of Atherosclerosis**

Twenty-one New Zealand male rabbits (3.2–4.7 kg) were fed a 0.25%-cholesterol, 2.0%–peanut oil–

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**Figure 2.** Schematic illustration of delivery catheter. Stent is mounted between the distal balloon and the silk suture (arrowhead). Warm normal saline is injected through the lumen and exits through the slot, which warms the stent up to 55°C, immediately converting the stent from 1.6-mm diameter to the desired external diameter, which was selected to be either 2.5 or 3.5 mm.
enriched rabbit chow diet (Purina 5326, ICN Nutritional Biochemicals, Warrensville Heights, Ohio) throughout the entire course, resulting in serum total cholesterol values of 441 ± 362 mg/dl (mean ± SD) and high density lipoprotein cholesterol values of 28.6 ± 17.3 mg/dl. After 1 week on the diet, abrasion of the arterial intima was performed, via a distal right femoral arteriotomy, from the thoracic aorta to the right femoral artery with a 3F Fogarty balloon, as described by Baumgartner.4

Percutaneous Transluminal Angioplasty and Implantation in Atherosclerotic Rabbits

Six to 10 weeks after inducing atherosclerosis, the rabbits were prepared in a manner similar to the normal rabbits (described above), including penicillin, ketamine, xylazine, heparin, and aspirin 90 mg mouth each day from 2 days before until 30 days after implantation. Ninety milligrams of acetylsalicylic acid is the equivalent of 19.1–28.4 mg/kg orally each day, which was within the range that has been shown to inhibit platelet aggregation without affecting endothelial cell prostacyclin production in rabbits.5 This was checked in each atherosclerotic rabbit by testing platelet aggregation to ADP using platelet-rich plasma with the Monitor IV Plus platelet aggregometer (Helena Laboratories, Beaumont, Texas).6 Platelet aggregation to 20 mg/ml ADP was decreased from a 100% normal response to a mean of 56.2% (range, 34–78%) with a monophasic reaction, confirming inhibition. A midline neck incision was made and anesthetized subcutaneously with 6 ml 0.25% bupivacaine with 1:400,000 epinephrine, and a 5F introducer sheath was inserted into the right carotid artery using an arteriotomy. A 2.5-mm diameter, 20-mm length USCI Dilica angioplasty catheter (USCI) was introduced over a 0.016-in. steerable guidewire into the infrarenal aorta. Five milliliters of Renografin 60 (Squibb Diagnostics, New Brunswick, New Jersey), diluted 50%, was injected during cineangiography, with a 2-mm grid lead rule placed at the level of the lumbar spine. All of the local pressure gradients were measured across the stenosis during gentle withdrawal of the catheter.

A 2.0-cm segment of the right common and external iliac arteries underwent angioplasty, using the 2.5-mm balloon because this was 11% larger than the measured 2.25-mm mean diameter of the iliac arteries of normal rabbits of the same breed and weight. The balloon was inflated to 8 atm pressure for 60 seconds three times; then arteriography and pressure gradient measurements were repeated. The delivery catheter with the mounted endoprosthesis was thin and flexible, which permitted rapid introduction from the right carotid artery, around an acute angle with the arch of the aorta, into the descending aorta over a steerable guidewire using standard techniques. A 2.5-mm diameter endoprosthesis (reduced to 1.6-mm diameter by mounting it on the delivery catheter) was introduced over a 0.014-in. steerable guidewire into one half of the dilated segment, either the right common or external iliac artery, selected randomly. Then 10 ml 75–80° normal saline was injected manually at a rate of 2–3 ml/sec to convert the endoprosthesis to 2.5-mm diameter; then the pressure gradients were measured. Using a similar technique, a 2.0-cm long segment of infrarenal aorta was dilated to 3.5-mm diameter because this was 6% longer than the measured 3.30-mm mean diameter of the aorta in normal rabbits. Then, pressure gradients along the aorta were measured after PTA, and a 3.5-mm diameter endoprosthesis was implanted in a randomly selected half, followed by pressure measurements and angiography.

The rabbits were followed up with serial intravenous DSA with a 2-mm grid ruler. The first DSA was obtained after 6 weeks; however, there was visible narrowing at this time, so angiograms were obtained every 2 weeks, and in subsequent groups angiograms were obtained every week. A second injection with a 60° oblique view was added, using up to 3 ml/kg of MD-76. The DSA films were measured using a mechanical caliper accurate to 0.001 in. (0.0025 mm) (Brown and Sharpe, North Kingston, Rhode Island). To measure stenosis, a percentage was calculated where the numerator was the diameter of the lumen measured at the site of maximum stenosis in the stent and angioplasty segments, and the denominator was the diameter of the implanted endoprosthesis (equal to the diameter of the angioplasty balloon) measured on the initial nonsubtraction film before contrast was administered. The patency of side branches was assessed during the postimplantation angiogram and follow-up DSA.

After the final DSA, the rabbits were sacrificed at 6 (n=4), 8 (n=4), 12 (n=3), and 20 weeks (n=5) using the established AVMA guidelines on euthanasia. The arteries underwent perfusion and pressure fixation, and then were prepared for SEM and histologic analysis, as described above. There were three anesthetic deaths with pneumonia, which were analyzed to ascertain the effects of angioplasty alone, and two deaths from pneumonias that occurred 2 weeks after angioplasty and stenting.

Statistical Analysis

Before balloon angioplasty and stenting, the percentages of stenosis seen on angiogram were normally distributed. Therefore, after inducing atherosclerosis, the presence of statistically significant stenosis (compared with 0%) was evaluated by a one-sample t test for the aorta and the right iliac artery. Differences in pressure gradients were compared between data pairs obtained at three time points (before PTA, after PTA, and after stent implantation) using the nonparametric Friedman test and multiple comparison procedures because the data were frequently not normally distributed.7 Likewise, the Wilcoxon signed-rank test was used to compare restenosis in the stent site with the corresponding PTA site at each week and to compare restenosis at each follow-up week with the first.

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measurement after the procedure. This was done separately for the right iliac artery and aorta in each rabbit at every follow-up DSA, in the anteroposterior plane, the 60° oblique plane, and the arithmetic mean of both planes. To account for these multiple comparisons, a significance level of 0.01 was used for each comparison. Spearman correlation analyses were used to correlate the DSA results of the anteroposterior plane with the 60° oblique plane angiograms. The mean percentages of restenosis over time for each of the two treatments were compared using a repeated-measures analysis of variance on the natural logarithm scale to obtain normality of the data.8

To detect any possible interaction between the two adjacent treatments in the atherosclerotic rabbits (angioplasty plus stenting versus angioplasty alone), the treated arterial segments were divided into two groups—one where the stent was randomly assigned to be upstream and one with the stent to be downstream. The percentage of restenoses in the upstream stents were compared with those of the downstream stents, separately for the aorta and right iliac artery, at each follow-up DSA with a paired t test.

The mean neointimal thicknesses in the short-implant duration rabbits were compared with those of the long-implant duration rabbits using the unpaired t test. This test was applied separately in the aorta and right iliac artery stents for the normal rabbits (6–8 weeks vs. 8 months) and in the iliac artery for the atherosclerotic rabbits (6–8 vs. 20–21 weeks). A one-way analysis of variance was used to compare the neointimal thickness in the three implant duration groups (5–8, 12, 20–21 weeks) in the aorta for the atherosclerotic rabbits.

Results

**Normal Rabbits**

In each of seven normal rabbits, a 3.5-mm diameter stent was delivered by catheter, then activated to expand in the aorta; similarly, a 2.5-mm stent was implanted in the right iliac artery. These endoprostheses were able to be delivered transluminally to the arterial segments precisely. There was no detectable migration, spasm, vessel wall defect, or acute occlusion. Follow-up DSA showed wide patency and stable positioning of the intravascular stent without delayed migration; there was no erosion or dilation of the vessels. Table 1 summarizes the degree of stenosis observed during DSA of the stent and adjacent control (angioplasty) sites in normal rabbits. After 6 weeks, there was minimal stenosis inside the stents, with a mean of 6.9% in the 2.5-mm iliac artery endoprosthesis (n=7) and 9.4% mean stenosis in the endoprostheses in the aorta (n=7), which was not statistically different than the control sites. After 8 months, there also was minimal stenosis inside the endoprostheses, with a mean of 13.1% in the 2.5-mm stent (n=4) and 13.6% in the 3.5-mm stent (n=4), which was not statistically different than the control sites or the results at 6 weeks (Figure 3).

Gross pathologic examinations of the normal rabbits showed a thin, translucent, white fibrous tissue layer over the endoprosthesis (Figure 4). The smooth neointimal surfaces were identical at 6 weeks and 8 months, translucent, glistening, and without defects.

### Table 1. Normal Rabbits: Percent Stenosis of the Titanium-Nickel Intravascular Stent Implantation and Control Sites

<table>
<thead>
<tr>
<th>Location</th>
<th>Treatment</th>
<th>Time</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
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<td>7</td>
<td>6.9</td>
<td>5.4</td>
<td>4.2</td>
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<tr>
<td></td>
<td></td>
<td>3 mo</td>
<td>4</td>
<td>9.9</td>
<td>2.6</td>
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<tr>
<td></td>
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<td>10.2</td>
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<td>8 mo</td>
<td>4</td>
<td>13.1</td>
<td>10.7</td>
<td>14.0</td>
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<tr>
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<td></td>
<td>6 wk</td>
<td>7</td>
<td>5.8</td>
<td>5.6</td>
<td>3.9</td>
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<tr>
<td></td>
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<td>7.6</td>
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<td>6 mo</td>
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<td>9.7</td>
<td>10.2</td>
<td>8.4</td>
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<tr>
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<td></td>
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<td>4</td>
<td>9.8</td>
<td>11.5</td>
<td>8.3</td>
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<tr>
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<tr>
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<td>9.4</td>
<td>9.7</td>
<td>6.5</td>
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<td>9.2</td>
<td>5.7</td>
<td>8.8</td>
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<tr>
<td></td>
<td></td>
<td>3 mo</td>
<td>4</td>
<td>6.9</td>
<td>6.3</td>
<td>5.9</td>
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<td>-1.0</td>
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*†There is no statistical difference in percent stenosis between stent and control: *p=0.42, †p=0.83.
or thrombus. The vessel wall appeared normal, without fibrosis, erosions, or visible irregularities. Histopathologic examination of the neointima at 6 weeks showed a somewhat loose matrix of collagenous tissue, with a variable orientation of fibers, covered by a thin layer of flat cells. In between bundles of fibrous tissue, both in the neointima and between coils of wire, were numerous smooth muscle cells (myofibroblasts). The neointima contained occasional clusters of extravascular erythrocytes and small foci of hemosiderin. There were dilated vascular channels, sparsely in the neointima, and small vessels in between the coils of wire, in gaps larger than 50 μm. There were occasional macrophages and foreign body cells adjacent to the titanium-nickel alloy.

Six weeks after implantation, the neointimal layer measured 102.7±10.5 μm for the aortic stents and 139.6±15.2 μm for the stents in the right iliac arteries. The thickness of the medial layer varied from normal to moderately atrophied. After 8 months, the fibrous tissue in the neointima appeared more compact, tending to be oriented parallel to the luminal surface (Figure 5). There were fewer smooth muscle cells in the fibrous tissue of the neointima, covered by a thin layer of flat endothelial-like cells. Similar to the results at 6 weeks, there were occasional dilated vascular channels, rare foci of hemosiderin, few macrophages, and rare foreign body cells. The gaps in between coils of wire were all larger than 10 μm and contained smooth muscle cells with fibrous tissue; there were blood vessels in spaces larger than 50 μm. Eight months after stenting, the neointima measured 145.1±126.1 μm for the aortic endoprostheses and 152.5±71.8 μm for the endoprostheses in the right iliac artery (Table 2); there was no statistically significant change in neointimal thickness from 6–8 weeks to about 8 months after implantation. Further thinning of the medial layer was seen, varying from mild to considerable atrophy, with increased fibrous tissue in the media. The adventitia appeared similar to that of intact vessels.

Small opaque particles, less than 1 μm in size, sparsely stippled the tissues at the implant site. These particles were seen at the implant sites in our previous canine study and contained 96.3–97.6% titanium and 2.4–3.7% nickel. There was no evidence of atherosclerosis in the stented segments of the normal rabbits, and the adjacent arteries were normal. SEM showed a smooth, complete, and confluent layer of flat, polygonal, endothelial-like cells after 6 weeks. At 8 months, these cells were oriented with their long axes parallel to the direction of blood flow (Figure 6), without surface thrombus or defects.
Atherosclerotic Rabbits

The atherosclerotic rabbits developed stenotic lesions, which were detected with digital subtraction angiography 6 weeks after induction. Before PTA, there was 36.5±14.2% stenosis (mean±SD) in the right iliac artery and 28.8±13.8% stenosis in the aorta (Table 3). Histopathologic study of the intact lesions after inducing atherosclerosis demonstrated fibrous intimal hyperplasia, smooth muscle cell proliferation, fibromuscular capping, foam cells, acellular ground substance and cholesterol clefts (Figure 7). There were areas of acellular ground substance and foci of calcification in the atheroma. SEM showed almost complete endothelialization of the luminal surface. The nonendothelialized remainder of the luminal surface had fibrous tissue covered with microscopic aggregates of platelets, leukocytes, and red blood cells.

The local pressure gradients along the lumen changed during PTA and endoprosthesis implantation (Table 4). In the right iliac artery, the mean (±SD) initial pressure gradient was 28.2±16.4 mm Hg. This decreased to 13.8±11.0 mm Hg after PTA and decreased further to 8.3±9.5 mm Hg after stenting. A significant (p<0.001) overall effect due to the procedures was found, with significant pairwise reductions from before to after PTA (p<0.05) and from after PTA to after stenting (p<0.05). In the aorta, the mean initial pressure gradient was 2.8±5.0 mm Hg, which changed to 3.8±3.5 mm Hg after PTA and decreased to 1.5±2.2 mm Hg after stenting. A significant (p=0.019) overall effect was found, with no significant pairwise reductions in pressure gradients. Postprocedure angiograms showed that all stents were patent.

Five rabbits died from a few hours to 2 weeks after the procedure; autopsy showed hemorrhagic pneumonia in these rabbits, which was due to Pasteurella multocida and was sensitive to penicillin. All rabbits were subsequently treated with procaine and benz-

| Table 2. Normal Rabbits: Thickness of Neointimal Layer Over Stent (n=7) |
|-----------------|-----------------|-----------------|
|                 | Aorta stent     | Iliac stent     |
| Implant duration (wk) | Mean±SD | Range  | Mean±SD | Range  |
| 6                | 95.2±40.2       | 58.8–181.3      | 128.8±41.2  | 102.9–205.8 |
| 8                | 110.1±46.1      | 53.9–220.5      | *          | *      |
| 31               | 331.6±152.3     | 68.6–519.4      | 256.9±107.2 | 73.5–298.9 |
| 27               | 85.2±29.8       | 44.1–142.1      | 138.6±59.4 | 83.3–269.5 |
| 33               | 55.9±18.6       | 29.4–88.2       | 96.0±49.0  | 39.2–186.2 |
| 33               | 107.5±103.8     | 14.7–362.6      | 118.4±25.9 | 83.3–181.3 |
| Total†           | 102.7±10.5      | 68.6–181.3      | 139.6±15.2 | 73.5–181.3 |

Thickness measured in μm.
*Suboptimal histologic sections preclude measurement.
†p=NS, no statistical difference in neointimal thickness between short (about 6 weeks) and long (about 8 months) implant duration groups.
Figure 6. Scanning electron micrograph of the luminal surface 8 months after implantation in normal rabbits. The cells form a smooth, complete monolayer and are elongated in the direction of blood flow (arrow). This confluent covering was stable from 6 weeks to 8 months, without surface defects or thrombus. There is a leukocyte attached to the surface (arrowhead), which is a normal finding on the native endothelial surface. Bar represents 10 μm.

Thine penicillin G (150,000 units each) intramuscularly every other day for 1 week; there were no further deaths or evidence of infection at any of the implantation sites.

There was a loss of several local side branches during endoprosthesis implantation and follow-up in the atherosclerotic rabbits. The 2.5-mm stent implant sites had 21 local side branches from 0.3 to 1.0 mm in diameter; six had decreased flow, and five became occluded immediately after implantation, whereas late occlusion occurred in three side branches. The 3.5-mm stent implant sites had 18 local side branches from 0.3 to 1.2 mm in diameter; five had decreased flow, and three became occluded immediately after implantation, whereas late occlusion occurred in two side branches. Entrapment of plaque in between coils and pushing open intimal flaps are technical possibilities with intravascular stents; however, there were no detectable complications during angiography. The luminal surface of the treated atherosclerotic segments appeared smooth.

Follow-up DSA demonstrated recurrence of stenosis, particularly in the right iliac artery, in both the control and in the stented arterial segments (Figure 8). In the stents, the restenosis was smoothly tapered, without abrupt transitions, and occasionally was continuous with restenosis in the angioplasty control area. The data observed in the anteroposterior plane correlated with the 60° oblique angiogram data (0.53 ≤ Spearman correlation coefficients ≤ 1.00). Because the former are more complete, they are reported in Figure 9. By repeated-measures analysis of variance on the natural logarithm of percent restenosis (n=11), it was shown that the right iliac artery sites restenosed during the first 4 weeks after the procedure (p<0.001 for the anteroposterior

Table 3. Atherosclerotic Rabbits: Percentages of Stenosis Before Angioplasty and Stenting

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Mean (%)</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right iliac artery</td>
<td>21</td>
<td>36.45*</td>
<td>14.21</td>
<td>34.7</td>
<td>12.2</td>
<td>61.9</td>
</tr>
<tr>
<td>Aorta</td>
<td>21</td>
<td>28.77*</td>
<td>13.77</td>
<td>31.1</td>
<td>9.3</td>
<td>54.0</td>
</tr>
</tbody>
</table>

*Statistically significant stenoses compared with 0%, p<0.001.
plane, the 60° oblique plane, and the mean restenosis over both planes) with no statistically significant difference in restenosis between the stented areas and control areas. In the aorta, the repeated measures analysis of variance (n=7) indicated that there was no significant restenosis during the first 6 weeks after the procedure in the anteroposterior plane, the 60° oblique plane, and the mean over both planes. There was a trend toward the restenosis in the stented area to be greater than in the control area for the anteroposterior plane, 60° oblique plane, and mean over both planes (p=0.09, 0.028, and 0.017, respectively). Beginning at 8 weeks, there was an increased amount of restenosis in both areas, with the control area having greater values than the stented areas. However, these differences were not statistically significant and most likely were due to the fewer rabbits (n=3–8) at the longer follow-up times. The treated vascular segments were divided into two groups—one where the stent was upstream and the other with the stent downstream. There was no statistically significant difference in percentage restenosis in the upstream stents versus the downstream stents, either in the aortas or the iliac arteries; there was no detectable downstream effect. During the final angiogram and at autopsy, the patency rate was 56.3% (nine of 16) in the 2.5-mm stents and 100% (16 of 16) in the 3.5-mm stents.

Gross pathologic examination of the stents in the atherosclerotic rabbits after 8 weeks was similar to the neointima in the normal rabbits, with a smooth, translucent surface that was free of defects (Figure 10A). By 20 weeks, the neointima appeared thicker, being opaque with an ivory color and the surface had minor irregularities, but no thrombus or defects were visible (Figure 10B).

Histopathology showed rapid formation of a neointimal layer, which eventually became atherosclerotic. At 2 weeks, there was a surface thrombus along the balloon angioplasty site. In the control area (angioplasty alone), the local thrombus was as thick as 500 μm; over the stent, the local thrombus layer was 60–200 μm thick, with a mean of 120 μm. At 2 weeks, there were signs of early reorganization; the microthrombus became invaded by macrophages and smooth muscle cells (Figure 11). Six weeks after angioplasty and stent-

![Image](https://circ.ahajournals.org/)

**Figure 7.** Photomicrograph of the intima and media of the aorta 8 weeks after inducing atherosclerosis. Smooth muscle cell proliferation is seen in the neointima (luminal surface at the top), with fibromuscular capping (long arrow) and acellular ground substance. Foam cells (short arrow) and fibrous tissue are superficial to the medial layer. Trichrome stain; bar represents 100 μm.

<table>
<thead>
<tr>
<th>Table 4. Atherosclerotic Rabbits: Pressure Gradients Before PTA, After PTA, and After Stenting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery</td>
</tr>
<tr>
<td>Right iliac</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

PTA, percutaneous transluminal angioplasty. Pressure gradients measured in mm Hg.

*†‡Statistically significant decreases compared in medians with before PTA, *p<0.001, †p<0.05, ‡p=0.019.
ing, the local thrombus adjacent to the wire was exten-
sively reorganized; the erythrocytes were less num-
rous, and smooth muscle cells became more abundant.

The mean (±SD) neointimal thickness after 5–8
weeks measured 247.2±181.0 µm for the aortic stents
and 218.2±77.1 µm for the stents in the right iliac
artery (Table 5). After 20 weeks, the mean neointi-
mal thickness was 320.6±167.5 µm for the aortic
stents and 308.4±188.7 µm for the stents in the right
iliac artery. Comparing across the implant duration
groups, there was no statistically significant differ-
ce in neointimal thickness in the iliac or aortic
stents. Twenty weeks after the procedure, the neo-
tima consisted of fibrous intimal hyperplasia, smooth
muscle cells, and fibromuscular capping (Figure 12).
In many areas, the neointima contained foam cells,
cholesterol clefts, and acellular ground substance,
similar to the histopathology at intact atherosclerotic
areas. In addition, there were dilated vascular chan-
nels in the neointima first seen at 6 weeks and
increasing as the thrombus became reorganized.
Adjacent to the implant wire, there were scattered
macrophages and rarely a foreign body cell, yet no
acute or chronic inflammatory reactions were detected.

There were 10–220 µm gaps in between the indi-
vidual coils of wire. These contained smooth muscle
cells with collagen; blood vessels were observed in
gaps larger than 40 µm. The medial layer was fre-
cently atrophied, as thin as 20 µm, with mild-
to-moderate fibrosis, occasional foam cells, and calc-
fications. The vessel adventitia and adjacent
retroperitoneum appeared normal. One-centimeter
serial sections of the lungs, liver, spleen, and kidneys
showed rare areas of pneumonia, mild fatty hepatic
infiltration, and an infrequent segmental infarct in
the kidneys. The latter were found only in rabbits
after denudation of the endothelium using the Fog-
artery balloon catheter. With regard to the injection of warm saline, which was shown to heat the stent up to 55°C for less than 1 second, no specific pathologic changes were detected.

SEM of the atherosclerotic sites after angioplasty and stenting showed that within a few hours, a fibrinous network was deposited on the luminal surface of the stent. Within 6 weeks, the majority of the surface was covered by a smooth monolayer of polygonal endothelial-like cells, and a small percentage was fibrinous material. After 20 weeks, the confluent monolayer extended over virtually the entire luminal surface of the endoprosthesis. The cells were elongated with their axes parallel to the direction of blood flow, similar to the native intimal endothelial cells. There were rare nonendothelialized areas, which were exposed in small islands and covered by microscopic aggregates of platelets and leukocytes (Figure 13). This appearance was similar to the intact atherosclerotic lesions, which lacked endothelium on scattered small islands of their luminal surface. The luminal surface was smooth, continuous, and without abrupt transitions or surface thrombus.

**Discussion**

Balloon PTA has been established as safe and effective and has become a standard treatment for stenotic atherosclerosis in peripheral, renal, and coronary arteries. However, there are acute and chronic complications. In the coronary arteries, acute occlusion is observed in approximately 4% of cases, requiring emergency coronary artery bypass grafting in 2.5% of patients. The major long-term complication is recurrent atherosclerotic stenosis, which is seen in 25–35% of patients after coronary angioplasty, particularly within the first 3–4 months. Clinically
significant restenosis is seen in approximately 25% of patients after iliac artery angioplasty and in 40% after femoropopliteal angioplasty within the first year.14,15 Recent clinical reports have demonstrated that intravascular endoprosthetic stents can be effective for treating acute symptomatic dissection or acute occlusion after balloon angioplasty.16-18

Endoprosthetic stents would become more widely applicable if they were shown to prevent atherosclerotic restenosis after angioplasty.

Using the normal canine iliac artery as a model, we were able to demonstrate feasibility and safety of a 5-mm diameter nitinol endovascular stent but could not test efficacy against atherosclerosis. This study

### TABLE 5. Atherosclerotic Rabbits: Thickness of Neointimal Layer Over Stent (n = 16)

<table>
<thead>
<tr>
<th>Implant duration (wk)</th>
<th>Aorta stent</th>
<th>Iliac artery stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Range</td>
</tr>
<tr>
<td>5</td>
<td>598.5±226.7</td>
<td>137.2–1024.1</td>
</tr>
<tr>
<td>6</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>6</td>
<td>74.8±28.4</td>
<td>44.1–117.6</td>
</tr>
<tr>
<td>6</td>
<td>359.4±176.4</td>
<td>58.8–646.8</td>
</tr>
<tr>
<td>7</td>
<td>245.0±164.3</td>
<td>98.0–499.8</td>
</tr>
<tr>
<td>7</td>
<td>109.4±27.1</td>
<td>63.7–156.8</td>
</tr>
<tr>
<td>8</td>
<td>155.4±125.2</td>
<td>29.4–387.1</td>
</tr>
<tr>
<td>8</td>
<td>188.1±82.0</td>
<td>78.4–284.2</td>
</tr>
<tr>
<td>Total‡</td>
<td>247.2±181.0</td>
<td>218.2±77.1</td>
</tr>
<tr>
<td>12</td>
<td>264.6±107.8</td>
<td>151.9–460.6</td>
</tr>
<tr>
<td>12</td>
<td>154.7±52.7</td>
<td>93.1–249.9</td>
</tr>
<tr>
<td>12</td>
<td>84.6±15.5</td>
<td>49.0–107.8</td>
</tr>
<tr>
<td>Total‡</td>
<td>168.0±90.7</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>338.2±134.8</td>
<td>102.9–666.4</td>
</tr>
<tr>
<td>21</td>
<td>85.9±15.0</td>
<td>63.7–117.6</td>
</tr>
<tr>
<td>20</td>
<td>554.6±186.0</td>
<td>215.6–886.9</td>
</tr>
<tr>
<td>20</td>
<td>281.4±65.3</td>
<td>102.9–362.6</td>
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<tr>
<td>20</td>
<td>342.7±112.2</td>
<td>176.4–524.3</td>
</tr>
<tr>
<td>Mean‡</td>
<td>320.6±167.5</td>
<td>308.4±188.7</td>
</tr>
</tbody>
</table>

Thicknes measured in μm.

*Suboptimal histologic sections preclude measurement.
†Occluded.
‡p=NS, no statistical difference in neointimal thickness among the three groups in the aorta or between the two groups in the iliac artery.
evaluated a new design for the nitinol endoprosthesis stent—a flat, low-profile wire in a small-diameter coil. With the custom catheter, we were able to easily deliver the stent in the vascular system with reliable expansion to the predetermined diameter, either 2.5 or 3.5 mm. As a control study, we tested implantation in normal rabbits, observing that the neointimal layer became more fibrous and less cellular from 6 weeks to 8 months, with no evidence of intimal hyperplasia or atherosclerosis. The neointimal layer was thin and stable, comparing favorably with a recent study that demonstrated a neointima of smooth muscle cells and fibrous tissue, measuring $62.3 \pm 10.7 \mu m$ over the Wallstent after 3–6 months in the aortas of normal rabbits.19 In the present study, the cellular response to the 2.5- and 3.5-mm nitinol stents at the implantation sites was similar to other inert metallic stents in normal animals, confirming safety and feasibility. As a result of these controls, we were able to compare balloon angioplasty alone versus stenting after balloon angioplasty in a rabbit model of atherosclerosis.

During the induction of atheromatous plaques, the rabbits increased their serum cholesterol by 10-fold and developed six major features of atherosclerosis: intimal smooth muscle cell proliferation, increased fibrous tissue and acellular ground substance, lipid laden foam cells with cholesterol clefts, and fibromuscular capping.20,21 The lesions were not identical to atherosclerosis in humans, having fewer calcifications, less acellular ground substance, and more complete endothelialization; also, although there were obvious, significant angiographic stenoses, the degree of stenosis was less than the amount seen in clinical cases. In this model of atherosclerosis, balloon angioplasty causes histologic changes that are similar to those reported in humans.20–23 Faxon et al24 has shown that these rabbits consistently develop atherosclerotic restenosis within 4 weeks after balloon angioplasty. We used each rabbit as its own control to eliminate the variability in atherosclerosis among rabbits, randomly assigning arterial segments to one of the two treatments to control for any possible downstream effects. The aspirin dose was in the proper range to leave endothelial cell production of prostacyclin intact while inhibiting platelet aggregation.5 Aspirin was continued for the first 30 days because previous studies showed neointimal healing during this time frame. The 20-week follow-up was believed to be an adequate duration because the percentage of restenosis stabilized after 8 weeks in the iliac arteries and after 14 weeks in the aortas. This is comparable to

Figure 12. Photomicrograph of a longitudinal histologic section of the stent in the right iliac artery of an atherosclerotic rabbit 20 weeks after angioplasty plus stenting. The luminal surface is toward the top (L). Panel A: Fibrous intimal hyperplasia and smooth cell proliferation has occurred in the neointima. Panel B: Higher power magnification demonstrates macrophages, foam cells, and cholesterol clefts (arrow) in the thickened neointima. Trichrome stain; bars represent 200 μm, and the space previously occupied by the stent wire is labeled S.
restenosis in humans, which usually occurs within 3–4 months after angioplasty.\textsuperscript{12,13,25}

The diameter of the stent was selected to match the angioplasty balloon, having a ratio ranging from 1.0 to 1.2 to the intact arterial diameter (with a mean of 1.06 in the aorta, and 1.11 in the iliac artery), to avoid the complications of undersized and oversized stents, such as thrombosis and intimal hyperplasia.\textsuperscript{16,26} There was a significant decrease in the pressure gradient after stenting, consistent with producing an improved tubular shape to the lumen and possibly resulting from some prevention of vessel

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**Figure 13.** Scanning electron micrographs of the aortic luminal surface over the stent 20 weeks after angioplasty plus stenting in atherosclerotic rabbits. Panel A: Surface is covered with a smooth monolayer of elongated endothelial-like cells. There are microscopic thrombi attached to small islands of non-endothelialized areas (arrowhead). Panel B: Higher magnification shows that the attached microscopic aggregates consist of platelets and leukocytes (arrow). Bars represent 100 μm.
wall recoil after PTA, tacking down a fine intimal flap or pushing aside segments of protruding atheroma.16,27 This demonstrates an active, physical function of the endoprosthesis, supporting effectiveness against acute symptomatic arterial dissection after angioplasty. Our data suggest that in patients with acute arterial dissection causing hemodynamically significant intimal flaps after balloon angioplasty, stenting will not further increase the risk of restenosis.

There were statistically equivalent restenosis rates, comparing angioplasty plus stenting versus angioplasty alone, occurring during the first 8 weeks in the iliac arteries and within the first 14 weeks in the aortas. In the 2.5-mm stents, the restenosis stabilized at approximately 80% versus the 3.5-mm stents in which the restenosis stabilized at approximately 30%; although the latter represents complete loss of the initial gain in lumen diameter after angioplasty plus stenting, it is not as hemodynamically significant as in the smaller arteries. The larger arteries tolerated atherosclerotic thickening of the neointima, as all of the aortas (16 of 16) remained patent. The smaller arteries behaved differently, with occlusion in seven of 16, although it cannot be determined which treatment site closed first, the stent or the control area.

The rabbits were randomized into two treatment groups—one that had the stent upstream and one that had the stent downstream; comparing these two groups detected no downstream effect, so arterial segments treated with angioplasty alone and those treated with angioplasty plus stenting behaved independently. Using each rabbit as its own control reduced the variability among rabbits and allowed a high statistical power of detecting differences 15% or greater in restenosis rates. For example, at 12 weeks, the power was 99% for the 2.5-mm and 90% for the 3.5-mm stent implantation sites. Therefore, the lack of significant differences between angioplasty control versus angioplasty plus stenting was very unlikely to be a type II error. The stent was designed to be 7 mm in length because the neointima became thicker distally in previous studies,2 yet the length was adequate to observe and evaluate recurrent atherosclerotic stenosis. In clinical cases, the arterial segment that requires angioplasty may be longer than the segment that requires stenting, so the study design simulates uses in humans.

The pathophysiology of restenosis after balloon angioplasty is not well understood; two theories of the possible mechanisms have been postulated. The first may be summarized as an accelerated atherosclerotic response to the balloon’s controlled vascular injury. The second theory of restenosis proposes that the local thrombus deposited after balloon trauma undergoes pathologic reorganization into atherosclerotic tissue. These two mechanisms may act simultaneously, the first occurring at the luminal surface and the second developing in thrombus that is deposited in the crevices of the atheroma as well as in the surface thrombus, which is routinely seen after balloon angioplasty. The mechanisms may act to a variable extent, depending on the exact histologic trauma at the angioplasty site in each individual case. The histopathology of the stents in the atherosclerotic rabbits supports the hypothesis that the local thrombus adjacent to the stent becomes invaded by smooth muscle cells that reorganize to form a neointima and then eventually develops atherosclerosis. The local microthrombus around the nitinol wire became invaded by smooth muscle cells and macrophages within 2 weeks postimplantation, with deposition of fibrous tissue. The cell population of the neointima shifted within 6 weeks, with smooth muscle cells, collagen, and new blood vessels replacing the microthrombus. Micrometry measurements showed that the neointimal layer formed within the first 6–8 weeks, with no significant further increase at 20 weeks, resulting in a mean value at 20 weeks of 308.4±188.7 and 320.6±167.5 µm for the stents in the iliac arteries and the aortas, respectively. Within 20 weeks, there was atherosclerosis in the neointima, with significant restenosis. In atherosclerotic rabbit aortas, Rollins et al28 reported that after 8 weeks the intimal proliferation adjacent to the Gianturco stent wires was histologically similar to the intimal plaques in intact areas; however, it is not possible to test for restenosis because there was no balloon dilatation. In atherosclerotic rabbit iliac arteries, Robinson et al29 observed abundant proliferation of smooth muscle cells and foam cells in the neointima at 4 weeks, with a neointimal thickness of 436±143 µm after angioplasty plus stenting versus 532±221 µm after angioplasty alone (control). In atherosclerotic rabbit aortas, Robinson et al30 reported the neointimal thickness over the stent measured 384±234 µm at 4 weeks and increasing to 451±173 µm at 8 weeks. It is not possible to extrapolate the hemodynamically significant stenosis directly from the mean neointimal thickness measurements because the latter uses a sample that averages out segments with maximum stenosis and histologic sections include only a small fraction of the vessel wall.

Our angiographic results agree with observations in atherosclerotic animal models and results of recent clinical trials. In atherosclerotic rabbits, Robinson et al29 observed that iliac arteries treated by stenting after angioplasty had improved lumen diameters, with measurements of 1.70±0.26 mm immediately after stenting versus 1.07±0.35 mm in the contralateral iliac artery immediately after angioplasty alone (control). This difference diminished over time, resulting in a 1.38±0.19 mm lumen in the stent versus 0.94±0.35 mm in the control iliac artery at 4 weeks, which represents a 48.5% loss of the initial increase in lumen diameter after stenting.29 Palmaz et al27 has reported that 6-month follow-up angiograms showed an average neointimal thickness of 800 µm after balloon expandable stenting of iliac arteries in humans. Percutaneous transluminal atherectomy has been performed in an area of restenosis in a Medinvent Wallstent in a patient’s super-
ficial femoral artery; the histopathology showed smooth muscle hyperplasia, foam cells, and acellular ground substance in the thickened neointima (U. Sigwart, personal communication). Zollikofer et al.\(^{31}\) has described stenosis inside a Wallstent placed in a polytetrafluoroethylene hemodialysis shunt, leading to eventual occlusion. Our study differs from two experiments that used an atherosclerotic rabbit model.\(^{39,32}\) Palmaz et al.\(^{32}\) design used rabbit aorta that had no discrete angiographic stenoses before stenting and compared 77-μm thick plaque at the areas with the balloon expandable stent with 345-μm thick plaque in the control areas. Those results showed the neointima over the stent measured 66±23 μm at 8 weeks and 98±36 μm at 24 weeks, although only three rabbits survived 24 weeks. The overall plaque thickness was a mean of 441 μm at the stent, where most of the plaque was abluminal, compared with 430 μm in the intact areas of atherosclerotic aorta.\(^{32}\) The design of the study by Rousseau et al.\(^{39}\) used atherosclerotic rabbit aortas but, similar to the study by Palmaz et al, did not involve balloon angioplasty. Those results showed that the nondilated, stented atherosclerotic rabbit aortas developed a 31±6-μm thick neointima at 1 week, which increased to 85±9.6 μm at 8 weeks and contained fibrosis, fibromuscular capping and smooth muscle cells. Because the atherosclerotic rabbit arteries have a stable plaque thickness that will not restenose without balloon angioplasty,\(^{24}\) it is difficult to extrapolate from those two studies to angioplasty patients or to compare with the present study.

Endothelialization prevents thrombus formation and has been hypothesized to prevent intimal hyperplasia.\(^{33}\) In the present study, endotheliallike cell covering of the surface was almost complete, yet restenosis was not prevented, which is consistent with the current concept of atherogenesis.\(^{34}\)

The results from atherosclerotic models cannot be directly extrapolated to humans because human atheromatous plaques have a higher percentage of nonendothelialized luminal surface than do atherosclerotic rabbits; unlike dogs or normal rabbits, humans do not completely endothelialize vascular grafts.\(^{35}\)

We initially believed that the physical barrier of the stent and the fibrocellular layer in the neointima may prevent smooth muscle migration and proliferation. However, smooth muscle cells are capable of infiltrating spaces as thin as 10 μm, with nutrient vessels penetrating gaps as small as 40 μm. Also, the “fibroblasts,” “spindle cells,” and “myofibroblasts” of the neointima are not guardians of a thin neointima but are derived from smooth muscle cells and are capable of becoming atherosclerotic. Smooth muscle cells and fibrous tissue have been consistently observed in histologic sections of neointima over the various stents in the literature,\(^{1,2,19,26,28–33}\) although the myofibroblasts may regress over time in the absence of atherogenic stimuli.\(^{36}\) Once the wires of the stent have been incorporated into the vessel wall, the benign metallic alloy is relatively far from the luminal surface, away from the site of action of the atherogenesis during blood flow over the neointimal surface, so the eventual cellular reactions in the neointima may be less dependent on the configuration and composition of the stent. Ideally, an endoprosthetic stent should have no restenosis. Realistically, perhaps the restenosis rate inside stents should be comparable to the risk of restenosis after balloon angioplasty, repeated in patients when necessary, which is (approximately 30% of 30%)\(^{34–12}\) less than 10%. Our results predict that this will be difficult to achieve in small diameter arteries, but neointimal atherosclerosis may be tolerated better in larger diameter vessels.

Although results from rabbits that have experimentally induced atherosclerosis can not be directly extrapolated to humans, it appears that a discrete endoprosthetic stent may not prevent diffuse atherosclerotic vascular disease. The same factors that cause atherosclerosis were present after stenting; the smooth muscle cells in the neointima were the same that cause restenosis after balloon angioplasty, and the neointima eventually became atherosclerotic.

Acknowledgments

We would like to thank Drs. Earl Shirey and Yoichi Sugita for their early work on the titanium-nickel intravascular endoprosthesis. We are indebted to Scott Solano of USCI, to Sue Wesolowski for technical assistance in digital subtraction angiography, to Dr. James McMahon for EDAX preparations, and to Claire Martinez for manuscript preparation. We are grateful to Dr. Yukihiko Nose, Dr. Patrick Whitlow for insight into clinical technique, Dr. Norman Ratliff for reviewing histopathology, and to Dr. Bernadine Healy for review and encouragement.

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KEY WORDS • angioplasty • restenoses • intravascular stents • prostheses • atherosclerosis
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