A New Balloon-Expandable Tantalum Coil Stent: Angiographic Patency and Histologic Findings in an Atherogenic Swine Model

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The angiographic patency and histologic characteristics of a new balloon-expandable tantalum stent were studied after implantation intervals ranging from 1 to 32 weeks in athrogenic miniature swine peripheral and coronary arteries. Stents were placed in 34 arteries (10 coronary and 24 iliac arteries) in a total of 13 swine. Two swine died within 24 h of stent implantation. Follow-up angiography was performed before death was induced in 11 swine (8 coronary and 19 iliac arteries) and revealed 100% patency without evidence of lumen stenosis, thrombosis, or migration of the stents. The neointimal thickening was maximal at 4 weeks after stent implantation and was at its minimum at 52 weeks after implantation with reendothelialization of the stents generally complete at that time.

The development of percutaneously implantable endovascular prostheses or stents is intended to address two major problems associated with percutaneous balloon angioplasty: 1) abrupt occlusion of the dilated vessel leading to emergency surgery, and 2) restenosis or recurrence of the arterial stenosis or occlusion. The incidence rate of abrupt occlusion after balloon angioplasty of the dilated artery requiring emergency surgical revascularization ranges from 2% to 5% (1-4).

It is hoped that stents can effectively reverse abrupt arterial occlusion after coronary angioplasty, allowing either elective surgical revascularization or continued medical therapy without concomitant myocardial infarction. The clinical application of stents as effective “bailout” devices not only would increase the overall safety and efficacy of routine coronary angioplasty but also would expand the indications for balloon angioplasty to patients currently not considered candidates because of the high risk of death or limb loss should abrupt occlusion occur.

Restenosis of the dilated lesion occurs in approximately 30% of patients within 6 months after elective coronary angioplasty (5,6). A reduction of the restenosis rate would reduce the need for repeat procedures and, by sustaining the immediate benefits of angioplasty, would reduce the overall costs of the procedure. Palmaz et al. (7) reported the results of implantation of a tubular balloon-expandable stainless steel mesh stent in the iliac arteries of 154 patients followed up for an average of 6 months [range 1 to 24]. Two patients experienced early thrombosis and occlusion, but no patients had late restenosis as determined by angiographic and clinical variables.

A preliminary report by Sigwart et al. (8) suggested that restenosis of the stented coronary artery was not observed in 12 patients with a self-expanding stainless steel mesh stent who underwent an angiographic follow-up study at 3 to 6 months; however, restenosis of this coronary stent was a significant problem in a large series (9) of patients followed up for an average of 6 months. In that study (9), early restenosis occurred as complete occlusion due to thrombosis within the 1st 2 weeks in 21 (22%) of 95 patients. Late restenosis, presumed to be due to intimal hyperplasia and smooth muscle proliferation and defined by quantitative angiography as a 0.72 mm reduction in the minimal lumen diameter, occurred in 32% of the patients.

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To more realistically assess the restenosis rate and the tendency for a newly developed balloon-expandable tantalum coil stent to cause fibrointimal and smooth muscle proliferation, we selected as the animal model for this study Yucatan miniature swine fed a high cholesterol diet because of their propensity to develop atherosclerotic stenoses within 8 weeks of balloon endothelial injury (10). The purpose of this study was to evaluate the angiographic patency rate, ease of use, and histologic findings of this balloon-expandable tantalum coil stent implanted in coronary and iliac arteries of atherogenic Yucatan miniature swine.

Methods

Balloon-expandable coil stent. The stent used in this study (Wiktor stent, Medtronic) was composed of tantalum wire (diameter 0.005 in. [0.013 cm]) wound tightly in a helical pattern over a deflated coronary balloon angioplasty catheter. The stent is 15 mm long and does not significantly change in length after balloon expansion because of the redundant coil configuration (Fig. 1).

Animal model. Male or female Yucatan miniature swine (n = 13) weighing 15 to 20 kg were placed on a diet of 3,700 kcal/day consisting of standard Purina mini-pig chow with 2% of the calories added as raw cholesterol and 15% of the calories added as lard. After 2 weeks on this diet, the animals were sedated with ketamine, 20 mg/kg intramuscularly, and intubated. General anesthesia was obtained with sodium pentobarbital administered intravenously at 15 mg/kg and titrated to effect. A carotid artery cutdown was performed by sterile technique and an 8F vascular sheath (Cordis) was placed in the carotid artery. Heparin, 10,000 U, and low molecular weight dextran, 250 ml, were given intravenously. This protocol was approved by our institutional Animal Use Committee on October 27, 1988 and conformed to the position of the American Physiologic Society on research animal use.

Stent implantation. After baseline coronary and peripheral angiography were performed, bretylium tosylate, 100 mg, was administered intravenously as prophylaxis against ventricular arrhythmias before coronary stents were placed. With use of standard balloon angioplasty and guide wire techniques, the stent-mounted balloon catheter was positioned in the selected coronary artery segment (left anterior descending = 9, left circumflex = 1) or iliac artery segment (external = 18, internal = 6). An attempt was made to use a stent size approximately 10% to 15% larger than the diameter of the target artery to reduce the risk of stent migration. The balloon was inflated twice to between 6 and 8 atm for 30 s to fully expand the stent. Suction was then applied to deflate the balloon, and it was withdrawn into the guiding catheter. Immediate postimplantation angiography of the stented vessel was then performed.

Follow-up care and treatment. After stent implantation, the catheters were removed and the carotid arteriotomy was repaired. The animals received 80 mg of aspirin daily in their food and were continued on the high cholesterol diet. Two swine died within 24 h of stent implantation and underwent postmortem examination of the stented vessels. Eleven swine were killed after angiographic study of the stented arteries (8 coronary, 19 iliac) at intervals of 1 (n = 1), 2 (n = 2), 4 (n = 2), 6 (n = 3) and 32 (n = 3) weeks. Death was induced after the final angiogram with a lethal injection of potassium chloride while the animal was under general anesthesia. The stented arteries were pressure perfused at 100 mm Hg with Trump's solution for 20 min and then harvested for histologic analysis.

Angiographic analysis. At follow-up angiography, the minimal lumen diameter of the stented artery segment was compared with the diameter of the proximal segment of the artery measured with calipers. The percent lumen narrowing or dilution of the stented segment of the artery was calculated to determine if intraluminal narrowing had occurred. If side branches were within the stented segment, any compromise in flow or lumen narrowing was noted. Evidence of intravascular thrombus was defined as an intraluminal filling defect, and evidence of stent migration was determined by
noting the relation of the implanted stent to arterial side branches in the target artery.

Histologic analysis. Each specimen was embedded in methyl methacrylate and cross-sectioned with a low speed diamond cutting circular saw (Reuteleri) (11). Serial 1-mm thick sections were obtained from the stented segments and from the nonstented vessels adjacent to the proximal and distal ends of the stent. The stent wires were then carefully removed from the cut sections, and methylmethacrylate was removed with acetone. The sections were reembedded in paraffin, cut into sections 3 to 5 μm thick, and stained with hematoxylin-eosin and Richardson’s trichrome-elastin stain. The presence of Factor VIII-related antigen on the intimal surface of the stent was studied with standard immunoperoxidase techniques (12).

Elastin-stained sections were positioned on the stage of a projection-light microscope. The image was then magnified 25 times onto a piece of opaque white paper, and a pencil tracing was made of the section’s original lumens and component layers of the arterial wall (13). Neointimal thickness was measured with use of computer analysis (Summasketch-MacMeasure, Apple) techniques. For each 4-μm section from the stented portion of the harvested artery, the maximal neointimal thickness was recorded. All such measurements (for each 4-μm section of an individual stent) were then averaged to obtain the average maximal neointimal thickness for that stent specimen.

Statistical analysis. The mean thickness of the neointimal layers was compared between the five groups defined by the duration of the stent implant by using analysis of variance. A p value ≤ 0.05 was considered to represent a significant difference. Measurements are presented as mean values ± SD.

Results

Early deaths and stent implant complications. In two swine, early death occurred within 24 h of the stent implantation. Both animals had recovered from anesthesia and were observed to ambulate normally in their cages. On postmortem examination of the stented arteries (two coronary and five dia sten incs), there was no evidence of either swine or exogenous thrombus. One animal had evidence of panniculitis, which was believed to be the cause of death. No cause of death was determined for the remaining animal.

One potential problem during stent implantation is the possibility of stent embolization, which did occur in one swine. The guiding catheter became disengaged from the coronary ostium after the balloon with the stent mounted on it was passed into the coronary artery. The balloon catheter and stent then prolapsed out of the coronary artery, and the stent became dislodged during attempts to withdraw the balloon and stent back into the guiding catheter. Because of the stent’s radiopacity, the device could be clearly seen on fluoroscopy at the aortic root bifurcation and was easily retrieved by grasping the end of the wire stent with endovascular biopsy forceps. As the stent wire was withdrawn, the coil configuration unwound itself, allowing the stent to be removed from the vascular sheath as a single strand of wire. Another stent was placed in this swine’s coronary artery without complication by using a different guiding catheter.

Angiographic follow-up (Table 1). Follow-up angiography was performed on stents implanted for 1 week to 8 months and demonstrated 100% patency of the arteries (Fig. 2). Angiographically, there was no significant narrowing in any stent segment (>10%) with respect to the proximal native artery diameter. At follow-up the mean lumen diameter in the stented segment was 1.9 ± 0.4% larger than the diameter of the native artery. There was no angiographic evidence of thrombosis, migration of the stents or compromise of side branches. The stent was easily visible with fluoroscopy during implantation, and could be placed in mid to distal coronary segments with excellent ability to track over 0.014-in. (0.06-em) angioplasty guide wires.

Histologic findings. Neointimal thickness was measured for the stented arterial segments harvested at 1 week (n = 2), 2 weeks (n = 4), 4 weeks (n = 5), 6 weeks (n = 7) and 32 weeks (n = 9). The mean neointimal thickness values for each harvest interval are compared in Figure 3. Representative histologic findings are illustrated in Figures 4 and 5.

Specimens examined 1 week after stent placement revealed organization of nonocclusive thrombus adherent to the intimal surface of the stents with islands of immature neointimal cells. The process of neointimal formation appeared to commence within the portion of the thrombus bordering the neointima. The neointimal thickness at 1 week averaged 192 ± 8.5 μm. An accumulation of red cells in the troughs formed between the struts and the depressed inner arterial surface was frequently noted.

By 2 weeks, thrombus covering the stent struts had been replaced by cells presumed to be myointimal in origin at most sites (Fig. 5A). Neointima at this time was still immature and heavily cellular with sparse scaffolding by collagen bundles and averaged 204 ± 7.5 μm among these specimens. At 4 weeks, stent struts were fully embedded within a maturing neointimal layer containing abundant collagen bundles and fewer myofibroblasts (Fig. 5B). The neointimal layer was thickest along the stent struts and was thinner in the areas between the struts. Media underneath the stents was found to be consistently attenuated and was associated with the development of mild fibrosis. The lumens of the stented segment was completely covered with a monolayer of cells with morphologic characteristics of endothelium and positive staining for Factor VIII-related antigen.

The thickness of the neointimal layer measured 269.6 ± 19.5 μm and reached its maximum in these specimens harvested at 4 weeks after stent placement; then the value was significantly larger (p < 0.05) than that in the groups at 1, 2, 6 and 32 weeks after stent implantation. A mature continuous layer of neointima covered the dilated and patent stented segment at 6 weeks. The thickness of neointima measured
212 ± 45.5 µm. Neovascularity and blood elements were altogether absent.

In the specimens studied 32 weeks after stent placement, stent wires were coated with a very thin layer of neointima (105 ± 18.1 µm thick) that was significantly smaller than that of the other groups (p < 0.05) (Fig. 5, C and D). The neointima appeared to have further atrophied and now consisted principally of collagen with a minimal cellular component. Reendothelialization of the lumen of the stented segment was generally complete in these specimens.

At each harvest interval, no differences were noted between coronary and peripheral arteries with regard to the pattern or extent of myointimal proliferation, damage to the media or damage to the internal elastic lamina. In neither the coronary nor the peripheral stented segments were there any foci of granuloma formation or segmented leukocytes, including eosinophils.

Discussion

Dotter (14), in an effort to further advance percutaneous revascularization of occlusive peripheral vascular disease, published a landmark paper in 1969 describing prolonged patency of >2 years' duration of a stainless steel coil spring implanted in canine peripheral arteries. Subsequently, various percutaneous endovascular prostheses have been developed, including a heat-sensitive expanding nitinol coil (15, 16), a stainless steel wire formed in a zigzag configuration (17), a self-expanding stainless steel mesh stent (18, 19), a balloon-expandable stainless steel coil stent (20, 21), and a balloon-expandable tubular stainless steel stent (22–24), all demonstrating successful implantation and patency in nonatherosclerotic animal models.

Mechanisms of stent failure. Human clinical trials (7–9) of coronary and peripheral stents have indicated that stents have a bimodal failure curve. That is, the early failures, which occur within the 1st 2 weeks, appear to be due to thrombosis of the stent and should be prevented or significantly reduced with adequate systemic anticoagulation. The second group of stent failures, which occur after weeks to months, are due to stenosis of the lumen of the stented segment caused by excessive intimal thickening. It has been suggested that factors that promote this excessive intimal thickening include an excessive amount of thrombus deposited on the stent's surface because of the inherent thrombogenicity of electropositively charged metals and repeated trauma to the endothelium of the artery from the stent.
which stimulates a high turnover of collagen and smooth muscle cells (25).

Previous studies in animal models. Recognizing that canine and other nonatherosclerotic models may not accurately reflect the biologic response of human atherosclerotic arteries to these foreign bodies, several investigators have implanted stents in rabbit atherosclerotic models (26–28). The findings in the rabbit model suggested differences among the devices. The balloon-expandable stainless steel coil (27) and the balloon-expandable stainless steel tubular slotted stent (26) maintained patency without significant restenosis at the implanted sites, whereas the thermally sensitive self-expanding nitinol coil (28) failed to prevent recurrent stenosis at the site of implantation in a rabbit model.

The present study. With the propensity for atherogenic miniature swine fed a high cholesterol diet in conjunction with endothelial injury to develop stenotic lesions that histologically closely resemble postangioplasty restenosis lesions in humans (10), we believed that these animals would be an excellent model to test arterial potency and study the healing response after implantation of a stent. Our hypothesis was that if this stent acted as an irritant causing repeated injury to the native artery, it would cause a fibroproliferative healing response culminating in stenosis at the site of stent implantation. The results of this study suggest that the Medtronic-Wiktor stent does not incite an excessive proliferative response of smooth muscle cells and fibrous tissue leading to stenosis of the stented segment of the artery.

Angiographically, there was no evidence of arterial narrowing >10% in any stented segment and in most cases...
Figure 4. Representative histopathologic features of the full cross-sectional area of a stented coronary artery at 4 weeks (A) and 32 weeks (B) after implantation. Richardson's trichrome stain.

Figure 5. Histologic studies of stented coronary segments at 2, 4 and 32 weeks after implantation. A, At 2 weeks. The stent strut (asterisk) appears to be completely covered by an immature neointimal layer. The media appears to be compressed beneath the strut. Note the marked cellularity of the neointima. B, At 4 weeks. The stent struts (asterisks) appear to be completely covered by a layer of maturing neointima with significant cellularity. The maturation process is more pronounced toward the endoluminal surface. The separation between the neointimal layer and arterial media is artificial. C, At 32 weeks. The strut wires are coated with a very thin layer of neointima. The neointima has further atrophied and now consists principally of collagen with a minimal cellular component. Richardson's trichrome stain.

the slight overdilation of the stented segment persisted at follow-up angiography. There were no instances of compromise of any side branches or stent thrombosis with only daily aspirin given as long-term anticoagulant therapy. Finally, there was no evidence of stent migration.

Histologic examination of the stented arteries revealed an early increase in intimal thickening as the stent wires became covered with a fibrin mesh. This intimal thickening was maximal at 4 weeks after stent implantation and subsequently decreased to a minimum thickness at 32 weeks after implantation. There was evidence of complete reendothelialization of the stented segments by histochemical staining at 32 weeks.

Advantages of tantalum. This tantalum stent has the advantage of being easily seen with fluoroscopic imaging in contrast to the relatively poor visibility of stainless steel devices. The coil configuration allows the stent to be balloon expandable and confers superior longitudinal flexibility compared with that of the relatively rigid tubular slotted devices. This longitudinal flexibility permits the stent mounted on a balloon catheter to track over standard angioplasty guide
wires in tortuous arteries, and, once the stent is deployed, to conform to the natural contour of the artery.

**Conclusions.** This balloon-expandable tantalum coil stent shows no evidence of causing an excessive proliferative healing response leading to stenosis of the prosthesis in this animal model of atherosclerosis. This fact, combined with the advantages of excellent fluoroscopic visibility to enhance accurate placement, longitudinal flexibility to facilitate trackability over guide wires, and conformability once deployed to the natural contour of the native artery and balloon-expandability to allow direct deployment analogous to standard balloon angioplasty catheters, makes this device unique and encourages us to proceed with human clinical trials.

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**References**