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EXPERIMENTAL STUDIES

Polymeric Stenting in the Porcine Coronary Artery Model: Differential Outcome of Exogenous Fibrin Sleeves Versus Polyurethane-Coated Stents

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Objectives. **In a porcine coronary model, fibrin film soaked for 3 h in heparin was used as a circumferential coating on a tantalum stent to assess the effect of this naturally occurring biopolymer on arterial healing. The results were compared with those obtained with medical grade polyurethane-coated stainless steel stents.**

Background. **Thrombus plays an important role in healing after arterial injury and may affect the development of neointimal hyperplasia. Manipulation of the initial thrombus may alter the healing response. To study this, we placed a template of fibrin in a porcine coronary artery restenosis model.**

Methods. **Thirty-four fibrin film stents were delivered in 20 swine. Oversizing was avoided, to prevent deep arterial injury, by placement of optimally sized stents. Initial patency of the stented vessel was confirmed by angiography.**

Results. **Three fibrin-stented swine died within 48 h; in each, the stent was occluded with a fibrin/red blood cell mass. In two of these three, a portion of the exogenous fibrin had become detached from the stent and partially occluded the lumen. Of the remaining 31 stents, all were patent at elective sacrifice at 28 days. Eighty-four percent had a diameter stenosis <50%, and the mean (±SD) diameter stenosis was 32.3 ± 13%. There was no evidence of significant foreign-body giant-cell reaction. These results contrasted with the medical grade polyurethane-coated stents placed according to the same protocol without oversizing. Twelve of these stents were placed; six swine died of thrombotic occlusion within the 1st 48 h. At elective sacrifice at 28 days, the remaining polyurethane-coated stents were occluded by marked neointimal hyperplasia.**

Conclusions. **Fibrin film-coated stents seem promising as a template for modifying the local response to arterial injury and for potentially decreasing restenosis rates.**

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Intracoronary stents are finding increasing use for the treatment of suboptimal results of conventional dilation or for prevention of restenosis in selected patient subsets (1–5). The primary problems with current metallic stents include subacute closure and restenosis. These problems have encouraged interest in other stent materials such as polymers. Synthetic polymers, either biostable or biodegradable, would have the potential advantage of providing mechanical support for intimal dissections but also could act as a vehicle for local drug delivery to prevent restenosis. Initial experience with various synthetic polymers in different animal models produced variable results (6,7). With some biodegradable polymers in a porcine model, severe tissue reaction has been identified (6,7). Polyurethane has been widely used for vascular applications, including permanent pacemaker leads. Given the wide experience with this polymer, we considered polyurethane as a potential stent coating. Another alternative is the native biopolymer fibrin. Native fibrin is deposited after arterial injury, colonized and reabsorbed, and it may serve as a template for the degree of eventual neointimal thickness (8,9). The goals of this study were to assess the response of the arterial wall to exogenous fibrin sleeves placed in a porcine coronary artery model and to compare it with a medical grade polyurethane-coated stent sleeve.

Methods

Animals. All studies were conducted with the approval of the Animal Care and Use Committee of the Mayo Clinic. A juvenile, domestic, crossbred swine coronary model was used, as previously described (10). Swine were fed a normal laboratory chow diet without cholesterol supplementation. Premedication with a single dose of aspirin (650 mg) and verapamil (sustained release, 120 mg) was administered within 24 h before coronary arterial stenting. Ketamine (12 mg/kg body weight) and xylazine (8 mg/kg) were given intramuscularly for general anesthesia. Atropine (1 mg) was

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used intramuscularly to decrease oropharyngeal secretions, and flocillin (1 g) was given prophylactically for infection.

Arterial access was obtained through carotid arterial cutdown after infiltration of the ventral neck region with 10 ml of 1% xylocaine (10). The right external carotid artery was exposed, and an 8F hemostatic sheath was placed for arterial access. A single heparin bolus of 10,000 U was administered through the sheath.

Placement of coronary stent. After carotid artery cutdown, the coronary angioplasty balloon with the stent was positioned in the coronary artery over a standard guide wire with fluoroscopic guidance. Oversizing was avoided to prevent deep arterial injury (10). Stents were placed in the right coronary, circumflex or left anterior descending coronary arteries. Fluoroscopy with injection of contrast material immediately after implantation of the coil confirmed adequate coil expansion and vessel patency. The carotid arteriotomy was repaired with standard techniques or ligated if repair was not possible. The neck wound was closed with interrupted sutures, and the animals were returned to their quarters for observation. No antiplatelet agents or additional anticoagulants were used after the initial heparin dose.

At 28 days, the animals were killed with a commercial intravenous euthanasia solution (Sleepaway, Fort Dodge Laboratory, 10 ml through an ear vein). The hearts were removed immediately, and the coronary arteries were fixed by pressure perfusion (100 mm Hg) with 10% neutral buffered formalin for 24 h. After fixation, the stented coronary segments were dissected free. Sections were made at 2-mm intervals perpendicular to the long axis of the vessel with the stent still in place. The residual metal fragments were then removed, and the tissue from each segment was embedded and stained with hematoxylin-eosin and elastic-van Gieson. All histopathologic measurements were made by an experienced cardiac pathologist (W.D.E.) with digital microscopy.

The major and minor axes of both the original and stenotic (residual) vessel lumens were measured, as were the areas of the original and stenotic lumens. The percent area of stenosis was calculated as % Stenosis = 100 × (1.0 − [Stenotic lumen area/Original lumen area]). The minimal lumen diameter was also measured.

The relation between vessel injury and neointimal response was measured from the elastic-van Gieson–stained sections, as previously described (8,10). Vessel injury at each wire site was measured with a previously described ordinal injury score. This score increases with the depth of arterial injury and varies from least injury (0) through maximal injury (3). Mean arterial injury score for any given section was calculated as mean injury at all wire sites in that section: Mean injury score = (Sum of scores for each wire/Number of wires present).

The neointimal thickness at each wire site was measured, and the mean thickness for all wire sites was then used to calculate the injury response. For each injured artery there was, therefore, a mean injury score and a mean neointimal thickness.

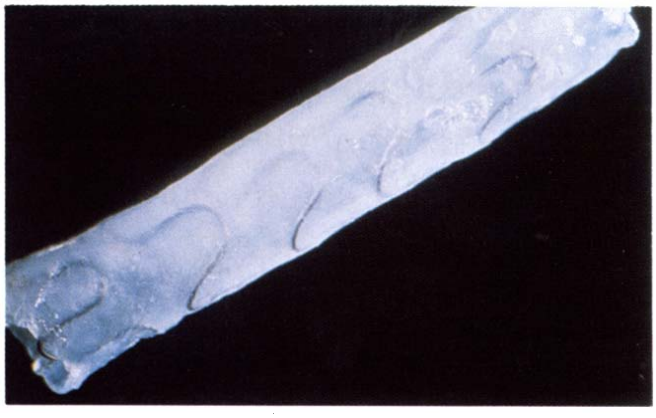

Figure 1. Fibrin sleeve configured as a thin, balloon-expandable cylinder. Embedded within the fibrin is a tantalum metal wire stent. The viscoelastic properties of the fibrin make it easily able to be crimped on an angioplasty balloon and expanded in a coronary artery as a long-term implant.

Experimental groups. There were two groups: fibrin-coated tantalum sleeve stents (group 1), and medical grade polyurethane-coated sleeve stainless steel stents (group 2).

Fibrin-coated tantalum stents. Fibrin was prepared for placement on the tantalum stent as follows. Porcine fibrinogen was isolated from pig whole blood with standard overnight cryoprecipitation methods. Whole blood was collected with citrate phosphate dextrose or citrate phosphate dextrose adenine anticoagulant solution. The whole blood was centrifuged for 10 min at 4,500 × *g*, and the plasma was transferred to an attached satellite bag. The plasma was frozen at −70°C for a minimum of 12 h. The frozen plasma was then placed in a refrigerator at 4°C and allowed to thaw 6 to 12 h until all residual ice crystals were gone. The plasma was centrifuged for 10 min at 4,500 × *g* at 4°C. The supernatant plasma was siphoned into satellite bags, and concentrated fibrinogen in a measured concentration of 500 to 800 mg/dl was left.

The fibrin was placed on a standard balloon expandable stent (Wiktor, Medtronic) as follows. Concentrated porcine thrombin, 1,000 U/ml, was used to precipitate the fibrinogen. The fibrin was then formed on the tantalum stent by dripping the fibrinogen solution and thrombin solution from separate syringes directly on the stent. Polymerization of the fibrin occurred around the stent; this formed a fibrin mass completely encasing the stent (Fig. 1). The fibrin was compressed to a thin (0.005-in. [0.012 cm]) film and then soaked in a heparin solution for 3 h. The devices were then crimped onto standard collapsed angioplasty balloons and delivered to the coronary artery.

Polyurethane-coated stents. The synthetic polymer films were biostable medical grade polyurethane, synthesized as follows. The films were cast from solvent by pouring the solvent-dissolved polymer over a 0.005-in. tantalum wire that was bent in the form of a sine wave, with an amplitude of 1 cm and a length of 1 cm. Curing was achieved in an oven at 50°C for 48 h. The films were removed by first covering

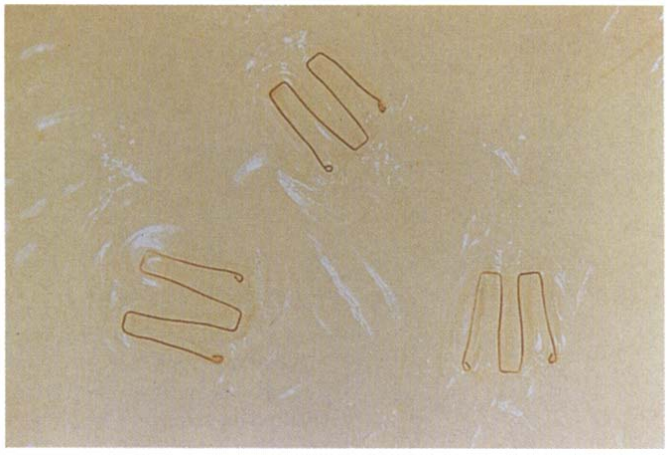

Figure 2. Medical grade polyurethane films were prepared by pouring the solvent-dissolved polymer over a 0.005-in. wire bent in the form of a sine wave. After curing, films containing the wire were cut and wrapped around angioplasty balloons.

them with 100% reagent alcohol and then cutting around the edges of the circular container. Each film was between 0.003 and 0.005 in. (0.007 to 0.012 cm) thick (Fig. 2).

Individual films were prepared for implantation by cutting a rectangle around the tantalum sine waves. The tantalum was entirely covered by the polyurethane film as a result of the casting process. The films were then wrapped around standard (collapsed) 3.0-mm angioplasty balloons, ready for delivery to the coronary arteries using standard over-the-wire techniques. Inflation of the balloon resulted in unwrapping of the film-tantalum combination, and withdrawal of the balloon caused the film to form a cylinder lining the wall of the artery ~1 cm in length.

Statistical methods. The slopes and intercepts for combined arterial segments were determined with linear regression according to standard methods (Systat). This analysis allowed direct comparison of the arterial injury–response relation.

Results

Group 1. Thirty-four fibrin film stents were delivered in 20 swine (Table 1). All swine had patent vessels at angiography 15 min after stent placement. Three of these animals died within 48 h; at pathologic examination, the three stents were occluded, presumably resulting in an arrhythmic death. In each of these three swine, the occlusion was related to a fibrin/red blood cell mass. In two of them, a portion of the exogenous fibrin had become detached from the stent and partially occluded the lumen. This may have resulted in the subsequent occlusion.

Of the remaining 31 stents, all were patent at elective sacrifice at 28 days (Fig. 3). The minimal lumen diameter of the stented segments was 1.53 ± 0.46 mm (range 0.93 to 3.05). The distribution of the minimal lumen diameter is shown in Figure 4. Mean diameter stenosis was 32.3 ± 13%, and mean area stenosis was 52.6 ± 16.6%. The distribution of the area and diameter stenoses is shown in Figure 5. Eighty-four percent of the segments had a residual diameter stenosis <50%, and there were no occlusions.

Histologically, the fibrin was structurally intact, and it was completely endothelialized in all stented segments. The degree of neointimal thickening during the time after implantation was similar to that previously reported in this porcine model. There were no large collections of foreign-body giant cells. Finally, local vascular integrity was maintained, without medial necrosis (Fig. 3).

Mean neointimal thickness was 0.56 ± 0.19 mm (range 0.29 to 0.04). Although this model was not intentionally oversized, the degree of arterial injury varied (Table 1). The relation between neointimal thickness, neointimal area and

Table 1. Mean Injury Score, Neointimal Thickness and Stenosis After Implantation of Fibrin Stent

Vessel No.	Animal No.	Vessel	Mean Injury Score	Mean Neointimal Thickness (mm)	Diameter Stenosis (%)
1	1	LCx	1.86	0.36	19.1
2	1	RCA	2.0	0.29	15.6
3	2	LCx	3.0	0.72	54.6
4	2	RCA	2.5	0.77	42.5
5	3	LAD	2.14	0.44	22.7
6	3	LCx	2.29	0.62	21.7
7	3	RCA	3.0	0.95	59.5
8	4	LAD	2.4	0.53	30.4
9	4	LCx	2.8	0.59	34.7
10	4	RCA	3.0	0.84	21.2
11	5	LAD	3.0	0.84	57.5
12	5	LCx	3.0	0.73	24.5
13	5	RCA	3.0	0.88	51.5
14	6	LCx	2.33	0.36	23.7
15	6	RCA	1.33	0.34	14.9
16	7	LCx	1.88	0.35	26.7
17	8	LAD	2.2	0.33	21.7
18	9	LAD	2.0	0.39	23.1
19	10	LAD	2.0	0.59	28.7
20	10	RCA	2.5	0.70	39.2
21	11	LCx	2.43	0.36	31.7
22	12	RCA	2.2	0.38	35.0
23	13	LCx	1.83	0.33	25.8
24	13	RCA	2.0	0.48	27.4
25	14	LCx	3.0	0.84	54.6
26	14	RCA	2.67	0.67	28.1
27	15	LCx	2.33	0.52	25.3
28	15	RCA	2.0	0.37	14.8
29	16	LCx	3.0	0.65	41.9
30	16	RCA	2.6	0.59	39.6
31	17	RCA	2.5	0.78	44.7
Mean ±SD				0.56 ±0.19	32.3 ±13

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

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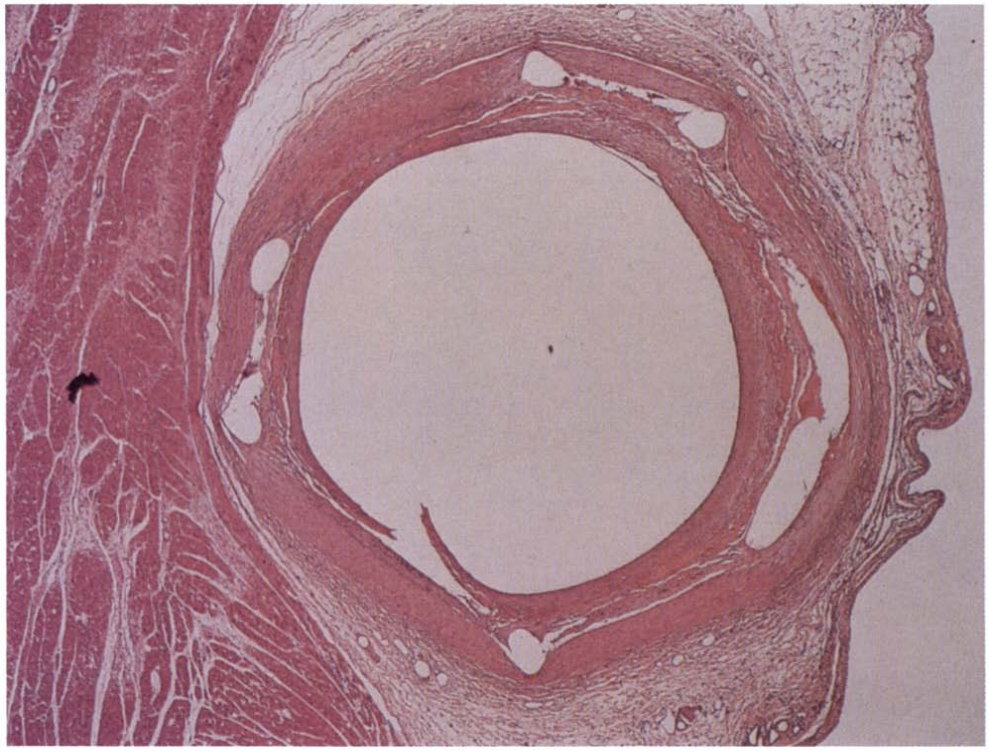


Figure 3. Fibrin stent at 28 days. A thin layer of fibrin remains, with only mild neointimal thickening. Hematoxylin-eosin ×7.5, reduced by 15%.

injury score is shown in Figure 6. The regression equation was area = 0.36 × injury score − 0.30. Even with more severe injury scores (>2.0), the mean neointimal thickness typically remained <1 mm.

Group 2. Twelve circumferentially coated polyurethane metallic stents were placed. Six of these swine died within the 1st 48 h after implantation. At elective sacrifice at 28 days, the remainder of the stents were occluded. A mass of neointimal thickening completely obliterated the lumen in each. The area and diameter stenosis, therefore, were 100% in each.

Histologic examination documented an intense foreign-body inflammatory reaction with multinucleated giant cells in each stent, in addition to severe neointimal thickening and occlusion (Fig. 7). The relation between neointimal thickness and degree of arterial injury could not be calculated because the stent was occluded in each.

Figure 4. Distribution of minimal lumen diameter in 31 porcine coronary arteries with fibrin film stents.

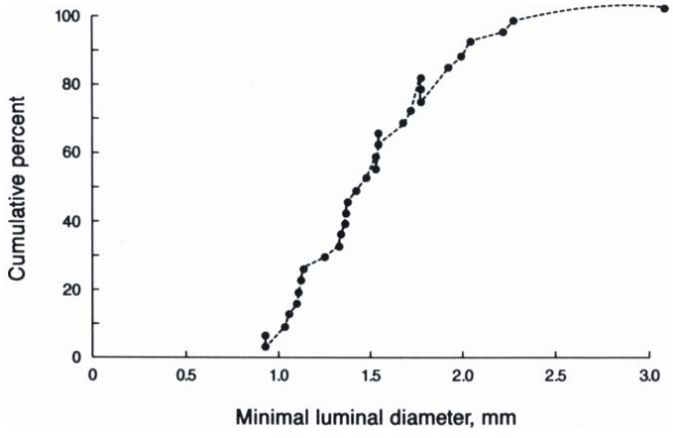
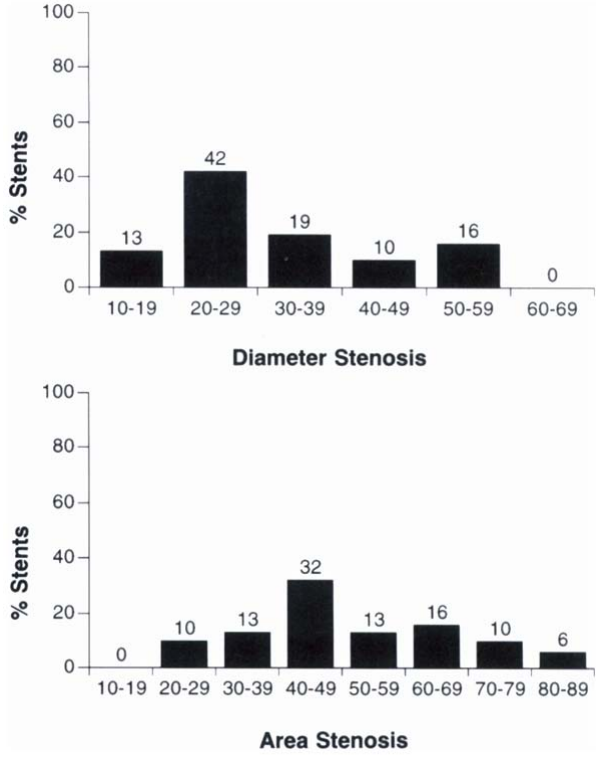


Figure 5. Distribution of diameter (top) and area (bottom) stenosis in 31 porcine coronary arteries with fibrin film stents.



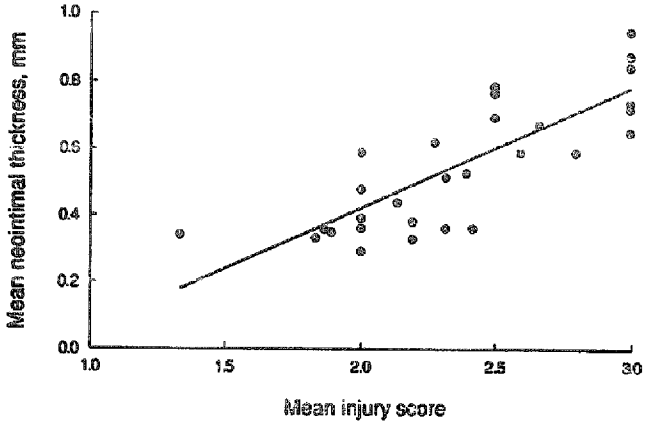


Figure 6. Injury-neointimal thickness regression line for the fibrin sleeve stents. Although there is a persistent relation, as previously described, between arterial injury and thickness, it is less than that previously described (8). Even with more severe injury, the thickness remained typically <1 mm.

Discussion

Intracoronary metallic stents are being used with increasing frequency to treat dissections and abrupt closure during percutaneous transluminal coronary angioplasty and potentially to decrease restenosis rates (1–5). Because of the potential problems of permanent intraarterial metallic implants, including acute and subacute thrombotic closure and the finding that restenosis remains a substantial problem with current metallic designs, there has been interest in the development of polymeric stents. These could be either biostable or biodegradable and could potentially be used as vehicles for local drug delivery and as a scaffold to treat dissections or abrupt closure.

Multiple polymeric materials are being tested for intracoronary implants. We have reported the initial outcome of polyethylene terephthalate stents in a porcine coronary model without oversizing (6). Of seven swine surviving 4 to 6 weeks after stent implantation, the stented segment was occluded in each, with massive neointimal thickening. In that stent model, there were two histologic patterns: a chronic foreign-body inflammatory response and a central neointimal response. The latter was morphologically similar to that seen in human restenotic tissue obtained at the time of directional atherectomy. Subsequently, in a similar porcine coronary model in which three other polymers were used (polyglycolic/polylactic acid, polycaprolactone and polyhydroxy butyrate valerate), similar severe tissue reactions were also found, including extensive fibromuscular hyperplasia, multinucleated giant cell formation and medial necrosis (7). Whether these severe reactions are the result of breakdown products or result from the process of degradation itself is uncertain.

Present study. In this study, we compared two other polymers—a biostable, biocompatible polyurethane and a "natural" fibrin film. Polyurethane has been used extensively for vascular applications and is the most widely used polymer for construction of permanent pacemaker leads. It has, however, not been widely used for arterial applications in small vessels. Despite its relative biocompatibility, polyurethane resulted in the same findings as previously described with other polymers in this model—vessel occlusion and a foreign-body inflammatory response with multinucleated giant cells. Neointimal thickening at 28 days was marked and occluded all the stents; in addition, there was a high rate of thrombotic occlusion within the 1st 48 h.

These results are in striking contrast to the results with fibrin. In 31 of the 34 stents, lumen patency was maintained at 28 days, without severe local tissue reaction and without severe neointimal thickening. The residual stenoses were <50% in most swine treated with these circumferentially coated fibrin stents. There were various degrees of neointimal thickness but less than previously reported. Typically in this model increasing degrees of arterial injury result in a linear increase in neointimal thickness. This finding was also confirmed in this study. In addition, the healing response with the fibrin sleeve was similar histologically to that with native fibrin; however, the implanted fibrin did last until sacrifice at 4 weeks, whereas native fibrin usually lasts <2 weeks (9).

In the fibrin stent group, three swine died within 48 h, and stent occlusion was found in each. In two of these, there was partial detachment of the fibrin from the stent and partial occlusion of the lumen. In the third animal, no such structural problem was identified. None of the swine had received any anticoagulant therapy after the implant. The fibrin-coated stents had been soaked in heparin for 3 h before final balloon preparation. Future studies will be needed to identify the requirement for this soaking or need for more anticoagulation.

Fibrin in medical applications. The use of fibrin for medical applications has been well described (11–22). Initial applications included its use as a dural substitute in patients with head injuries (21). It has also been used as a glue or spray for hemostasis, for reinforcing and sealing suture and staple lines, as an internal organ liner, and as a substrate for in vitro endothelialization of vascular grafts (13,17–19,23). The latter application has the most similarity to the use described in this study—as an implantable template to control or modify the healing response after arterial injury (19). In polytetrafluoroethylene vascular graft applications, fibrin glue, which contained human fibronectin and aprotinin and tranexamic acid (inhibitors of fibrinolysis), promoted the formation of a sheer stress-resistant endothelial cell monolayer (19). Even after 24 h of perfusion, most of the graft surface was still covered by endothelial cells. In addition, species-specific fibrin seems to produce little local tissue reaction.

In addition to sealing biologic surfaces and promoting endothelialization with little tissue reaction, fibrin also has the potential to act as a delivery vehicle. The matrix varies widely depending on the conditions under which it is formulated. Variations in ionic strength, pH and fibrinogen and

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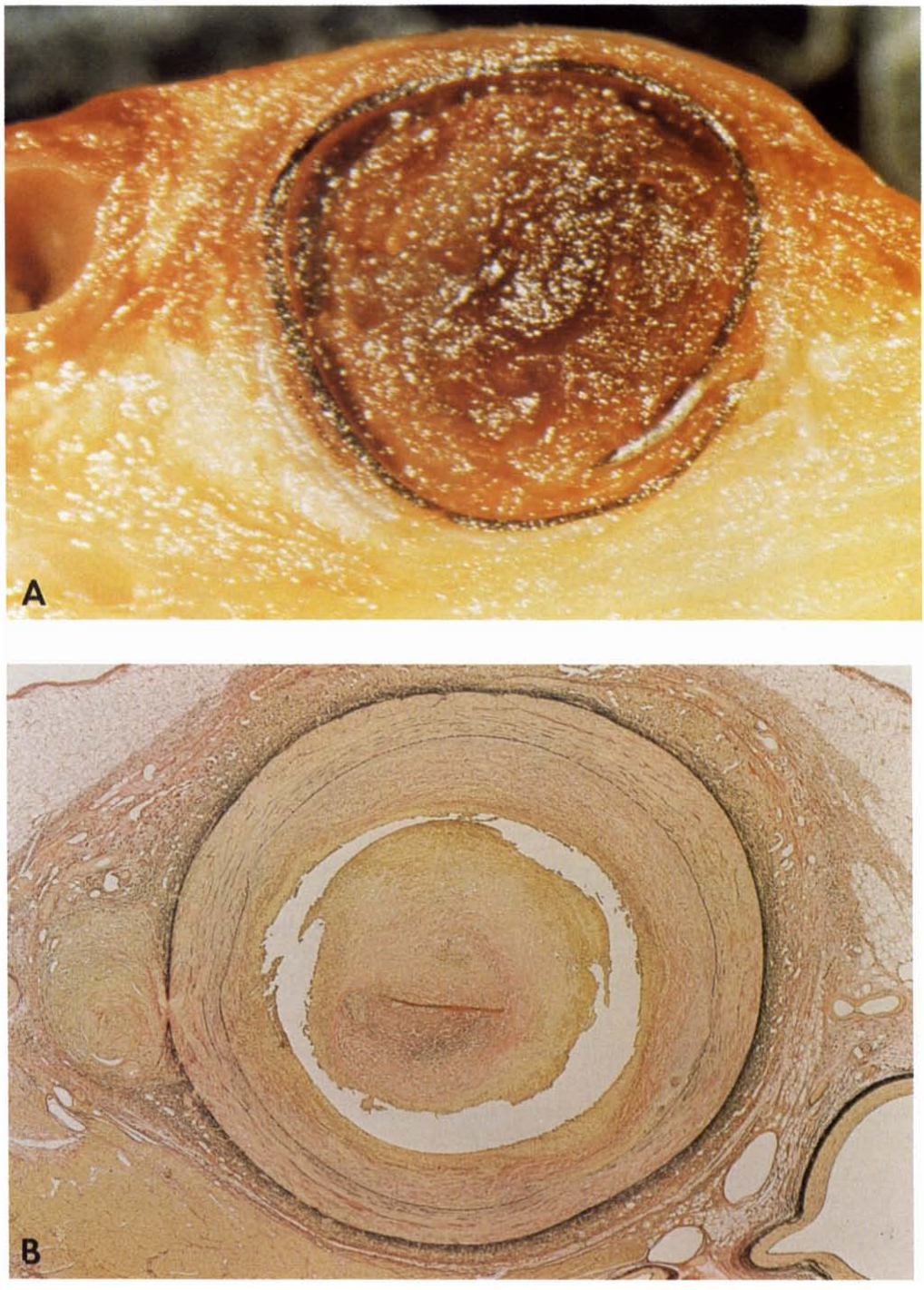

Figure 7. A, Gross microscopic photograph of polyurethane-coated stent with complete occlusion. B, Microscopic photograph of stent at 28 days with vessel occlusion related to a large amount of neointimal hyperplasia. Elastic-van Gieson ×5, reduced by 24%.

thrombin concentration affect whether the final fibrinogen is coarse or fine, although the first two variables are the most important. Depending on the matrix size, the fibrin could be used to incorporate microcapsules of various sizes for local drug delivery.

Fibrin biodegradation. The biodegradation of fibrin has been studied (14,22). The reabsorption is both enzymatic (fibrinolysis) and cellular (phagocytosis). The rate of reabsorption varies and depends on formulation, matrix size and cross-linking. In the present series, at 1 month the exogenous fibrin seen was still present, although it was colonized. Presumably by varying the formulation, reproducibly controlled degradation can be achieved.

There are several potential concerns about fibrin, including issues of donor infection, specific formulation, immunologic response and optimal delivery vehicle. The use of species-specific fibrin has not been associated with significant reactions. Whether more minor reactions may be important is unclear. The fibrin sleeve used did not prevent the development of at least some neointimal formation in the current series. It did, however, prevent the uniform occlusion and severe tissue reaction seen with other polymers

we have studied. Whether the various neointimal formations that were present in this series resulted from impurities in formulation, immunologic reactions or other factors cannot be determined.

Conclusions. This report evaluates the initial experience with fibrin as a naturally occurring biopolymeric coating for intracoronary stents in a porcine coronary injury model. In contrast to medical grade polyurethane and other biopolymers studied in this model, patency of the stented segment was maintained in all animals, and the previously observed neointimal and foreign-body tissue reaction were significantly decreased.

The potential of fibrin as a stent or sleeve needs further evaluation. Substantial problems need to be addressed, including issues of donor source, specific formulation and delivery. It does seem promising, however, as a natural template for arterial healing that could potentially decrease the local tissue response seen with other polymers or devices and that could modify the "restenotic" process after arterial injury.

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