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AJNR Am J Neuroradiol 1997, 18 (2) 271-277

<http://www.ajnr.org/content/18/2/271>

This information is current as
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Experimental Arteriovenous Fistulas: Treatment with Silicone-Covered Metallic Stents

Glen Geremia, Mati Bakon, Luke Brennecke, Michael Haklin, and Bruce Silver

PURPOSE: To determine the efficacy of silicone-covered metallic stents in the treatment of experimentally created carotid-jugular fistulas. **METHODS:** Carotid-jugular fistulas were surgically constructed in six mongrel dogs. Silicone-coated, self-expanding metallic stents were placed across the fistula holes within the carotid artery, and carotid angiography was performed before, immediately after, and 4 and 8 weeks after stent placement. Fistula specimens were resected 2 months after stent placement and analyzed by means of gross and light microscopy. **RESULTS:** Angiography revealed complete closure of all fistulas immediately after stent deployment. The fistulas remained closed and all carotid arteries remained patent. Marked stenosis within the carotid lumen was seen along the proximal and distal ends of the stents. Gross and micropathologic specimens of the carotid-jugular fistulas revealed fibrous connective tissue and collagen across the fistula holes. Proliferative fibrous connective tissue, collagen, and fibromyoblasts were located at either end of the stents. The wires of the stents indented the intraluminal surface of the carotid arteries. **CONCLUSIONS:** Silicone-covered stents were effective in closing all experimentally created carotid-jugular fistulas. With further refinements and variations in technique, covered stents may prove a viable alternative to current endovascular devices.

Index terms: Fistula, arteriovenous; Interventional instruments, stents; Animal studies

AJNR Am J Neuroradiol 18:271-277, February 1997

Previous investigators have had some success in treating experimentally created fistulas with porous metallic stents (1). The metallic wire mesh of the stents acted as a scaffold for the ingrowth of fibrous connective tissue through the stent pores. Because of the porous structure of these stents, the fistulas were not closed immediately; however, fibrous reactive tissue eventually filled the pores and resulted in fistula closure over time. In the current experiment, silicone-covered nonporous stents were

investigated to determine their effectiveness in the acute and permanent treatment of experimentally created fistulas.

Materials and Methods

Experimental arteriovenous fistulas were created in six mongrel dogs, each weighing approximately 30 kg. The surgical procedure for handling these dogs complied with the guidelines established by our hospital's institutional animal care and use committee. The surgical technique used to create arteriovenous fistulas in the necks of mongrel dogs has been described previously (1).

Stent Procedure

The dogs were allowed to heal for 1 week after fistula creation before arteriography was initiated. Selective carotid arteriography was performed via the transfemoral approach with a standard 5F catheter. At the finish of this diagnostic study, the 5F catheter was exchanged for a 7F stent delivery system by using an exchange guidewire. A single, silicone-covered metallic stent (Wallstent, Schneider USA, Minneapolis, Minn) was deposited intravascularly into the carotid artery so that it covered the fistula hole. Placement of the stent was done with an insufflator at

Received March 18, 1996; accepted after revision August 5.

Supported in part by Schneider Inc, Minneapolis, Minn.

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AJNR 18:271-277, Feb 1997 0195-6108/97/1802-0271

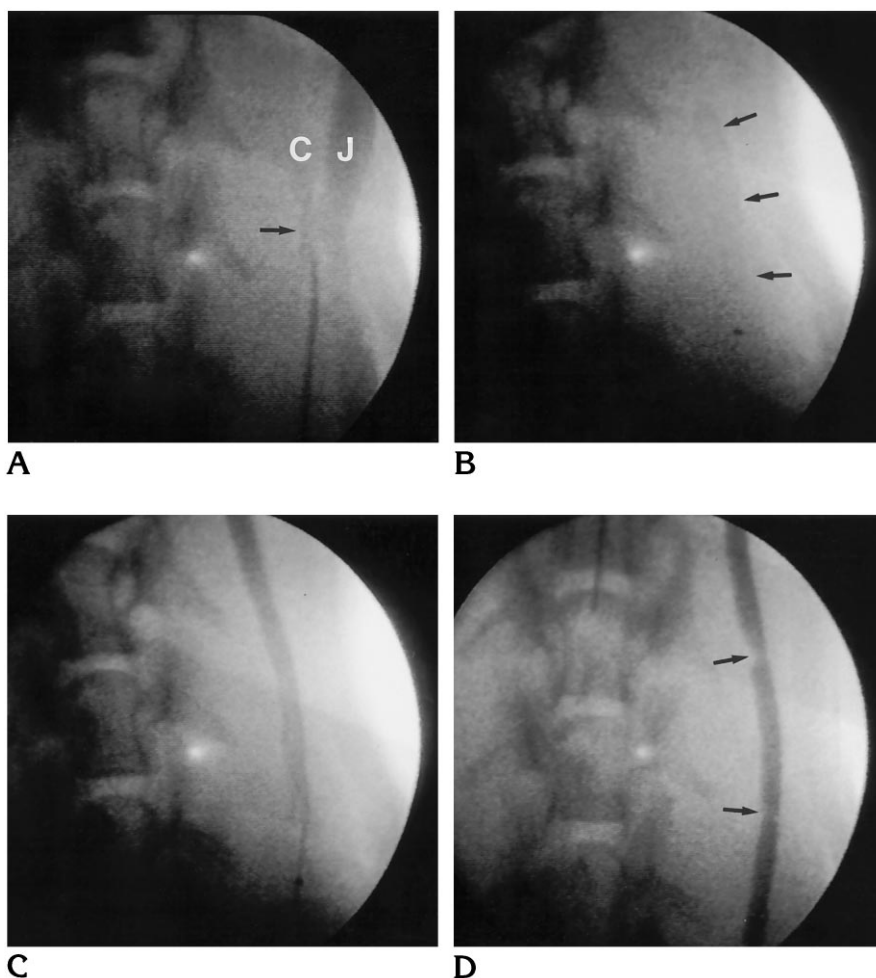
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Fig 1. A, Arteriogram shows the catheter lying within the carotid artery proximal to the fistula (*arrow*). The jugular vein lies lateral to the carotid artery. (C indicates the carotid artery; J, the jugular vein.)

B, The stent (*arrows*) lies within the carotid artery and across the fistula hole.

C, Arteriogram immediately after stent placement shows the fistula is closed. The carotid artery remains widely patent.

D, Carotid arteriogram 8 weeks after stent placement shows the fistula remains closed. The carotid artery is patent. However, focal areas of stenosis (*arrows*) are seen within the carotid artery and lie at the proximal and distal ends of the stent.



3 atm of pressure while an overlying rolling membrane was retracted. Arteriography was performed immediately after and 4 and 8 weeks after stent deployment. The arteriovenous specimen was resected 8 weeks after stent placement.

The metallic wire of the stent is made of Elgiloy (Elgiloy Ltd Partnership, Elgin, Ill), a nonmagnetic, corrosion-resistant, cobalt-chromium-iron-molybdenum alloy whose biocompatibility makes it suitable for surgical instruments and implants. After the Elgiloy wire is braided to construct the stent, the fabrication is heat treated to enhance the tensile and fatigue strength of the wire braid. The wire has a diameter of 0.0035 inches and the stent measures 42 mm in length by 5 mm in diameter unconstrained. The wire-braided stent is then coated with a thin film of silicone, which is applied by dipping the tubular stent mesh into a bath of liquid silicone that solidifies when air dried. The result is a film of silicone encasing the wires and filling the pores of the stent. The wires were completely coated end-to-end with silicone. The best results are achieved by oversizing the stent by approximately 1 mm more than the diameter of the native vessel (2). Since the native carotid artery of a dog measures approximately 4 mm in diameter, a stent of 5 mm in diameter was chosen. The stent is

mounted on a delivery system that consists of coaxial catheters. The exterior tube serves to constrain the stent until retracted during delivery (rolling membrane). The interior tube of the coaxial system contains a central lumen that will accommodate a 0.038-inch guidewire.

Histologic Process and Photography

The process by which the stented fistula specimens were prepared for micropathologic examination has been described previously (1). After processing and embedding, the paraffin blocks were cut into approximately 5- μ m-thick sections. Three slides from each of the sections were cut, and one slide from each section was stained with hematoxylin-eosin, Masson's trichrome stain, and Verhoeff's elastin stain, respectively.

Results

All fistulas were closed immediately after the silicone-coated stent was placed within the carotid artery (Figs 1 and 2), and they remained closed and unchanged throughout the study. Intraluminal narrowing of at least 50% in diam-

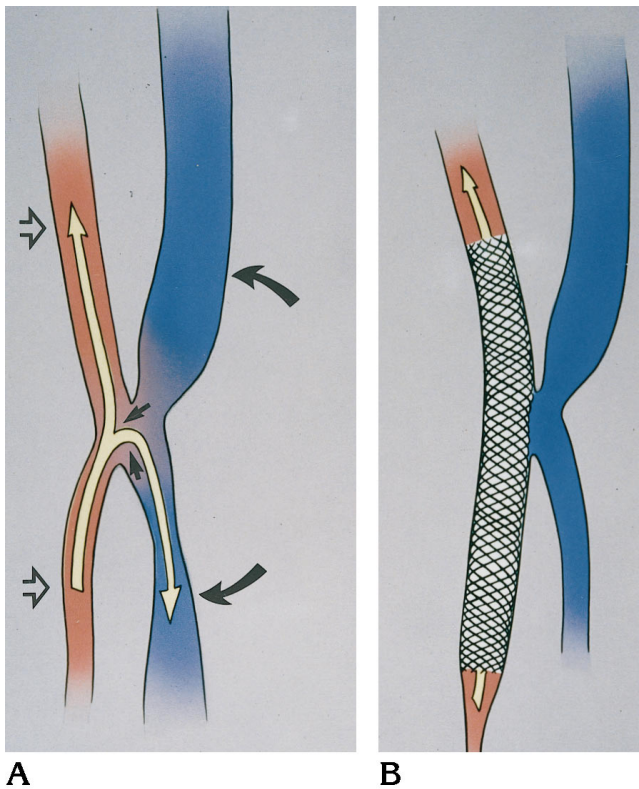


Fig 2. Illustration shows the changes present at the fistula site after stent placement.

A, Before stent placement, blood/contrast material is shunted from the carotid artery (*open arrows*) through the fistula (*small arrows*) and into the jugular vein (*large arrows*).

B, Immediately after placement of the silicone-coated stent, the fistula is closed. The carotid artery remains widely patent. Blood and contrast material within the carotid artery no longer communicate directly with the jugular vein.

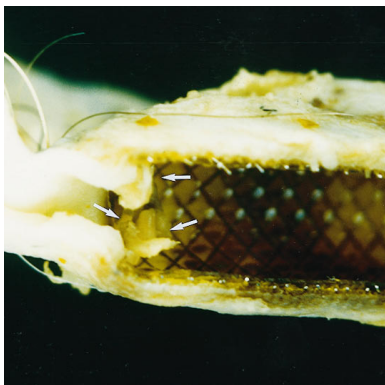
eter was seen within the carotid artery at the proximal and distal ends of the stent, but all carotid arteries remained patent.

The arteriovenous fistula specimens were resected 8 weeks after stent placement. Longitudinal sectioning with removal of half the arterial wall revealed fibrous connective tissue (organized thrombus) along the free edge of the silicone-coated stent (Fig 3). Cross sections through the edge of the stent revealed proliferative neointima surrounding the ends of the stent wire (Fig 4).

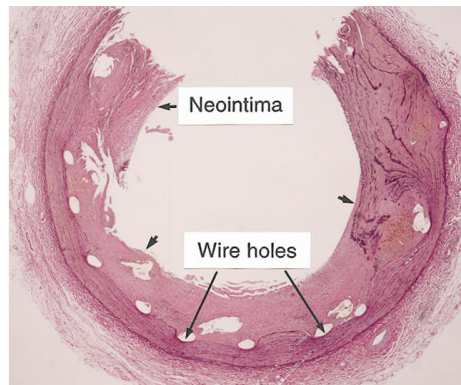
Gross and histopathologic cross sections through the stent-containing portion of the carotid artery were obtained (Fig 5). These revealed a minimal degree of neointima deep to the silicone film and adjacent to the stent wires. The silicone coating acted as a barrier that prevented complete encasement of the stent wires by neointima. There were mild impressions on the intraluminal surface of the arterial wall made by the outward pressure of the stent wires. The sections through the fistula hole revealed a glistening, white, organized fibrotic matrix that entirely filled the hole (Fig 6). This "connective tissue plug" consisted of fibrous connective tissue with fibroblasts and macrophages. Vascular spaces of various sizes were also noted. The increased amount of mature collagen and the decreased cellularity along the fistula margin suggested that the margins of the fistulas were thrombosed first.

Discussion

Arterial prostheses heal more slowly in humans than in the experimental animals tested thus far, but mongrel dogs have provided the best simulation of the human condition for



3



4

Fig 3. Gross longitudinal pathologic section through the stent containing a segment of the carotid artery. White, organized fibrous material (*arrows*) overlies the free edge of the silicone stent. The glistening coat of silicone fills the interstices of the wire mesh.

Fig 4. Cross section through the carotid artery at the stent-carotid interface. A prolific amount of neointima (*arrows*) lies deep to the stent wire (*holes*) and encircles the inner lumen of the carotid artery (Verhoeff's van Gieson's elastic stain, original magnification $\times 5$).

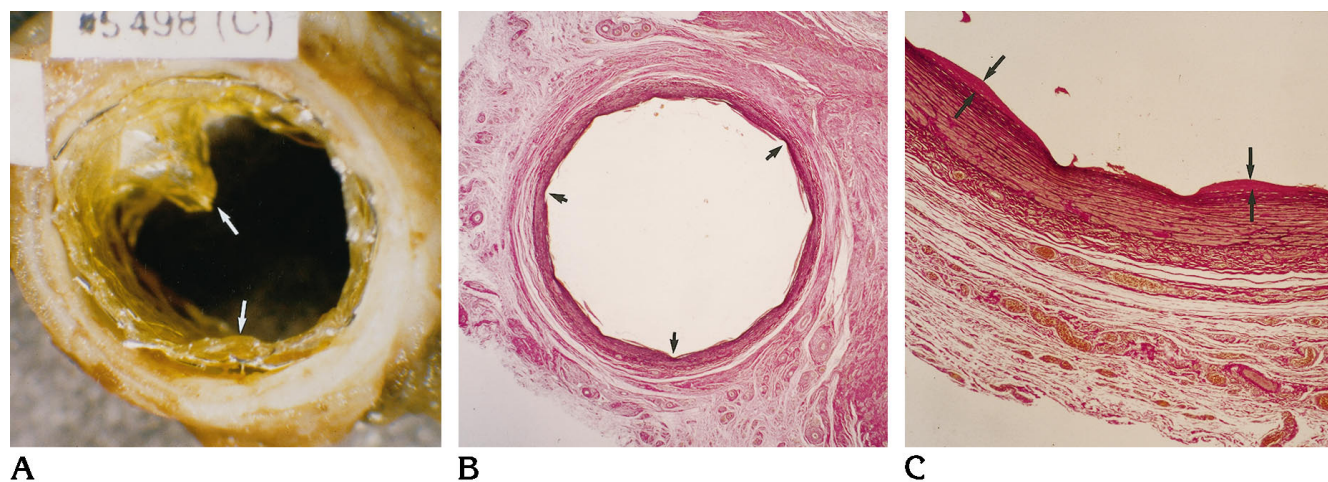


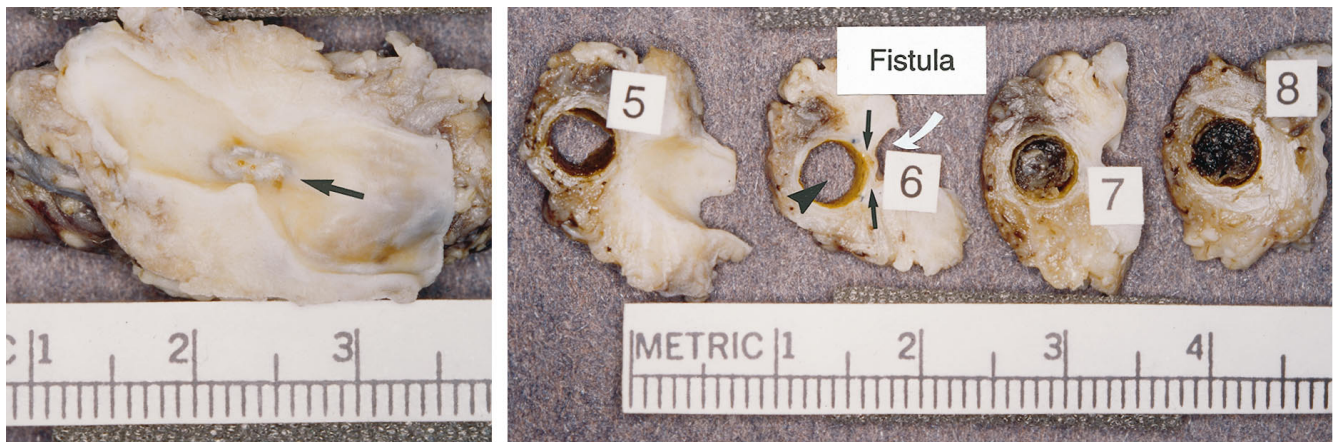
Fig 5. A, Cross section through the carotid artery shows the silicone-coated metallic stent within the lumen. A thin layer of silicone (arrows), free of endothelial ingrowth, lines the intraluminal surface of the carotid artery. B, Cross section through the carotid artery approximately 5 mm from the fistula hole, after the stent wires have been removed. Arrows indicate indentations in the luminal surface of the carotid artery (Verhoeff's van Gieson's stain, original magnification $\times 2.5$). C, Photomicrograph shows a small amount of neointimal proliferation adjacent to the wire indentations (arrows) (Verhoeff's van Gieson's stain, original magnification $\times 10$).

studying ingrowth of fibrous tissue following implantation of a vascular graft (3). Previous researchers have had some success using porous metallic stents to close experimentally created arteriovenous fistulas in the carotid arteries of mongrel dogs (1). These porous metallic stents (Wallstents) did not produce immediate closure of the fistulas but rather eventual closure in 60% (3 of 5), which was due to fibrocellular tissue filling the pores between stent wires with eventual plugging of the fistula holes. Our study was modeled after this experiment. The only difference was in the construction of the stent. We added a silicone coating to the same type of porous metallic stent (Wallstent), but all other conditions of the two experiments were constant and unchanged. It was our intention to examine the effectiveness of coated stents in the hope that the fistulas would occlude immediately.

The wire mesh of the stents was covered by a fine film of nonporous silicone. Placement of these covered stents within the carotid artery and across the fistula hole resulted in immediate and complete closure in 100% (%) of the fistulas. In contrast, in the prior experiment, porous metallic stents placed across a fistula hole resulted in no immediate change in flow across the fistula (1); closure of the fistula or reduction of flow across the fistula hole was only seen on follow-up arteriography 4 to 8 weeks after stent placement.

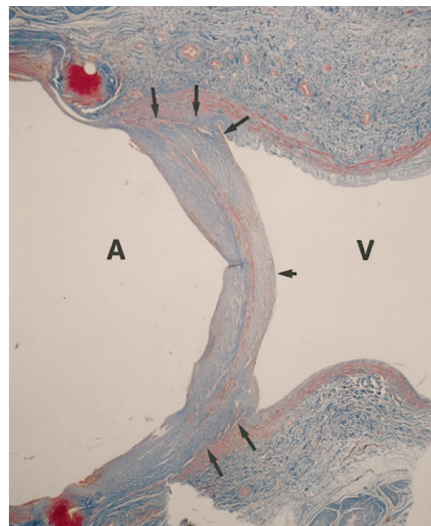
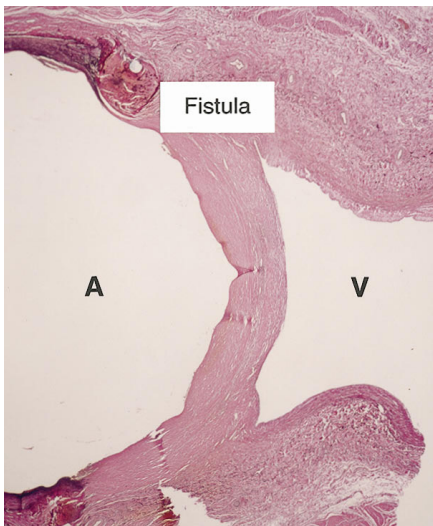
Fibrous connective tissue overgrowth across the fistula hole is a common finding in experiments with both coated and noncoated stents. More mature, less cellular elements (collagen) are present near the perimeter of the fistula with less mature, more cellular (fibroblasts) elements noted at the center of the hole. This finding is best appreciated on the histologic sections with Masson's stain (Fig 6D) and suggests that the reparative process begins at the margins of the fistula and proceeds in a centripetal fashion. In the current experiment, this attempt by the body to heal the experimentally created fistula took place despite the successful, complete closure of the fistulas effected artificially by the silicone-covered stents.

Treatment of experimentally created arteriovenous fistulas with coated (nonporous) stents has been attempted before stents coated with autologous vein grafts were used in the treatment of arteriovenous fistulas created in Labrador dogs (A. Wakhloo, M. Schumacker, J. de Vries, et al, "Coated and Non-coated Stents in Treatment of Carotid AV Fistulas and Aneurysms: An Experimental Study," presented at the annual meeting of the American Society of Neuroradiology, St Louis, Mo, June 1992). These stents eventually became encased in fibrocellular tissue without significant narrowing of the vessel lumen. When the vein graft was attached with cyanoacrylate, complete thrombosis of the stented vessel was noted 1 week



A

B



C

D

Fig 6. Carotid-jugular fistula.

A, Gross en-block specimen of the stent-containing carotid artery, jugular vein, and fistula. The jugular vein is filleted open. A thin glistening layer of endothelium can be seen overlying the fistula hole (arrow). Deep through this fistula hole lies the silicone-coated stent within the carotid artery.

B, Cross sections through the fistula hole. Section 6 lies at the center of the fistula (curved arrow indicates jugular vein; arrowhead, carotid artery lumen). Thick white fibrous connective tissue occupies the fistula site (straight arrows).

C, This section is through the center of what previously was the patent fistula. There is a solid area of collagen and fibrosis between the carotid artery (A) and jugular vein (V). On both the arterial side and the venous side, the segment of collagen and fibrosis was covered by endothelium (Verhoeff's van Gieson's stain, original magnification $\times 5$).

D, The margin of the fistula (long arrows) contains blue material (collagen) that is darker (more mature and less cellular) than the less mature, cellular fibroblasts in the central area (short arrow). This indicates that the margins of the fistula were first to thrombus and organize (Masson's Trichrome stain, original magnification $\times 5$). (A indicates carotid artery; V, jugular vein.)

after implantation as a result of immunologic rejection and distinct foreign-body reaction. In our experiment, the stented carotid arteries remained patent; however, there was significant fibroproliferative reactive change at the edges of the coated stent that caused significant narrowing of the vessel, as seen at angiography.

Stenosis of a stented vessel is a well-known phenomenon. Theories espoused to explain it include trauma resulting from outward pressure of the stent, as seen with the self-expandable stents (Wallstent and Gianturco Z stent), or from inflation of a delivery balloon (such as Palmaz, Strecker, Gianturco, or Robin). The stenosis is related to cellular proliferation within the

vessel wall, stimulated by interactions among platelets adherent to the damaged intima, endothelial cells, and smooth muscles (2, 4-6). In the present experiment, the fibroproliferative response seen within the carotid artery at the edge of the stent may have been caused by trauma related to outward pressure from the Wallstents. However, no fibroproliferative tissue was noted in the similar, prior experiment, in which non-coated metallic stents were used. Possibly, the coating of silicone to the ends of the stent acted as a nidus for thrombus deposition and/or significantly altered blood-flow dynamics conducive to the proliferation of fibrous tissue.

The substructure (porosity) of the silicone

material may also have contributed to the local tissue proliferative response. Previous experiments have shown that porosity may be an essential requirement for patency of synthetic vascular prostheses that have a small internal diameter (7). Porosity refers to the presence of pores within the synthetic graft material that may promote patency by providing a scaffold for ingrowth of endothelium to line the inner wall of a prosthetic graft (8, 9). Increased permeability of vascular grafts has been shown to enhance tissue incorporation. Pores may be required for the transfer of fluids and ions in prostheses that will enhance endothelial growth. The endothelial layer along the intraluminal surface of a vascular prosthesis provides a protective measure against the development of thrombus formation by virtue of its smooth surface and nonthrombogenic properties. Stimpson et al (10) evaluated the long-term patency of silicone-rubber vascular prostheses with a 6-mm internal diameter and 18- to 30- μ m pore size on canine aortic interposition and arteriovenous grafts. Six prostheses (6-mm internal diameter by 8-cm length) were studied as arteriovenous grafts over a period from 2 weeks to 10 months after placement. The porous walls of the silicone rubber prostheses were incorporated with capillaries and fibrohistiocytic cellular elements at 2 weeks after implantation. This cellular incorporation was unchanged at the 2.5-year follow-up.

Okoshi et al (11) performed an experiment using two types of small-diameter (1.5 mm) vascular grafts with varying degrees of porosity. They carried out an in vivo evaluation of porous versus minimally porous polyurethane-polydimethylsiloxane (PU-PDMS) vascular grafts implanted as infrarenal aortic replacements in male Sprague-Dawley rats. The patency rates at 2 weeks and at 3 months were 0% (0 of 7) and 0% (0 of 1), respectively, for the minimally porous grafts and 72% (8 of 11) and 8% (1 of 12), respectively, for the porous grafts. Another series of 15 more highly porous luminal surface grafts were fabricated, which exhibited a 73% patency at 3 months with a fully endothelialized surface at pathologic examination. The authors concluded that porosity is a significant factor for graft patency in small-diameter vascular prostheses.

In a separate study, Okoshi et al (12) compared two types of (PU-PDMS) vascular grafts with an internal diameter of 1.5 mm. These grafts were of low porosity (hydraulic perme-

ability of 2.7 ± 0.4 mL/min per square centimeter) and of medium porosity (hydraulic permeability of 39 ± 8 mL/min per square centimeter). Three months after implantation, patency was 8% for the low-porosity grafts (1 of 12) and 76% for the medium-porosity grafts (12 of 17). The only patent low-porosity graft revealed neointimal hyperplasia and incomplete endothelialization. All but one patent medium-porosity graft showed a glistening neointima with complete endothelialization.

The nonporous silicone material that covered the wire mesh of the stents used in our experiment prohibited an ingrowth of endothelium. The lack of a protective endothelial lining deep to the silicone surface could have led to thrombus aggregation and subsequent fibroproliferative tissue reaction.

In conclusion, silicone-covered stents were effective in the treatment of all experimentally created arteriovenous fistulas. Significant stenosis of the carotid artery was seen at the proximal and distal ends of the stents. Fibroproliferative tissue was identified as the cause, and perhaps this reaction was due to localized trauma to the vessel during stent deployment. The abrupt transition from the smooth endothelial lining of the native vessel to the shelflike ridge at the end of the covered stent may have promoted platelet aggregation. Furthermore, the lack of porosity of silicone prohibited the ingrowth of a protective layer of endothelium, which also may have contributed to platelet adherence.

The endovascular stent used in this experiment is not suitable for current neuroendovascular applications. Its size (7F) would need to be reduced and its lack of flexibility would need to be corrected. Nevertheless, our experiment shows the feasibility of treating arteriovenous fistulas acutely with covered stents; it is hoped that these results will encourage further development of the covered stent for neurovascular indications.

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