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Biocompatibility of 1-French Polyethylene Catheters Used in Interventional Neuroradiology Procedures: A Study with Rats and Dogs

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This study was designed to investigate the thrombogenicity, inflammatory response, and endothelial response to the presence of sterilized, 1-French polyethylene catheters implanted into the arterial system and subcutaneous tissues of 18 rats and two dogs. At time periods ranging from 1 week to 6 months, repeat angiography was done, the animals sacrificed, and the tissues containing the catheter removed for histologic study. In the subcutaneous tissues the catheter became encased in a very thin (less than 0.5 mm) coating of fibrous tissue with no evidence of inflammation. In large vessels, the catheter at all time periods appeared identical both angiographically and histologically to that at the time of implantation. In small to medium-sized vessels a slight increase in vessel size (25% increase in diameter of the rat iliac) was observed angiographically. On histologic evaluation, there was evidence of myointimal hypertrophy, which was asymmetrically placed, centered around the position of the catheter. There was no evidence of thrombi or of incorporation of the catheter itself into the hypertrophic tissue.

In dogs and rats, an implanted 1-French polyethylene catheter is well tolerated: the animals showed no evidence of thrombotic, thromboembolic, or inflammatory complications. Myointimal hypertrophy was observed in small to medium-sized arteries, which is of unknown significance.

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Several years ago Merland and colleagues [1–3] reported the use of an implantable microcatheter system for use in interventional neuroradiologic procedures. Benefits of this system include: (1) the capability of permanently attaching balloons to the catheter so that there can be no inadvertent detachment, (2) elimination of the traction necessary for detachment once the balloon is properly placed, (3) the ability to deflate an implanted balloon at a later date if so desired, and (4) the capability of retrieving the entire system, if necessary. This system may also be used with a detachable balloon, allowing the option of detachment or implantation without detachment if detachment appears difficult or hazardous. The centerpiece of this report is a 1-French extruded polyethylene catheter that is flexible, shapable in steam, does not kink easily, and has a low coefficient of friction when used in a coaxial system. Its inner diameter of 0.2 mm will allow the delivery and retrieval of contrast medium and nonpolymerized hydroxyethyl methylacrylate (HEMA).

Initial clinical experience with this system has been good [1–4], but little is known about the biocompatibility of such intraarterial devices and their long-term effects. This study was undertaken to evaluate the effects of implantation of this catheter in the arterial system of experimental animals.

Materials and Methods

The 1-French (0.33 mm OD/0.2 mm ID) polyethylene catheter was obtained in bulk from Balt (Paris, France), cut into appropriate lengths, and gas sterilized prior to implantation. Latex balloons were obtained from Ingenor (Paris, France), and HEMA from Polysciences

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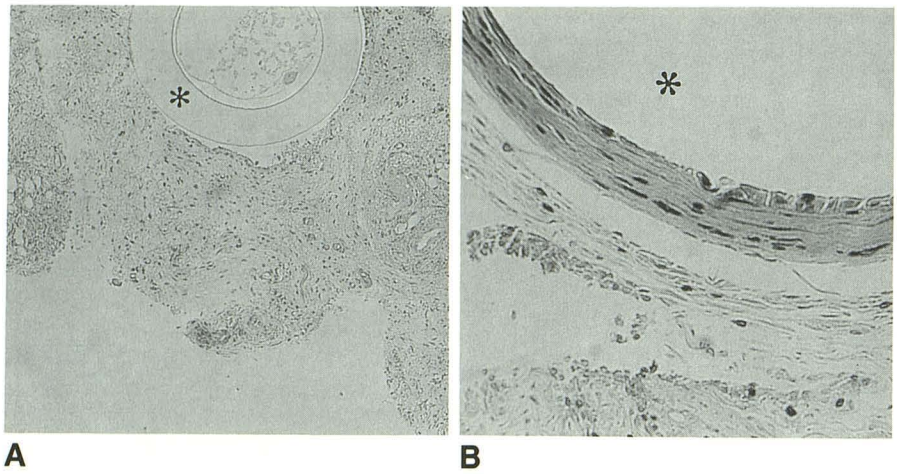


Fig. 1.—Subcutaneous rat tissue containing a catheter implanted for 2 weeks (*A*) and 6 months (*B*).

***A*, Catheter (*asterisk*) is surrounded by loose connective tissue in *A* and by a very thin band of fibrous tissue in *B*. H and E stain, ×150.**

***B*, Trichrome stain, ×630.**

(Warrington, PA). The HEMA was prepared according to the published method of Goto et al. [5].

Eighteen rats (700 g) and two 20-kg mixed-breed dogs were obtained commercially, housed in the animal care center of the University of Wisconsin, and used under a protocol approved by the University of Wisconsin Animal Care Committee. All procedures were performed under sterile conditions and general anesthesia (rats; chloral hydrate 300 mg/kg IP: dogs; induction with IV 5% pentobarbital (1 ml/5 lbs body weight), and maintained with 1–2% isofluorane and 100% oxygen after intubation.

Prior to implantation each catheter was filled with nonionic contrast material (Iohexol 300 mg I/ml), and the distal end was occluded with a 4-mm segment of stainless steel suture (1–0). In rats the catheter was introduced into the arterial system via a cutdown on the left common carotid artery. Under fluoroscopic control, the distal end of the catheter was advanced into a common femoral artery, the common carotid artery was then ligated at the catheter insertion site. The proximal end of the catheter was tied in several tight knots and implanted in the subcutaneous tissues of the neck.

At time intervals of 2 days (six rats), 2 weeks (four rats), 2 months (four rats), and 6 months (four rats), aortic arch arteriograms were obtained with a film-screen technique via a carotid approach (cutdown on the right common carotid artery; 22-gauge Angiocath (BD); 0.75 Iohexol 300 mg I/ml). The animals were then sacrificed, and tissues containing the catheter (subcutaneous implantation site, occluded carotid artery, aorta, iliac artery, and femoral artery) were removed from each animal and fixed in formalin for histologic staining.

In the two dogs, latex balloons were permanently attached to the catheter [6], and introduced intraarterially through a 16-gauge sheath needle (Jelco) placed in a common femoral artery. The balloons were positioned into either a surgically created aneurysm on a common carotid artery [7] or a subscapular artery. The balloons were inflated with HEMA, the proximal end of the catheter tied in several tight knots, the coaxial delivery system removed, and the proximal end of the catheter implanted in the subcutaneous tissues near the arteriotomy site. Two months after implantation, arteriograms were obtained (femoral approach; 4-French pigtail catheter, 15 ml Iohexol 300 mg I/ml), the animals were euthanized with Buthenasia (1 ml/10 lbs body weight), and the tissues containing the catheter and balloons fixed in formalin for histologic evaluation.

All histologic samples were embedded in paraffin, sectioned at a thickness of 10 μm, and stained with H and E, Trichrome, or EVG (elastin).

Results

We evaluated the effects of implantation of this catheter at the subcutaneous implantation site, the thrombosed occluded artery (common carotid artery ligated at the time of catheter insertion), the small arteries (1–6 mm in diameter), and the large arteries (greater than 6 mm in diameter). The results are as follows.

Subcutaneous Tissues

At periods of 2 days (n = 6) and 2 weeks (n = 4), the catheter was surrounded by scattered inflammatory cells and loose connective tissue (Fig. 1A). Four weeks after implantation (n = 4), this had converted to a loose fibrous reaction completely surrounding the catheter (not shown). Two months after implantation (n = 4) this fibrous reaction had matured into a dense, thin (less than 1 mm) fibrous coating of the catheter (Fig. 1B). Only four giant-cell granulomas were seen. No infectious complications were encountered. In both dogs, the catheter was found to be completely intraarterial (proximal end in the common femoral artery), indicating that it had pulled back from its implantation site. There was no evidence of bleeding, thrombosis, or arterial injury at any of the arteriotomy sites.

Thrombosed Arteries

The catheter was implanted in the thrombosed left common carotid artery, which was ligated at the time of catheter insertion in each of the 18 rats. Two days after implantation (n = 6), the catheter was surrounded by fresh thrombus (Fig. 2A), which was more organized and fibrous 2 weeks (n = 4) and 2 months (n = 4) after implantation and arterial occlusion (not shown). Six months after implantation and arterial occlusion (n = 4), the previous arterial lumen was filled with dense fibrous tissue that was closely applied to both the arterial wall and to the implanted catheter (Fig. 2B). There was no evidence of inflammatory reaction or recanalization.

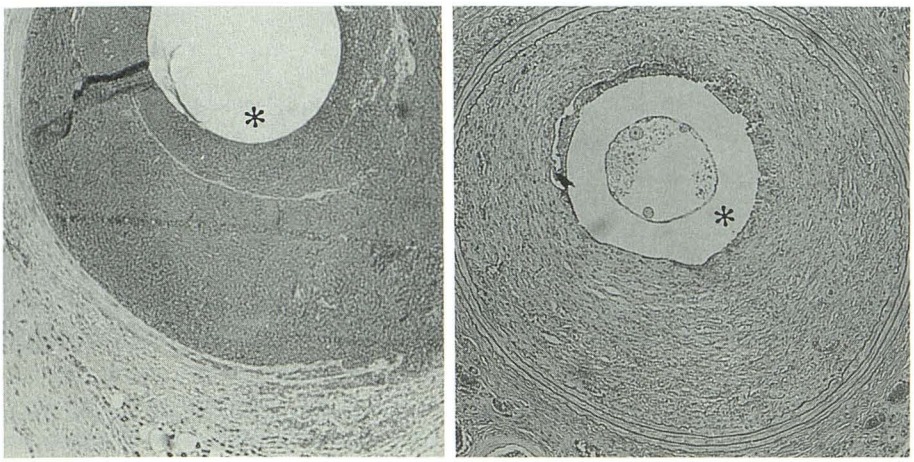


Fig. 2.—*A* and *B*, Cross sections of rat common carotid arteries containing catheter (*asterisk*) at 2 days (*A*) and 6 months (*B*) after carotid ligation with catheter in vessel lumen. The catheter is surrounded by fresh thrombus containing intact red blood cells in (*A*) and by well organized fibrous tissue in (*B*). (H and E, ×140)

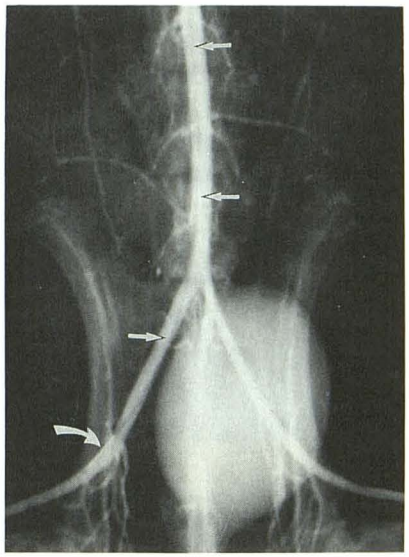


Fig. 3.—Anteroposterior aortogram of rat with catheter in place in the arterial system for 2 months. Catheter is seen as a faint filling defect in the lumen (*straight arrows*) terminating in the external iliac at the metallic marker (*curved arrow*). Note size discrepancy of external iliac and common femoral arteries.

Large Arteries

Large arteries were defined as those greater than 6 mm in diameter, or at least 18 times the diameter of the catheter. In these vessels (the aorta and iliac arteries of dogs ($n = 2$), the catheter did not change significantly with time. The arteriographic, gross, and histologic appearance of the catheter and the vessel walls was nearly identical to that on the day of implantation, without evidence of clots, vascular reaction, fibrin coating, or inflammatory reaction.

Small Arteries

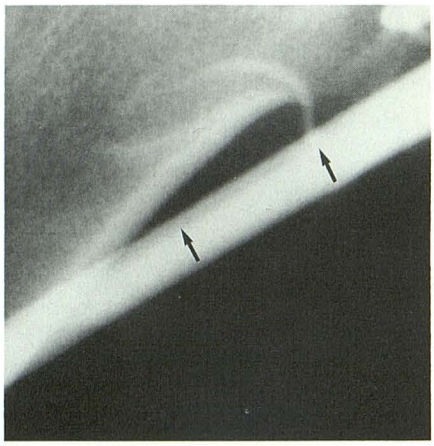
Small arteries were defined as those 1–6 mm in diameter, or 3 to 18 times the diameter of the catheter. Two days ($n = 6$) and 2 weeks ($n = 4$) after implantation, there was no detectable change in the angiographic or histologic appearance of the artery with the exception of the presence of the catheter as a filling defect in the angiogram (not shown). There was no detectable thrombus around the catheter, and no angiographically detectable disruption of the flow in the artery.

Gross and histologic analysis of the catheter and the artery showed them each to be indistinguishable from normal specimens.

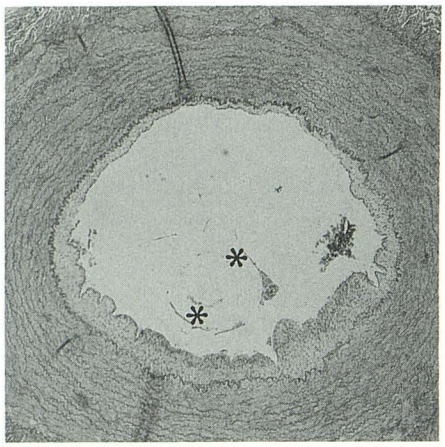
At time periods of 2 months ($n = 4$) and 6 months ($n = 4$) after implantation, however, there was angiographic evidence of an increase in the size of the artery containing the catheter, which extended distally to the distal tip of the catheter in the rat femoral and iliac arteries (Fig. 3). There was still no angiographic evidence of thrombus around the catheter or of significant obstruction to flow (Figs. 3 and 4A). At gross examination, there was no detectable abnormality in the arterial specimen, and the catheter was identical to a new, never implanted catheter. On histologic examination, there was evidence of myointimal hypertrophy of the femoral, carotid, and subclavian arteries in both dogs and in the aorta, iliac, and femoral arteries of six of the eight rats (Fig. 4). This myointimal hypertrophy generally occupied a small portion of the vessel wall immediately adjacent to the location of the catheter (Fig. 5), and was manifested as a plaque of thickened cells with a covering of endothelium. In both dogs, the intimal reaction was circumferential about the vessel but had an asymmetry so that the most thickened portion of the reaction was located adjacent to the catheter (Fig. 5). There were segmental areas of discontinuity of the internal elastic lamina adjacent to, but not directly beneath, this reaction (Fig. 5).

Discussion

The presence of the small catheter in the subcutaneous tissues at the implantation site was well tolerated. In these locations, the catheter has good biocompatibility, causing no inflammatory response. Only a few foreign body type granulomas were seen. These may have arisen because of a contaminant such as talc from the surgical gloves; however, they also have been reported as a result of surface irregularities such as gas bubbles in the implanted material surfaces [8]. In our study of the subcutaneous implantation sites, the catheter showed all the characteristics of an implanted inert



A



B

Fig. 4.—*A*, Arteriogram of dog femoral artery containing catheter in place for 2 months. Catheter is visible as a small filling defect (*arrows*).

B, Cross-sectional specimen from same femoral artery (EVG stain, ×140). Catheter (*asterisks*) is free within the lumen. Note asymmetric myointimal hypertrophy.

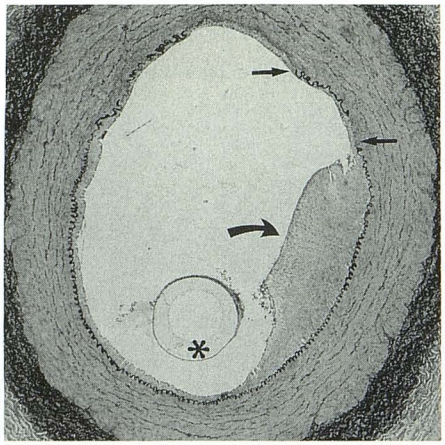


Fig. 5.—Cross section of a dog common carotid artery (EVG stain, ×140) containing catheter (*asterisk*) in place for 2 months. Note areas of discontinuity of internal elastic lamina (*straight arrows*), asymmetric myointimal hypertrophy (*curved arrow*), and thin acellular coating of catheter.

material [8], and become surrounded with a thin wall of dense fibrous tissue. Although we did not observe any infectious complications, the presence of a foreign material such as this in the subcutaneous tissues of an animal less resistant to infection than are rats and dogs might serve as a nidus for infection. The catheter did pull back to lie completely within the artery in both dogs, which we believe was related to the mobility at the femoral implantation site. Although this caused no complications in these dogs, caution should be used in implanting this catheter at mobile sites in the human (e.g., brachial artery).

Within the arterial lumen, the catheter itself was very well tolerated. There was no angiographic evidence of thrombotic or embolic complications. The catheter remained free of thrombus as evidenced by its appearance on arteriography and at gross and histologic examination. This is most likely related to a combination of the high shear forces acting on the catheter surface in the artery [9], to the Vroman effect [10, 11] or to platelet passivation [9]. High-shear forces strip tiny thrombi and platelet aggregates from the catheter surface before they are large enough to be detected radiographically, clinically, or at autopsy. No studies have been done with this catheter in low-shear (venous) conditions to assess the importance of this effect. The Vroman effect describes the coating of a foreign material in contact with blood by protein components from serum, which serve as a protective layer, preventing the deposition of platelets and thrombin. In most systems reported, these proteins are primarily albumin, fibrinogen, and globulin [12], but these change with the makeup of the polyethylene surface (crystalline vs amorphous) [13], and the surface of this catheter material has not yet been investigated. Platelet passivation describes the covering of a foreign material with a "platelet carpet," a thin layer of adherent platelets that coat the surface and prevent further interaction with blood components. Electron microscopic evaluation of the catheter material to investigate this possibility is currently underway in our laboratory.

Small arteries (rat femoral with a diameter of 1 mm and rat iliac with a diameter of 2 mm) that contained the catheter showed an increase in the lumen diameter as measured angiographically. This increase in diameter was seen consistently in arteries containing the catheter, but was not limited to the location of the catheter. That is, the increase in size of the artery extended beyond the tip of the catheter. This change in vessel size corresponded to a change in vessel diameter equal to the diameter of the catheter (control rat common femoral = 1.0-mm diameter; catheter containing common femoral artery = 1.3-mm diameter), but this corresponds to a greater change in cross-sectional area than would be expected on a volume displacement basis. It is not known at this time whether this is related to changes in the flow dynamics, to changes in the catheter position, or to local irritation of the vessel wall by the catheter inducing the release of trophic substances responsible for vasodilation. The latter possibility is particularly intriguing when the internal changes in the arterial wall are taken into account.

Some small vessels (1–6 mm in diameter) that contained the catheter for more than 1 month showed myointimal hypertrophy, which was asymmetric and centered around the position of the catheter. This was observed in rat aorta and common iliac arteries (four of eight and six of eight, respectively) and in the dogs' common femoral, common carotid, and subclavian arteries that contained the catheter. Larger arteries such as the dogs' aorta and iliac arteries were not affected. This hypertrophic reaction of the vessel wall to the catheter was not apparent angiographically; it produced no significant decrease in the size of the lumen (the lumen diameter as measured angiographically actually increased), and there was no irregularity of the vessel wall detected on the angiograms even when they were reviewed in retrospect.

It was more pronounced in the dogs than in the rats, and it increased in magnitude with time in the rats.

The exact nature of this vessel-wall reaction is the subject of ongoing research in our laboratory. It has many characteristics similar to the intimal reaction seen after damage to the endothelium of arteries [14]. It may indeed represent a response of the vessel to irritation or damage by the catheter, although its presence did not correlate with the areas of discontinuity of the internal elastic lamina. A similar phenomenon has been reported in the aorta of rabbits in which a more rigid polyethylene catheter (1–2 mm in diameter) had been implanted [15]. In that study [15], two types of intimal reactions were observed: large lipid-laden plaques located at the ends of the catheter, and small slightly elevated fibrous plaques, which contained no lipid, along the course of the catheter where minimal trauma to the vessel wall would be expected. The myointimal reaction in the present study appears to be of the latter type.

This reaction occurred only in arteries containing the catheter and was centered at the location of the catheter. In arteries of the two dogs studied it was circumferential about the vessel, but with a greater thickness adjacent to the catheter. It is tempting to speculate that this might represent an attempt to incorporate the catheter into the vessel wall (i.e., endothelialization of the catheter), as has been reported in the aorta of rabbits [15]. We, as yet, have no evidence of that occurring with this microcatheter system, although in one case (Fig. 5) the catheter appeared to be covered by a thin coating and may have been displaced from the edge of the hypertrophic reaction by the fixation and mounting process.

Conclusions

This implantable 1-French polyethylene catheter system was well tolerated in the animals in our study. There was no evidence of thrombosis, thromboembolism, or of inadvertent vessel occlusion. In the subcutaneous tissues at the implantation site the tissue and catheter showed the characteristics of an implanted inert material, with no inflammatory or infectious complications. In small and medium-sized arteries containing the catheter there was an arterial-wall reaction manifested as asymmetric myointimal hypertrophy. This reaction had an appearance similar to the fibrous plaques reported previously [15], and had no angiographically detectable consequences. Further studies are necessary to investigate the long-term consequences of this reaction. We have no evidence at present to make us suspect that these lesions are the harbinger of premature atherosclerosis of vessels containing the catheter.

In some instances, the clinical use of this catheter system has allowed us to perform procedures that were not possible with other systems [1–4]. This system eliminates two of the main hazards associated with balloon occlusion; that is, premature detachment and the traction necessary to accomplish balloon detachment. Clinical follow-up of the patients treated with this system has showed no evidence of complication related to the intravascular catheter (some patients are 5 years posttreatment), but further monitoring will be necessary to document safety.

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