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Platinum Coil Coatings to Increase Thrombogenicity: A Preliminary Study in Rabbits

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Summary: The authors investigate a modification of the Gugliemi detachable coil. They have developed a rabbit model and coating technique to test differences in thrombogenicity of platinum coils with a variety of polyurethanes.

Index terms: Aneurysm, intracranial; Interventional instrumentation, coils; Interventional neuroradiology, experimental; Animal studies

Intracranial aneurysms are known to affect at least 2% of the world's population. Annually in North America the rupture of saccular aneurysms accounts for 25 000 new cases of subarachnoid hemorrhage (1). Over the last decade, endovascular treatment has become an accepted alternative to surgical therapy for the management of aneurysms, which, because of their size, their morphology, or the patient's medical condition are felt to be either unclippable or to pose an unacceptable risk for traditional operative treatment.

Until recently, the endovascular treatment of intracranial aneurysms was based upon the use of detachable balloons employed either for occlusion of an aneurysm's parent artery or for blockage of the aneurysm lumen (2). Balloons have in numerous instances been inadequate for treatment, especially when parent artery preservation was required. This deficiency is largely due to the inability of available balloons to adapt to the irregular shape of most aneurysms.

With the availability of steerable (ie, nonflow-dependent) catheters capable of accessing the intracranial circulation came the possibility of obliterating an aneurysm lumen by filling it with soft metallic coils. However, these devices also proved to have limited capabilities, largely because of the inability prior to delivery to determine accurately whether a given coil would remain confined within an aneurysm. Gugliemi and his associates' development and description of a technique that allows controlled delivery and detachment of soft platinum coils has, however, renewed interest in the use of coils as devices for the treatment of intracranial aneurysms (3, 4).

As currently used, the major mechanism for obliteration of aneurysms with the Gugliemi detachable coil (GDC) is dense packing of the aneurysm with platinum coil. Multiple coils are required to obliterate most aneurysms, and for the treatment of large or giant aneurysms several meters of platinum often must be inserted. Each time a coil is deposited there is some risk of injury, either to the aneurysm or to its parent artery, of displacement of previously placed coils, or of thrombus. Also, the time required to insert, position, and detach multiple coils may be considerable and, in general, longer procedure times are associated for a variety of reasons with an increase in morbidity. Thus, despite its considerable theoretical and proved practical advantages (ie, controlled delivery, detachment by electrolysis, and the potential for electrothrombosis), the GDC, for optimal application, requires further modification. Increasing the thrombogenicity of the GDC is one approach that might make it possible to achieve successful aneurysm obliteration with less need for complete mechanical packing of the aneurysm lumen.

As the first step in evaluation of this approach, we have developed a rabbit model and coating technique to test differences in the thrombogenicity of platinum coils coated with a variety of polyurethanes.

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Materials and Methods

Coil Preparation

Three polyurethanes were used for coating the platinum coils. One of the polymers is a relatively thrombogenic polyurethane (PEU-PEO), which is composed of 55 wt% hard segment of methylene bis(*p*-phenyl isocyanate) and butane diol (Becton-Dickinson Polymer Research, Dayton, OH). The soft segment was poly(ethyleneoxide) (PEO) (molecular weight = 1450). A mildly thrombogenic polyurethane (PEU-PTMO) (Pellethane 2363–80A, Dow Chemical Co., Midland MA) and a sulfonate-grafted modification of the polymer (PEU-PTMO-Sulf) were also used. The base polymer consisted of approximately 50% hard segment of methylene bis(*p*-phenyl isocyanate) and butane diol with a soft segment of poly(tetramethylene oxide) (PTMO) (molecular weight = 1000). The sulfonated version had 14% of the urethane nitrogens grafted with propyl sulfonate chains. The sulfonate groups have been reported to make the polymer considerably less thrombogenic than the PEU-PTMO polymer. The physical and blood-contacting properties of the PEU-PTMO and the PEU-PTMO-Sulf polyurethanes as well as the PEU-PEO polyurethanes have been previously reported (5, 6).

Thirty-two platinum coils measuring 2 mm by 20 mm were divided into four equal groups. Group I was uncoated and served as a control group. Group II was coated with PEU-PTMO-Sulf; group III, with PEU-PEO; and group IV, with PEU-PTMO. To assure complete coating, the coils were positioned at the end of their introducers, and then the introducer with the coil within it was placed in a 1% solution of the polymer and dimethylacetamide for 2 hours. The introducer-coil system was then removed from the solution, allowed to drain for 1 hour, and placed in a vacuum oven at 50°C for 48 hours to ensure removal of all of the dimethylacetamide. The control coils were not coated but were moved to the end of their introducer and repackaged to assure the same handling for all of the coils. Scanning electron micrographs of randomly selected coils confirmed the presence of coatings on the coils. All coils were repackaged and sterilized prior to use in the rabbits.

Thrombogenicity Testing

White New Zealand rabbits weighing approximately 4 to 5 kg were used under a protocol approved by the Animal Care Committee. General anesthesia was induced with an intramuscular mixture of Ketamine, Acepromazine, and Rompin, and then after endotracheal intubation was maintained with a 1.0% to 2.0% halothane and 100% oxygen mixture. At the end of the experiment euthanasia was induced with an intravenous injection of sodium pentothal. A total of 16 rabbits (32 carotid arteries) were studied.

Bilateral 5-cm incisions were made in the anterolateral aspect of the neck to expose a 3-cm length of both the right and left common carotid arteries. A 2.5-mm doppler probe (Crystal Biotech, Hopkinton, MA) was placed around each carotid artery. Local 1% lidocaine was applied externally both to prevent and to relieve vasospasm. Following placement of the doppler probes on both common carotid arteries, a 5-cm incision was made in the right groin, and under direct visualization an 18-gauge angiocath was inserted into the femoral artery. Through this "sheath" a Tracker 18 catheter (Target Therapeutics, San Jose, CA) 60 cm in length was introduced and, under fluoroscopic control, was placed into one of the carotid arteries so that its tip was at least 5 cm proximal to the position of the external doppler probe. Baseline velocity measurements from the doppler probe were obtained both before and after placement of the Tracker catheter in the carotid artery. These were recorded on a strip recorder (Gould Inc., Cleveland, OH) for measurement.

A single 2 × 20-mm platinum coil was deposited into the carotid artery through the Tracker catheter so that the position of the coil was just proximal to the doppler probe. All coils were introduced with a coil pusher, and in no instance was detachment by electrolysis employed. Following coil placement the catheter was then pulled into the descending aorta. Velocity measurements were recorded constantly following coil placement until the velocity had either declined to zero or a time interval of 30 minutes had elapsed. The Tracker catheter was then used to catheterize the opposite common carotid artery; the procedure was then repeated in an identical manner. There was no difference in the amount of force necessary to deliver any of the coils in the four groups. Upon completion of the experiment, the animals were killed using a barbiturate overdose. The segment of each carotid artery containing a coil was removed and was placed into either formaldehyde or glutaraldehyde for fixation. Coils from each group were examined with scanning electron microscopy. The types of coating applied to individual coils were unknown to the individuals performing the rabbit experiments.

Results

The coils coated with PEU-PEO (group III) caused significantly faster occlusion of the carotid artery than did coils in the other three groups (Table 1). Although there were many observations for which the exact time from coil placement to vessel occlusion was not known, it was known that the time to occlusion was greater than 30 minutes. Thus, the data are right censored, and because of this a survival analysis technique was used to test for homogeneity among the groups. The test of equality over the

TABLE 1: Comparison of coil thrombogenicity as measured by occlusion time

	Occlusion < 30 min	Patent > 30 min
Group I	4/10	6/10
Group II	2/6	4/6
Group III	8/8	0/8
Group IV	3/8	5/8

four groups using the log-rank test was significant at the 0.05 significance level (Chi-square = 8.254, $P = 0.041$). Because this test was significant, indicating that differences exist among the four groups, pairwise comparisons using the log-rank test were made to determine which pairs in the groups were different. These results are summarized in Table 2.

There were three pairs that showed meaningful differences at the 0.05 level of significance: groups I and III; groups II and III; and groups III and IV. The variation between group I and group III was highly significant; those between group II and III and group III and IV were just barely significant.

Scanning electron micrographs taken following fixation and removal of the coils from the carotid arteries demonstrated an increase in the amount of complex cellular material on the PEO–PEU-coated coils (group III) as compared with coils in the other groups.

Discussion

Early clinical experience has confirmed several advantages of the GDC coil over other devices currently available for use in the endovascular treatment of saccular intracranial aneurysms. Most important among these are controlled coil delivery and the ability both to place and then to detach a coil while inducing little mechanical stress or strain on either the aneurysm or its parent vessel. A relative disadvantage of the technique is the necessity to fill the entire volume of an aneurysm with strands of platinum coil for complete aneurysm obliteration. Because of this requirement and the mechanical limitations in pushing coils longer than 40 cm from the site of their introduction into the intracranial circulation, placement of multiple coils is required for the satisfactory treatment of most aneurysms. Besides lengthening procedure time, the placement, positioning, and detachment of multiple coils likely adds to the chance of injury both to the aneurysm and to its parent artery. The use of multiple coils also introduces the risk of displacement and migration of previously placed coils.

TABLE 2: Pairwise comparison of coil groups

	Chi-square	*P*
Group I vs II	0.014	0.91
Group I vs III	6.779	0.0092
Group I vs IV	0.005	0.945
Group II vs III	4.404	0.036
Group II vs IV	0.014	0.906
Group III vs IV	4.129	0.042

Further advancement of the endovascular treatment of saccular intracranial aneurysms might be achieved by increasing the thrombogenicity of the GDC coil so that more complete aneurysm thrombosis would occur without the need of replacing the complete volume of the aneurysm with platinum wire.

The addition of either dacron or silk fibers to platinum coils is an effective means of significantly increasing their thrombogenicity. When longer than 2 or 3 cm, however, fibered coils, because of the friction between the coil and the catheter lumen, become extremely difficult to push through catheters placed within tortuous vessels. In addition, rapid thrombosis such as that induced by fibered coils is undesirable because of what would seem to be the high risk of embolic complications occurring as the result of dislodging thrombus from either the coil or the aneurysm during coil manipulation or retrieval. Such an event rarely occurs with the use of the GDC coil in its current configuration.

As an approach to making the GDC coil more thrombogenic, the concept of coating the platinum with a mildly thrombogenic material that would not affect the mechanical properties of the coil was developed. Polyurethane block copolymers have been used for many biomedical applications and offer excellent physical properties and generally good biocompatibility (7). Polyurethanes are composed of an elastic soft segment—usually a long chain diol—and a hard segment of a diisocyanate and a chain extender. The urethane linkage and chain extender allows the grafting of various functionalities such as alkyl or hydrophilic chains, sulfonate or carboxylate groups, or amino acid sequences, to alter blood compatibility and physical and surface properties (8–10). The three polyurethanes used in this study have varying levels of thrombogenicity.

Our results show that the GDC coils coated with the PEU-PEO polyurethane caused significantly faster vascular occlusion than did either the uncoated coils or the coils coated with the other two polyurethanes. Scanning electron micrographs taken of the coils after their removal from the carotid arteries confirmed the presence of more cellular material on the PEU-PEO coils than was present on the other groups of coils. (Fig. 1) We are encouraged by these results and as the next step in this investigation will compare

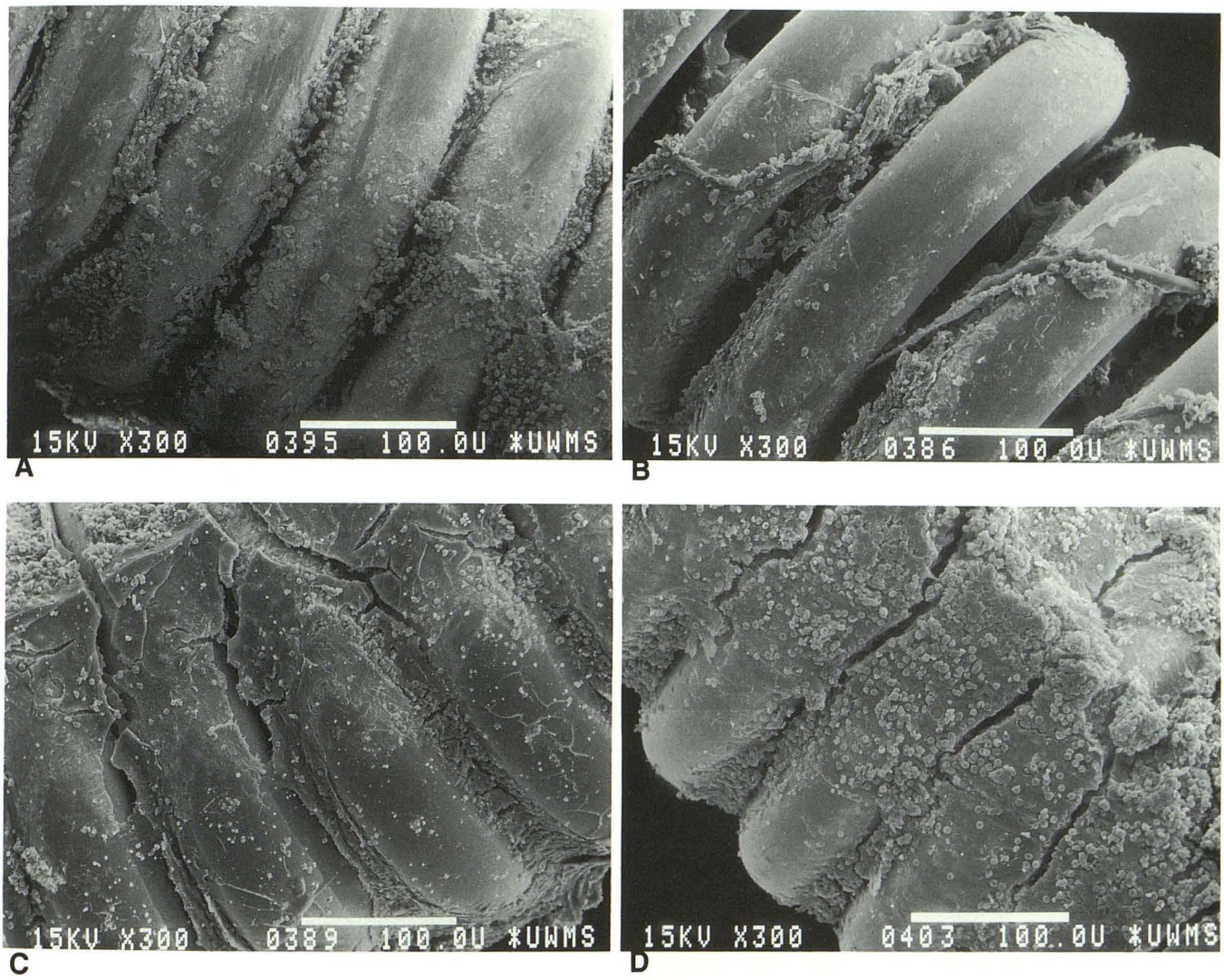

Fig. 1. Scanning electron micrographs of platinum coils following their removal from the carotid artery.
A, Uncoated coil.
B, PEU–PTMO-Sulf-coated coil.
C, PEU–PTMO-coated coil.
D, PEU–PMEO-coated coil.
The PEU-PTMO-Sulf polyurethane (*B*) is the least thrombogenic of the materials used for coating of the coils. This coil was coated with the lightest covering of thrombus. The coil coated with PEU-PEO polyurethane (*D*), the most thrombogenic of the polyurethanes used, was coated with the heaviest covering of thrombus.

the effectiveness of coated and uncoated GDC coils in the treatment of experimental canine aneurysms. The ultimate object of these studies is to develop a system of implants which can be designed to have biologically functional capacities (eg lesser or greater degrees of thrombogenicity) or properties which attract or repel various cellular elements.

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Please see the Commentary by Halbach on page 799 in this issue.