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## **Histologic effects of collagen-filled interlocking detachable coils in the ablation of experimental aneurysms in swine.**

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# Histologic Effects of Collagen-Filled Interlocking Detachable Coils in the Ablation of Experimental Aneurysms in Swine

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**PURPOSE:** To assess the histologic changes produced by platinum microcoils with an inner core of cross-linked bovine collagen in experimentally induced aneurysms in swine, and to assess the feasibility of the system for the delivery of the collagen. **METHODS:** Bilateral pouch aneurysms were created in the side wall of the common carotid artery in seven barnyard pigs. Eight aneurysms were treated with coils designed with an interlocking detachment mechanism: in four of these, the coils had an inner core of collagen; in the other four, the platinum microcoils had a similar design but without the collagen mandrel. The packing density of the coils within the aneurysm was approximately the same for both types of coils. The other six aneurysms were left untreated and served as controls. Angiograms were obtained at the time of treatment (2 weeks after the aneurysms were created) and at 1, 4, and 8 weeks after treatment. All animals were killed 8 weeks after the treatment (10 weeks after the aneurysms were created). Arteries and aneurysms were resected en bloc and fixed for histopathologic study. **RESULTS:** The interlocking detachment mechanism worked well. Little difference was noted between the two types of coils in their ability to effect complete aneurysmal thrombosis (three of four aneurysms treated with collagen-core coils and two of four aneurysms treated with conventional coils). The collagen-core coils stimulated new collagen formation in areas proximal to the coils, and more fibroblasts were noted near the collagen-core coils than near the conventional coils. **CONCLUSION:** Local fibroblast proliferation and collagen production were stimulated by heterologous cross-linked collagen embedded in microcoils in this experimental model. Such biologic stimulation holds promise for improving the endovascular cure rate of aneurysms in humans.

**Index terms:** Aneurysm, embolization; Animal studies; Interventional instruments, coils; Interventional materials, embolic agents

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Endovascular techniques for the treatment of intracranial aneurysms have been evolving for more than 20 years. Early investigators used various types of detachable balloons (1-3). This initially promising method has recently been superseded by catheter-delivered platinum microcoils (4-7). By far, the most promising variety of microcoil has been the Guglielmi de-

tachable coil, which relies on electrolysis for its deployment (8-12). The Guglielmi coil is currently the subject of an ongoing multicenter trial, with early results verifying its promise as the definitive treatment for some aneurysms. The major limitation of this coil is its decreasing effectiveness as orifice and aneurysmal size increase. Thus, the very aneurysms for which this therapy was first proposed, large and surgically difficult lesions, are those that respond least favorably to its use. Such aneurysms, treated with Guglielmi detachable coils, have a higher rate of recanalization, regrowth, and rupture (13).

Certain technical considerations may explain these processes. Recanalization is less likely if the coils can be packed tightly within the aneurysm, so as to occupy a higher proportion of the

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Study design for testing collagen-filled coils in experimentally created aneurysms in swine

Group	1				2				3				4	
Animal	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Aneurysm site	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Embolitic material	None	CIDC	None	CIDC	None	IDC	None	IDC	IDC	CIDC	IDC	CIDC	None	None

Note.—CIDC indicates collagen-filled interlocking detachable coils; IDC, conventional interlocking detachable platinum coils.

lumen. As coil packing proceeds, however, the previously deployed coils reach a high density and overlap one another, hindering the ability to see where subsequent coils are placed. Ideal coil positioning is thus compromised, and the aneurysm may not be filled optimally. Additionally, as packing nears the orifice, chances of coil herniation into the parent artery with secondary parent artery thrombosis or distal embolization increase. The wider the orifice, the more likely the occurrence of deleterious events. These factors may lead to fewer coils per unit volume being delivered into large aneurysms than into smaller, narrow-necked aneurysms. If it were possible to ensure that the coils would not migrate or herniate, then denser packing could be obtained and better results could be expected. At this time, technical considerations preclude this tactic. Alternatively, if an additive chemical or biologic material could be found that would allow fewer coils to produce the same ablative effect, the same result would be achieved and procedural morbidity would be decreased. Collagen has been proposed as an endovascular agent that might promote the production of fibrosis within berry aneurysms.

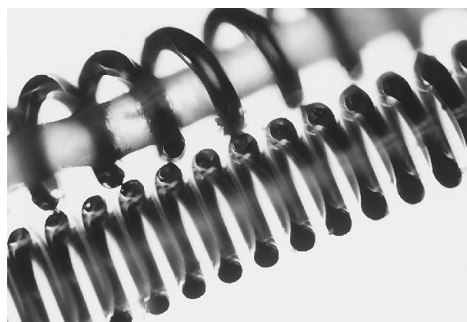
In a pilot study, prototype collagen-coated coils were implanted in surgically created aneurysms in swine. The implantation produced increased fibrosis compared with the uncoated control coils (14). On the basis of these results, we developed an improved coil design for collagen delivery. We wound the coil around a core of collagen so that a controlled volume and surface area of collagen would be exposed to blood within the aneurysm after deployment by any detachment mechanism. We then compared the cellular effects produced by collagen-filled interlocking detachable coils in the aneurysm to those produced by conventional interlocking detachable platinum coils. We secondarily were able to assess the deployment characteristics of an interlocking detachment

mechanism. The results of these experiments form the basis of this report.

### Materials and Methods

Under an approved protocol, seven adult barnyard pigs were procured through our Institutional Animal Care and Use Facility. All surgical and angiographic procedures were performed with sterile techniques while the animal was under general anesthesia. The animals were maintained in accordance with the National Institutes of Health Guide to the Care and Maintenance of Laboratory Animals (15). Fourteen aneurysms were surgically created in the side wall of the common carotid artery (one aneurysm on each common carotid artery in each pig) by means of autologous external jugular vein grafts by techniques described previously (14). All animals had aspirin (325 mg/d) for 2 weeks after surgery. The aneurysms produced were 6 to 7 mm in length and 5 to 6 mm in maximum width. The orifices averaged 4 to 5 mm. Arteriography was done at 2, 3, 6, and 10 weeks after the aneurysms were created. All animals were killed after the last arteriography was performed (10 weeks).

The animals were divided into four groups, three with two animals each (four aneurysms per group) and one with a single animal (two aneurysms). A study design was developed (see Table) in which one aneurysm in each pig in the first two groups, and both aneurysms of the last group were used as patency controls. In this plan, collagen-filled coils and conventional interlocking detachable platinum coils were compared directly in two animals and each coil type was compared directly with no coils in four animals (two animals for each coil type). Aneurysms designated by the study protocol for embolization were embolized 2 weeks following their creation. One aneurysm from each pig of group 1 and group 3 was packed with interlocking detachable microcoils (Target Therapeutics, Fremont, Calif) containing cores of Zyderm collagen (Collagen Corp, Palo Alto, Calif). At the same time, each animal in group 3 had its second aneurysm packed with simple coils with interlocking detachment mechanisms (Fig 1). Each animal in group 2 had one aneurysm packed with conventional interlocking detachable platinum coils. The resulting coils were 0.018 inches in diameter (coil lengths and helical diameters were as follows: 20 cm, 8 mm; 15 cm, 5 mm; 8 cm, 4 mm; and 6 cm, 3 mm, respectively).



1

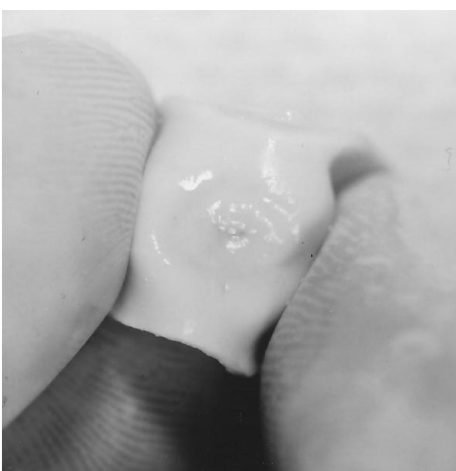


2

Fig 1. Collagen core within platinum coil (top) and standard platinum coil (bottom).



3



4

Fig 3. Control aneurysm.

Fig 4. Aneurysm with collagen-core platinum coil 6 weeks after embolization. Connective tissue fills the aneurysm, and there is a smooth, glistening surface at the site of the former orifice.

All embolizations were performed from a transfemoral route by a single operator. Coils were delivered until the coils approached the aneurysm's orifice. The degree of coil packing was approximately similar for all aneurysms (75% + 15% of aneurysmal size), but unavoidably differed slightly owing to variations in aneurysmal size. In total, of the 14 aneurysms, 6 served as controls, 4 were embolized with collagen core interlocking detachable coils (collagen-filled coils), and 4 were embolized with simple interlocking detachable coils (Figs 2-4). There were no immediate complications.

After the animals were killed, the parent vessels and aneurysms were resected en bloc, their gross features were noted, and they were fixed for histopathologic study. Aneurysms packed with coils were embedded in hydroxyethyl methacrylate, and staining was accomplished by using mineralized bone stain. A circular diamond saw was used for sectioning and the sections were hand polished to 30 μm thickness to preserve the relationships of coil to soft tissue (Harrington Arthritis Research Institute, Phoenix, Ariz). This special attention to technique allowed us to confirm deposition of new collagen on the heterologous implant. Aneurysms without coils were stained with hematoxylin-eosin. Histologic specimens were reviewed by an experienced vascular pathologist.

## Results

### *Detachment Properties*

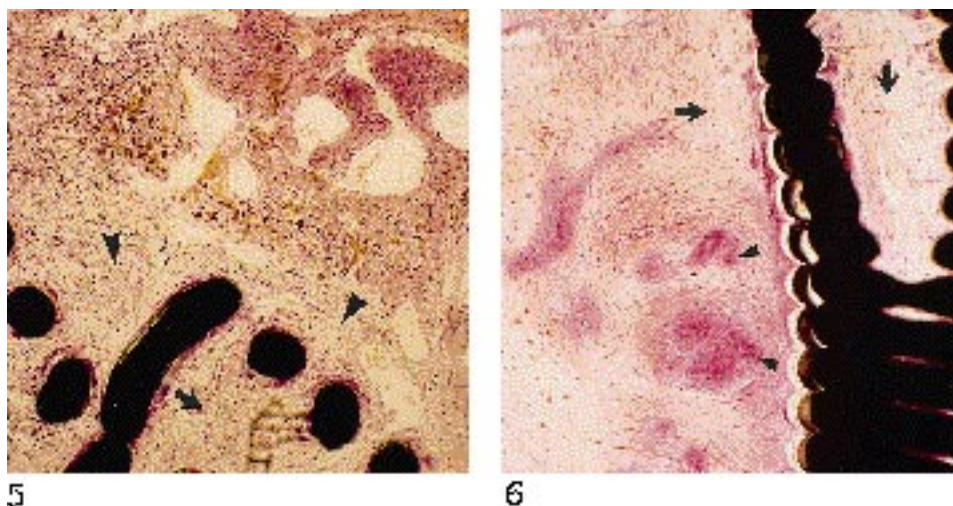
The interlocking detachment system performed well. Coils could be withdrawn until detached, and there was no hindrance to smooth detachment. There was a slight increase in the stiffness of the collagen-core coils unless briefly presoaked in physiological saline. If presoaked in saline, no difference was detectable between the two coil types.

### *Angiography*

All animals underwent arteriography 2 weeks after the aneurysms were created. One of the aneurysms in the animal in group 4 had thrombosed; there had been surgical difficulties in the creation of this aneurysm. The second aneurysm in this animal was patent at the time the animal was killed (10 weeks after the aneurysm had been created). All other aneurysms (12 of 12) were patent at 2 weeks. Arteriography at 3,

Fig 5. Histologic section (mineralized bone stain) of aneurysm treated with collagen-filled coils. Background collagen stains green. Highly cellular tissue infiltrates the collagen core (arrow) and extends outside the coil into neocollagen (arrowheads).

Fig 6. Histologic section (mineralized bone stain) of aneurysm treated with conventional platinum coils (no collagen). No background collagen is seen, and a loose connective tissue matrix fills and surrounds the coil (arrows). Neovascularity is seen in proximity to the coil (arrowheads). Note poor cellularity.



6, and 10 weeks showed that all other nonembolized aneurysms remained patent, although two of the remaining four were 10% to 20% smaller at 10 weeks than at 2 weeks. Three of four aneurysms embolized with collagen-filled coils were completely occluded at angiography at 3, 6, and 10 weeks (1, 4, and 8 weeks after embolization). The fourth aneurysm was partially (83% of aneurysmal volume) occluded. Two of four aneurysms embolized by the conventional interlocking detachable platinum coils were angiographically occluded at 3, 6, and 10 weeks. The remaining two aneurysms were partially (75% of aneurysmal volume) occluded. There were no parent artery thromboses in any group.

### Histopathology

Light microscopy was performed on all specimens (6 to 8 weeks after embolization for embolized aneurysms). Compared with aneurysms treated with the conventional coils, aneurysms embolized with collagen-filled coils showed more new collagen in proximity to the coil and within the heterologous collagen. Within and near this neocollagen, there was a notable increase in the number and density of fibroblasts. At sites more remote to the coils, there was little if any difference in the amount of neovascularity, fibroblastic invasion, or collagen deposition (Figs 5 and 6).

### Discussion

The theoretical approach to endovascular therapy for cerebral aneurysms has heretofore

relied primarily on the creation of a thrombus within the aneurysmal lumen. This approach is inherently flawed, as thrombus has no permanency. In defense of this theoretical premise of filling the lumen of the aneurysm, any permanent device capable of totally filling the aneurysmal lumen would have an advantage over other devices; therefore, a balloon, perfectly sized and shaped to fill the aneurysmal lumen, would be a superb agent. Aneurysms, however, seldom have configurations matching balloon designs (16–18). Pulsatile wave propagation also is promulgated unchanged across liquid environments, necessitating some solidification technique to mitigate against this phenomenon. Coils fail to completely fill the aneurysm with biologically inactive material, and rely, in large part, on thrombus to cause their effects (13, 19). Thrombus, as a dynamic biological material, may and should lyse over time, with secondary recanalization occurring as a natural and expected event. This combination of events often leads to recanalization and regrowth of the aneurysm.

In contradistinction to these therapies, surgical clip ligation relies on the total exclusion of the weakened portion of the vessel from the circulation. In theory, and indeed in practice, this has produced excellent results, even given the invasive nature of the procedure. Despite the rapid and extreme advances in the microsurgical therapy of cerebral aneurysms, morbidity and mortality remain significant, especially for ruptured aneurysms and aneurysms in anatomically challenging locations (20, 21). Giant, large, and wide-necked aneurysms con-

tinue to defy safe surgical therapy, regardless of location (20).

Our project revolves primarily around the use of a biologically active agent for enhancement of fibrogenesis of an ongoing physiological event (thrombosis). As an embolic agent, platinum coils are inherently poor at causing thrombosis, partially because they are biologically inert and offer no demonstrated propensity for converting thrombus to a biologically stable, fibrotic end point (13, 19). Advantages of coils as embolic agents relate primarily to malleability, a physical property, which results in easy delivery to sites distal in tortuous vessels (4-7). As previously alluded to, thrombus itself is an only transient condition on the pathway to a more stable histologic resolution and eventual ablation of the aneurysmal lumen.

If we are to reinforce the neck and orifice of an aneurysm, we must either take advantage of the direct mechanical forces or enhance the biological processes responsible for maintaining tensile strength. Since our approach to the structure is biological then consideration of our building materials is paramount. Collagen is one, and perhaps the most ubiquitous, of all biological building materials present in all human tissues. Tissues deficient in collagen have poor tensile strength, whereas those rich in collagen resist tearing and shearing, probably because collagen-rich tissues are also rich in fibroblasts and fibrous matrix, which allow the tissues a method of continuous repair. If thrombus is a necessary progenitor in the production of strong fibrous tissue, collagen also fulfills this requirement (22-24). Once collagen is present, promotion of fibroblastic ingrowth occurs, with fibroblasts producing even more collagen and promoting the formation of strong, mature connective tissue (25, 26). These conditions should be ideal for the development of a high-tensile-strength cap to the orifice of an aneurysm treated by endovascular methods.

Our study had a limited scope, and was not designed to answer all questions related to the endovascular therapy of berry aneurysms. One potential biological enhancement to a promising but unproved therapy was evaluated for its effects in an admittedly flawed aneurysmal model. The animal and the method of aneurysm creation are subject to criticism. Although swine have clotting mechanisms similar to humans, their mechanisms of converting thrombus to connective tissue are incompletely understood

(27). A surgically created sidewall aneurysm is not a spontaneous aneurysm, and the trauma induced by the surgical procedure may produce fibrogenesis in and of itself. Finally, humans and swine may differ in many other undefined ways as relate to connective tissue, aneurysms, and blood flow. Collagen can be modified in many ways. Optimization of the collagen configuration must be accomplished. If not collagen, then other basic natural building blocks may be useful. Further research in the area of biological enhancement of physical embolization techniques is continuing and promising.

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