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The Nature of Thrombosis Induced by Platinum and Tungsten Coils in Saccular Aneurysms

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PURPOSE: To compare the efficacy and biocompatability of electrolytic and mechanically detachable embolization coils of two metal types. **METHODS:** Experimental saccular aneurysms in pigs were used to assess embolization induced by platinum or tungsten coils. Longitudinal angiographic and histologic studies were performed on treated and untreated (control) aneurysms to compare thrombosis and cellular responses after embolization with electrolytically detachable platinum coils and with mechanically detached tungsten coils. **RESULTS:** Fewer tungsten than platinum coils were needed to induce thrombosis. The inflammatory response within the aneurysmal lumen was more florid in embolized aneurysms than in control aneurysms. No difference was found in the timing or extent of accumulation of eosinophils, lymphocytes, or polymorphs between the two coils used. Giant cell responses were more marked in treated aneurysms; tungsten coils more than platinum coils. The amount of collagen and fibrosis present increased over the study period and was similar in treated and control aneurysms. **CONCLUSION:** The coil type influenced the initial cellular response but had little effect on the rate or degree to which blood clot within the aneurysm was replaced by fibrous tissue.

Index terms: Aneurysm, embolization; Interventional instruments, coils; Animal studies

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Recent advances in coil embolization techniques, including the introduction of detachable coils, have dramatically increased their clinical use for endosaccular packing of intracranial aneurysms (1). Long-term isolation of saccular aneurysms from the circulation depends on stable intraluminal occlusion. Initial obliteration of the lumen is provided by a combination of coil mass and induced thrombosis, but for long-term permanent obliteration of the aneurysm the blood clot needs to be replaced by fibrous tissue. One study describing microscopy of the coil/thrombus complex in humans (2) reported only incomplete fibrous replacement of blood clot in giant aneurysms several months after the coils were inserted.

In the absence of human data, histologic changes after various endosaccular embolization techniques have been studied in experimental aneurysms (3). These investigations have shown that the thrombotic properties of different coils vary according to the design, coating, and materials used in their construction (4–6). Other studies have shown that stable aneurysmal thrombosis is associated with the formation of an endothelium-lined layer of connective tissue between the aneurysm and parent artery months after embolization, but they have not established the time needed for arterial wall healing (7, 8).

This study was performed to compare the type and stability of intralumenal thrombus formed both spontaneously and after embolization with detachable platinum or tungsten coils and to determine the rate at which osteal healing occurs in experimental aneurysms.

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Materials and Methods

Twenty-three experimental aneurysms were surgically constructed from vein allographs anastomosed to the carotid artery of female pigs (25 to 30 kg) using the technique established by German and Black (9) and modified as described in an earlier article (10). A 4.5-mm-diameter punch was used to make a standard arteriotomy so that the neck of all the aneurysms was the same size. Some variation in the size of the aneurysmal lumens was inevitable, since the width depended on the dimensions of the vein graft. The completed aneurysms therefore measured 10 to 14 mm in length and 5 to 6 mm in width. Surgery, angiography, and coil embolization were performed with the animals under general anesthesia, which was induced and maintained through inhalation of halothane with a mixture of nitrous oxide and oxygen.

After surgery, patency of the aneurysms was documented by selective carotid angiography, performed by percutaneous transfemoral catheterization. Embolization of 18 aneurysms (10 with platinum and eight with tungsten coils) was performed 0 to 3 days after surgery via the same route. A 5F or 6F guide catheter was placed in the carotid artery and the aneurysms were catheterized with an appropriate microcatheter for delivery of platinum Guglielmi detachable coils (GDCs) (Target Therapeutics, Fremont, Calif) or tungsten Mecanique des Spirales (MDS) tungsten coils (Balt Extrusion, Montmorency, France). Angiography alone was performed in five control animals in whom aneurysms were left untreated. Coils were placed until the aneurysmal lumen no longer filled with radiographic contrast material. This end point, rather than a dense packing with coils, was used to compare the ability of the two coil types to induce intralumenal thrombosis.

Follow-up angiography was performed in all animals at 2 weeks (8 to 18 days), after which nine animals were killed. Angiography was repeated at 4 weeks (24 to 30 days) in seven animals and at 7 weeks (44 to 56 days) in the remaining seven animals. After the final angiographic study, the animals were killed and the aneurysms removed. The aneurysms were sectioned transversely, midway between the fundus and neck, and the coils were removed by gentle traction to minimize disturbance of the thrombus prior to being embedded in paraffin wax. The fixed specimens were sectioned perpendicular to the long axis of the parent vessel, stained with hematoxylin-eosin, Masson trichrome, or reticulin, and examined by light microscopy.

The intralumenal thrombus was assessed for the number of neutrophil polymorphs, eosinophils, lymphocytes, and giant cells and the extent of collagen formation, fibrosis, and vascularization within the aneurysmal lumen. The presence of endothelium at the aneurysmal neck was also recorded. These assessments were scored from 0 to 3, with 3 being the most cellular, by an investigator who was blinded to the treatment group of each specimen. Statistical analysis of the resulting scores was performed using Student's *t* test for matched groups.

Results

Angiographic Results

Coil embolization achieved 100% occlusion in 10 aneurysms (GDCs, four of 10; MDSs, six of eight). Residual filling was evident as a neck remnant only (ie, >95% occlusion) in five aneurysms (GDCs, four of 10; MDSs, one of eight), as a larger residuum into which coils could not be placed without obstructing the parent artery in three aneurysms (GDCs, two of 10; MDSs, one of eight). All subtotally occluded aneurysms were completely thrombosed on subsequent angiography and all five untreated aneurysms spontaneously thrombosed over the study period (Fig 1). In all, 38 GDCs were used in 10 aneurysms (mean, four; range, three to six coils) and 16 MDSs were used in eight aneurysms (mean, two; range, one to four coils).

Histologic Results

Blood clot in various stages of resolution was present in nine of 11 aneurysms examined up to 26 days after surgery, but had been completely replaced in all aneurysms examined after 26 days. Within the lumen of the aneurysm there was a granulation-tissue response with capillary ingrowth and proliferation and progressive replacement of the blood clot with increasingly collagenized fibrous scar tissue. There was no difference in the timing, degree, or rate of progress of this fibrous replacement of blood clot in control animals or those treated with MDS or GDC coils.

In addition to the fibrotic reaction replacing the intralumenal blood clot, an inflammatory response was present within the granulation-tissue response composed predominantly of neutrophil polymorphs, eosinophils, and lymphocytes (Fig 2). With both types of coil, the inflammatory response was significantly greater than in the control animals, although there was no statistical difference in mean cellularity scores between aneurysms treated with GDC or MDS coils (Table). As would be expected, the inflammatory response was greatest in the first few weeks; the difference in pooled mean scores between treated and untreated aneurysms being statistically different in those examined in the first 28 days but not thereafter.

In a number of cases, there was also a prominent foreign-body type giant cell reaction related either to the coils themselves or to other

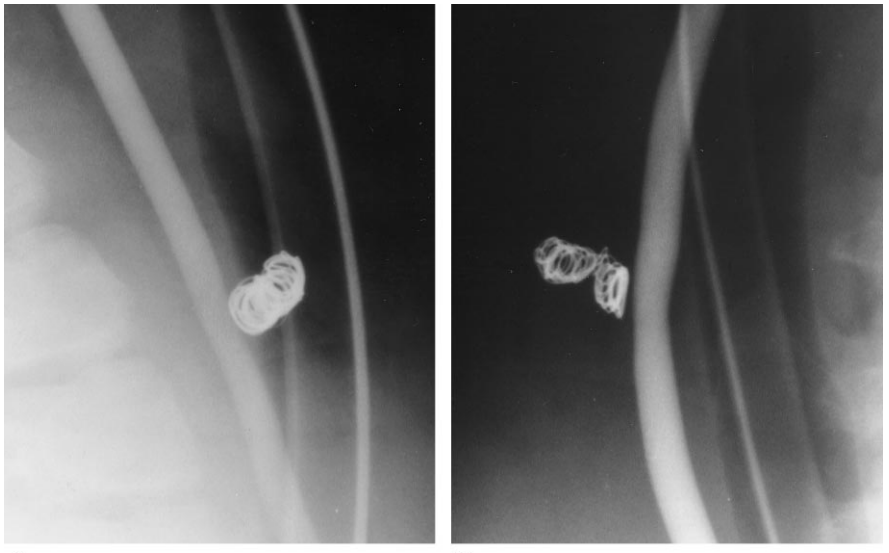

Fig 1. Angiograms 6 weeks after embolization with GDCs (*A*) and MDSs (*B*). Note complete healing of the parent artery wall and the looser coil packing in *B*.

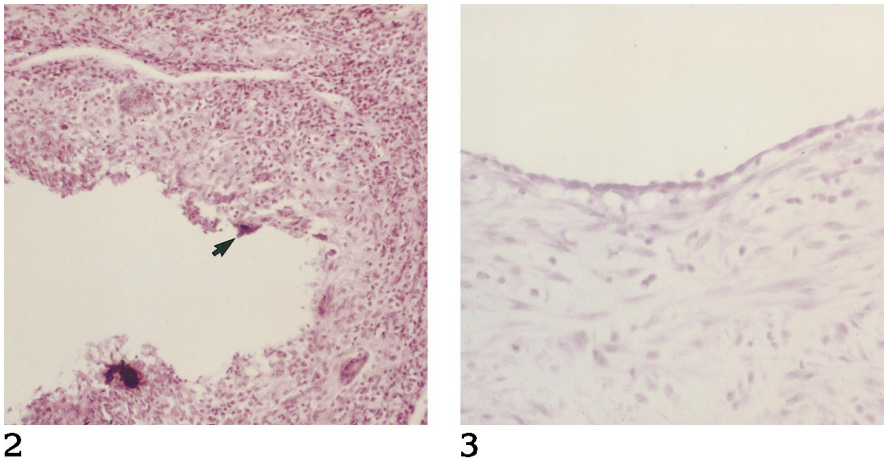

Fig 2. Microscopic appearance of the inflammatory infiltrate surrounding a platinum coil after the coil has been removed. There is a dense, predominantly lymphoid infiltrate within cellular fibrous tissue, and a giant cell (*arrow*) is present adjacent to the space from which the coil has been removed (hematoxylin-eosin, original magnification ×125).

Fig 3. Microscopic section of the thrombosed aneurysmal neck 6 weeks after treatment with tungsten coils. There is a single layer of endothelium covering cellular fibrous tissue, which contains a scant lymphoid inflammatory infiltrate and shows little evidence of organization. An endothelium cover was always present 3 weeks after thrombosis (hematoxylin-eosin, original magnification ×375).

Cellularity scores for aneurysms treated with GDCs and MDS coils

Type of Aneurysm	Polymorphs/Eosinophils/ Lymphocytes			Giant Cells			Collagen/Fibrosis		
	n	Mean	SEM	n	Mean	SEM	n	Mean	SEM
Control aneurysms	15	0.47	0.12	5	0.40	0.40	10	2.40	0.16
Aneurysms treated with GDCs	30	1.15*	0.23	10	1.20	0.34	20	2.50	0.12
Aneurysms treated with MDS coils	24	1.05*	0.22	8	1.69*	0.34	12	2.62	0.13
Control aneurysms examined <28 days after surgery	12	0.46	0.14	4	0.50	0.50	8	2.37	0.18
GDC + MDS-treated aneurysms examined <28 days after surgery	36	1.22**	0.18	12	1.63*	0.31	24	2.54	0.10
GDC + MDS-treated aneurysms examined >28 days after surgery	12	0.72	0.24	6	1.00	0.36	8	2.58	0.15

Note.—Each cell type was given a score from 0 to 3. The scores for inflammatory cells (polymorphs, eosinophils, and lymphocytes) were summed. Comparisons were made between treated and untreated (control) aneurysms and between control aneurysms examined less than 28 days after surgery and coil-treated aneurysms examined before and after 28 days after surgery. n indicates the number of observations made.

* $P < .05$

** $P < .01$

foreign material within the aneurysmal lumen. Such a reaction was found in both treated and untreated aneurysms, but was more pronounced in MDS-treated aneurysms, reaching statistical significance at the 5% level compared with untreated control animals; but in the GDC-treated aneurysms, the giant cell reaction was not significantly different from that seen in the control animals (Table).

At the neck of the aneurysm, the initial fresh thrombus was progressively replaced by fibrous tissue ingrowth from the margins. Fibrous obliteration of the neck occurred more rapidly than resolution of the intralumenal blood clot and was present, together with endothelial overgrowth, as early as 14 days after coil embolization (Fig 3). As with fibrous replacement of the clot, the rapidity and extent of this process were not influenced by the presence or type of coil used.

Discussion

The experimental aneurysm used in this study has some shortcomings as a model of intracranial aneurysms, since most human aneurysms are in the subarachnoid space and arise at arterial branch points, not as lateral pouches. However, the model has been widely adopted because no satisfactory intracranial animal model is currently available and because the surgery involved is relatively simple. The surgical technique used in this study was most similar to that used by Ahuja et al (6) in dogs and allows the construction of a standard aneurysm of relatively uniform size and shape. The reproducibility of the model makes it more suitable for comparative studies of endovascular treatments rather than of aneurysmal hemodynamics or pathophysiology (11).

This model in pigs has a propensity for spontaneous thrombosis (12) and early rupture (10). For the latter reason, embolization was performed without the traditional interval for maturation of the anastomosis. The absence of this delay was not associated with additional morbidity. In this study the MDS coils were more thrombogenic than the GDC coils at least in their ability to induce thrombus, since residual luminal filling was evident in two of eight aneurysms in which MDSs were used compared with six of 10 aneurysms in which GDCs were used, and embolization was achieved with fewer coils. Electrothrombosis, which potentially enhances GDC thrombogenicity (7), appears to have little effect on the induction of thrombus or its nature, although we did not compare GDCs with mechanically detached platinum coils.

We are aware of two previous reports of microscopy after coil embolization of aneurysms in the pig (7, 13). In the report by Guglielmi et al (7), microscopy of a single aneurysm 2 months after treatment with GDCs showed the coils were surrounded by abundant well-organized thrombus, numerous foreign-body giant cells, and chronic inflammation within the clot. The neck was entirely occluded by organized thrombus with an endothelial lining to the luminal surface. Dawson et al (13) compared the histology of aneurysms embolized with Dacron-fibered and collagen-coated platinum coils at 3, 6, 9, and 12 weeks after embolization. The aneurysms treated with collagen-coated coils developed a more mature collagen-rich fibrous scar as early as 3 weeks after treatment. These authors comment that the longer the interval since embolization the more fibrous the scar, but they did not present detailed longitudinal data. Residual thrombus was present in aneurysms treated with fiber coils for up to 12 weeks.

Our results show that the initial inflammatory response after thrombosis is influenced by the embolization device used, but this difference in cellularity between embolized and spontaneously thrombosed aneurysms was less apparent with the development of fibrosis and collagen. This would suggest that in the long term the coil type has little influence on the replacement of the initial blood clot by fibrous scar, at least for uncoated coils.

This observation is indirectly supported by studies of delayed microscopy. Histologic changes 6 months after embolization with GDCs were studied by Mawad et al (8) in dogs. The lumen contained richly vascularized fibrous tissue between the coils that was dense and collagenized at the periphery. There was a mild foreign-body response consisting of a few histiocytes and giant cells. The center of larger aneurysms contained less organized fibrous tissue with newly formed capillaries and prominent fibroblasts, suggesting that maturation occurred from the periphery. The aneurysmal neck was covered by tissue organized in three layers; a superficial layer of endothelium, beneath which smooth muscle cells were arranged in two separate layers. Also in the dog, Graves et al (4) found highly organized thrombus com-

posed of collagenized fibrin and fibrous tissue adherent to the wall of aneurysms embolized with platinum coils with and without attached silk fibers. Only a limited inflammatory reaction was present and the neck was lined with a cell layer continuous with the endothelial cell lining of the parent artery. The aneurysms were examined up to 158 days after treatment, but no longitudinal comparison of the histologic changes was described.

Rabbits were used for the construction of experimental aneurysms in two recent reports (M. P. Marks, C. C. Tsai, A. M. Norbash, H. Chee, K. S. Waggie, and G. K. Steinberg, "In Vivo Evaluation of Coils for Endovascular Therapy"; and J. Reul, U. Spetzger, C. Fricke, et al, "Treatment of Experimental Bifurcation Aneurysms with Detachable Platinum and Tungsten Coils: Angiographic and Histologic Results" both presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, May 1995.) Two months after embolization with platinum, tungsten, and nitinol coils, Marks et al found the coils to be covered by an endothelial overgrowth that was thickest over the platinum coils. They also examined the coils 24 hours after placement and found a layer of fibrin that was thinnest on the tungsten coils. However Reul et al performed microscopy 3 and 4 months after embolization with tungsten and platinum coils and found no endothelialization at the aneurysmal neck with open spaces between loops of intraluminal coils. A bifurcation model was used in their study, in which the hemodynamic influence of blood flow more closely simulates human aneurysms. The lateral wall aneurysm model used in our study has little tendency toward recanulation and therefore the potential effect of coil compaction and recanulation on thrombus stability could not be assessed.

It can be concluded that the type of metal and design of coils influence the induced thrombus in the short term. More longitudinal studies are needed to show the effect of coil design on the formation of fibrosis, since, bearing in mind species variations, the current evidence suggests that initial occlusion of the aneurysmal neck does not ensure stability as maturation of the coil/thrombus complex takes place.

Acknowledgments

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