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Long-term Angiographic and Histopathologic Findings in Experimental Aneurysms of the Carotid Bifurcation Embolized with Platinum and Tungsten Coils

J. Reul, J. Weis, U. Spetzger, T. Konert, C. Fricke, and A. Thron

PURPOSE: To evaluate the long-term outcome of endovascular occlusion of arterial aneurysms effected with metal coils. **METHODS:** Microsurgical methods were used to produce carotid bifurcation aneurysms in 20 rabbits and the radiologic and histologic changes were examined. Eight of these aneurysms were occluded with electrically detachable platinum coils (Guglielmi detachable coils [GDCs]) and nine were treated with mechanically detachable tungsten coils (mechanical detachable system [MDS]). Three aneurysms remained untreated and served as controls. One animal died of embolic complications 12 hours after endovascular treatment. After observation periods of 3 to 6 months, the remaining animals were examined by intraarterial digital subtraction angiography and subsequent fixation and light and electron microscopy. **RESULTS:** Large open spaces without signs of thrombosis were found between the loops of the coil baskets in 12 aneurysms (six treated with GDCs and six treated with MDS) regardless of the observation period. In very densely packed aneurysms (four cases with complete occlusion as determined by angiographic criteria), the coil surfaces were for the most part covered by thin cell layers; however, complete endothelialization was never seen. In aneurysms with an initial partial occlusion of 70% to 90%, coil compaction and/or recanalization was a consistent finding. A comparison of the radiologic findings with the histologic aspect revealed that the degree of occlusion was often overrated on the radiographs (in eight of 17 cases). In general, the fibrous tissue reaction appeared to be slightly more pronounced in aneurysms occluded with tungsten coils. **CONCLUSIONS:** Platinum and tungsten coils were not always effective in causing endoluminal thrombosis leading to long-term occlusion by organized thrombus.

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

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Endovascular treatment with detachable coils is an accepted method for the occlusion of cerebral arterial aneurysms that otherwise would require high-risk surgery or that cannot be treated at all by surgery (1-4). It has been suggested that this new technique may be a promising general alternative to neurosurgical

management of small berry aneurysms even though the long-term outcome of endovascular treatment with coils has as yet not been studied sufficiently either in experimental animals or in large-scale clinical trials. Moreover, little is known about the degree of embolization achieved by this method and the cellular reactions to the endovascular coils. Only a small number of experimental studies of the effects of endovascular coils on arterial aneurysms have been performed thus far.

Human cerebral berry aneurysms are usually found at arterial bifurcations (5, 6). Therefore, to study the effects of endovascular treatment with detachable coils, we used an established model for small berry aneurysms with microsurgically created arterial bifurcation aneurysms in rabbits (7-10).

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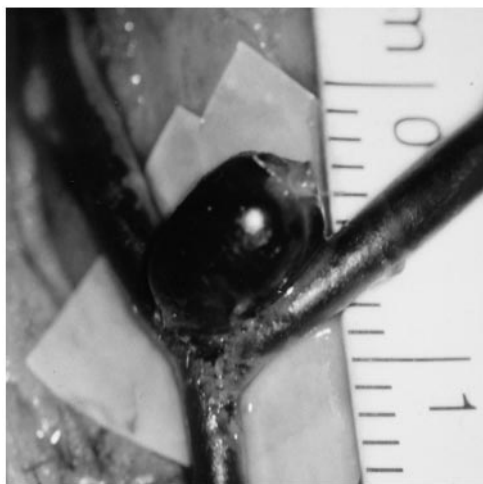


Fig 1. Intraoperative photograph of a typical carotid bifurcation aneurysm in the rabbit. The aneurysm is about 8 mm in length and shows a well-delineated neck. The diameter of the parent vessel is about 2 mm.

Materials and Methods

In 20 bastard chinchilla rabbits (weight, 4 to 5 kg), experimental bifurcation aneurysms were created microsurgically using a technique described by Forrest and O'Reilly (8). The arteriotomies were modified and the sutures uptied to achieve variously sized aneurysmal domes and necks (Fig 1). The aneurysms were produced by means of a venous graft pouch derived from the right jugular vein. The microsurgical procedure has been described in detail elsewhere (11). After 3 weeks, intraarterial angiography via a transfemoral approach was performed. The sizes of the aneurysms were determined on the angiographic films according to Zubillaga et al (4) by using a caliper ruler. The diameters of the aneurysms ranged from 3 to 14 mm (Tables 1 and 2). The diameters of the parent vessels were about 2 mm, which is similar to the human anterior and middle cerebral artery. At that time, eight aneurysms were occluded by use of electrically detachable coils (Guglielmi detachable coils [GDCs]). Nine aneurysms were treated with mechanically detachable tungsten coils (mechanical detachable system [MDS]). Because the packing density of the coils in human cerebral artery aneurysms varies considerably, four of the experimental aneurysms (two of each group; animals 1, 9, 14, and 16 in Table 1) were packed very densely (Fig 2); the remaining aneurysms were occluded only partially (Table 1). Tungsten coils are more rigid and probably more thrombogenic than platinum coils because their surface is not as smooth (Fig 3); therefore, they were packed together less closely. Three unembolized aneurysms served as controls; their walls were covered by normal endothelium as determined by scanning electron microscopic criteria (see below), and the lumina were patent throughout the observation period.

Control angiography was performed after 3 to 6 months in 16 animals. The degrees of occlusion were determined independently by two experienced neuroradiologists. The degree of occlusion was determined to be *complete* (100%) if no residual lumen was detectable by angiography. If a residual lumen was visible on the angiograms, occlusion was considered to be *incomplete*, and for these cases three further categories were defined: *almost complete* (90% to 100% occlusion, only a very small residual pouch at the neck); *partial* (70% to 90% occlusion, small but clear residual lumen at the neck of the aneurysm); or *minimal* (70% or less occlusion, estimated by comparing the open lumen with the total size of the aneurysm). Dome and neck sizes were also determined on the angiograms.

Immediately after the second angiographic examination, the animals were killed. Simultaneously, a perfusion fixation of the arteries was performed to avoid postmortem coagulation artifacts. To avoid mechanical alterations of the neck and of the coil surface, the carotid arteries were opened along the long axis opposite the aneurysmal neck under microscopic control. The aneurysms, the adjacent blood vessels and other tissues, as well as the brains were examined macroscopically, photographed, postfixed, and dissected. In addition, the size of the remaining lumen was estimated by microscopic examination using the same categories as for the angiographic analysis (size of the residual lumen in relation to the total size of the aneurysm). The results of the gross pathologic analysis were documented photographically. The aneurysmal walls and the adjacent blood vessels were divided into several segments. Segments from each case were examined by scanning electron microscopy. In the four cases with detectable tissue between the coils (see below), pieces of these tissues were embedded in epoxy resin and examined by light and transmission electron microscopy according to standard protocols. Additional segments from two of these aneurysms were frozen in liquid nitrogen; cryostat sections from these blocks were stained with hematoxylin-eosin.

Results

A synopsis of the angiographic, gross pathologic, and electron microscopic results is presented in Tables 1 and 2.

Aneurysms Embolized with Platinum Coils (Eight Cases)

Initial angiographic findings showed two aneurysms that were judged to be completely occluded, three that were almost completely occluded, and three that were partially occluded immediately after the embolization procedure.

Control Angiographic Findings.—Three animals were examined after 3 months, and five rabbits were examined after 6 months with fol-

TABLE 1: Angiographic and pathologic findings in experimental bifurcation aneurysms created in 17 rabbits

| Animal | Type of Coil | Aneurysm Diameter, mm | Dome-to-Neck Ratio* | Occlusion | | Increase or Decrease Relative to First Follow-up† | Degree of Occlusion at Gross Pathology | Increase or Decrease Relative to Second (Control) Follow-up† | Observation Period |
|--------|--------------|-----------------------|---------------------|-----------------|------------------|---|--|--|--------------------|
| | | | | First Follow-up | Second Follow-up | | | | |
| 1 | MDS | 3 | > 1 | C/AC | C | I | C | N | 3 mo |
| 2 | MDS | 6 | > 1 | P | MO | D | MO | N | 3 mo |
| 3 | MDS | 4 | > 1 | P | ... | ... | P | N* | 12 h |
| 4 | MDS | 9 | 1.0 | P | MO | D | MO | D | 6 mo |
| 5 | MDS | 10 | > 1 | P | MO | D | MO | D | 6 mo |
| 6 | MDS | 7 | > 1 | P | MO | D | MO | N | 5 mo |
| 7 | MDS | 6 | > 1 | P | P | N | MO | D | 6 mo |
| 8 | MDS | 8 | 1.0 | P | MO | D | MO | N | 3 mo |
| 9 | MDS | 7 | 1.0 | AC | MO | D | MO | D | 4 mo |
| 10 | GDC | 4 | > 1 | P | C | I | AC | D | 3 mo |
| 11 | GDC | 8 | > 1 | AC | MO | D | MO | N | 6 mo |
| 12 | GDC | 12 | > 1 | P | P | N | MO | D | 6 mo |
| 13 | GDC | 6 | 1.0 | AC | AC | N | P | D | 6 mo |
| 14 | GDC | 4 | > 1 | C/AC | AC | N | MO | D | 6 mo |
| 15 | GDC | 5 | 1.0 | P | AC | I | AC | N | 5 mo |
| 16 | GDC | 6 | 1.0 | C | P | D | MO | D | 3 mo |
| 17 | GDC | 5 | 1.0 | AC | MO | D | MO | N | 3 mo |

Note.—MDS indicates mechanical detachable system with tungsten coils; GDC, Guglielmi detachable coils (platinum); C, complete; AC, almost complete; P, partial; and MO, minimal occlusion.

* Dome-to-neck ratio was set to 1 if the diameter of the aneurysmal neck was large (more than two thirds of the dome diameter), and was >1 if the diameter of the neck was two thirds of the diameter of the dome or less.

† Relative to first follow-up examination compared to A1; I indicates increase; D, decrease of occlusion; N, no change.

TABLE 2. Findings at angiography and electron microscopy in experimental bifurcation aneurysms created in 17 rabbits

| Animal | Coil Configuration at Control Angiography | Coil Configuration at Gross Pathology | Electron Microscopy |
|--------|---|---------------------------------------|--------------------------------------|
| 1 | Basket | Occluded | Cells, endothelium |
| 2 | Dime | Compacted | Fibrin, thrombocytes, no endothelium |
| 3 | ... | ... | Fibrin, thrombocytes |
| 4 | Dime | Compacted | Fibrin, thrombocytes, no endothelium |
| 5 | Basket | Compacted | Fibrin, thrombocytes, no endothelium |
| 6 | Basket | Compacted | Fibrin, thrombocytes, no endothelium |
| 7 | Basket | Basket | Fibrin, thrombocytes, no endothelium |
| 8 | Dime | Compacted | Fibrin, endothelium |
| 9 | Dime | Compacted | Fibrin, no endothelium |
| 10 | Basket | Basket | Fibrin, no endothelium |
| 11 | Dime | Compacted | Fibrin, thrombocytes, no endothelium |
| 12 | Basket | Compacted | Fibrin, thrombocytes, no endothelium |
| 13 | Dime | Compacted | Fibrin, no endothelium |
| 14 | Dime | Compacted | Thrombocytes, no endothelium |
| 15 | Basket | Basket | Fibrin, no endothelium |
| 16 | Basket | Compacted | Fibrin, endothelium |
| 17 | Dime | Compacted | Fibrin, no endothelium |

Note.—At initial angiography, the coils were arranged in a basket formation for optimal occlusion of the aneurysm. Dime describes the reconfiguration of the coils due to the rearrangement and compaction resulting in an appearance similar to a roll of coins. Coil configuration at posttreatment angiography was that of a basket in all cases.

Fig 2. A, Intraarterial angiogram obtained by using a microcatheter (Tracker 10, Target Therapeutics, Fremont, Calif) shows a typical bifurcation aneurysm (animal 16).

B, Control angiogram obtained immediately after dense packing with platinum coils (the coils were packed until no additional coil could fit into the lumen) shows a small peripheral rim of contrast; however, the neck is completely excluded from the parent circulation.

C, Control angiogram obtained 3 months after occlusion shows slight enlargement of the arteries. The coils were compacted at the dome of the aneurysm and a partial recanalization of the neck can be seen (arrows).

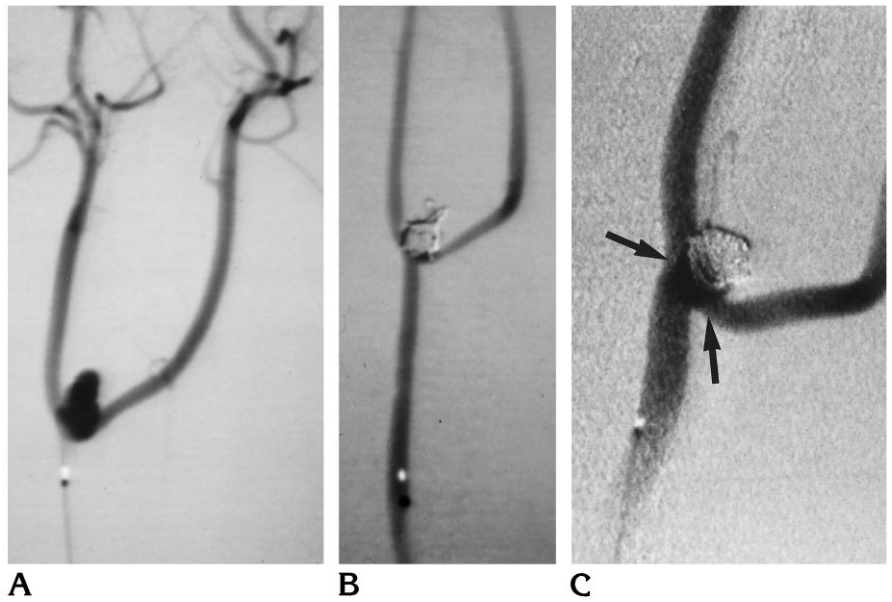
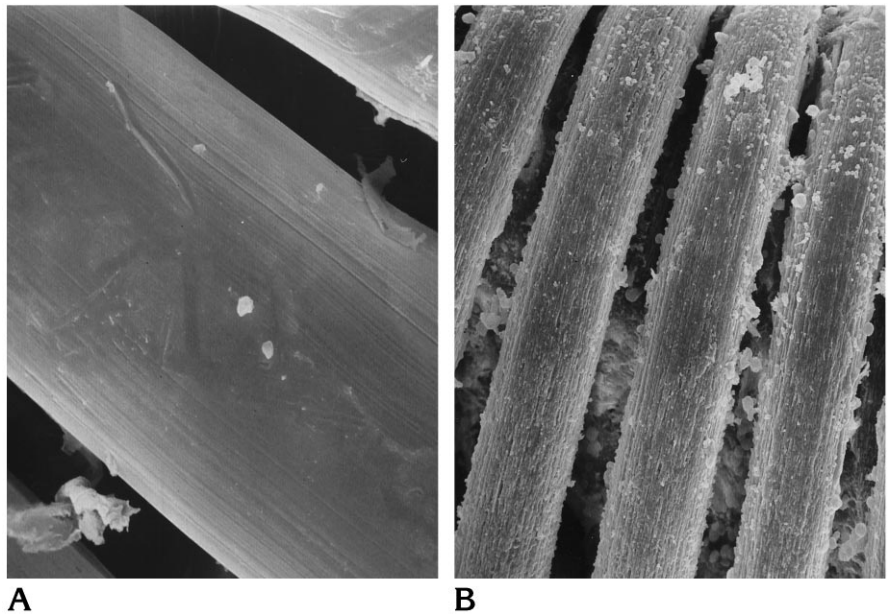


Fig 3. High-magnification scanning electron microscopic examinations of a platinum coil (A) (magnification $\times 1000$) and tungsten coil (B) (magnification $\times 400$). The surface of the tungsten coil is rougher than that of the platinum coil.



low-up angiography. Three aneurysms remained unchanged, an increase in the occlusion rate was seen in two cases, a decrease due to coil compaction and recanalization of the neck was seen in three cases (Fig 2), and three cases were unchanged.

Gross Pathologic Findings.—In six aneurysms, the coils were rearranged and had lost the basket configuration. The central lumen and the neck of these aneurysms were open and the

coils appeared uncovered. The coils in the lumen of these aneurysms were not covered by any tissue and there were large open spaces without thrombosis between the loops of the coils (Fig 4). In contrast to the angiographic findings, the residual lumen appeared larger, even in the case (animal 15) in which there was an angiographically increased occlusion rate. In only one case were the coils covered by a transparent layer of neointima.

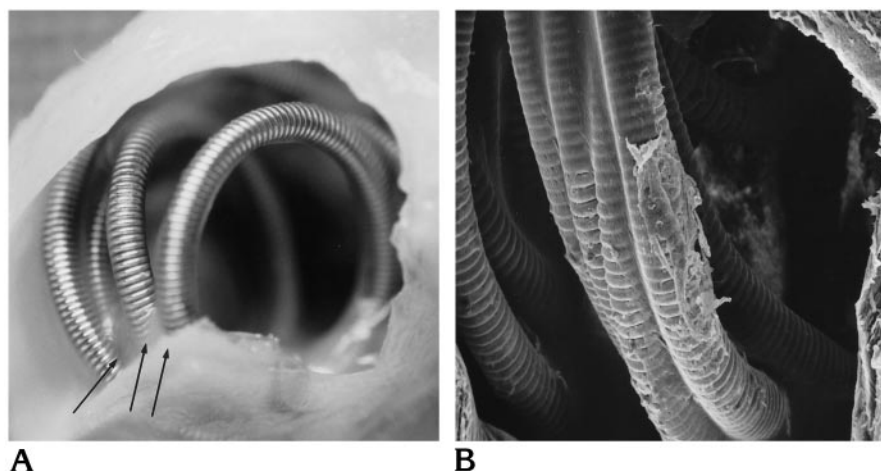


Fig 4. A, Gross pathologic examination of the ostium (neck) of the aneurysm (animal 16) shows a considerable compaction of the coils with reorganization of the initially created basket to a more "roll-of-coins" type configuration (magnification $\times 15$). The degree of reopening is much higher than is suggested on the angiographic films. The coils appear blank without thrombotic material between the spaces or endothelialization. Only at the contact zone to the aneurysmal wall is a smooth, transparent tissue layer visible (arrows).

B, Scanning electron microscopic examination (magnification $\times 40$) (animal 17) shows the surface of the coils covered by a thin layer of protein (fibrin). However, the spaces between the loops are not occluded. Even at higher magnification, no cobblestone pattern was visible.

Aneurysms Embolized with Tungsten Coils (Nine Cases)

Initial Angiographic Findings.—Of these aneurysms, two had been occluded completely and, in seven, partial occlusion (70% to 90%) was found immediately after embolization. One animal died 12 hours after embolization as a result of a stroke with prominent right hemisphere necrosis. An embolus appeared to be the cause of necrosis, because a hemorrhagic component was observed in the necrosis.

Control Angiographic Findings.—One animal was killed after 4 months and one animal had to be killed 5 months after surgery because of an infection unrelated to the surgical or interventional procedure. Three aneurysms each were examined by angiography after 3 and 6 months, respectively. An increase in occlusion rate was found in only one case, one aneurysm was unchanged, and a decrease in the occlusion rate was seen in six cases.

Gross Pathologic Findings.—One aneurysm was completely excluded from the parent circulation by a neointimal layer of connective tissue. In one aneurysm, there was still a basket configuration; however, no intimal layer was visible. Coil compaction was found in six aneurysms. In contrast to the platinum coils, there was more reactive connective tissue between the coil loops in the fundus, and in two aneurysms the coils were covered by a smooth, transparent layer of soft tissue.

Because the pathologic results were similar in both groups, the findings are presented in summary. The walls of both the control aneurysms

and the partially recanalized aneurysms were covered by a glistening layer of membranous tissue similar to the adjacent arterial wall, suggesting continuous endothelialization.

In more than half the cases of partial occlusion, a compression of the coil basket with an open aneurysmal neck was seen (Tables 1 and 2). Compared with the degree of occlusion estimated after angiography, the gross examination revealed a decreased occlusion rate in these cases, suggesting an overestimation of the occlusions on the basis of the angiographic results (Table 1).

Of the four aneurysms with detectable tissue between the coils and a neointimal layer (one platinum and three tungsten coils), two (one platinum and one tungsten coil) were subjected to histologic analysis. No major inflammatory reaction was seen. The thin layer between the coils consisted of granulation tissue with numerous capillaries.

Each of the 17 aneurysms was examined by scanning electron microscopy (Table 2). In addition, three cases (one GDC, two MDS) were analyzed by transmission electron microscopy. In the above-mentioned four cases with detectable tissue between the coils, these tissue layers were covered by cells that showed a cobblestone pattern by scanning electron microscopy. This pattern is typical, but not specific for endothelial cells. Focally, these cells were covered by amorphous material, presumably fibrin, and thrombocytes. In the remaining cases, no signs of endothelialization were present. Few thrombocytes adhered to these coils. The surfaces of

the tungsten coils were not as smooth as those of the platinum coils.

Discussion

Endovascular occlusion of cerebral arterial aneurysms with detachable coils has been proposed as an alternative to neurosurgical management (2–4). Even though initial clinical results of endovascular occlusion were encouraging (2, 4, 12), follow-up control studies after 6 and 12 months showed recanalization frequencies of 30% or higher. In a considerable number of cases, only subtotal or partial occlusion was possible, depending on the configuration of the aneurysm and especially on the size of the neck (4). The aneurysms that were occluded incompletely initially remained unchanged without any further thrombosis (2, 4).

Incompletely clipped aneurysms are likely to bleed again (13–24) and thus may be at risk for recurrent subarachnoid hemorrhage. So far, clinical long-term results of large-scale controlled studies of endovascular occlusion of bifurcation aneurysms with detachable coils are lacking. Experimental data are also rare, which is why we performed the present study of surgically created bifurcation aneurysms in rabbits. Most intracranial aneurysms in humans are located in or close to arterial bifurcations, such as the basilar tip. In several previous studies, the model systems did not closely mimic the situation in human cerebral aneurysms, because the aneurysms were not located at bifurcations but instead were placed somewhere along the course of the arteries, even though hemodynamics are very different at bifurcations than at other parts of blood vessels (1, 25–28). Moreover, it is important to consider the blood coagulation profile of the experimental animal, which is quite different from that in humans and dogs and is actually not very well studied in pigs. Thus, results of studies using large blood vessels in dogs or pigs are not necessarily applicable to humans.

Mechanisms of blood clotting in rabbits have been studied extensively (7, 29–40) and found to be similar to those in humans. The anatomy of the circulation of the head and neck in rabbits is well known (41). Forrest and O'Reilly described an experimental model of bifurcation aneurysms using the rabbit common carotid artery and a pouch created microsurgically from a segment of the jugular vein (8). This model has

been used in a small number of rabbits to test the efficacy of embolization approaches with fiber-coated coils (7). In the present study, 20 aneurysms were produced by a slightly modified technique.

Nine aneurysms were embolized with tungsten coils, which are thought to be more thrombogenic than platinum coils. Eight aneurysms were occluded with electrically detachable platinum coils. Observation periods of 3 and 6 months were chosen to detect long-term changes, including organization of thrombi and endothelialization.

Surprisingly, virtually no intraluminal thrombi were found adhering to the coils. In only four cases (the ones with the most densely packed coils) were the spirals covered by granulation tissue. On the intraluminal surface of this tissue, cells arranged in a cobblestone pattern, presumably endothelial cells, were seen by scanning electron microscopy. The proliferation of granulation tissue appeared to be more prominent in the aneurysms treated with tungsten coils (three of nine) than in those occluded with platinum coils (one of eight), despite the less dense packing of the tungsten coils, and may be a result of the irregular surface of these coils (Fig 3). Unfortunately, antisera specifically directed against antigens of rabbit endothelial cells are not available thus far to confirm the endothelial differentiation of the cells covering the tissue by immunohistochemistry. However, in most treated aneurysms (13 of 17), the intraluminal surfaces of the coils were not covered by any tissue, and only small, fresh blood clots and aggregated thrombocytes were found to adhere to the coils.

Most aneurysms showed some degree of recanalization, regardless of the degree of the initial coil packing (Figs 2 and 4). In the majority of cases, measurement of the degree of embolization by use of the angiographic films led to an overestimation of the occlusion as compared with the direct measurements of the specimens collected immediately after angiography and perfusion fixation.

These results indicate that in the present experimental system of bifurcation aneurysms in rabbits, platinum and tungsten coils are quite ineffective in causing endoluminal thrombosis that leads to long-term occlusion by an organized thrombus. To achieve a minor degree of proliferation of granulation tissue, complete filling of the aneurysms with coils is necessary;

and even in these cases, recanalization can take place. Future modifications of the coil surfaces might enhance the thrombogenic potential of the material.

The present data differ from results obtained by others who found a higher degree of thrombosis and fibrosis between the coils, leading to a higher degree of occlusion (28). However, those groups used different experimental animals and different surgical approaches to produce aneurysms (see above).

Nevertheless, a favorable outcome with regard to lack of repeat hemorrhage of recently ruptured cerebral berry aneurysms treated by endovascular approaches has been reported (F. Vinuela, "Summary of the Multicentric Study Results of the Treatment of Cerebral Aneurysms Using the GDC System," presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995). However, detachable coils as a means to treat cerebral berry aneurysms were introduced only 3 years ago. Therefore, the observation periods in these studies are restricted. Large-scale clinical trials with long-term follow up of the patients are necessary to determine the efficacy of endovascular occlusion therapy. These trials should include autopsy studies on patients treated by coil embolization with long-term survival and later death of unrelated causes. In such cases, the degree of occlusion as well as the cellular reactions to the coils can be determined with certainty.

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