Microsurgically produced bifurcation aneurysms in a rabbit model for endovascular coil embolization

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Endovascular coil embolization in the treatment of cerebral aneurysms is an evolving method. However, little is known about the permanent occlusion rate and long-term outcome. At present, the treatment of choice for aneurysmal subarachnoid hemorrhage is microsurgical clipping of the aneurysm without alteration of the distal blood flow.10,27 Intraaneurysmal balloon occlusion was abandoned because of major disadvantages,20 but the failures of this therapeutic concept appear to have been forgotten. Although essential problems have not yet been resolved with this technique, coil embolization has been introduced with enthusiasm, and the number of endovascularly treated aneurysms is increasing rapidly. Coil embolization will likely be established as an accepted method in the treatment of cerebral aneurysms.6,16–18,28

The purpose of this experimental study was to address some of the unsolved problems related to coil embolization of arterial aneurysms. Therefore, it was necessary to establish an appropriate experimental model of bifurcation aneurysms that resembles the clinical situation in humans as closely as possible. Various techniques have been used to produce experimental aneurysms in animals, including intramural injection of sclerosing agents, feeding of β-aminopropionitrile, and induced hypertension.15,32,35 The majority of experimental aneurysms, however, were produced microsurgically.4,8,9,11–14,19,24,25,29,34,38 Previously, several authors have described venous pouch aneurysms, but most studies have involved sidewall aneurysms. However, Forrest and O’Reilly8 and O’Reilly, et al.,25 introduced an important modification to the surgical production of bifurcation aneurysms. Their model consists of anatomically positioning venous pouches within an artificial arterial bifurcation. The hemodynamic parameters in this model are very similar to those in human bifurcation aneurysms, which clearly outnumber sidewall aneurysms in the cerebral vasculature.26,30

The present experimental animal model allows the radiological and histopathological evaluation of coil embolization of bifurcation aneurysms. Of special interest is the degree of radiologically demonstrated occlusion in aneurysms treated by endovascular obliteration compared with the eventual histopathological findings. It is also important to gain experience with the predictive value of radiological follow-up examinations. Additionally, a standardized analysis of the various coil systems and the different coil surface materials is possible,8,19,28 encouraging the development of new materials that improve epitheliogenic or thrombogenic capacity and optimize the degree of permanent aneurysm occlusion.

Key Words • experimental aneurysm • animal model • coil embolization • endovascular instrumentation • subarachnoid hemorrhage • rabbit
Materials and Methods

Animal Model

The study was conducted according to current German regulations and guidelines for animal experiments and was approved by our institutional review committee. Chinchilla rabbits weighing between 4 and 5 kg were preanesthetized by intramuscular injection of 5 mg/kg xylazine 2% and 30 mg/kg ketamine 10%. Male and female animals were used. Anesthesia was achieved and continued intravenously with a mixture of xylazine and ketamine (0.2 ml/kg/hour). Mechanical ventilation was not necessary because of sufficient spontaneous breathing of the rabbits. All surgical procedures were performed under sterile conditions using microsurgical techniques. Perioperative single-shot antibiotic prophylaxis (Tardomyocel comp III, 0.5 ml/kg) was administered subcutaneously. To minimize interindividual technical deviations, the surgical procedures were always performed by one of the authors (U.S.) and the coil embolizations by another (J.R.).

Surgical Procedures

The anesthetized rabbits were placed supine on a heated plate to maintain normothermia and fixed with the neck slightly extended. A midline skin incision was made, extending from the angle of the mandible to the manubrium sterni. The right external jugular vein was isolated, and a 1- to 1.5-cm segment without any side branches was resected and kept in heparinized saline. Both common carotid arteries (CCAs) were exposed and isolated for a segment of at least 5 cm. To prevent vasospasm, the operative field was continuously irrigated with a diluted solution of nimodipine. The left CCA was proximally ligated with a 6–0 suture and was cut obliquely after temporary distal occlusion was achieved. The lumen was rinsed with heparinized saline. The right CCA was temporarily closed with atrumatic clips and a longitudinal arteriotomy was performed. The new bifurcation resulted from a partial end-to-side anastomosis of the left CCA to the proximal part of the arteriotomy of the right CCA (Fig. 1), using interrupted monofilament 10–0 vicryl sutures and a BV No. 6 needle. For the production of various aneurysm neck configurations two different forms of arteriotomy were used. In 13 rabbits, a straight arteriotomy (5–6 mm) of the right CCA and a straight longitudinal cut (3–4 mm) at the distal end of the left CCA were performed to create a well-defined, narrow neck of the aneurysm. In 50 rabbits the arteriotomies were elliptical (5–6 mm), and V-shaped wedges (2–3 mm) from the distal ends of the left CCA were resected to produce a wide aperture, resulting in a broader aneurysm neck (Fig. 2). Next, the venous segment was fitted exactly within the remaining aperture of the newly created bifurcation. An atrumatic clamp was placed at the end of the grafted vein segment and all clips were removed. The axial bloodstream promptly inflated the venous pouch, and a saccular aneurysm arose. Then, the clamp at the distal vein segment was opened briefly to remove captured thrombi. Finally, the dome of the aneurysm was ligated with a 6–0 vicryl suture, resulting in a berry-shaped bifurcation aneurysm (Fig. 3). In 11 animals, the dome of the aneurysm was coated with a drop of cyanoacrylate glue to prevent reopening of visible small side branches of the bulging venous segment. The skin incisions were closed with absorbable 4–0 sutures, and the animals were allowed to recover in a heated cage. The rabbits were observed daily for general status and respiratory and motor functions.

Neuroradiological Procedures

Two to 3 weeks after surgery, digital subtraction angiography (DSA) and coil embolization were performed after anesthesia had been induced in the rabbits and without mechanical ventilation. For DSA and endovascular treatment, the femoral arteries were surgically exposed and a No. 3 French catheter was introduced. If the created bifurcation and the aneurysm were verified, coil emboliza-
tion was performed consecutively. Endovascular occlusions were performed using mechanically detachable coils (MDCs; Balt, Montmorency, France) made of tungsten; and electrically detachable platinum coils also known as Guglielmi detachable coils (GDCs; Target Therapeutics, Fremont, CA). We used MAG 2F/3 and Tracker 10 catheters for MDCs and GDCs, respectively. The femoral arteries were routinely ligated after removal of the catheter, and the skin incisions in the groin were closed. The rabbits were observed in a routine follow-up protocol, and final DSA was performed 3 or 6 months after coil embolization. Three untreated rabbits with documented aneurysms were kept as controls.

Angiographic studies were obtained and aneurysm occlusion was estimated by two independent investigators to be complete (95%–100% obliteration) or incomplete (< 95% obliteration). The occlusion rates estimated in the initial DSA were then compared to the final angiographic occlusion rate 3 or 6 months later.

**Histopathological Features**

Immediately after final DSA, the rabbits were killed by perfusion fixation with a mixture of 3.5% glutaraldehyde and phosphate buffer that was injected intraarterially through the angiographic catheter. Thereafter, gross pathological examination of the brain, vessels, and aneurysm was performed. The degree of morphological aneurysm obliteration was evaluated and compared to the angiographic findings of two independent investigators. After being embedded in paraffin the aneurysms were cut and examined by light microscopy to evaluate the degree of thrombosis and fibrosis between the coil loops. Scanning electron microscopy was used to study 17 aneurysms, especially to determine the degree of endothelialization of the coil surfaces.

**Results**

Sixty-three animals underwent operation (Table 1). Fifteen rabbits (24%) died during the study and were excluded. Of these, four animals died intraoperatively or immediately postoperatively due to severe blood loss or problems with anesthesia. Six rabbits died or had to be killed in the course of the experiment because of complications from infections (four pneumonias and two wound infections). Five other animals were killed because of the following neurological deficits: 1) tetraplegia in two cases, one immediately postoperatively and one after coil embolization.

**Table 1**

<table>
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<tr>
<td>embolization not feasible</td>
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</tr>
<tr>
<td>total</td>
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<tr>
<td>MDCs</td>
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</tr>
<tr>
<td>total</td>
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GDCs = Guglielmi detachable coils; MDCs = mechanically detachable coils.

![Fig. 2. A microsurgical end-to-side anastomosis with both common carotid arteries is performed and a venous pouch is fitted into the created bifurcation. *Left:* Schematic drawing. *Right:* Intraoperative photograph.](image)
embolization; 2) hemiplegia during coil embolization in one animal; 3) severe respiratory problems in one animal immediately postsurgery, probably caused by an inadvertent lesion of the trachea or by a bilateral lesion of the recurrent laryngeal nerves; and 4) trophic disorder and mutilation of the right leg in one rabbit following occlusion of the femoral artery.

Fourteen animals (22%) were excluded from further evaluation, because inadvertent vessel occlusion was demonstrated on DSA. Unilateral CCA occlusion could not mimic the situation of a bifurcation aneurysm as required, and bilateral CCA occlusion inevitably caused aneurysm obliteration. In one rabbit, mechanically induced vasospasm during selective angiography for coil embolization caused transient unilateral occlusion of the left CCA. Repeat angiography 6 days later revealed secondary occlusion of the artery and the aneurysm. After deaths and exclusions, thirty-four surgically produced carotid bifurcation aneurysms (54%) remained to test endovascular therapeutic approaches. In four aneurysms, coil embolization was not feasible because of an aneurysm size of less than $2 \times 2$ mm. Three rabbits with demonstrated aneurysms were kept as controls. Follow-up angiography 3 and 6 months later showed that all three aneurysms in the control group were still patent and completely unchanged in size.

Altogether, 26 bifurcation aneurysms were successfully treated by coil embolization (Fig. 4 upper left and right), 16 rabbits with GDCs and 10 with MDCs. Histopathological evaluation was performed in 17 animals, nine of which had been treated with MDCs and eight with GDCs (Table 2).

![Fig. 3. Intraoperative photograph showing a microsurgically produced arterial bifurcation aneurysm. All temporary clips were removed and the axial bloodstream inflated the venous pouch resulting in a berry-shaped aneurysm. The aneurysm dome was ligated with a 6–0 suture.](image)

![Fig. 4. Angiographic findings. Upper Left: Digital subtraction angiography (DSA) 4 weeks postoperatively confirming the microsurgically produced bifurcation aneurysm. Upper Right: Initial DSA immediately after embolization with Guglielmi detachable coils demonstrating an incompletely obliterated aneurysm with partial occlusion of the neck. Lower Left: Final DSA 3 months after coil embolization demonstrating complete radiological aneurysm occlusion. Lower Right: Photograph obtained during gross pathological examination of the same coil-embolized bifurcation aneurysm showing incomplete occlusion of the aneurysm and recanalization without permanent thrombotic or epithelial occlusion. The microsurgically produced bifurcation was cut longitudinally and the aneurysm is viewed from the base to the dome. Original magnification \( \times 12 \).](image)

**Surgical Procedures**

On average, 32 interrupted sutures (range 28–37) were needed to create the bifurcation and fix the venous pouch. The mean duration of the entire surgical procedure was 185 minutes (range 115–260 minutes). Intraoperative
measurements showed a mean CCA diameter of 2.3 mm (range 1.9–2.5 mm). The mean size of the microsurgically produced aneurysms was 5.8 ± 4.3 mm (range 2.3–6.5 mm). The straight arteriotomy of the right-sided CCA resulted in a markedly higher rate of spontaneous vessel and aneurysm occlusion. In the 13 animals with straight arteriotomies, eight occlusions (62%) occurred (three unilateral and five bilateral inadvertent occlusions of the CCA and the aneurysm). In the 50 rabbits with elliptical arteriotomies, only six occlusions (12%) were seen on DSA (one unilateral and five bilateral occlusions).

Coil Embolization

In total, 26 microsurgically produced arterial bifurcation aneurysms were coil embolized. In the group of rabbits embolized with platinum coils (GDCs), six (38%) of 16 aneurysms appeared to be occluded completely at the time of the initial angiography. Final DSA 3 to 6 months later demonstrated complete occlusion in four (25%) of 16 aneurysms (Fig. 4 lower left). In three completely obliterated aneurysms in the GDC group, compaction and recanalization occurred; however, one incompletely occluded aneurysm showed secondary total occlusion on DSA. In the group of aneurysms treated with tungsten coils (MDCs), complete occlusion in three (33%) of 10 aneurysms was found on angiography, but no complete occlusions were seen in final DSA. All aneurysms embolized with MDCs showed coil compression and compaction resulting in partial recanalization at final angiography (Table 2).

Histopathological Studies

Gross pathological investigation 3 to 6 months after coil embolization revealed an incomplete occlusion in all 17 bifurcation aneurysms. Recanalization with open spaces between the coil loops was a constant finding, even in the three aneurysms that were completely occluded according to angiographic criteria (Table 3). Morphologically, no thrombi were found in the coil basket, irrespective of the degree of coil density. The GDC- and MDC-treated bifurcation aneurysms showed no fibrosis or organized thrombotic material between the loops of the coils (Figs. 4 lower right and 5 right), resulting in a honeycomb recanalization from the base to the dome of the aneurysm. Histological investigation demonstrated that in 13 of 17 cases the coils were not covered by any tissue. In only four cases, a thin layer of granulation tissue covered the surface of the coils (Fig. 6), but no endothelium was detected. Gross pathological estimation of the degree of aneurysm occlusion generally showed a lower occlusion rate than that estimated in final angiography.

Discussion

Theoretical Considerations

The goal of surgical and endovascular treatment of cerebral arterial aneurysms is the complete and permanent exclusion of the aneurysm to prevent regrowth and rebleeding. Ideally, complete endovascular aneurysm occlusion should be followed by endothelialization across the aneurysm base. Only by this partial reconstruction of the arterial wall is complete and probably permanent occlusion achieved. However, clinical studies have led to controversial results because endovascular coil embolization frequently attained only an incomplete obliteration of the orifice and sac of the aneurysm, provoking a discussion about the fate of residual aneurysm necks.

Although estimates of the risk of hemorrhage or rehemorrhage from remnant aneurysms vary, there is a considerable risk of rebleeding, especially in cases of aneurysm regrowth from a residual neck, as found in partially clipped aneurysms. The location of the aneurysm remnant plays an important role in the dynamics of regrowth and rebleeding. Angiographic and color Doppler flow measurements have demonstrated a characteristic
Coil embolization of experimental bifurcation aneurysms

<table>
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<th>Investigation Method</th>
<th>Incomplete Occlusion</th>
<th>Complete Occlusion</th>
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<td></td>
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<td>gross pathology</td>
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*Incomplete refers to aneurysm obliteration < 95%; complete denotes aneurysm obliteration 95% to 100%. Abbreviations: GDCs = Guglielmi detachable coils (eight animals); MDCs = mechanically detachable coils (nine animals).

A major disadvantage of coil embolization is the unsolved problem of complete and permanent occlusion of the aneurysmal base. Endothelialization and intimal pro-

Pattern with defined in- and outflow zones. According to these studies, a residual neck in the aneurysm inflow zone will tend to have a higher risk of regrowth compared to a residuum in the outflow zone. It is also important to note that experimental sidewall aneurysms have a completely different flow pattern within the aneurysm sac compared to bifurcation aneurysms. Sidewall aneurysms demonstrate a slow blood flow and often stasis of the flow with consequent thrombosis. However, aneurysms in humans are known to arise most frequently in arterial bifurcations. Therefore, our experimental model was designed to mimic closely human bifurcation aneurysms, which allows a partial transfer of the results to clinical circumstances.

Animal Model

The size of the orifice and sac, the anatomy of the vessels, and the hemodynamic profile are important factors in the pathogenesis of aneurysms. In our experimental bifurcation aneurysm model, the mean diameter of the rabbit CCA (2.3 mm) is in the range of the anterior cerebral artery (1.0–3.0 mm) and the middle cerebral artery (2.4–4.6 mm) in humans. Likewise, the mean experimental aneurysm diameter (5.8 × 4.3 mm) is the same as the average size of cerebral aneurysms in humans.

The modification of the aneurysmal neck by straight incision of the CCA was not practical, because of the high spontaneous occlusion rate (62%) seen on follow-up angiography. The use of elliptical vessel incisions in our ongoing study will further improve the overall rate of patent bifurcation aneurysms suitable for coil embolization in future.

The blood clotting system and thrombus formation in canine models have already been studied in detail. Spontaneous occlusion of the CCA or of the experimental aneurysm occurred in previous studies only in the early postoperative course. If the bifurcation remained patent, there was no spontaneous thrombosis or any change in aneurysm size. Confirming these results, the three control aneurysms in our study also were still patent after 3 and 6 months and showed no change in size.

A disadvantage of the present method is the inevitable long-term care of the animals with a high risk of losing several rabbits due to secondary complications. Postoperative infections, repeated anesthesia for neuroradiological follow-up investigations, and the procedure of coil embolization itself presented additional risks. The ratio of animals remaining for the final evaluation (63 undergoing operation vs. 26 coil embolizations: 41%) was relatively low. However, this ratio will improve because the majority of the pitfalls were seen in the beginning of the learning curve, and the technique of straight arteriotomy is no longer used.

Endovascular Procedures

At present, a general problem of endovascular therapy is the known instability of initial coil packing and complete occlusion of the aneurysm is not always possible without running a high risk of inadvertent vessel occlusion or coil migration. Recanalization of the initially completely occluded lumen occurs with consecutive blood flow into the aneurysm sac. We confirmed this phenomenon in all histomorphologically evaluated aneurysms of our series, demonstrating open spaces and no organized thrombi between the loops of the coil basket (Figs. 4 lower right and 5 right).

The mechanism of increased compaction of coil material in follow-up angiographic studies is still unknown, but continuous compression by the “waterhammer effect” alone is an insufficient explanation. It appears possible that the basket of coils will initially be filled with thrombi, leading to preliminary occlusion of the aneurysm by a clot. However, without an epithelial layer covering the thrombus, the permanent axial bloodstream could wash out the thrombotic material. In the recanalized aneurysm the coils could move closer together, resulting in the visible compaction frequently seen on follow-up angiography. Recanalization was a constant finding of histomorphological examination in our series, and no organized thrombotic material was seen in the dome of the aneurysm or between the loops of the coils (Fig. 5). Obviously, this has to be confirmed in further histological studies.

A major disadvantage of coil embolization is the unsolved problem of complete and permanent occlusion of the aneurysmal base. Endothelialization and intimal pro-
literation across the aneurysm neck and between the coils could not be demonstrated in the present and a few other histopathological investigations in animal models. In only four rabbits in our series the coil surface was partially covered by thin layers of granulation tissue (Fig. 6). However, in the majority of the cases (13 of 17), the surface of the coils was not covered. Recently, these experimental results were confirmed by two human autopsy cases that showed no endothelialization across the coil-embolized aneurysm neck.

It is interesting to note that in experimental studies with collagen-coated microcoils, reendothelialization across the aneurysm neck combined with intraluminal organization of the thrombus and solid scar formation was detected. However, these results were found using experimental sidewall aneurysms, which have a completely different hemodynamic profile from microsurgically produced bifurcation aneurysms. But even if reendothelialization does occur, the lack of proper reconstruction of the whole vessel wall, which is the main problem of endovascular treatment, will still remain. By clipping the aneurysm neck, such a reconstruction is achieved by the approximation and gathering of all layers of the vessel wall. This safe and permanent restoration is not attainable with any of the embolization procedures. Intraluminal coil occlusion causes only an interruption of the in- and outflow tracts, but the weak point—the defect of the vessel wall—is not treated sufficiently. Therefore, the internal occlusion of the aneurysm sac alone without reconstruction of the vessel wall is of questionable value. On the basis of this knowledge, endovascular stents were used in recent studies to overcome these obstacles. However, in spite of the initial favorable results, stents are not usable at present because of their limited flexibility and the complex anatomy of cerebral arterial bifurcation aneurysms.

Radiological Versus Histopathological Findings

According to angiographic criteria the density of initial coil packing seemed to be an important factor for the long-term results. Therefore, aneurysm occlusion should be achieved by a very dense coil packing with complete obliteration of the aneurysm from the dome to the neck. The ideal condition will then be a reendothelialization of the aneurysm base providing a permanent occlusion. To avoid recanalization of the embolized aneurysms the coils are usually packed as closely together as possible. Tungsten coils are more rigid than platinum, and because of this technical feature the coils in the MDC group were packed less closely. The dense packing should inhibit the washout of the thrombotic material around the coils. Our results confirm this assumption, because all MDC-embolized aneurysms demonstrated compaction and recanalization on final angiography. Four GDC-treated aneurysms, however, showed complete occlusion on final angiography (Table 2). It is remarkable, however, that no aneurysm was found to be completely obliterated on histopathological examination (Figs. 4 lower right and 5 right). Actually, there was recanalization with open spaces between the coil loops even in the aneurysms that seemed to be totally occluded according to angiographic criteria.

Our morphological results demonstrate a general overestimation by angiography of the degree of aneurysm occlusion. The rate of aneurysm occlusion was always estimated as higher on DSA than was actually proven by the gross pathological specimens. In the clinical routine, the degree of aneurysm occlusion and the density of coil packing are monitored by angiography, even though the metal coils cause a massive local x-ray extinction, making it difficult to estimate the degree of aneurysm obliteration. We should be aware that the radiological picture of the coil material within the aneurysm is a two-dimensional image of a complex three-dimensional structure. Moreover, the metallic artifacts of the coils, especially in densely packed aneurysms, could mask minor amounts of contrast media in recanalized sections of the aneurysm sac. Thus, angiography does not appear to be the optimum diagnostic tool for follow-up investigations of the degree of aneurysm obliteration. This limitation of angiography compared to morphological examination should be taken into account in further studies using experimental aneurysms and also in the clinical assessment of coil embolization. The unresolved question of coil embolization is whether angiographically proven aneurysm occlusion is only a “radiological/optical” illusion.

Conclusions

The present animal model with microsurgically produced carotid bifurcation aneurysms can be used to test different coil systems and new surface materials for the endovascular obliteration of human cerebral aneurysms. Hemodynamic conditions and the blood clotting system are very similar in rabbits and humans, and experimental aneurysms have the same size and configuration as human cerebral bifurcation aneurysms. We found a considerable discrepancy in the radiological analysis of obliteration compared to the histopathological findings. The incomplete aneurysm occlusion seen in every gross pathological specimen that we examined demonstrates an overestimation of the occlusion rate by radiology. These findings show that significant improvements are necessary in the endovascular treatment as well as in the radiological monitoring of coil embolization procedures.

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References

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