Histological Findings in Coil-packed Experimental Aneurysms 3 Months after Embolization

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OBJECTIVE: Knowledge regarding tissue reactions within coil-packed aneurysms is poor. The purpose of this study was to analyze histological changes in a chronic experimental bifurcation aneurysm model that might explain the protective effect of Guglielmi detachable coils.

METHODS: The aneurysms were produced by means of a venous graft pouch at a surgically created bifurcation of the carotid artery in the neck of rabbits. After 3 weeks, embolization with Guglielmi detachable coils was performed in the treatment group but not in the control group (seven rabbits each). At the time of embolization, six of seven treated aneurysms were completely occluded according to radiological criteria. Twelve weeks later, all aneurysms were explanted after final angiography. Histological examinations were performed with coils in situ.

RESULTS: Six of seven embolized aneurysms demonstrated complete occlusion in final angiography. But gross pathology revealed that all specimens had differently sized open cavities between the coils. In only two cases, these spaces were very small and the aneurysmal sacs were filled with coils and tissue by more than 90%. Light microscopy demonstrated intraluminal granulation tissue and strong chronic inflammatory wall thickening with numerous foreign body cells at the interface between coils and tissue. Coils were partially incorporated into the aneurysmal wall, sometimes close to the surface and occasionally even outside the wall within the surrounding tissue.

CONCLUSION: The protective effect of Guglielmi detachable coil treatment in our chronic experimental bifurcation aneurysms results from formation of intraluminal granulation tissue and wall thickening attributable to chronic inflammation. (Neurosurgery 50:379–385, 2002)

Key words: Aneurysm, Animal study, Foreign body cells, Guglielmi detachable coils, Histology, Light microscopy

Endovascular coil embolization has become an established method in the treatment of saccular intracranial aneurysms. Although achievement of total occlusions and therefore long-term prognosis is uncertain (12, 13, 21, 23), the number of coil-treated patients increases each year. Some radiological and clinical reports (3, 5, 6, 11, 18, 22) of results after coil embolization have been published during recent years, but knowledge regarding the state of the tissue within the coil-packed aneurysm remains poor.

Only a few human case reports (2, 12, 13, 16, 17) and some experimental studies (1, 9, 10, 15, 21, 23, 25) that describe histopathological findings after coiling have been published. Included are the human case reports by Manabe et al. (12, 13) and Bavinzski et al. (2), as well as the experimental sidewall aneurysm series by Tenjin et al. (25), and the recently published study by Bavinzski et al. (1) describing bifurcation aneurysms in rabbits on the basis of light microscopic histopathological sections with coils in situ. The scarceness of respective reports may be explained by difficulties obtaining such sections because of differences in the density of packed coils and aneurysm soft tissue (15).

In this experimental study, we describe the light microscopic histopathological findings in a series of experimental bifurcation aneurysms 12 weeks after coiling. The results are

compared with published clinical and experimental results, with a special focus on the visible chronic inflammation reaction of the tissue.

MATERIALS AND METHODS

Surgical procedure

In 14 male New Zealand chinchilla rabbits, bifurcation aneurysms were microsurgically created according to the technique of Forrest and O'Reilly (8). The aneurysms were produced by means of a venous graft pouch at a surgically created bifurcation of the carotid artery in each animal's neck.

Interventional procedure

After 3 weeks, intra-arterial angiography via a femoral artery approach was performed in seven rabbits. All aneurysms were patent and had a diameter between 10 and 15 mm. At that time, the aneurysms were occluded via microcatheter by use of Guglielmi electrically detachable platinum coils (GDCs). All sacs were densely packed. At the end of the coiling procedure, six aneurysms were completely occluded (>90%) according to radiological criteria. In one case, coil embolization was incomplete because of technical problems. None of the animals received perioperative anticoagulation therapy. After 12 weeks, at final angiography the six previously full embolized aneurysms were still completely occluded according to radiological criteria, and the one primarily incompletely embolized aneurysmal sac was still partially open. Thereafter, the aneurysms were perfused with 0.9% saline to avoid postmortem coagulation artifacts, and they were explanted and fixed in 4% paraformaldehyde.

Control group

Seven aneurysms were not coiled. Their patency was proven 3 weeks after creation by color Doppler ultrasound only, because our former experiments had not demonstrated a histological difference between aneurysms investigated by angiography and Doppler ultrasound versus those investigated only by use of ultrasound. Twelve weeks later, the aneurysms were perfused with 0.9% saline, explanted, and fixed in 4% paraformaldehyde.

Histopathological technique

After fixation in 4% paraformaldehyde, all specimens (coiled and not coiled) were dehydrated in graded ethanol during a 4-day period and embedded in glycol-methacrylate hard plastic (Technovit 7200 VLC; Heraeus Kulzer, Wehrheim, Germany) in accordance with the technique described by Donath and Breuner (7).

The polymerized blocks were cut by use of an automatically cooled sawing machine. The thickness of the diamond saw blade was 0.1 mm. The area of the specimen to be investigated (vertical through the orificium) was brought to the surface by sawing, and the other side of the block was made parallel. The prepared blocks were then mounted between slides and sawed into sections 0.25 to 0.3 mm thick.

Before staining, automatic grinding and polishing of the slide preparation to a final thickness of 0.02 to 0.04 mm were performed with 1200- and 4000-grain sandpaper. During the procedure, water cooling was necessary at all times. All specimens were stained with hematoxylin and eosin.

RESULTS

Gross pathology of the control group

All seven untreated bifurcation aneurysms of the histopathological control group remained completely open 15 weeks after surgical creation.

Gross pathology of the embolized aneurysms

Final angiography directly before the animals were killed demonstrated the aneurysm-parent arteries complex patent in all cases (*Fig. 1*). According to angiographic criteria, six of seven aneurysms appeared completely occluded.

Immediately before (or after, in two cases) fixation in paraformaldehyde, the carotid bifurcation was opened and the aneurysmal orifice as well as the surface of the aneurysmal sacs were inspected and photographed.

In all specimens, different-sized intra-aneurysmal cavities between the coil loops were visible via the orifice. In two cases, these spaces were very small. The aneurysmal sacs were filled with coils and tissue by more than 90%. The largest intra-aneurysmal cavities were found in the aneurysm, which had been incompletely coiled. The coil loops were usually visible very close under the surface of the aneurysmal sac, but in some cases they were also outside and within the surrounding tissue.

Light microscopic findings of the control group

The aneurysms were created from a venous pouch with a wall thickness of approximately 0.02 mm (*Fig. 2*). Because of the arterial blood pressure, the thickness of the aneurysmal (venous) wall was increased adaptively to approximately 0.2 mm, but its trilaminar character remained intact. Intima and media were fibrotic with a proliferation of the smooth muscles of the native venous vessel wall. In isolated cases, unabsorbed sutures with surrounding foreign body cells (FBCs) were still visible.

Light microscopic findings of the embolized aneurysms

The complicated sawing and grinding procedures allowed examination of only two to four slides per aneurysm. The histopathological finding was uniform in all slides, including those from the incompletely coiled aneurysm.

Twelve weeks after application of platinum coils into the experimental aneurysmal sac, the aneurysmal lumen was incompletely obliterated by cellular and vascularized granulation tissue consisting of fibrocytes, numerous vessels, and capillaries. Even within the coils, the same histology was found (*Fig. 3*). At the luminal side of the intra-aneurysmal granulation tissue, a thin endothelium-like cell layer could be detected (*Fig. 4*).

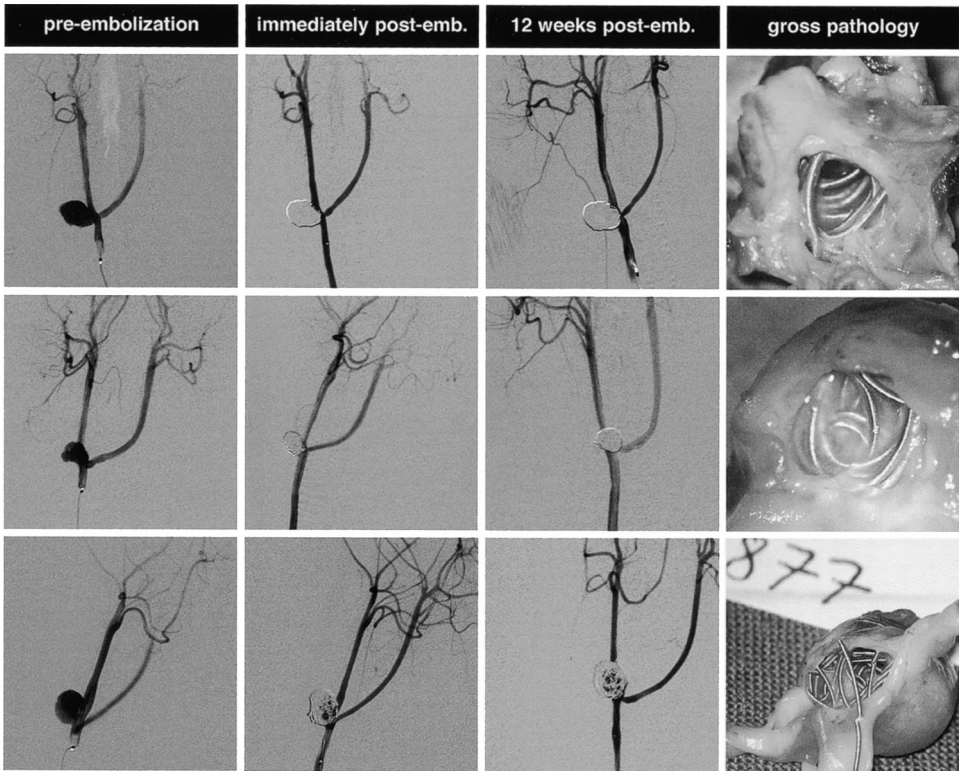

FIGURE 1. Representative series of pre-embolization, immediate postembolization, and 12-weeks postembolization angiograms for the different findings in gross pathology; coil diameter = 0.015 inch. *Top* and *middle rows*, despite complete occlusion of the aneurysms (according to angiographic criteria) in the immediate and the 12-weeks postembolization angiograms, gross pathology revealed that spaces between the coil loops were visible via the aneurysm orifice in all specimens 12 weeks after treatment. *Middle row*, in two of seven aneurysms the cavities were very small. The aneurysmal sacs were more than 90% filled with coils and tissue. Bottom row, the largest intraaneurysmal spaces were found in the aneurysm that demonstrated incomplete occlusion in angiograms both immediately postembolization as well as at 12 weeks postembolization.

Figure 5 shows coil loops within an unobliterated cavity of the aneurysm. They also were found often covered and filled by cellular and vascularized granulation tissue.

In many places, the platinum coils were incorporated in the aneurysmal wall. In some cases, they were located directly below the surface covered only by a small tissue layer, and sometimes they were even outside the aneurysmal sac, within the surrounding fatty tissue (*Fig. 6*). Because of the tension of the coil loops, the aneurysmal wall developed multiple bulges after embolization (*Fig. 7*).

Twelve weeks after treatment, the histology of the aneurysmal wall in the neighborhood of the incorporated platinum coils was completely different as compared with the control group (*Figs. 7* and *2*). There was a severe chronic inflammation with numerous FBCs at the interface between coils and tissue (*Fig. 8*) and a loss of the native trilaminar character of the aneurysmal wall. The thickness of the aneurysmal wall was at least 2.5 mm (as measured in the incompletely coiled specimen).

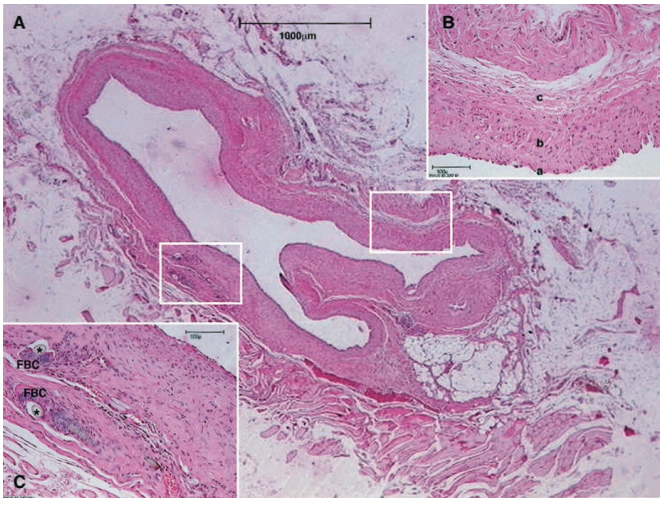

FIGURE 2. *A*, control group aneurysm; cross section of the arterial wall and the adjacent aneurysm. At the rim of the aneurysm is a localized foreign body reaction with several multinucleated giant cells. *B*, cross section of the aneurysmal wall at a higher magnification. The wall is much thicker than a normal venous blood vessel wall. Beneath a thin endothelial cell layer (*a*), there is a thick tunica media composed of smooth muscle cells and connective tissue (*b*). This is the result of an adaptation process to the elevated (arterial) blood pressure. *c*, tunica adventitia. *C*, localized foreign body reaction (*FBC*) at the site of the unabsorbed sutures (*) (hematoxylin and eosin).

DISCUSSION

Gross pathology

According to the literature (9, 10, 15, 25), between 2 and 6 months after coiling, sidewall aneurysms are completely occluded in most cases, and a repair (endothelialization) of the arterial wall at the aneurysmal orifice is visible (9, 10, 15, 25). Bifurcation aneurysms, however, analyzed in the present study, are like native human intracranial aneurysms, hemodynamically quite different from sidewall aneurysms (19, 20,

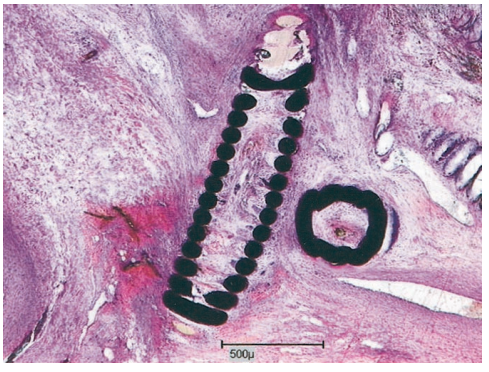

FIGURE 3. Twelve weeks after application of platinum coils into an experimental aneurysmal sac, the aneurysmal lumen was filled by rich cellular and vascularized granulation tissue consisting of fibrocytes, numerous vessels and capillaries (hematoxylin and eosin).

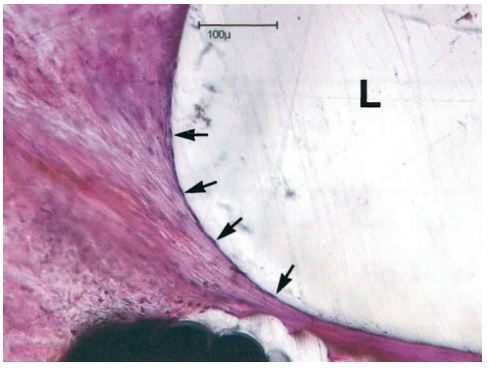

FIGURE 4. At the luminal side (*L*, unobliterated cavity) of the intra-aneurysmal granulation tissue, a thin endothelium-like cell layer (*arrows*) could be detected (hematoxylin and eosin).

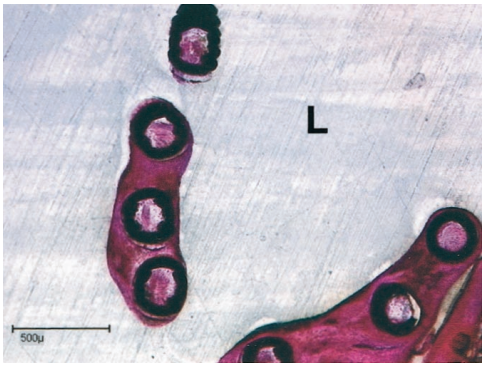

FIGURE 5. Coil loops within an unobliterated cavity (*L*) of the aneurysm. Often they were found to be covered and filled by rich cellular and vascularized granulation tissue (hematoxylin and eosin).

24), and unlike sidewall aneurysms, bifurcation aneurysms do not tend to thrombose spontaneously (4, 14, 24). Almost all experimental bifurcation aneurysms have been created in rabbits (1, 21, 23). Only Macdonald et al. (10) used dogs.

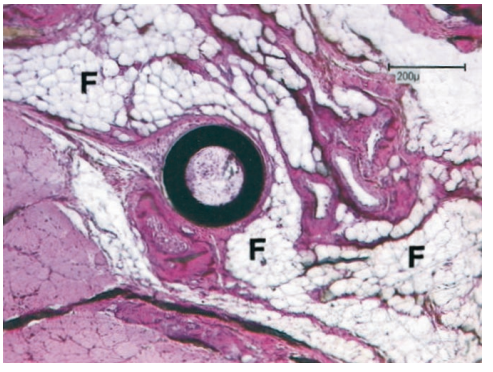

FIGURE 6. Sometimes the platinum coils were outside the aneurysmal sac within the surrounding fatty (*F*) tissue (hematoxylin and eosin).

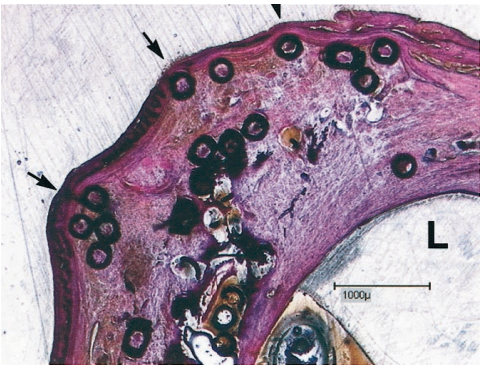

FIGURE 7. The structure of the aneurysmal wall was markedly changed. Because of the tension of the coil loops, the aneurysmal wall developed multiple bulges (*arrows*) after embolization. *L*, unobliterated cavity (hematoxylin and eosin).

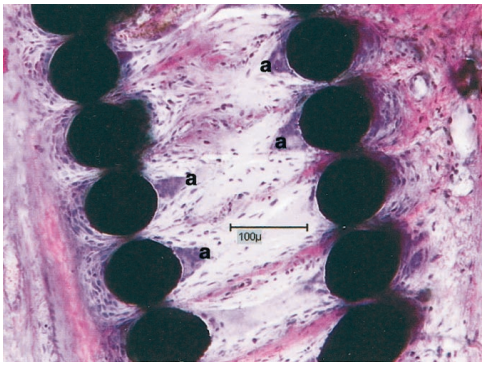

FIGURE 8. Twelve weeks after treatment, there was a severe chronic granulating inflammation with numerous FBCs (*a*) at the interface between coils and tissue and a loss of the native trilaminar character of the aneurysmal wall (hematoxylin and eosin).

Although angiographic control 3 to 6 months after coil embolization has demonstrated complete or almost complete occlusion of the aneurysms, macroscopic examination revealed that in numerous specimens, the aneurysmal sac was

not occluded by connective tissue (1, 10, 21, 23). In the present study, only two of six angiographically completely occluded aneurysmal sacs were filled almost completely with tissue.

In the literature, there are only seven human case reports (2, 12, 13, 16, 17) regarding the gross pathology of coil embolized intracranial aneurysms more than 1 month after treatment. Only two of seven aneurysms (2, 17) were obliterated completely according to angiographic criteria. Of these, the occlusion was confirmed (2) in the gross pathology of one specimen.

Light microscopic findings

In both experimental (1, 21, 25) and human case reports (2, 12, 13), light microscopic histopathological studies of aneurysms with coils in situ are rare. Furthermore, only a few articles have described light microscopic histopathological observations after removal of the coils in human (17) as well as in experimental aneurysms (4, 15).

Although experimental sidewall (4, 15, 25) and bifurcation (1) aneurysms, as used in the present study, are completely different in hemodynamics (19, 20, 24), the intra-aneurysmal histopathological findings of richly vascularized fibrous tissue surrounding and bridging the coils 3 months after coil embolization seems quite similar (1, 4, 15). This histopathological picture is consistent with the findings reported in human aneurysms (2, 12, 13, 17).

Three months after coiling, vascular healing of the neck of experimental sidewall aneurysms can be observed (15, 25). The orifice is covered by a new trilaminar vascular wall (15, 25). In experimental bifurcation aneurysms, Bavinzski et al. (1) described also a new vascular wall covering the luminal side of the intra-aneurysmal granulation tissue composed of cells resembling endothelium and muscle cells (in 17- and 24-week-old specimens). Three months after the treatment of experimental bifurcation aneurysms, Reul et al. (21) used electron microscopy to find tissue layers between the coils that were covered by cells revealing a cobblestone pattern. This finding is typical, but it is not specific for endothelial cells. In the present study, 12 weeks after coiling, an endothelium-like thin cell layer at the luminal surface of the dense intra-aneurysmal granulation tissue also could be observed (*Fig. 4*) in all coiled aneurysmal sacs. This endothelial cell layer did not cover and close the aneurysmal orifice, however, as found in sidewall aneurysms (15, 25). Therefore, this layer should not be described as a new vascular wall. Among the human case reports (2, 12, 13, 17), only one aneurysm with a small neck (2) covered by an endothelial lining was found 40 days after embolization.

The histopathological structure of the wall of human berry aneurysms is different from the structure of the aneurysmal wall in this experimental study. In human aneurysms, the wall consists mainly of dense collagen tissue with thrombotic material of different ages on the inner surface. Only at the entrance of the aneurysm does the wall contain some remnants of an arterial wall, e.g., smooth muscle cells and fragments of the internal elastic membrane. In this study, the experimentally induced wall of the aneurysm consists at first of a normal venous blood vessel wall that adapts to a higher arterial blood pressure through thickening of the smooth muscle cell layer in the tunica media. After coil embolization of the experimental aneurysm, the aneurysmal wall becomes disorganized by the invasion of capillaries and fibroblasts, organizing the thrombotic material and initiating a chronic foreign body reaction in the neighborhood of the coils. These histopathological results in the present experimental study are consistent to a high degree with the findings in human aneurysms. Eight months after the embolization of human aneurysms, the coils also were embedded in granulation tissue (2, 12, 13), and at 54 months, they were partially incorporated in the completely changed aneurysmal wall (2). In all human aneurysms (2, 12, 13, 17), as well as in experimental aneurysms (1, 4, 15) including those in the present study, numerous inflammatory cells, especially FBCs, were found close to the outer and inner surface of the coils. Byrne et al. (4) counted FBCs in control and GDC-embolized sidewall aneurysms and found no significant difference. However, their histopathological investigation was performed after removal of the coils. Therefore, the results of Byrne et al. (4) may not be representative of the inflammatory reaction at the interface between coils and surrounding tissue. Reul et al. (21) observed no major inflammatory reaction in light microscopic investigations of experimental bifurcation aneurysms 3 months after coil embolization, but they did not state the part of the aneurysmal sac or wall for which this observation was made.

There seems to be uniform histopathological presence of numerous giant cells at the outer and inner surface of platinum coils in human and experimental aneurysms. Therefore, induction of wall thickening resulting from chronic inflammation with FBCs must be studied.

CONCLUSION

Twelve weeks after coil embolization, human and experimental bifurcation aneurysms frequently are not totally obliterated with tissue, although the aneurysmal sac often is completely occluded according to angiographic criteria. The coils are partially embedded in granulation tissue. The histological structure of the thickened aneurysmal wall is completely changed, with a loss of its native trilaminar character. Usually there are numerous FBCs at the interface between coil and tissue. The reaction of chronic inflammation with FBCs may cause thickening of the aneurysmal wall, making this an important protective mechanism to prevent aneurysm rupture.

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COMMENTS

The authors created 14 terminal aneurysms in 14 rabbits in the region of the carotid arteries. They left seven aneurysms as controls and embolized the other seven with standard Guglielmi detachable coils (GDCs). In all but one animal, they achieved dense aneurysm packing and angiographically complete aneurysm occlusion. They harvested the aneurysms 12 weeks after the procedures, then correlated anatomic and histological findings between the seven controls and seven aneurysms embolized with GDCs. The authors also performed angiographic evaluation of the aneurysms before collection and compared them with pre-embolization angiograms.

The histological findings observed in these terminal aneurysms in rabbits are very similar to those described in the histopathological evaluation of aneurysms embolized with GDCs in clinical practice.

If the GDCs produce an intra-aneurysmal hemodynamic "quiescent" environment, the GDCs will elicit a slow but steady clot organization and transformation into granulation tissue. This hemodynamic achievement is more readily achieved in lateral than in terminal aneurysms. The aneurysm inflow zone (the area of the neck of the aneurysm with the strongest dynamic stress because of a blood-flow-water-hammer effect) is the area where aneurysm recanalization resulting from coil compaction is more often observed in clinical practice.

The histopathological findings in this article clearly demonstrate that clot organization and maturation in a terminal aneurysm are basically the same as in lateral aneurysms, if the aneurysms have been densely packed with GDCs. The dense packing and control of the aneurysm inflow zone in both types of aneurysms allows the intra-aneurysmal clot to mature into granulation tissue and effects fibrous and colla-

gen transformation (not demonstrated in this article by use of immunohistochemistry techniques).

This article also demonstrates the validity of the new type of basic science research in interventional neuroradiology incorporating tissue engineering and molecular biology. An increasing number of articles are being published regarding modification of the surface of GDCs with the addition of polymers, growth factors, cytokines, and so on to accelerate and intensify intra-aneurysmal clot maturation and collagen transformation. This new generation of endovascular coils may improve long-term anatomic results through reduction in coil compaction and aneurysm re-formation.

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This is an elegant study by Böcher-Schwarz et al. The authors examined histopathological changes in 14 venous pouch bifurcation aneurysms in a rabbit model 3 months after coil embolization. Six of seven aneurysms were fully occluded according to angiographic criteria at the time of treatment. None of these aneurysms developed recanalization or compaction; they remained fully occluded at 3 months as demonstrated by angiography. One of seven aneurysms was incompletely embolized and remained partially occluded after 3 months.

The histological findings demonstrated incomplete reendothelialization of the intraluminal aneurysm surface. Small intercoil cavities with a chronic granulomatous response remained within the cavity. In addition, the wall of the aneurysm demonstrated coil incorporation with considerable wall thickening. This may be the protective event that prevents recurrent rupture of human cerebral aneurysms.

This article is important in that the histological findings of coil embolization in bifurcation aneurysms are clearly different from those in experimental sidewall aneurysms. These findings, however, must be juxtaposed against the risk of aneurysm rebleeding and recanalization. All six aneurysms with initial angiographic occlusion remained occluded at 3 months, despite the histological findings. The risk of rupture of an experimental bifurcation aneurysm may approach zero. Because of the lower blood pressure in the rabbit, this aneurysm model may be limited in its elucidation of histological findings in aneurysms that recanalize or regrow. The aneurysm wall in this model was a trilaminar venous wall that hypertrophied in response to arterial pressurization. Coil embolization resulted in chronic inflammation and further wall thickening. This may be a different response than in an arterial berry aneurysm in which the wall is not trilaminar initially.

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The authors produced venous pouch bifurcation aneurysms in rabbits. The experimental group was embolized with GDCs 3 weeks after surgical creation of the aneurysm. The investigators used special fixation techniques to allow for light microscopic histological examination 12 weeks after coiling. This study documented the presence of intraluminal granulation tissue and evidence of aneurysmal wall thickening associated with chronic inflammation. This and other studies have documented that angiographic obliteration may occur despite the presence of histopathologically identifiable spaces between coils. The authors suggest that the thickening of the aneurysmal wall as a result of this inflammation may be an important protective measure to prevent aneurysm rupture. Because there are no data to support this conjecture, the importance of complete angiographic obliteration for any therapeutic intervention should continue to be the accepted standard.

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