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# Histologic and Morphologic Comparison of Experimental Aneurysms with Human Intracranial Aneurysms

T. Abruzzo, G. G. Shengelaia, R. C. Dawson, III, D. S. Owens, C. M. Cawley, and M. B. Gravanis

***PURPOSE:*** **Vein pouch aneurysms are the most commonly created experimental lesions in neuroendovascular research. We sought to determine whether an experimental aneurysm that is derived from a pancreatic elastase–digested arterial sac (EDASA) models the histology and morphology of human cerebral aneurysms more accurately than the vein pouch aneurysm does.**

***METHODS:*** **EDASAs were created in the common carotid arteries of four rabbits, and vein pouch aneurysms were created in the common carotid arteries of four pigs. Five recently ruptured human cerebral aneurysms were obtained at autopsy. Identical histologic preparations were made for all specimens, and a vascular pathologist performed blinded histologic analyses. Morphologic dimensions were measured with a micrometer at 40-fold magnification.**

***RESULTS:*** **In each human cerebral aneurysm, there was complete absence of internal elastic lamina and tunica media, and none showed evidence of mural inflammation or neointimal proliferation. Average wall thickness was 51 $\mu$m. All vein pouch aneurysms had a well-developed internal elastic lamina and tunica media, and all exhibited profound inflammation and neointimal proliferation. Average wall thickness was 290 $\mu$m. EDASAs were devoid of internal elastic lamina, their tunica medias were mildly atrophic, and the sac walls contained only mild inflammation and neointimal proliferation. Average wall thickness was 46 $\mu$m.**

***CONCLUSIONS:*** **EDASAs model the morphologic and histologic characteristics of human cerebral aneurysms more accurately than vein pouch aneurysms do.**

Most experimentally created saccular aneurysms currently used in interventional research are vein pouch models. Several variations exist, but all vein pouch aneurysms are microsurgically constructed by grafting a segment of autologous vein to a surgically created arteriotomy (1–11). Although some types of vein pouch aneurysms accurately model the geometry and hemodynamics of cerebral aneurysms, all spontaneously manifest histologic changes that are not found in true saccular arterial aneurysms. It has been suggested that these changes are a consequence of surgical trauma, promoted by the presence of an anastomotic suture line in the neck of the vein pouch construct (12). We believe these changes also reflect a specific remodeling process that underlies the physiological adaptation of venous tissue to arterial hemodynamics. Accordingly, we think that an experimental aneurysm that is wholly arterial and that is devoid of suture lines would provide a more accurate histologic model.

We have recently described a novel technique for the creation of wholly arterial saccular aneurysms in rabbits (12). So as not to neglect the importance of hemodynamics in vascular biology, the carotid bifurcation was used as an anatomic substrate. Rabbits were selected as the species for this model because their coagulation system is similar to that of humans, and the size of the rabbit carotid artery closely approximates the size of the human middle cerebral artery (8, 13, 14). Our technique involves conversion of the external carotid artery to a saclike stump by suture ligation and division. The sac is subjected to elastolysis by the endoluminal incubation of pancreatic elastase. As reported previously, greater than 80% of the resulting structures remain angiographically patent after 6 weeks (Fig 1).

To determine if pancreatic elastase–digested arterial sacs simulate the histologic and morphologic properties of human cerebral aneurysms more accurately than do vein pouch aneurysms, thereby permitting a more reliable prediction of clinical responses to

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From the Departments Radiology (T.A., G.G.S., R.C.D., D.S.O.), Neurosurgery (C.M.C.), and Pathology (M.B.G.), Emory University School of Medicine, Atlanta, GA.

Address reprint requests to T. Abruzzo, MD, Department of Radiology, Emory University School of Medicine, 1364 Clifton Rd NE, Atlanta, GA 30322.

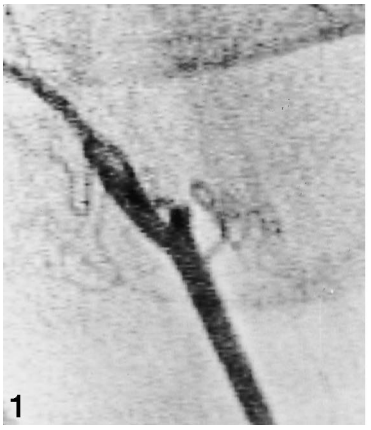


FIG 1. Carotid angiogram in a rabbit 2 weeks after the external carotid artery was converted into an EDASA.

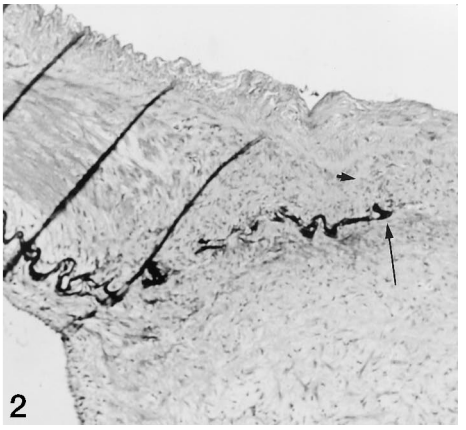


FIG 2. Cross section at the neck of a human cerebral aneurysm. The internal elastic lamina is seen as a deeply stained, undulating band coursing between the tunica intima and tunica media of the parent artery. Abrupt termination of the internal elastic lamina (*long arrow*) and the tunica media (*short arrow*) is seen at the margins of the saccular orifice (orcein; original magnification ×40).

intervention, the histologic and morphologic features of pancreatic elastase–digested arterial sac aneurysms (EDASAs), vein pouch aneurysms, and human intracranial aneurysms were analyzed by direct examination of histologic preparations. A standard profile for the comparison of experimental data was created from a review of published clinicopathologic series.

## Methods

### *Establishment of Standards for Comparison of Experimental Data*

We reviewed the literature to determine the histologic and morphologic features that are most characteristic of human cerebral aneurysms. Between 1940 and 1997, six major clinicopathologic series of human intracranial aneurysms were reported (15–20). Collectively, these series described the detailed histopathology of more than 340 aneurysmal specimens. One study included the morphologic measurements of 45 human cerebral aneurysms (18). The histologic and morphologic features that were most consistently reported were used to create a standard profile for comparison of experimental data. Four essential histologic traits were included in this profile: 1) Complete absence of internal elastic lamina in the sac of the aneurysm, with abrupt termination of the internal elastic lamina of the parent artery at the margins of the saccular orifice. 2) Complete absence of the tunica media in the sac of the aneurysm, with abrupt termination of the tunica media of the parent artery at the margins of the saccular orifice. 3) Absence of an inflammatory reaction in the walls of the aneurysmal sac. 4) Marked paucity of cellular elements in the sac wall and absence of fibromuscular neointimal proliferation. According to Suzuki and O'Hara (18), the average wall thickness of a saccular human cerebral aneurysm that is less than 5 mm in diameter is between 50 and 100 $\mu$m.

### *Specimens of Experimental Aneurysms*

All protocols were approved by the Institutional Animal Care and Use Committee of Emory University in accordance with the National Institute of Health guidelines. Four EDASAs of the common carotid artery bifurcation were created in three New Zealand white rabbits while they were under general endotracheal anesthesia (in one rabbit bilateral aneurysms were constructed). As described previously, each aneurysm was constructed by converting the external carotid artery into a saclike stump 0.75 cm long (12). In every case, 60 U of porcine pancreatic elastase was incubated in the lumen of the external carotid artery stump for 45 minutes.

Four jugular vein pouch aneurysms of the side wall of the common carotid artery were created in four adult pigs while they were under general endotracheal anesthesia. The aneurysms were constructed by suturing a linear segment of autologous jugular vein, measuring 1.25 cm in length, to an oval common carotid artery arteriectomy, measuring 5 mm in diameter. A modification of the surgical technique described by German and Black (1) and Kerber and Buschman (2) was used. The anastomotic suture line on the jugular vein graft was angled obliquely so that the inflow substreams were parallel to the long axis of the aneurysm rather than perpendicular to it. The details of this technique have been described in previous reports (21, 22).

All experimental aneurysms were left to mature for a period of 2 weeks, at which time, luminal patency was confirmed by angiography. In every case, the aneurysm was angiographically patent. Immediately after completion of angiography, the animals were killed by pentobarbital overdose, and the aneurysms were perfusion-fixed in 10% formalin, harvested, and embedded in paraffin blocks.

### *Specimens of Human Cerebral Aneurysms*

The formalin-fixed, paraffin-embedded specimens of five recently ruptured human intracranial saccular aneurysms, located at branch points in the circle of Willis, were obtained from five different autopsies. In each case, the maximal diameter of the aneurysmal sac measured between 5 and 10 mm.

### *Histologic Preparations*

Histologic preparations were made for all specimens in identical fashion by cutting 5-$\mu$m-thick longitudinal sections from paraffin blocks of formalin-fixed tissue. Multiple sections of each specimen were stained with hematoxylin-eosin. Separate sections were stained with orcein for elastic tissue studies.

### *Histopathologic and Morphometric Analysis*

A vascular pathologist blinded to the source of each aneurysmal specimen performed histologic examinations to describe the features of each specimen in relation to the four established standards of comparison described above. The presence or absence of endoluminal thrombus in each specimen was determined by microscopic examination of hematoxylin-eosin–stained sections. The morphologic dimensions of each aneurysmal specimen were estimated by measuring longitudinal sections through the specimen's central axis of symmetry at 40-fold magnification. Each measurement was taken twice (each time by a different investigator) with the same calibrated micrometer. Wall thickness was measured and recorded separately for the dome and neck of each aneurysm. In each aneurysmal specimen, the wall thickness at the dome ($WT_D$) was calculated as an average of the values of the wall thickness measured at three different sites: the apex of the dome, the

**TABLE 1: Aneurysmal morphology**

| Type of Aneurysm | Average Wall Thickness at Dome, μm | Average Wall Thickness at Neck, μm | Combined Average Wall Thickness, μm |
|---|---|---|---|
| Human (n = 5) | 51 | 52 | 51 |
| Vein Pouch (n = 4) | 228 | 350 | 290 |
| Elastase (n = 4) | 44 | 49 | 46 |

Note.—Wall thickness was measured and recorded separately at the dome and neck of each specimen as described in the Methods section. For each type of aneurysm, the average wall thickness at the dome and the average wall thickness at the neck are reported as an average of the individual values for each specimen in that group. For each type of aneurysm, the combined average wall thickness was calculated as the average at the dome and neck for the group.

**TABLE 2: Aneurysmal histology**

| Type of Aneurysm | Attenuation or Absence of Tunica Media at Dome | Attenuation or Absence of Internal Elastic Lamina at Dome | Intramural Inflammation | Cellular Composition of Aneurysmal Wall |
|---|---|---|---|---|
| Human (n = 5) | 5/5 | 5/5 | 0/5 | Disorganized acellular bundles of fibrillary collagen, occasional smooth muscle cells and fibroblasts. |
| Vein Pouch (n = 4) | 0/4 | 0/4 | 4/4 | Extreme cellularity with massive neointimal proliferation of smooth muscle cells and fibroblasts; prominent intramural mononuclear and neutrophilic infiltrates. |
| Elastase (n = 4) | 0/4 | 4/4 | 0/4 | Moderate cellularity contributed primarily by smooth muscle cells with an occasional fibroblast; occasional mononuclear cell but little evidence of an inflammatory reaction. |

Note.—A vascular pathologist blinded to the source of each aneurysmal specimen performed histologic examinations to describe the features of each specimen in relation to the established standards for comparison of experimental data outlined in the Methods section. The results are summarized for each type of aneurysm as a group.

right lateral wall of the dome, and the left lateral wall of the dome. The wall thickness at the neck ($WT_N$) was calculated as the average of the right and left $WT_N$.

## Results

### *Human Cerebral Aneurysms*

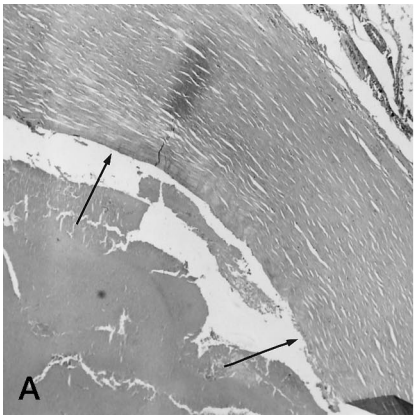
The histologic and morphologic data that we obtained from specimens of human cerebral aneurysms were in agreement with the findings reported in the six series that we reviewed (Tables 1 and 2). In all our specimens of human aneurysms, there was abrupt termination of tunica media and internal elastic lamina at the margins of the saccular orifice (Fig 2). None of our human specimens showed evidence of intramural inflammation, and in each case the aneurysmal wall was profoundly depleted of cellular elements (Fig 3A and B). In every section examined, the sac wall contained vast expanses of acellular collagenous tissue. Fibromuscular proliferation and neointimal thickening were not detectable in any of our human aneurysms. In our five specimens of human aneurysms, the average wall thickness at the neck was 52 μm, and the average wall thickness at the dome was 51 μm. In all five human specimens, firmly adherent thrombus covered the point of rupture and extended along the luminal surface of the aneurysmal cavity. In three of the five specimens, greater than one third of the aneurysmal cavity was filled with thrombus in various stages of organization.

### *Vein Pouch Aneurysms*

The histologic features of our vein pouch aneurysms were consistent with those reported by Stehbens (3, 5). In all the vein pouch aneurysms examined, a well-developed internal elastic lamina and tunica media extended throughout the aneurysmal sac (Fig 4). The walls of the vein pouch aneurysms were extensively infiltrated by inflammatory cells, and extreme degrees of fibromuscular proliferation were observed. The fibromuscular proliferation, which encompassed an excessive accumulation of both vascular smooth muscle cells and collagen fibers, was not restricted to the intima but spanned the entire aneurysmal wall. Proliferating cells included both vascular smooth muscle cells and fibroblasts. The inflammatory cell infiltrate contained both mononuclear cells and neutrophils. In all the vein pouch aneurysms, the sac walls produced massive neointimal thickening, which encroached upon the lumen (Fig 5A). In our vein pouch aneurysms, the average wall thickness at the neck was 350 μm, and the average wall thickness at the dome was 228 μm. In two specimens of vein pouch aneurysms (50%), unorganized thrombus filled greater than one third of the luminal cavity.

### *Pancreatic Elastase–Digested Arterial Sac Aneurysms*

In all the EDASAs, there was an abrupt termination of the internal elastic lamina at the margins of



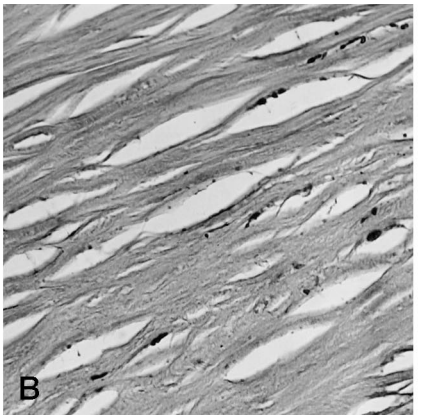




FIG 3. *A*, The wall of a human cerebral aneurysm. Absence of inflammation and a marked paucity of cellular elements are evident (*arrows* point to the luminal surface) (hematoxylin-eosin; original magnification ×40).

*B*, Same tissue section at a higher magnification emphasizes the highly acellular character of the human aneurysmal wall (hematoxylin-eosin; original magnification ×40).

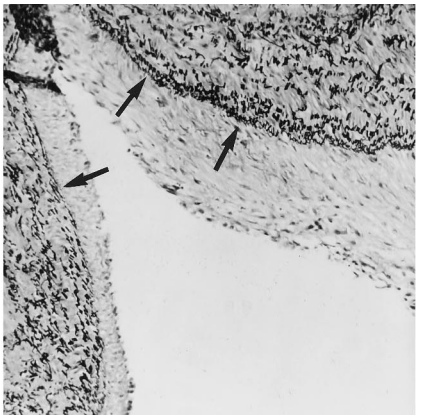
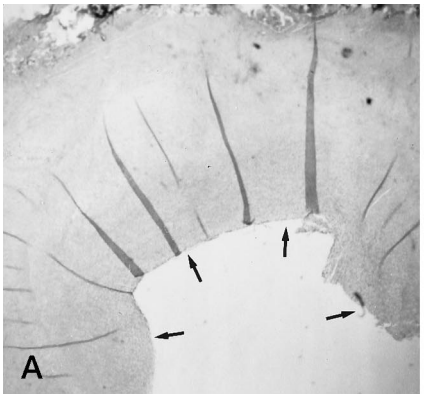
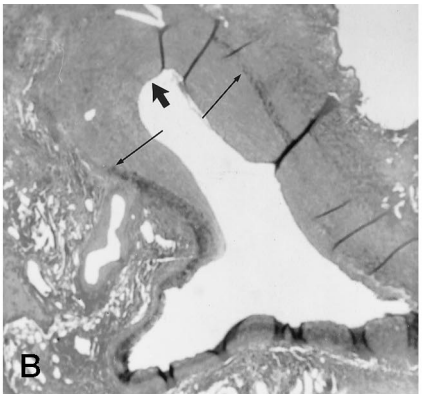


FIG 4. Cross section of swine vein pouch aneurysm. A well-developed internal elastic lamina is seen coursing throughout the aneurysmal sac (*arrows*) (orcein; original magnification ×40).



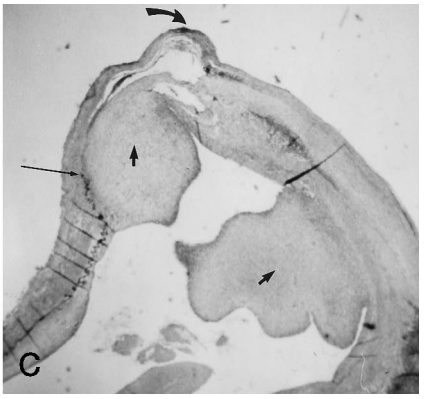




FIG 5. Longitudinal cross sections of aneurysmal specimens. Each cross section is taken through the specimen's central axis of symmetry (original magnification ×40).

*A*, Swine vein pouch aneurysm. The aneurysmal wall appears as a massively enlarged structure with extensive neointimal thickening (*arrows* point to luminal surface) (hematoxylin-eosin stain).

*B*, Rabbit EDASA. The aneurysmal wall is relatively thin, without significant neointimal accumulation (*short arrow* points to luminal surface). The internal elastic lamina terminates as it approaches the entrance of the aneurysmal sac (*long arrows*) (orcein stain).

*C*, Human cerebral aneurysm. The aneurysmal wall appears as a thin, attenuated structure, without significant neointimal thickening. The internal elastic lamina can be seen terminating at the margins of the saccular orifice (*long arrow*). Organized thrombus (*short arrows*) covers the point of rupture (*curved arrow*) and extends along the endoluminal surface of the aneurysmal dome (orcein stain).

the saccular orifice (Fig 5B). In each case, tunica media continued into the EDASA sac wall with some evidence of mild atrophy. The sac walls contained a mild inflammatory reaction and were moderately cellular, with a small degree of fibromuscular proliferation. The inflammatory cell population included both mononuclear cells and neutrophils. A mild degree of neointimal thickening, without luminal encroachment, developed in each of the EDASA sacs. In our EDASAs, the average wall thickness at the neck was 49 $\mu$m, and the average wall thickness at the dome was 44 $\mu$m. Unorganized thrombus filled greater than one third of the luminal cavity in two of four specimens.

## Discussion

Our results show that EDASAs model the histologic and morphologic characteristics of human cerebral aneurysms more accurately than do vein pouch aneurysms. As revealed by our study, EDASAs possess many of the features that are characteristic of human cerebral aneurysms, including absence of elastic tissue and an acellular sac wall that is relatively attenuated in thickness. Similar to human aneurysms, EDASAs express only mild degrees of mural inflammation and fibromuscular proliferation. In marked contrast to human aneurysms, vein pouch aneurysms have a well-developed internal elastic lamina and possess a highly cellular sac wall that is extensively thickened. Vein pouch aneurysms are further distinguished from human aneurysms in that they express extreme degrees of transmural inflammation and fibromuscular proliferation.

In this small series, angiographic patency at 2 weeks was equally excellent for vein pouch aneurysms (100%) as it was for EDASAs (100%). The high rate of angiographic patency observed for EDASAs at 2 weeks is in agreement with the results of our previous work (12). The discrepancy between angiographic pa-

tency and microscopic detection of endoluminal thrombus in postmortem specimens suggests that a substantial fraction of the clot detected microscopically formed ex vivo during surgical harvest of the specimen. The static pool of blood trapped within the lumen of the aneurysm during the cross clamping performed for harvest may have coagulated before perfusion fixation was initiated. Although we routinely administer heparin just before angiography, the window of therapeutic anticoagulation may have been exceeded in cases in which the time required for bilateral angiography and bilateral surgical dissection of the specimens was prolonged. Consequently, we believe that angiography reflects the in-vivo status of the aneurysmal lumen more reliably than does postmortem microscopic examination.

Previous pathologic investigations of vein pouch aneurysms have revealed findings similar to those reported here. Stebhens (3–5) performed detailed histologic studies of vein pouch aneurysms in sheep and rabbits, and found that rapid, spontaneous, and progressive fibromuscular neointimal proliferation begins within days after the experimental lesion is created. He reported that within 24 hours of the grafting procedure, venous pouches were extensively infiltrated by inflammatory leukocytes; fibrous neointimal thickening was grossly apparent within 10 days, and reached extreme proportions by 2 weeks. Progressive neointimal thickening continued without cessation for the entire period of experimental observation, which in some cases was longer than 2 years (5). Stebhens observed that vein pouch aneurysms older than 1 year exhibited extensive mural fibrosis throughout the aneurysmal sac (5). The extent of fibrosis and the aneurysmal remodeling closely approached the point of spontaneous histologic obliteration, a phenomenon that has never been observed in human conditions. Although the histologic features of aneurysms are highly dependent on hemodynamics, the sequence of histologic changes that Stebhens observed in side-wall vein pouch aneurysms was identical to that of vein pouch aneurysms grafted to the apex of an arterial bifurcation (4).

In vein pouch aneurysms, neointimal proliferation is expressed morphologically as thickening of the aneurysmal wall. Reflecting their lack of neointimal proliferation, EDASAs do not produce significant degrees of wall thickening. The results of human postmortem studies have consistently demonstrated that human aneurysms are structurally deficient, thin-walled structures (15–20). The thin, attenuated nature of the sac wall in cerebral aneurysms is an essential element of their pathogenesis that predisposes them to expansion and rupture. Extensive thickening of the sac wall in vein pouch aneurysms is highly atypical of saccular aneurysms, and probably interferes with their ability to grow and rupture (structural dynamics). Although progressive growth of vein pouch aneurysms has been reported in some studies, many authors have found that they do not undergo dynamic expansion (3–8). One study even found spontaneous shrinkage of a vein pouch aneurysm (23). Furthermore, spontaneous rupture of a vein pouch aneurysm has never been reported in the absence of wound infection or of mechanical failure of the anastomotic suture line. Presently, there is insufficient experimental data to make definitive conclusions about the structural dynamics of EDASAs, but it is likely that their structural dynamics will correspond closely with sac wall thickness. Sac wall thickness is an important predictor of aneurysmal behavior that must be considered in the design of experimental models. As shown in our study, the sac wall thickness of an EDASA (44 $\mu$m) is nearly identical to that of a human cerebral aneurysm (51 $\mu$m), while the average wall thickness of a vein pouch aneurysm is more than four times greater (228 $\mu$m).

The universal absence of neointimal thickening in the walls of saccular cerebral aneurysms has long been considered an essential pathogenetic feature of aneurysmal degeneration in the circle of Willis (15–20). Neointimal proliferation, the normal healing response of the arterial wall to injury, is distinctly absent at the apices of cerebral arterial bifurcations, where saccular aneurysms form (15). In many ways, neointimal hyperplasia and aneurysmal degeneration represent opposite ends of the same histologic spectrum. While neointimal hyperplasia involves mechanical augmentation of the arterial wall through the accumulation of vascular smooth muscle cells and extracellular matrix, aneurysmal degeneration involves mechanical failure of the arterial wall through the elimination of vascular smooth muscle cells and extracellular matrix. Clinicopathologic studies have suggested that aneurysmal lesions can be repaired and histologically obliterated through the process of neointimal proliferation (15, 24). Animal studies have supported this concept (25–27). If we consider histologic obliteration to be the therapeutic end point for the treatment of cerebral aneurysms, then neointimal proliferation and fibrosis are desirable therapeutic effects. In experimental aneurysms in which neointimal proliferation and fibrosis develop spontaneously, it is impossible to distinguish the effects of treatment from the natural history of the experimental lesion.

## Conclusion

Although the small number of experimental aneurysms examined in this study does not constitute a sufficient database for statistical analysis, our findings consistently showed marked similarities between EDASAs and human cerebral aneurysms. Our analysis suggests that vein pouch aneurysms may not reliably predict the responses of human cerebral aneurysms to therapeutic intervention. Unlike true saccular aneurysms, vein pouch aneurysms undergo a process of spontaneous healing through neointimal proliferation and fibrosis. This type of histologic behavior is highly atypical for true saccular arterial aneurysms. In EDASAs, on the other hand, inflammation and neointimal proliferation do not develop spontaneously. Consequently, EDASAs represent a

satisfactory model for the evaluation of aneurysmal tissue reactions to new interventional devices. Further study is warranted to fully characterize the acute and chronic histology of EDASAs.

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