

Assessment of experimental saccular aneurysm using selective angiography in common carotid artery of rabbits

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Abstract: In order to study the treatment of aneurysms, the technique of making experimental aneurysms in laboratory animals must be established. In our study, to examine the feasibility of making experimental aneurysm and selective angiography on the common carotid artery in rabbits and to determine the size of experimental aneurysm after surgery, saccular aneurysms were fashioned on the right common carotid artery in 17 rabbits using a vein pouch technique. Selective angiography of the common carotid artery was performed immediately after surgery, and at 1 week, 4 weeks, and 8 weeks after surgery. Also, histological changes in the aneurysms were observed. In 16 rabbits with established successful experimental aneurysm, no differences were found in diet intake and behavior before and after surgery. The patency of the carotid artery was confirmed by selective angiography. The average size of the aneurysm immediately after surgery was similar to that of 1 week postoperatively in selective angiography, however it increased with time at 4 weeks and 8 weeks. Histologically, infiltration of inflammatory cells and hemorrhage were found at the junction of the carotid artery and the vein pouch at 1 week, which disappeared at 4 weeks and 8 weeks. This study suggests experimental saccular aneurysm using the vein pouch technique might form aneurysms similar to that of the human in its properties such as increment of size, and selective angiography might be suitable for assessment of experimental aneurysm. Therefore, this animal model may be suitable for investigating new treatment methodologies for human aneurysms.

Key words: Rabbit, saccular aneurysm, selective angiogram

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Introduction

At least 5% of the human population in the USA harbors intracranial aneurysms, and 15~31% of these people have multiple synchronous aneurysms (Quigley *et al.*, 1988). There is extensive debate within the neurosurgical literature on criteria for surgical candidates, timing of surgery after

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an acute hemorrhage, and efficacy of different treatment modalities. Many treatment modalities have been available such as direct surgical obliteration of the aneurysm, surgical clamping of the aneurysm, ligation of the feeding vessel proximal to the aneurysm, and endovascular occlusion techniques using balloons or coils (Stehbens 1981b; Krings *et al.*, 2002). Moreover, advanced techniques have been continuously applied and tested in the treatment of aneurysm because established procedures sometimes yield insufficient, complicated or unreliable clinical results (Drake *et al.*, 1984; Heilman *et al.*, 1992; Szikora *et al.*, 1997; Byrne *et al.*, 1999). In order to develop new treatment methods, it is certain that establishment of an animal model of aneurysm must be the initiating event.

The purpose of this study is to demonstrate that an aneurysm can be reliably created in a common carotid artery utilizing the vein pouch technique and establish growth dynamics of experimental aneurysms in the rabbit model. Furthermore, this paper illustrates that the changes in aneurysm patency and size can be observed using histologic examination with light microscopy to detail anatomic changes of the aneurysm. Once the technique is proven, this animal model can be applied to study the development of new treatment methods with the use of selective angiography to assess the treatment methodologies.

Materials and Methods

Animals

New Zealand White Rabbits were supplied from the Samyuk Lab Animals, Inc. Animals were housed in the Large Animal Facility of the Department of Laboratory Animal Medicine, Yonsei University College of Medicine. The

temperature ($22\pm 2^\circ\text{C}$) and humidity ($55\pm 2\%$) were controlled and diet (Purina diet) and water were supplied *ad libitum*. The procedures in this experiments were reviewed by the "Committee for the Care and Use of Laboratory Animals" in Yonsei University College of Medicine according to the "Guide for Animal Experiments" edited by Korean Academy of Medical Science.

Experimental aneurysm

17 male rabbits, 3 to 3.5 kg, were anesthetized with 10 mg/kg of ketamine HCl (Ketalar, Yu-han Yanghang, Korea) by intramuscular injection and maintained with enflurane (Gerolan, Choongwae medical, Korea). During surgery, human SPO₂ probe (Hewlett-Packard, USA) was applied to rabbit's tail and SPO₂ was monitored and lead II of EKG, rectal temperature were monitored with anesthesia monitoring system (Hewlett-Packard, USA). The anterior neck is shaved and the animal is fastened to an operating table. The surgical area was scrubbed with povidone-iodine solution then draped in a sterile fashion. Under sterile conditions, a 4 cm midline incision was made from the manubrium to the submental area. A segment of the external jugular vein was isolated and freed by blunt dissection so as not to damage any of the associated neurovascular structures. To harvest the vein pouch, the jugular vein was ligated with 4-0 silk in 2 place adjacently and was cut between the first and the second ligatures and over a distance of 1 cm caudally from the second ligature, the third ligature of the jugular vein was made and the cranial part of the third ligature site was cut (Fig. 1A). The blood in the lumen of the harvested vein pouch was irrigated with lidocaine solution and heparinized saline. The vein pouch was placed on a heparinized, saline-soaked, gauze sponge while the recipient site on the artery was prepared. The sternocleidomastoid muscle was reflected laterally, exposing

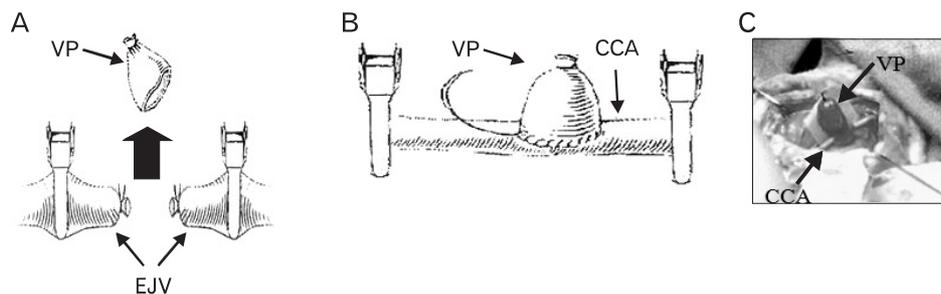


Fig. 1. Illustration of creating saccular aneurysm (A, B) and saccular aneurysm sewn onto the right common carotid artery (CCA) (C). The vein pouch is separated from the external jugular vein (EJV) (A). Then, after a transverse incision is made at the cervical region of the carotid artery, the vein pouch (VP) is sewn onto the common carotid artery with interrupted sutures. VP was attached to CCA (C).

the common carotid artery. A 3 cm segment of artery was cleansed of adventitia and isolated between bulldog clamps. A small square of thin latex (30×50 mm) was positioned beneath the isolated segment of artery. A transverse incision was made on the carotid artery with microscissors to be 2~3 mm wide. The open-end of harvested vein pouch was then anastomosed to dissected side of carotid artery (end to side anastomosis) with a single simple interrupted suture using 8-0 Ethilon (Ethicon, NJ, USA) (Fig. 1B). The base of the vein pouch aneurysm was surrounded with Gel-foam (Spongostan, Johnson & Johnson Medical, USA) and the whole segment was covered with a small gauze sponge. After commencement of manual compression to control bleeding, the bulldog-clamps were removed (Fig. 1C). Manual pressure was continued for 5 min. Finally, Gel-foam and small gauze sponge were removed carefully so as not to cause bleeding. Morphine was administered at extubation to all rabbits and was repeated at 4- to 6-h intervals during the next 12 h.

Selective angiography

The patency and the length of the aneurysm were determined by selective angiography via femoral artery cut-down immediately after surgery, and at 1 week, 4 weeks and 8 weeks respectively. The rabbits were divided into three groups. Angiography was performed immediately after surgery and at 1 week in 5 rabbits (group A). Same angiography was performed in 5 other rabbits (group B) immediately after surgery and at 4 weeks after surgery and remaining six rabbits (group C) immediately after surgery and at 8 wks after surgery. Rabbits were anesthetized with 10 mg/kg of ketamine HCl (Ketalar, Yu-han Yanghang, Korea) by intramuscular injection and maintained with enflurane (Gerolan, Choong-wae medical, Korea). During surgery, human SPO2 probe (Hewlett-Packard, USA) was applied to rabbit's tail and SPO2 was monitored and lead II of EKG, rectal temperature were monitored with anesthesia monitoring system (Hewlett-Packard, USA). Under aseptic conditions, skin incision was made on the inguinal region where pulsation was detected and the femoral artery was bluntly isolated. The distal portion of the artery was ligated while tension was applied to the proximal artery with 4-0 silk. The artery between the silk placement sites was punctured and a catheter (Fas-tracker 18, length: 150 cm, outer diameter: 2.5 F; Target Therapeutics Inc, USA) was introduced into the femoral artery. When 25% the catheter was introduced into the artery, and then the proximal silk was tied loosely. Under fluoroscopy (MCA - 501, C-arm

X-ray mobile type; Medison Korea), the catheter with guide wire (Seeker-16 Flexible guide wire, length: 175 cm, diameter: 0.016 inch; Target Therapeutics, USA) inserted was selectively introduced into the right common carotid artery. Ioversol (Optiray 320, Mallinckrodt Medical, USA) was used as the contrast agent (1,000 mg I/ug) was used as a maximum dosage for selection of carotid artery. The arteriogram of the experimental aneurysm in the right common artery was recorded with videotape using a videolink program (Mediface, Korea). Arteriogram being finished, the image of aneurysm recorded in the video tape was captured with a π view program (Mediface, Co., Seoul, Korea) designed for motion capture during videotape replay and then the width of aneurysms were measured with built-in caliper. To minimize the possibility of error caused by image angle, we capture the perpendicular aneurysm image to x-ray beam and measure the width of aneurysms. During procedures, 0.5 ml of saline was administered to flush the remnant contrast agent in the catheter after every injection of contrast agent. After angiography was performed the catheter was then retrieved and the femoral artery was ligated with 4-0 silk. Femoral artery access for follow-up angiography at 1 week, 4 weeks, and 8 weeks were accomplished by using proximal part of ligature site in same artery.

Histopathology

One rabbit was euthanized by overdose injection of a pentobarbital sodium at 1 week, 4 weeks and 8 weeks respectively. The common carotid artery was dissected and removed. Tissues were fixed in 10% neutralized buffered formalin solution and embedded in paraplast. Paraffin sections were stained with hematoxylin-eosin and examined with a light microscope.

Statistical analysis

Statistical analysis was performed using the SPSS statistical computer program. One way ANOVA was applied to data analysis.

Results

In 16 rabbits, experimental aneurysm was successfully established with 6% perioperative mortality rates. No differences were found in diet intake and behavior before and after surgery in 16 rabbits. One rabbit showed the sign of

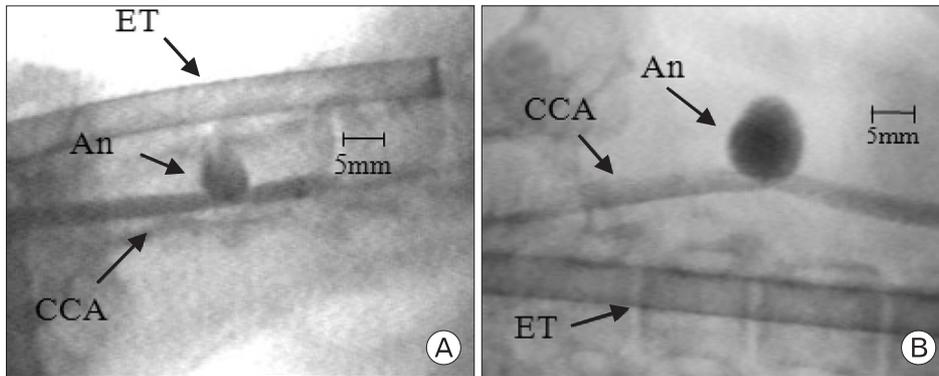


Fig. 2. Angiography of demonstrating aneurysm at 1 week (A) and 8 weeks after surgery (B). Contrast being injected, common carotid artery (CCA) was opacified with aneurysm (An). Note the size of aneurysm increased with time compared to that of endotracheal tube (5 mm, ET).

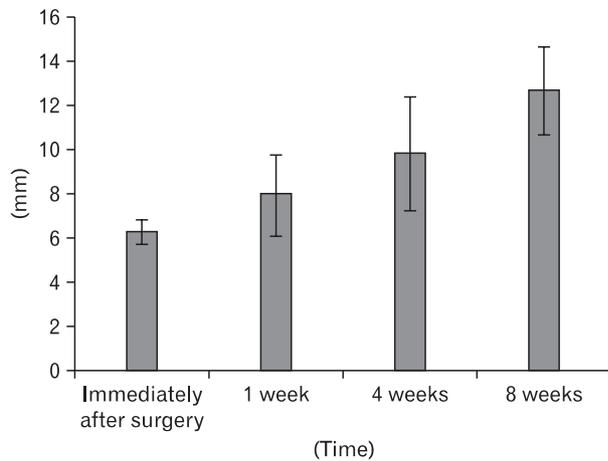


Fig. 3. Changes in aneurysm width determined by angiography. The width of aneurysm was significantly increased at 4 weeks and 8 weeks, respectively, compared to immediately after surgery.

anorexia, depression and dehydration at day 1 and diarrhea and weight loss was detected at day 3. These symptoms were exacerbated in spite of fluid therapy and antibiotic therapy. Therefore, 1 week after surgery, follow-up angiography could not be performed and there were no clinical signs of recovery, the rabbit was euthanized 2 weeks after surgery. There were no signs of post-surgical complications such as lameness in 16 rabbits due to the femoral artery ligation. The patency rates immediately after surgery was 87.5%. In 2 rabbits, the occlusion of the carotid artery was detected by selective angiography immediately after surgery and it was due to blood clot formation at the orifice of aneurysm. To recanalize the carotid artery, Fas-tracker 18 (Target Therapeutics, USA) catheter was located at the carotid artery near the orifice of aneurysm and the guide wire (Seeker-16 Flexible guide wire; Target Therapeutics, USA) was crossed into the aneurysm. Then, the catheter was introduced into the aneurysm through guide wire and 2 ml dose blousing of saline was performed

to recanalize the carotid artery. Though, small thrombus was flowed to peripherally, there were no signs associated with distal embolization of thrombus. Once the carotid artery was recanalized, the patency of artery was 100% and they were maintained until 8 weeks in 2 rabbits. The patency of the carotid artery in others was confirmed by selective angiography immediately after surgery. Selective angiography was successful in demonstrating the aneurysm (Fig. 2).

In 16 of the rabbits in which the vein pouch was grafted in the right carotid artery, the average width of the aneurysm determined by selective angiography immediately after surgery was 6.38 ± 0.52 mm, 8.06 ± 1.81 mm at 1 week, 9.93 ± 2.55 mm at 4 weeks and 12.72 ± 1.94 mm at 8 weeks, respectively. The width of aneurysm was significantly increased at 4 weeks and 8 weeks, respectively, compared to immediately after surgery ($P < 0.05$). Also, it was found that the width of aneurysm was significantly increased at 8 weeks compared to 1 week and 4 weeks respectively ($P < 0.05$) (Fig. 3).

In necropsy findings, the surrounding tissues were dislocated by the enlarged experimental aneurysm, however, the size of the aneurysms was within 15 mm that it might affect the function of surrounding tissues minimally (Fig. 4). Histologically, infiltration of inflammatory cells composed of neutrophils, lymphocytes and mild hemorrhage were found in the junction of carotid artery and the vein pouch at 1 week. This had disappeared at 4 weeks and 8 weeks. All specimens showed intact anastomosis. The endothelial surfaces were intact and continuous and the lumens were patent (Fig. 5).

Discussion

Currently available animal models for the study of treatment of aneurysms include rabbit, rat, dog and, more recently, in swine. Dogs have been consistently used

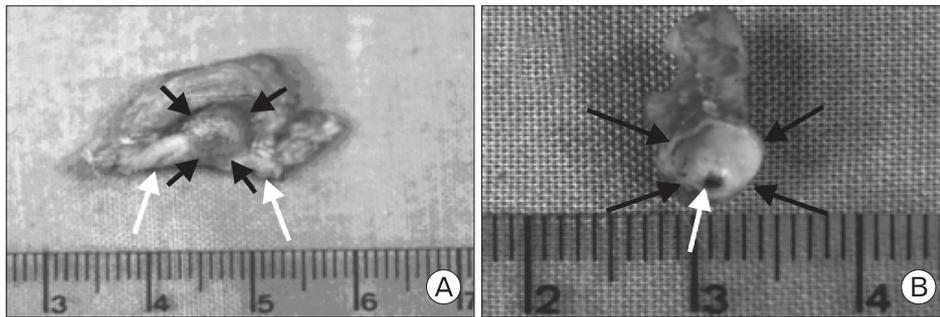


Fig. 4. (A) The gross findings of aneurysm 4 weeks after surgery. The surrounding tissue was dislocated by the aneurysm (black arrows) attached to common carotid artery (white arrows). (B) The cross-section view of aneurysm. There was a patent aneurysmal orifice (white arrow) in the aneurysm (black arrows).

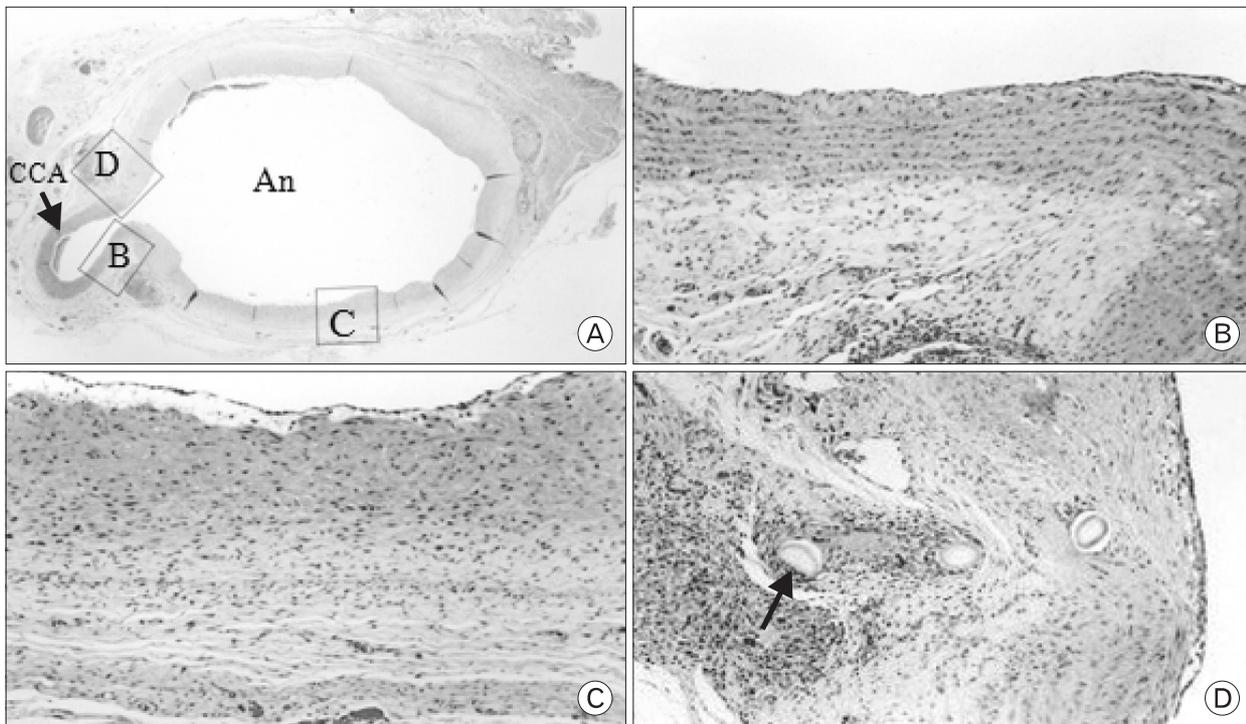


Fig. 5. Histologic finding of aneurysm 4 weeks after surgery. (A) Aneurysm (An) was attached to common carotid artery (CCA) (×10). (B, D) Junction of common carotid artery and aneurysm. Suture material (black arrow) was shown (×40). (C) Aneurysm wall. There was a mild infiltration of neutrophils and fibrosis (×40).

since the mid 1950s. Their ease of handling and reliable anesthesia contributes to their success as laboratory animals. The fibrinolytic system in canine blood is very active when compared to humans (Osterman *et al.*, 1976). Experiments have shown rapid lysis of autologous clot with early recanalization within 6-12 h after arterial occlusion (Bookstein *et al.*, 1974). Therefore, this natural tendency to rapid lysis of thrombus makes it difficult to extrapolate the results obtained in the canine model accurately to treatment of human aneurysms. The activity of the fibrinolytic system and the coagulation system is relatively similar in man and swine (Osterman *et al.*, 1976). Hence, many researchers have advocated the use of swine as an alternative to dogs for the

construction and treatment of experimental aneurysms. In swine, surgical construction of experimental lateral saccular aneurysms (Guglielmi *et al.*, 1994), bifurcation aneurysm and terminal aneurysms (Massoud *et al.*, 1994) are established successfully. However, Kirse *et al.* stated that dog and swine are clearly the most expensive laboratory animal and the rabbit model is somewhat cheaper, assuming the operation is done under noninhalation anesthesia. Also, they stated that rat could be used to study novel modalities for the treatment of aneurysms (Kirse *et al.*, 1996). However, as though aneurysm that constructed in the rat by vein pouch technique resembles most human aneurysms, this animal model has its limitation for the application of endovascular therapy because

the outer diameter of the common carotid artery in rats around 300~350 g is from 0.8 mm to 1.2 mm but the outer diameter of the catheter which commonly used for treatment of human intracranial aneurysm is 0.82 mm or larger. Also, it cannot be introduced into the femoral artery of the rat due to its small vessel size. Advantages of rabbits include the similarity of the size of their common carotid arteries to the human proximal middle cerebral artery. Furthermore, the rabbit is one of the non primates whose thrombotic and thrombolytic profiles are most comparable to those of humans (Heilman *et al.*, 1992). It is our intention to use this model to investigate the application of newly developed transarterial microwave irradiation with coiling of aneurysm. Therefore, rabbit was selected for its accessibility to aneurysm through femoral artery for investigation of newly developed endovascular treatment modalities.

In order to study the treatment of aneurysm, the technique of creating an experimental aneurysm in laboratory animals had to be established. Previously established methods include damaging the wall of the vessel by intramural injection or topical application of a noxious substance such as nitrogen mustard, hypertonic saline (White *et al.*, 1961), or calcium chloride (Gertz *et al.*, 1988), or by damaging the artery wall using laser energy (Quigley *et al.*, 1988) or inducing hypertension through medication, carotid ligation and the induction of lathyrism (Hashimoto *et al.*, 1987). However, the above techniques are unpredictable concerning the rate and size of aneurysm formation and take an extended time for aneurysm formation. The anastomosis of a vein pouch to the wall of an artery resembles saccular aneurysms found in humans both morphologically and histologically. The vein pouch, like an aneurysm, lacks an internal elastic lamina and a well-developed muscular media in rabbit model. It gave consistently reliable results with respect to the size of the aneurysm produced and also excellent patency rates (German & Black, 1954). The vein-pouch technique using the rabbit model was first described by Forrest and O'Reily and their paper described almost a 25% perioperative mortality and extremely low thrombosis rate (3%) and it was probably related to wide orifice related to the length of aneurysm (Forrest & O'reilly, 1989). Kirse *et al.* (1996) have shown in their study that vein-pouch technique using rabbit model could be successfully applied to the rat with 100% patency rates. However, One-third of the aneurysms showed varying degrees of partial apical thrombosis in the rats. In this study, 16 experimental aneurysms were successfully established with

6% perioperative mortality rates, the size of the aneurysm was easily determined from the size of harvested jugular vein, and the patency rate was 87.5% immediately after surgery. In 2 rabbits, the aneurysm was occluded temporarily, but it was recanalized quickly. Therefore, the patency rates are 100% at 1 week, 4 weeks and 8 weeks. Our 2 case of thrombosis at orifice of opening was probably related to the relative narrow orifice compared with the length of the aneurysm and subsequent reduction of blood supply to the aneurysm during manual compression to the aneurysm.

The current study was to demonstrate creation of reliable experimental aneurysms in the rabbit model and to demonstrate changes in patency and size with time. Increased growth was demonstrated with no early rupture of the aneurysm and histologic changes were not found to be similar to those in human saccular aneurysm. Therefore, this may be an excellent model for the investigation of new treatment modalities. This animal model using vein pouch technique can be used to study interventional modalities for the treatment of aneurysms.

Other researchers previously established a growth pattern of aneurysm in the rabbit and the rat respectively (Stehbens 1981b; Quigley *et al.*, 1988; Kirse *et al.*, 1996). It is generally accepted that most untreated intracranial aneurysms will get larger in human as they did in this model (Allcock & Canham, 1976). Also, in our study, the average width of the aneurysm was significantly increased at 4 weeks and 8 weeks compared to immediately after surgery and it is similar to the results of other study using vein pouch technique in rat (Kirse *et al.*, 1996). In this experiment, Serial angiograms could not be done in rabbits because angiographic procedures were not performed percutaneously. The femoral artery approach was achieved by cut-down because the diameter of femoral artery was too small to puncture percutaneously and after procedures the femoral artery was ligated after procedures. Therefore, it is limited to have more information on the changes in the same aneurysm angiographically. Though, in regard to determining the aneurysm size, configuration, and neck morphology, non-invasive techniques such as time-of-flight phase contrast and contrast enhanced magnetic resonance angiography has been reported (Krings *et al.*, 2002). However, in this study, we could not use MRI due to its limited accessibility.

Stehbens reported that experimental aneurysms in rabbit model designed to simulate saccular aneurysms grew, becoming almost spherical, and its walls initially thin and

transparent, thickened considerably within 8 weeks (Stehbens 1981a). Histologically, there was increased cellularity of perivascular tissues. The inflammatory response was resolved in acute phase, but phlebosclerosis developed in the aneurysms and progressed to severe fibrosis, calcification, ossification, mural thrombosis and lipid deposition resembling human atherosclerosis, with eventual loss of the media, in long term study (Stehbens 1981b). In our study, infiltration of inflammatory cells are composed of neutrophils, lymphocytes and along with mild hemorrhage were found in the junction of the carotid artery and the vein pouch at 1 week. These tended to decrease at 4 weeks and 8 weeks similar to the previous study. Other chronic changes seen by Stehbens were not observed due to the short period of the experiment. It is anticipated that selective angiography might be suitable for assessment of experimental aneurysm and apply to new treatment methodologies for human aneurysms because of its similar properties such as increment of size.

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