主　論　文

Histopathological study of balloon embolization:

Silicone vs. latex

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動脈瘤閉塞モデルの組織学的検討

―シリコンバルーンとラテックスバルーンの比較―

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Running title: Silicone vs. latex in balloon embolization

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ABSTRACT

Bilateral, Symmetrical, experimental aneurysms were produced with anastomosed vein flap in the carotid arteries of 24 mongrel dogs. Aneurysms were occluded with latex or silicone balloons on each side and observed angiographically from two weeks to two months. A histopathological study was performed subsequently using light and scanning electron microscopy. Rupture following balloon embolization occurred in five aneurysms, all of which were incompletely occluded by a silicone balloon. On subsequent angiogram, four silicone balloons and one latex balloon were found to have migrated into the aneurysm, resulting in aneurysmal expansion. Parent artery occlusion was more common with latex balloons than silicone balloons. Histopathologically residual fresh thrombi, less proliferation of fibroblasts within the aneurysmal cavity and poor endothelialization were present around the silicone balloon. These results suggest that the intraaneurysmal organization, as seen in the aneurysm occluded by the silicone balloon, will delay because the balloon is not fixed within the aneurysm, and that such free-floating and rotating balloon causes repeated aneurysm wall trauma, contributing to subsequent enlargement and rupture of the aneurysm. The superior anti-thrombogenic nature of silicone may be responsible for the bias of such phenomena toward the silicone balloon.

Key Words: Balloon embolization, Histopathological study, Silicone, Latex

INTRODUCTION

Recently, the technique of intravascular occlusion by detachable balloon for surgically inaccessible aneurysms has gained wide-spread usage. Although the development of catheters and balloons and advances in microcatheter techniques have made successful occlusion possible, several complications with rupture following balloon embolization have been reported[9,18]. Some cases of rupture occurred following incomplete aneurysmal occlusion, the cause of which has been thought to be aneurysmal wall injury due to the mechanical impact by a free-floating balloon within the aneurysm[9]. We suspect that such a destabilization of the balloon may be responsible for the delay in intraaneurysmal thrombosis and organization. We compared aneurysmal occlusion using a siicone or a latex balloons in experimentally created canine carotid artery aneurysms to determine which material was superior for clinical aneurysmal occlusion.

MATERIALS and METHODS

Creation of Experimental Aneurysms.

Thirty mongrel dogs, each weighing approximately 12 Kg, were used for this study under a protocol approved by the Nagoya University Animal Care Comittee. The dogs were anesthetized with ketamine hydrochrolide (3 mg/Kg intramuscularly) and pentobarbital (5 mg/Kg intravenously). The animals were intubated and allowed to breathe room air spontaneously. Anesthesia was maintained with additional doses of pentobarbital as required.

Each surgical procedure was performed under sterile conditions with the aid of an operating microscope.

A 6 cm midline skin incision was made in the neck, and the common carotid artery and the external jugular vein were isolated. After vascular clamps were placed both proximally and distally, a 8 mm elliptical arteriotomy was made in the carotid artery. The external jugular vein was incised longitudinally and an appropriate length was anastomosed to the carotid artery side-to-side using 9-0 nylon suture. The vascular clamps were removed, and the jugular vein was ligated proximally and distally to the anastomosis, thereby creating an aneurysm-like projection on the lateral aspect of the carotid artery[16,20,21]. This procedures was performed bilaterally and created symmetrical carotid artery aneurysms.

Angiographic evaluation.

The patency of the experimental aneurysm was confirmed by carotid angiography. Each aneurysm was embolized incompletely by either silicone or latex balloon. In each dog, one aneurysm was occluded by a silicone balloon and the other by a latex balloon during a single procedure within seven days after the creation of the aneurysm. Navigation and intraaneurysmal balloon placement was performed using an intravascular microcatheter technique identical to that used clinically. Silicone and latex balloons were alternated from right to left side for each case in fairness to laterality. Both detachable balloons were of the Debrun type, whose protruding tip contained a metal marker*, and self-sealing

was obtained by balloon neck ligation with latex threads. 5-hydroxyethyl methacrylate (HEMA)** was used as the hardening material within the balloon. Since almost all aneurysms were incompletely occluded, faint filling of the aneurysm was observed by angiography just after the occlusion. Repeat angiography was performed between two weeks to two months following the occlusion and then both aneurysms were removed. At the completion of the study each animal was sacrificed with an overdose of pentobarbital.

Histopathologic evaluation.

Harvested aneurysms were cut along the median line of the aneurysm, crossing the parent artery to divide it into two specimens; one was fixed with formaldehyde and stained with hematoxylin and eosin for light microscopy (LM), and the other was prepared for scanning electron microscopy (SEM). The specimens for SEM were fixed to demonstrate the orifice on longitudinal section. Processing for SEM included fixation for at least 24 hours with 2% glutaraldehyde in 100 mM potassium phosphate buffer, pH 7.2, containing 4% sucrose and rinsed thoroughly with the same buffer. They were postfixed for 60 min with 1% osmium tetroxide dissolved in the above buffer and then rinsed. Specimens were dehydrated with graded ethanols and critical-point-dried by the fluorocarbon method. The dried specimens were coated with gold in a vacuum evaporator prior to SEM[3]. By LM, the cross-sectioned specimen in the middle of orifice was examined for the thickness of cell layers (organized

tissue, fibroblasts and endothelial cells) covered on the luminal surface of the balloon, evaluated by measuring at the center of the arc-shaped lining cell bridge. The connection of the cell layers with the arterial lumen also was assessed. Organizing tissue between the balloon and the aneurysmal lumen was evaluated at the base of the aneurysm, not by its thickness, but by the number of cell layers as a developmental index of intraaneurysmal organization. The development of endothelialization was evaluated in two dimensions by the extension of fibroblasts and endothelial cells using SEM. The paired t-test and Fisher's t-test were used to compare results of silicone and latex balloons in individual dogs.

RESULTS

Angiographic Results (Table 1).

Sixty aneurysms were created in thirty dogs. Six cases were unsuccessful because of spontaneous thrombosis prior to balloon embolization or premature death due to the leakage from the anastomosis and were excluded from this study. Five of the remaining 24 cases in which balloon embolization was performed bilaterally were lost because of rupture of the aneurysms during follow-up. Rupture occurred six days after balloon embolization in three cases and seven days afterward in two cases. All ruptures occurred in the aneurysms embolized by silicone balloons. This was significantly more frequent than with latex balloons. Autopsy proved that the rupture was caused not from

anastomosis disruption, but from penetration of the dome by the balloon itself. Follow-up angiography revealed that complete embolization with patency of the parent artery was achieved in 28 aneurysms: 15 aneurysms were occluded by latex balloons and 13 were occluded by silicone balloons (Fig.1A). However, two aneurysms completely occluded by silicone balloon desmonstrated balloon migration (Fig.1B). Four aneurysms occluded by silicone and two by latex balloons exhibited residual intraaneurysmal space (Fig.1C). Except for two aneurysms occluded by silicone balloons, these aneurysms demonstrated balloon migration into the aneurysmal sac with enlargement of aneurysm. Complete parent artery occlusion occurred in five vessels, out of which four were on the side of latex balloon occlusion. The ten cases in which both aneurysms were successfully embolized and the parent artery could be preserved used for the histopathologic study.

Aneurysm Histopathology (Table 2).

Light microscopy revealed that the luminal surface of both types of balloon had been covered by fibroblasts and organized thrombus associated with an inflammatory reaction within two months. Although some of the latex balloon surfaces were covered with dense, completely organized thrombus within a month, most of the silicone balloons were covered with nothing but rough fibrous tissue and poor proliferating fibroblasts, even after six weeks. The thickness of lining cells was not measured in three aneurysms removed two weeks after embolization because fibroblasts had not yet extended into the middle of the orifice on both balloons. The

nearer to the edge of the orifice, the thicker the cell layers. On most latex balloons, these lining cell layers were smoothly continuous with endothelial cells lining the lumen of the parent artery. For eight of the ten silicone balloons, however, the cell layers were not continuous (Fig.2A). This difference in endothelialization between balloon types at the junction of orifice edge statistically significant. The thinnest cell layers on the latex balloon were thicker than those of silicone balloon in half of the cases. Three cases had almost the same thickness on both balloons, but there were no cases in which the thickness on the silicone balloon was more than that on the latex balloon (Fig.3A). The thickness of the covering cell layers measured in the center of the orifice was 0.22+0.05 mm on the silicone balloon and 0.42+0.14 mm on the latex one, which represents a statistically significant ($p<0.01$). Intraaneurysmal organization on the latex balloon was superior to the silicone balloon in seven out of ten cases. Two cases showed almost the same degree of fibroblast proliferation on the two balloons, and in only one case was a silicone balloon superior to the latex one. Intraaneurysmal organization was classifed into three grades: grade I, fresh thrombus present; grade II, collagenized fibrin and rough fibrous tissue; and grade III, dens fibroblast proliferation with highly organized mature thrombus [14,20]. According to this classification, more than half of the aneurysms occluded by a silicone balloon were grade II, while most aneurysms occluded by a latex one belonged grade III (Fig.3B).

By SEM (Fig.2B), endothelialization proceeded through the following stages. First, fibrous connective tissue with multilayers of fibroblasts were formed from thrombus adhering to the balloon surface (stage I); then endothelial cells appeared on the cell layers with inner connections exhibiting a "cobble stone appearance" (stage II); and subsequently, the endothelial cells made tight junctions with each other exhibiting a "mosaic pattern" (stage III)[7]. Seventeen aneurysms could be observed by SEM except for two which were occluded by a silicone balloon and one by a latex balloon whose surface had not yet been covered with any tissues (stage 0). The "Cobble stone appearance" was observed on the latex balloon surface more often than that of the silicone balloon, and the "mosaic pattern" which demonstrated complete endothelialization was found on two latex balloon surfaces but no silicone surface. The stage of fibrous tissue was more commonly observed with silicone than latex balloons.

Endothelialization at the orifice was delayed on silicone balloon more than on the latex balloon in all cases except one (Fig.4). In most cases, the balloon tail protruded into the parent artery(Fig.1A). Fibrous tissue was found to mount the tail or make a bridge adherent to the tail, and around the tail, fibroblasts were arranged as if delineating vortices, suggesting eddy current formation (Fig.2B). Such fibroblasts exhibited a tendency to proliferate as well as extend into the center of the orifice. However the top of tail was never covered on either balloons, even after two months.

DISCUSSION

Intraaneurysmal balloon embolization is the most desirable endovascular treatment for an aneurysm. One of the major purposes of balloon embolization is to protect the thin aneurysmal wall from bearing the hemodynamic stress directly. However occasionally the aneurysm can only be filled incompletely because of the disproportion between the irregular shape of the aneurysm and the smooth shape of the round or oval balloon. Even in such cases, it has been believed that spontaneous intraaneurysmal thrombosis is accelerated due to the decrease in the size of the aneurysm cavity and the stasis of intraaneurysmal blood flow[18]. Nevertheless, a few cases in which an aneurysm enlarged or ruptured following incomplete treatment with a balloon have been reported [9,18]. Most of the reported cases showed migration of the balloon just prior to rupture compared to the primary position [9,18]. This suggests that a nonthrombosed extra-balloon space persists between the balloon and the aneurysmal lumen even several days following occlusion.

Our study, which may be the first report to describe this phenomenon in an experimental model, disclosed 11% of embolized aneurysms (five out of 48 aneurysms) ruptured following balloon embolization. It is certain that this rupture rate is higher than seen clinically. One reason is that the lumen of the experimental aneurysm was not constructed from arterial wall, but rahter with a thin and stretchable vein. Moreover, the lumen of the aneurysmal sac, which is in direct contact with the tip of the balloon is stretched most, because our model was created

using a side-to-side anastomosis. If the experimental aneurysm had been created with an arterial flap or an end-to-side anastomosis with a vein graft[5], the rupture may have been lower. It may also be assumed that the aneurysm was embolized too early. Previous reports[7,20] have stated that it takes two to four weeks to lay the inner surface of an experimental aneurysm before the endothelialization is completed. Nevertheless, even in such conditions, it should be noted that there is an obvious difference in the postembolized behavior of silicone and latex balloon.

Both silicone and latex balloons are used commonly for intravascular aneurysmal occlusion, and their safety as a biomedical materials has been confirmed[10,19]. Anti-thrombogenesis is one of the most important factors for intravascular materials [10]. In fact, the aneurysmal orifice embolized by a balloon is likely to show a delay in endothelialization following thrombus organization compared to that of spontaneous obstruction or fibrin sealant injection [14]. Within two weeks, the balloon surface was not covered by any cells, despite the fact that proliferated fibroblasts or endothelial cells with "cobble stone appearance" already had covered the orifice of a complete thrombosed aneurysm.

Especially silicone is an excellent anti-thrombogenic material. The adhesiveness of clots is less than 50% of that of the latex, and coagulating time when blood is attaching to silicone material is also postponed to 20 minutes, which is 12

minutes longer than that of latex[10]. This high efficiency is thought to be due to the surface structure rather than tissue-affinity [10]. When the surface of the two balloons was observed on SEM (Fig.5), the silicone balloon exhibited a smooth and finely uneven surface with homogeneous structure, whereas the latex balloon was rough and porous with a lot of large and deep craters. The rough and porous surface may rheologically cause turbulent flow and hemostasis on a surface which easily sticks and entraps red blood cells and platelets into the craters. Our study disclosed that the silicone balloon exhibited delayed endothelializaion at the luminal surface and intraaneurysmal organization as compared to the latex balloon. As for silicone balloon, these facts suggest that anti-thrombogenesis inside the aneurysmal remnant space after incomplete balloon occlusion may decclerate the organizing process and that lack of adhesion of clots on the balloon surface may delay endothelialization. Takahashi et al [19] also have reported that latex is superior to silicon in promoting the proliferation of endothelial cells in an in-vivo study on the biological reaction of various biomedical materials. In the case of incomplete embolization, the delay in intraaneurysmal organizing and endothelialization of the orifice may cause persistent instability of the balloon. As seen more frequently in aneurysms occluded by silicone balloon, crack formation at the junction between the orifice edge and covering cells on the balloon surface and intraaneurysmal fresh thrombi may be indicators of delayed thrombotic organization and endothelial repair. The results of angiographic studies

demonstrated that postembolization aneurysmal rupture or enlargement occurred more frequently on the aneurysms embolized by silicone balloons. This suggests that if the occluded balloon has been moving intraaneurysmally to and fro in synchrony with pulsatile blood flow for a comparatively long time before intraaneurysmal thrombosis is completed, then the weakest wall at the base of the sac could be injured and ruptured by the repeated impact of the balloon. especially one with a protruding balloon tip containing a metal marker[9].

Strother et al [18] have reported that turbulent flow caused by changing intraaneurysmal hemodynamics associated with incomplete occlusion can increase hemodynamic stress on the aneurysm wall. Such a jet flow also may expand the remnant neck and allow regrowth of the aneurysm [12]. Black et al [1] also have pointed out that a broad orifice was less likely to result in spontaneous intraaneurysmal thrombogenesis. Since aneurysm wall trauma due to mechanical or hemodynamic stress can enlarge or rupture an aneurysm, we must assert that a silicone balloon is more hazardous for aneurysmal embolization than a latex one.

It should be noted that all aneurysmal rupture was observed between the 6th and 7th days following balloon occlusion. One contributing factors could be spontaneous fibrinolysis. Although intraaneurysmal thrombosis may occlude the aneurysm temporalily and fix the balloon into the aneurysm, subsequent thrombolysis may cause recanalization and release the balloon to injure the intima again. Actually, in some clinical cases [2,17] recurrence

of aneurysm following spontaneous thrombosis has been observed, and such a phenomenon has been explained on the same basis. In our study, angiography performed two weeks after embolization showed a shift in the position of the silicone balloon into the bottom of an aneurysm without a remnant neck. Nevertheless, this balloon moved subsequently. We observed only one case, but this fact suggests that thrombosis and thrombolysis may occur sequentially within the lumen. Repeated angiography could demonstrate whether complete or incomplete embolization has occured. In a case of incomplete embolizaion, it is very important that serial angiography should be performed to check the balloon position and detect regrowth early [8].

To prevent rupture following balloon embolization, complete filling of the aneurysm would be ideal [13]. However over-inflation of the balloon should be avoided as it could compromise the patency of the parent artery. A balloon, especially if it is latex, protruding into the lumen of parent artery is likely to cause turbulent flow in the region of stenosis, contributing to intraarterial thrombosis. Moreover a balloon tail protruding into the lumen of the parent artery also may be thrombogenic.

Another problem related to inflating the balloon is the material used as the content of balloon. When contrast materials only is used, spontaneous balloon deflation to increase the risk of recanalization may occur in an early stage following embolization [11]. However, permanent hardening material may affect the surrounding tissue as a mass effect by the balloon itself and may compress surrounding tissue, especially nerves in

the cavernous sinus [15]. Moreover, a latex balloon filled with HEMA may be toxic because of oozing through the semi-permeable membrane [11]. Such a dilemma exists whenever intravascular balloon aneurysmal embolization is performed and further study is necessary to establish the safest regimen of balloon embolization, the manner in which the spontaneous thrombosis can be achieved following incomplete embolization, and how to prevent thrombogenesis within the parent artery when the balloon protrudes intraluminally. However, human aneurysm vary widely in shape, size, thickness and density of the aneurysmal sac, etc. Moreover atherosclerotic change and the other ischemic conditions that predispose to aneurysms may well affect the outcome [9].

As incomplete aneurysmal embolization has a risk of rupture caused by repeated aneurysmal wall trauma by an unfixed balloon, the silicone balloon is more dangerous than the latex balloon. In order to avoid such mechanical trauma, other balloon embolization techniques, such as endosaccular clipping [13], which occludes the aneurysmal neck by placing a small balloon without filling the sac completely could be employed. In stead of a balloon, coil [6] and wire have been used for aneurysmal embolization [4] and recently, liquids also have been tried experimentally. Each of these materials also has the problem of distal embolization. So the choice of therapeutic material must be individualized. Improve results will depend on further developments in the materials and methods of intravascular aneurysmal embolization.

FOOT NOTE:

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Figure Legends

Fig.1A A case of complete balloon embolization. Carotid angiogram demonstrating an experimental aneurysm before treatment (A) and just after detachable balloon (latex) embolization (B). The aneurysm is still filled with contrast material. Subsequent angiogram taken a month after embolization (C) showing complete occlusion of the aneurysm. Note the balloon tail protruding into the parent artery.

Fig.1B A case of complete embolization with balloon migration associated with aneurysm enlargement. Carotid angiogram demonstrating an aneurysm before treatment (A) and after embolization by a silicone balloon (B). Subsequent angiogram taken two weeks later (C), showing that the balloon shift into the aneurysm with some rotation, and angiography performed two months later (D), showing further migration.

Fig.1C A case of persistent incomplete embolization. Carotid angiogram demonstrating an aneurysm before treatment (A) and after incomplete embolization by silicone balloon (B). Subsequent angiogram taken two months after embolization (C) showing that intraaneurysmal remnant space still exists.

Fig. 2A A light photomicrograph of a cross-section of an aneurysm embolized by silicone balloon (one month after embolization). The upper side is the internal lumen of the parent artery. A thin bridge (arrowheads) shows cell layers covering the surface of the balloon. Note a crack (arrow) at the junction between these

covering layers and the aneurysmal orifice. (HE x20)

Fig. 2B A sccanning electron photomicrograph of the orifice (two months after embolization by a silicone balloon). The surface of the balloon (silicone) has been covered with fibroblasts. The endothelial cells in the lumen of the parent artery run a wave course longitudinally and are divided at the orifice. Lining fibroblasts delineate vortices around the protruding balloon tail smoothly cover and precede the lumen of the parent artery (arrowhead), but form a crack at the margin of orifice. The protruding balloon tail and a part of latex ligature remain uncoated except for the regions of mounting fibroblasts (arrow). (x40) (A bar in right lower corner represents 100 microns.)

Fig. 3A A light photomicrograph of covering cell layers (six weeks after embolization). The layers on the latex balloon (right) are thicker than those of the silicone balloon (left). (HE x100)

Fig. 3B A light photomicrograph of the bottom of an aneurysmal sac (one months after embolization). Intraaneurysmal space embolized by a silicone balloon in grade II (left) demonstrates rough fibrous tissue and fresh thrombi, while that of a latex balloon shows good organization with dense proliferation of fibroblasts, in grade III. (HE x100)

Fig. 4 A scanning electron photomicrograph of the intraluminal surface of a balloon (two months after embolization). Endothelial

cells on the surface of a silicone balloon (left) show a "cobble stone appearance" (stage II), while endothelial cells on a latex balloon disclose a "mosaic pattern" with marked cell borders (stage III). (right). (x700) (A bar represents 10 microns.)

Fig. 5 A scanning electron photomicrograph of the balloon surfaces. Note the smooth surface of a silastic balloon (left) and the rough and porous surface of a latex one (right). (x700) (A bar represents 10 microns.)

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Table 1-A

Angiographic Results of Balloon Embolization of Experimental Aneurysm

n=24	silicone	latex
aneurysmal rupture after embolization	5	0 *
parent artery occlusion	1	4
complete aneurysmal embolization	13 (2)	15 (0)
incomplete aneurysmal embolization	4 (2)	2 (2)

( ) : associated with shifted balloon

* : $p<0.05$ in Fisher's exact test

Table 1-B

Histopathological Results of Balloon Embolization of Experimental Aneurysm

n=10	silicone	latex
Light Microscopy		
thickness of covering cell layers (mm)	0.23 ± 0.05	0.42 ± 0.14*
crack formation	8	3
intraanurysmal organization #		
grade I	1	0
grade II	6	2
grade III	3	8
Scanning Electron Microscopy		
stage of endothlialization #		
stage 0	2	1
stage I	4	2
stage II	4	5
stage III	0	2

: refer the text on these grading and staging

* : $p<0.01$ in paired t-test

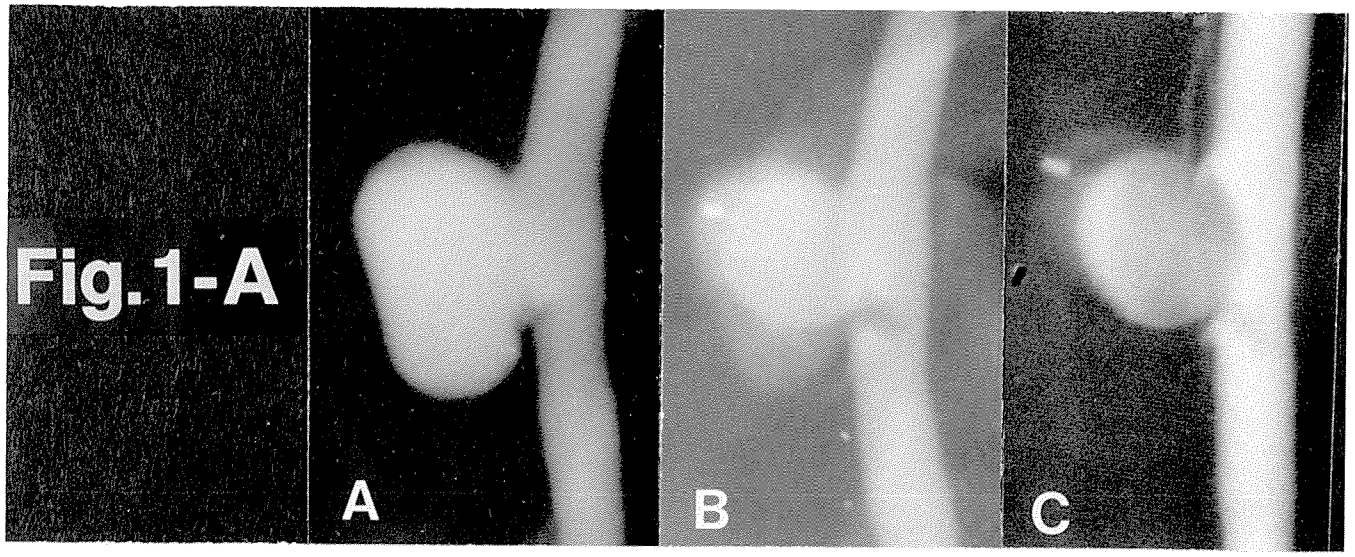
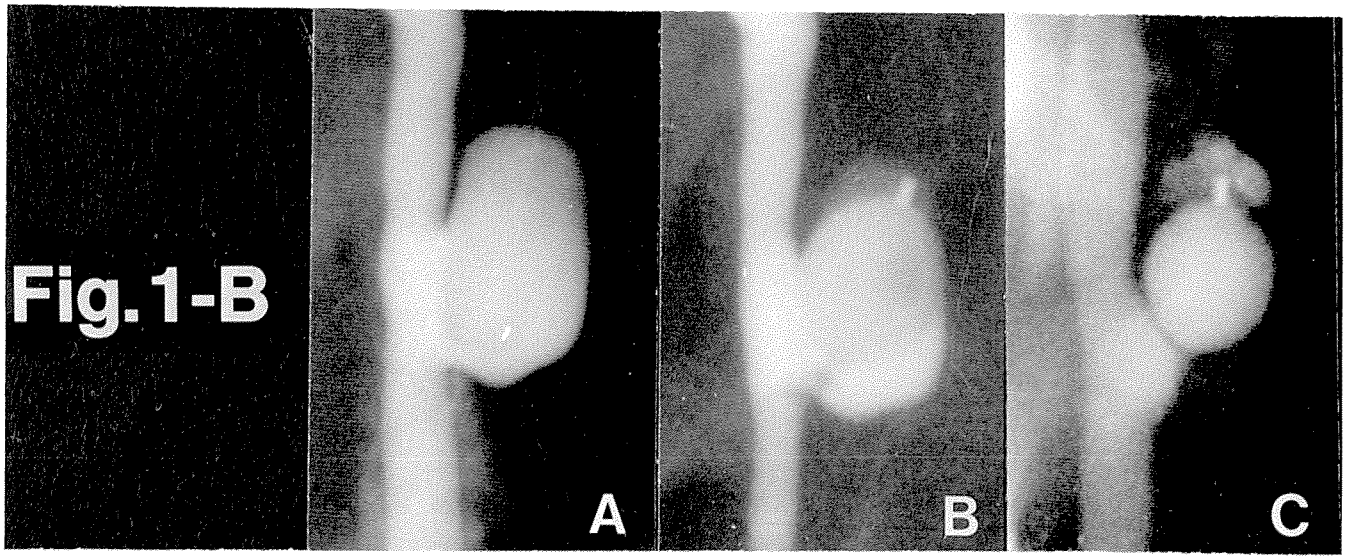


Fig. 1-A
A
B
C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A
B
C

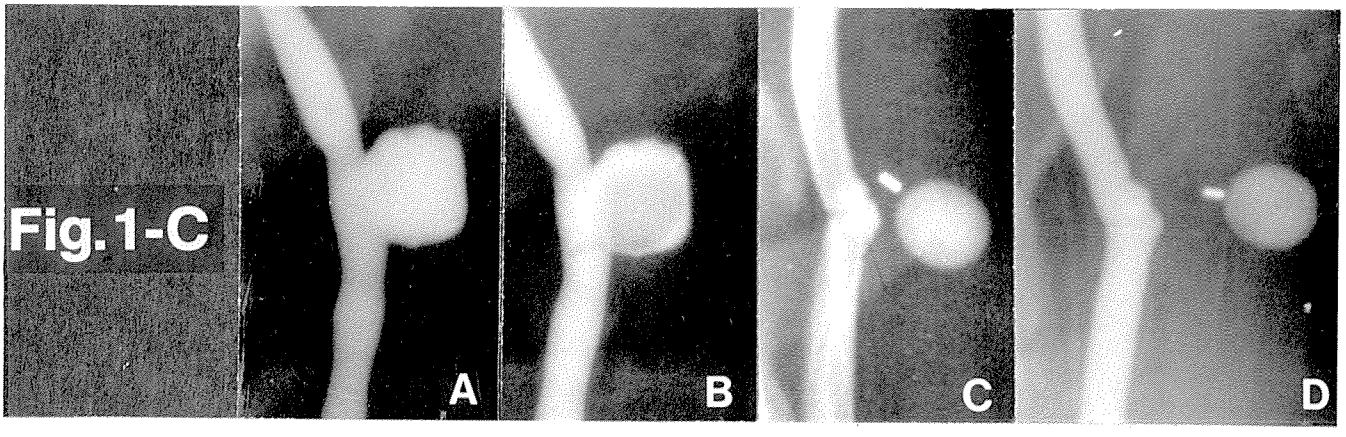


Fig. 1-C
A
B
C
D

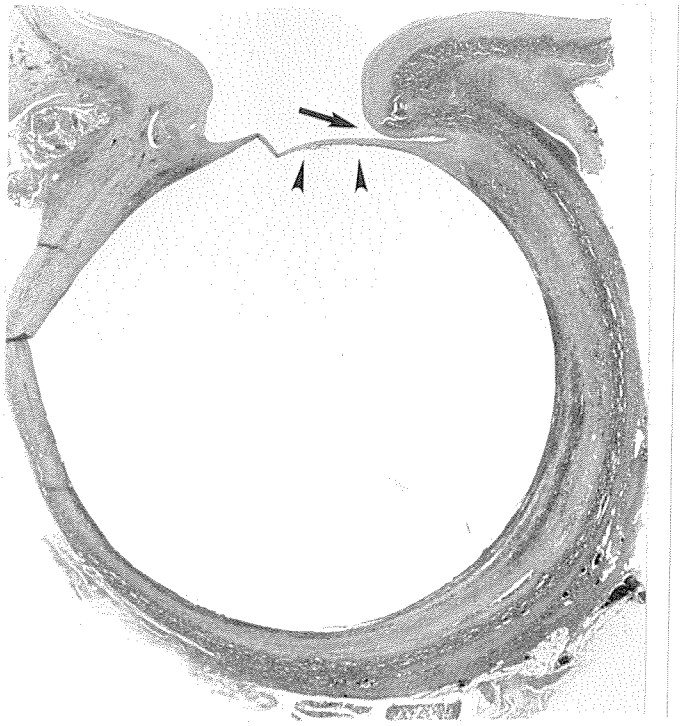


Fig. 2-A

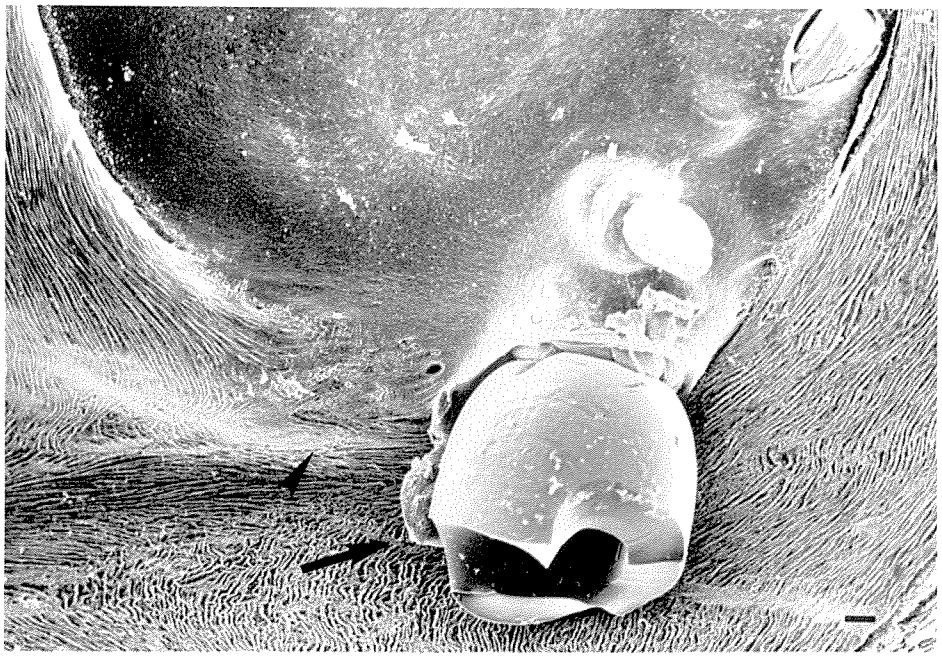
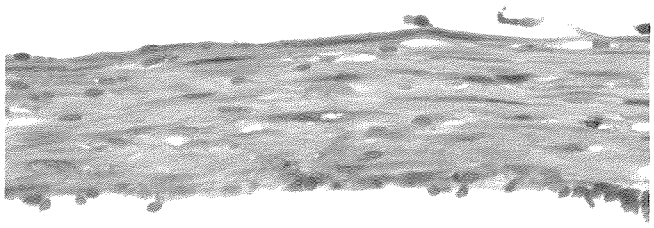


Fig. 2-B



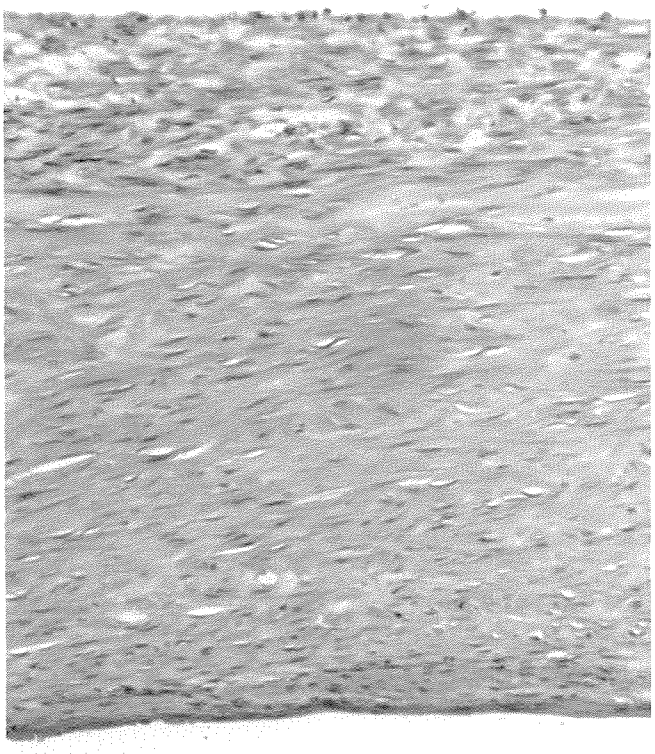


Fig. 3-A