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# Occlusion of canine aneurysms using microporous self-expanding stent grafts: Long-term follow-up

Shogo Nishi [a,*], Yasuhide Nakayama [b], Hatsue Ishibashi-Ueda [c], Yoshida Masato [d]

[a] Department of Neurosurgery, Interventional Neurosurgery, Spinal Surgery, Sapporo-Higashi Tokushukai Hospital, Sapporo, Hokkaido, Japan
[b] Department of Bioengineering, Advanced Biomedical Engineering Center, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka, Japan
[c] Department of Pathology, National Cerebral and Cardiovascular Center Hospital, Suita, Osaka, Japan
[d] Department of Neurosurgery, Nozaki Tokushukai Hospital, Osaka, Japan

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ABSTRACT

*Purpose:* The treatment of large or giant cerebral aneurysms by surgical and/or endovascular techniques is difficult and poses relatively high risks. Therefore, a microporous self-expanding (hybrid) stent graft composed of a thin, expandable, segmented polyurethane (SPU) membrane with micropores and a drug-delivery system was developed.
*Materials and methods:* A commercially available, self-expanding carotid stent was covered with a thin microporous SPU membrane fabricated by the dip-coating method and the excimer laser ablation technique, with an intraluminal coating of argatroban. Experimentally fabricated lateral-wall aneurysms in canine carotid arteries using venous pouches were occluded with the hybrid stent graft (bale-shaped pore density of 23.6%) on one side and a bare-metal stent on the other side without systemic antiplatelet therapy.
*Results:* Angiography at 1, 6, and 12 months of stenting revealed that all arteries were patent without marked stenosis without systemic antiplatelet therapy. All aneurysms treated with hybrid stent grafts remained occluded throughout the 12-month period, while among those treated by bare-metal stents, 2 of 3 aneurysms were occluded at 6 months (67%) and only 1 of 3 aneurysms were occluded at 12 months (33%). Histology revealed that the novel hybrid stent graft had less intimal hyperplasia than the bare-metal stent. The hybrid stent graft was useful for the successful occlusion of these canine carotid aneurysms, even at 12 months.
*Conclusions:* The novel hybrid stent grafts are expected to overcome the disadvantages of fully covered stent grafts and simple bare-metal stents, while combining both their merits, and appear to be useful in the treatment of large or giant cerebral aneurysms.



## 1. Introduction

Large, giant, or dissecting aneurysms with a broad neck occurring in the craniocervical area are difficult to treat surgically and/or endovascularly. The surgical treatment of such aneurysms involves direct aneurysm neck clipping [1,2], aneurysm trapping, proximal occlusion of the parent artery with or without a bypass [3], or a combination of clipping with coiling or a bypass [4]; endovascular treatment involves bare-metal, balloon-expandable, or self-expanding stent-assisted coiling [5–8]; use of simple covered stents [9,10]; use of flow-diverter stents [11–13]; or parent artery occlusion or trapping with or without a bypass [14,15]. Stent treatment is based on the assumption that the metallic struts induce alterations in the blood flow dynamics within an aneurysm, thereby inducing and promoting thrombus formation and fibrosis within the residual aneurysmal lumen [16,17]. However, aneurysms treated with stenting may be prone to recanalization or parent artery stenosis due to neo-intimal proliferation [18].

The recently developed pipeline embolization device (PED) is a self-expanding cylindrical mesh device with 48 individual cobalt chromium and platinum strands having 30–35% metal surface coverage, intended to be porous enough to preserve the patency of any branch vessels requiring coverage [11].

Microporous, self-expanding stent grafts have been developed for the occlusion of cerebral aneurysms, particularly extracranial and vertebrobasilar aneurysms. The newly developed stent graft is a hybrid of a bare-metal stent and a fully covered stent created by

* Corresponding author at: Department of Neurosurgery, Neuro-Intervention, Spinal Surgery, Sapporo Higashi-Tokushukai Hospital 14-3-1, Higashi, N33, Higashi-ku, Sapporo, Hokkaido 065-0033, Japan. Tel.: +81 11 722 1110; fax: +81 11 722 0378.
*E-mail address:* nishi@higashi-tokushukai.or.jp (S. Nishi).

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adjusting the porosity of the covering film, with a thin, expandable segmented polyurethane (SPU) membrane; micropores created by the excimer laser ablation technique for regulating endothelialization and intimal invasion; and a drug-delivery system at the membrane [19–21]. The present study examines the long-term occlusion efficacy of the experimentally fabricated hybrid stent in the treatment of canine carotid aneurysms.

## 2. Methods

### 2.1. Animals

For this study, experimental aneurysms were created in the carotid arteries of 12 female beagles (age, 12 months; weight, 13–15 kg). One month after aneurysm formation, each animal underwent placement of the novel microporous self-expanding stent graft in the carotid aneurysm of one side and a bare-metal self-expanding stent, on the other. Angiography was performed at 1, 6, and 12 months after stenting. Histological examination was performed after euthanizing the animals.

All animal experiments were performed in the acute setting under sterile conditions, in compliance with the Principles of Laboratory Animal Care (formulated by the National Society for Medical Research, Chicago, IL) and the Guide for the Care and Use of Laboratory Animals (NIH publication no. 86-23, revised 1985; National Institute of Health, Bethseda, MD). The research protocol (no. 09043) was approved by the ethics committee of the National Cerebral and Cardiovascular Center Research Institute.

### 2.2. Fabrication of aneurysms

Bilateral experimental side-wall carotid aneurysms were created in the carotid arteries of 12 female beagles by end-to-side anastomosis using an autologous venous pouch, as described previously [19–21]. The aneurysms measured approximately 5 mm in diameter at the neck and 10 mm in length. All procedures were performed under general anesthesia. The beagles were transmuscularly premedicated with ketamine chloride (dose range, from 150 mg/3 mL to 250 mg/5 mL per beagle), intubated endotracheally, and anesthetized with an intravenous administration of sodium pentobarbital at 50 mg/1 mL or 100 mg/2 mL according to the active motion. The carotid arteries and right external jugular vein on both sides were exposed under sterile conditions, and 2 venous pouches were created by one-sided ligation with threads after the harvesting of the right external jugular vein. The carotid artery and the venous pouch were anastomosed (side-to-end anastomosis) with discontinuous 7-0 nylon sutures, while the artery was temporarily clamped. After removing the clamp, the bleeding was controlled by additional suturing or local compression. The necks of the aneurysm were marked with radiopaque strings. After awakening from anesthesia, the dogs were allowed ad libitum access to food.

### 2.3. Fabrication of stent grafts

Bare-metal, self-expanding stents (Luminexx stents: diameter, 5 mm; length, 20 mm; Brad Inc., Murray Hill, NJ) taken out from their primary delivery systems were coated with an SPU film (Miractran, Tokyo, Japan) by dipping them in a tetrahydrofuran solution when sealed on a stainless mold (diameter, 5 mm). The thickness of the film was restricted to approximately 50 μm. Micropores were then created in the cover film by using a KrF excimer laser apparatus (L4500; Hamamatsu Photonics, Shizuoka, Japan). We created a bale-shaped pore type, with a pore size and interpore distance of 100 × 268 μm and 250 μm, respectively, to achieve an opening ratio of 23.6% (Fig. 1). The control stent comprised a bare-metal stent with an opening ratio of 86%. The outer surface of the SPU film of the microporous stent grafts was coated with argatroban (500 μg/cm$^2$), which was applied using a methanol solution (1% w/v); the solvent was subsequently

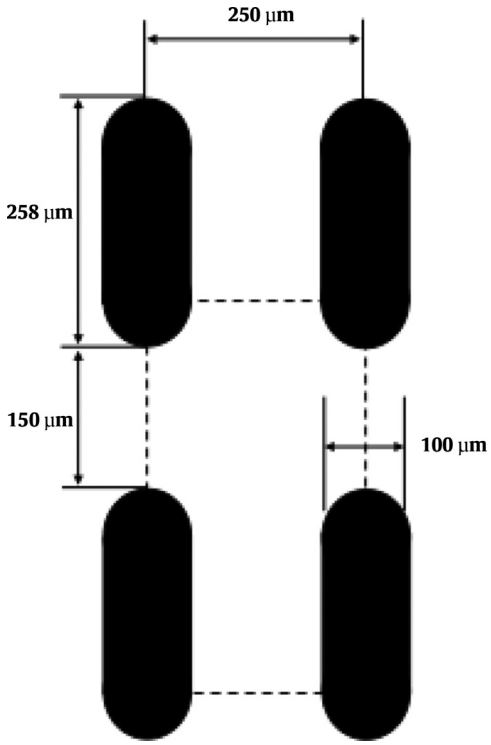


**Fig. 1.** Schema of the pore design. Pore diameter and the interpore distance were 100 × 268 μm and 250 μm, respectively, with an opening ratio of 23.6% (bale-shaped); the circumference at the 5-mm diameter was 15.7 mm.

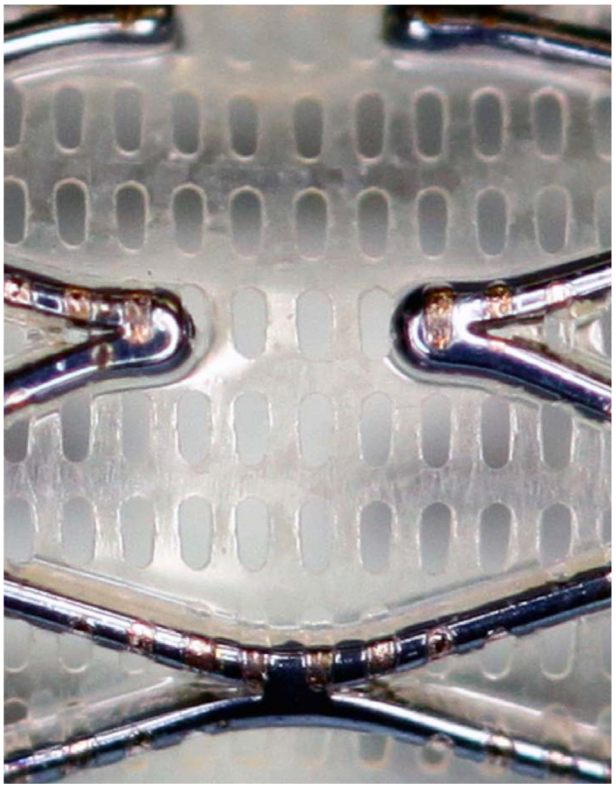

**Fig. 2.** Pore design in the hybrid microporous stent graft. Post-fabrication microporous stent graft showing bale-shaped micropores before remounting.