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A new-generation, low-permeability flow diverting device for treatment of saccular aneurysms

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Abstract
Objectives We report a preclinical comparative study of a 96-strand braided flow diverter.
Methods The 96-strand braided device was compared with the currently commercially available flow diverter with 48 strands. The devices were implanted across the neck of 12 elastase-induced aneurysms in New Zealand White rabbits and followed for 1 and 3 months (n=6 respectively). Aneurysm occlusion rates, parent artery stenosis and patency of jailed branch occlusions were assessed by angiography, histology and scanning electron microscopy studies.
Results It was feasible to navigate and implant the 96-strand device over the aneurysm orifice in all cases. At follow-up two aneurysms in the 48-strand vs. one in the 96-strand group were not occluded. This aneurysm from the 96-strand group however had a tracheal branch arising from the sac and showed a reverse remodelling of the vascular pouch at 3 months. In the occluded aneurysms, the parent artery was always completely reconstructed and the aneurysm orifice was sealed with neointimal tissue. No in-stent stenosis or jailed branch artery occlusion was observed.
Conclusions The 96-strand flow diverter proved to be safe, biocompatible and haemodynamically effective, induced stable occlusion of aneurysms and led to reverse remodelling of the parent artery.
Key points
- *Flow diversion has been introduced to improve endovascular treatment of cerebral aneurysms*
- *A new low-permeability flow diverter is feasible for parent artery reconstruction.*
- *The Silk 96 flow diverter appears effective at inducing aneurysm healing.*
- *The covered branches remained patent at follow-up.*

Keywords Flow diverter · Aneurysm · Stenting · Thrombus · Porosity · Pore density

Abbreviations

CCA	Common carotid artery
DSA	Digital subtracted angiography
FD	Flow diverter
PA	Parent artery
SEM	Scanning electron microscopy
VA	Vertebral artery

Introduction

The concept of flow diversion was introduced to improve endovascular methods for the treatment of cerebral aneurysms with larger segmental wall defects of the parent artery. In vitro and in vivo studies have demonstrated that stents with different porosity and pore density properties have a variety of interesting effects on intra-aneurysmal haemodynamics [1–4]. This led to the

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introduction of the flow diversion concept: a single endovascular, stent-like device, positioned across the aneurysm orifice will redirect blood flow to the parent artery and thus induce thrombosis of the aneurysm, whilst maintaining patency of adjacent branching vessels covered by the device.

The currently available flow diverter devices for intracranial aneurysm treatment have shown very promising results in parent vessel reconstruction and aneurysm healing in the clinical setting. These devices are braided structure tubular constructs, composed of a mesh of very fine strands. In clinical practice, data are available on the effectiveness of the Silk and the PED, both with a 48-wire braided structure. These data show that although the occlusion rate of treated aneurysms progressively increases over time, at 6 months it is approximately 76 % [5]. During the process of thrombosis the treated aneurysms may be unprotected from rupture, or in very large and giant lesions, the risk of rupture after treatment may even increase, likely by an inflammatory aneurysm wall reaction mediated by the quality of the induced intra-aneurysmal thrombus [6, 7]. When it comes to increasing occlusion rates, augmenting the haemodynamic power of flow diverters may theoretically allow this goal to be achieved.

Therefore, our purpose was to analyse the feasibility and effectiveness of a new-generation, higher braid profile flow diverter device with altered porosity and pore density properties in the treatment of experimentally created aneurysms in a rabbit model.

Materials and methods

Flow diversion devices

In this comparative study the products tested were braided flow diverter devices with different porosity and pore density properties. The basis device used was the Silk, which is a commercially available 48-wire braided mesh cylinder (called Silk 48 in this study) composed of a nickel-titanium (NiTinol) alloy and platinum microfilaments. Silk received the CE mark in January 2008. The study device was the Silk 96, a new-generation flow diverter with double the wire count of the original Silk. The Silk 96 presents with altered porosity, pore density and permeability properties, as shown in Table 1. Both are flexible, self-expanding devices specifically designed for parent artery reconstruction and aneurysm thrombosis.

Animal experiments

The ethics committee of the responsible Veterinary Authority approved all experimental protocols. Animals underwent two surgical procedures under general anaesthesia at two different time points: aneurysm induction and FD implantation. Twelve New Zealand White female rabbits were allocated to one of two similar study groups (six animals in each) according to the type of implanted device (Silk 48 or Silk 96). Each group was further divided into two subgroups according to the follow-up time, i.e. 4 weeks and 12 weeks following the FD implantation, respectively.

Table 1 Porosity, pore density and permeability data of flow diverters used in the study. The data are calculated for nominal 3.5-mm-diameter devices, unconstrained to a 3.75-mm diameter size (data provided by the manufacturer). The permeability of the devices was calculated according to the previously published formula [2]

	Silk 48	Silk 96
Mean strand size	0.034 mm	0.029 mm
Porosity	77 %	65 %
Pore density	12 pores/mm^2	40 pores/ mm^2
Permeability	178 μm^2	74 μm^2

Aneurysms were created according to the established elastase-induced aneurysm model [8]. Briefly summarised, under general anaesthesia, under sterile conditions, the right common carotid artery (CCA) of the animal was surgically isolated. An arteriotomy of 1–2 mm was made and a 5 F introducer sheath was advanced into the CCA in a retrograde fashion. Through the introducer sheath a 15-cm long microtube and a 2 F Fogarty balloon catheter were introduced. For elastase injection a microtube was used instead of a regular microcatheter, providing a much smaller dead space in the delivery system. The balloon was inflated at the origin of the right CCA and a seal test was performed by injection of contrast material. Keeping the balloon inflated, with the tip of the microtube close to the proximal end of the balloon, a mixture of 100 units of porcine pancreatic elastase (Worthington Biochemical Corp.), contrast material and saline solution at a ratio of 2:1:1 respectively was infused into the lumen of the isolated CCA segment and allowed to incubate for 20 min. At the end of the incubation period the stump was flushed with saline, and the balloon and microtube were removed. A control angiography was performed and the CCA was ligated permanently at the level of the arteriotomy.

The flow diversion treatment of the induced aneurysm was planned at a minimum maturation period of 3 weeks after aneurysm induction. Starting 2 days before FD implantation the animals were premedicated with aspirin (10 mg/kg PO) and clopidogrel (10 mg/kg PO); this regimen was continued for 4 weeks after endovascular treatment. Under general anaesthesia, the right femoral artery was surgically isolated and a 5 F introducer sheath was gently inserted. Animals were anticoagulated with 50 IU/kg of unfractionated IV heparin. Through a 5 F guiding catheter, the FD delivery

microcatheter, a Vasco 21 for the Silk 48 and a Vasco 25 (Balt International, France) for the Silk 96, was placed over a microguidewire in the subclavian artery. The FD was deployed across the neck of the aneurysm, and, in cases where the length of the device allowed, also covering the orifice of the vertebral artery. At the end of the procedure, the catheter and the introducer sheath were removed. The femoral artery was permanently ligated.

Angiographic evaluation of aneurysm occlusion was performed immediately following the FD implantation and before killing the animals, according to the scale proposed by Kamran et al. [9]:

0. No change in the endoaneurysmal flow;
1. Residual contrast medium filling more than 50 % of the pre-treatment aneurysm volume;
2. Residual contrast medium filling less than 50 % of the pretreatment aneurysm volume;
3. Residual filling confined to the neck region and not extending beyond the width of the neck;
4. No residual filling, i.e. complete obliteration of the aneurysm.

The incidence of parent artery stenosis was assessed at sacrifice with angiography and with histology.

Animals were followed up at 4 and 12 weeks. Before being killed, they were deeply sedated with IV propofol infusion. An intra-venous DSA of the right subclavian artery was performed by injecting a bolus of 12 ml of contrast agent through the cannulated left ear vein, as described previously [10]. Following angiography, a large dose of propofol was administered. In the areactive animal, the neck was dissected to open the large neck veins in order to exsanguinate the animal. The chest wall was surgically opened and the left ventricle of the heart was punctured. The left ventricle was continuously flushed with approximately 800–1,000 ml NaCl 0.9 % solution until the bleeding from the neck veins showed only minimal blood staining. The aortic arch with the supra-aortic trunks was then carefully dissected and fixed in 4 % buffered formalin. The samples were stored at 4 °C until histological preparation.

Tissue processing

Specimens were fixed in 4 % buffered formalin. After fixation the samples were rinsed in water and further dehydrated in an ascending series of ethanol (50 %, 70 %, 80 %, 90 % 96 %, 100 %) before being placed in xylene under vacuum. The infiltration of the samples proceeded under vacuum at 4 °C in methyl methacrylate. Embedding of specimens in methyl methacrylate (Methacrylic acid methyl ester, Fluka Chemie GmbH, Buchs, Switzerland; dibutyl phthalate, Merck-Schuchardt OHG, Hohenbrunn, Germany; Perkadox 16, Dr. Grogg Chemie AG, Stetten, Switzerland) was performed in customised Teflon forms. After polymerisation, the blocks were mounted on plastic frames and cut with a precision saw (Leica SP 1600®, Leica Instruments GmbH, Nussloch, Germany). Sections were mounted on acropal slides (Perspex GS Acrylglas Opal 1013, Wachendorf AG, Basel, Switzerland) and polished to 100– to 150-μm sections (Exakt® Mikroschleifsystem 400 CS, Exakt Apparatebau GmbH, Norderstett, Germany). Ground sections were surface stained with Giemsa in order to carry out the light microscopy. Neointimal thickness was measured as the distance between the device and the lumen.

For SEM, tissue samples were fixed with 2.5 % glutaraldehyde (Fluka, Bornem, Belgium) and washed with phosphate-buffered saline. The specimens were dehydrated with graded series of ethanol followed by critical point drying. The specimens were mounted and gold sputtered to achieve the surface conductivity required for SEM. SEM was performed on five samples (three Silk 48 and two Silk 96).

Histology and SEM analysis allowed for evaluation of endothelial coverage of the implants, aneurysm occlusion and intra-aneurysmal thrombosis.

Results

The rabbits in the two groups had similar ages and weights (mean weight 4.3±0.7 kg). Mean size of the created aneurysms was 3×6 mm with a mean neck size of 3 mm. Following implantation, the induced flow changes in the aneurysms were evaluated by DSA. Slowing down of the intra-aneurysmal flow after FD implantation as shown by increased contrast material residence time was observed in all except two cases, both from the Silk 48 group (Fig. 1). Immediate aneurysm occlusion was observed in two cases, one in each group. We observed no procedural thromboembolic events, vessel dissection or other adverse events.

The anatomical distance between the aneurysm and the vertebral artery did not allow for covering of the orifice of the VA with the FD in all cases. This was achieved only in three cases, all from the Silk 96 group, two from the 4-week and one from the 12-week survival subgroup. In these cases the VA remained patent both immediately after implantation and at sacrifice.

Aneurysm occlusions at sacrifice

At the 4-week sacrifice all aneurysms from both the Silk 48 and Silk 96 groups showed complete (grade 4) occlusion. At the 12-week sacrifice there were differences between the two groups. In the Silk 48 group, there were two aneurysms showing only partial thrombosis of approximately 30 % (grade 1) and 80 % (grade 2) occlusion of the aneurysm compared with its original size. In the Silk 96 group, there was only one aneurysm showing persistent patency. In this

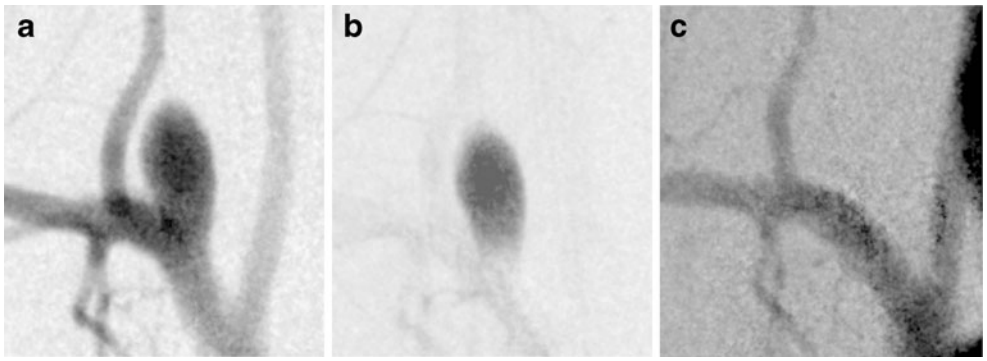

Fig. 1 **a** Digital subtraction angiography of the supra-aortic arteries of a rabbit, demonstrating an elastase-induced, large neck aneurysm. **b** Contrast material stagnation in the aneurysm after the implantation of a Silk 96 device. **c** Follow-up i.v. angiography at 4 weeks, showing the complete occlusion of the aneurysm, the patency of the subclavian branches and no signs of in-stent stenosis

case, the control angiogram demonstrated a tracheal branch originating from the aneurysm itself. The saccular part of the aneurysm was remodelled with reduction of the aneurysm pouch size, and the tracheal branch was still filling. At 4 and 12 weeks there was no angiographically proven in-stent stenosis or parent vessel occlusion in either group.

Histology and SEM evaluation

Twelve out of 12 samples were available for histology; the remaining two samples were processed only for SEM. Both the Silk 48 and Silk 96 groups were found to have induced thrombus formation at 4 weeks after stent implantation. The thrombus was organised and either layered or unstructured, independent of the type of flow diverter used (Fig. 2). At 12 weeks histology sections were available in four of the 6 samples (2 from each group). In the Silk 48 group, the partially occluded aneurysm showed a layered thrombus, occupying approximately 50 % of the original aneurysm volume. The second occluded aneurysm had shrunk and showed intraluminal fibrous tissue formation. In the Silk 96 group one aneurysm showed complete remodelling, showing only a fibrous transformation of the original carotid artery wall. In the second sample the aneurysm was no longer identified on the available sections, suggesting complete shrinkage. All the occluded aneurysms showed neointimal formation over the aneurysm neck.

Histology revealed a complete, uniform and similar endothelialisation over the FD surface in both groups at both follow-up time points, without signs of intimal hyperplasia and with a maximal neointimal thickness of less than 200 μm. Complete and smooth neointimal coverage was also proven by the SEM studies. In cases where the origin of the branching vessels was covered by the device, the strands of the FD were covered by endothelial cells and fine fibrin-like structures; however the pores of the device remained patent. The macroscopic and SEM studies also demonstrated the partial coverage of the aneurysm orifice by an endothelial layer in the aneurysms not occluded at 3 months (Fig. 3).

Discussion

In this study we describe the effectiveness results of a new-generation, lower porosity and higher pore density, 96-strand

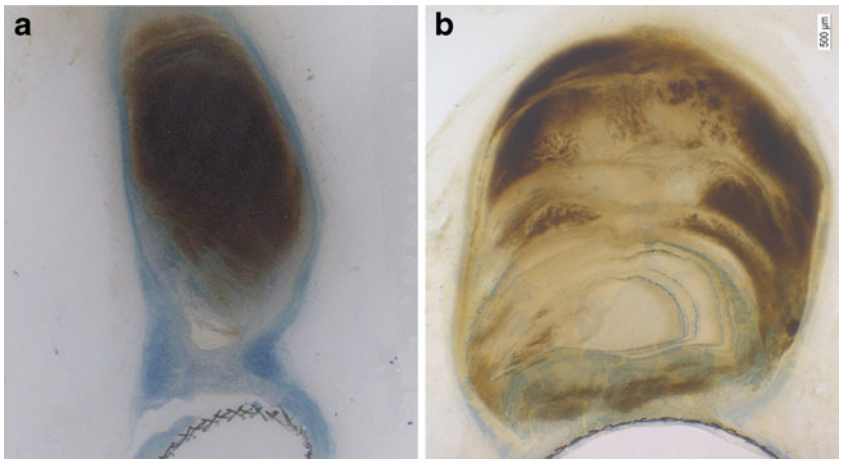

Fig. 2 **a** Homogeneous (no layering) pattern of intra-aneurysmal thrombus at 4 weeks. **b** Thrombus showing a distinct pattern of layering. Both aneurysms were treated with a Silk 96 device, but showed different morphology, a possible explanation for the difference in thrombus nature

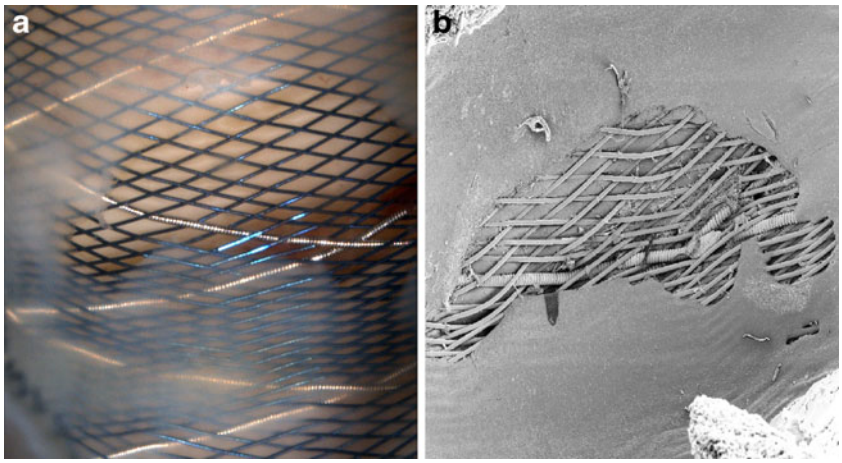

Fig. 3 Macrograph (**a**) and scanning electron microscopy picture (**b**) of the orifice of an aneurysm treated with a Silk 48 device at 12 weeks following implantation. The aneurysm remained patent. Note the partial endothelial coverage of the orifice, with the central portion not populated by the endothelial layer, allowing for persisting patency

braided flow diverter device in comparison to its commercially available predecessor, the Silk FD, in an elastase-induced rabbit aneurysm model. The new-generation FD device proved to be feasible and effective in parent artery reconstruction. The Silk 96 showed better performance in inducing aneurysm occlusion and arterial wall reverse remodelling.

Early in vitro studies revealed that stents are able to change intra-aneurysmal haemodynamics when placed across the orifice of aneurysms [1–4]. This flow-modifying effect of conventional balloon expandable and self-expanding stents is however usually not sufficient to induce aneurysm occlusion if applied alone. Such stent use is mainly to support endosaccular treatment. Meeting the clinical demand for endovascular parent artery reconstruction in certain aneurysm morphologies, the current technological advancements in the manufacturing of neuroendovascular devices led finally to the development of the currently available braided flow diverters. Compared with conventional intracranial stents, these FDs have a markedly lower porosity (60–80 %; proportion of open area to total area of the stent). Although they demonstrated great effectiveness especially in the treatment of "difficult" aneurysms [11–18], the rate of complete aneurysm occlusion at 6 months remains at 76 % [5]. This suggests still insufficient flow diversion under specific conditions. If flow diversion with a currently available device proves to be insufficient, a biologically active clot may remain, causing an inflammatory status and thus not allowing healing by reverse remodelling, or leading to aneurysm rupture [6, 7]. Complementary treatment options in such situations are limited to reducing or completely weaving off antiplatelet therapy, adding another or more FDs or occluding the parent artery—all options that require taking additional risks and increasing costs. There is thus a well-justified clinical need to increase the effectiveness of flow diversion.

A pragmatic way of increasing the flow-modifying effect across the aneurysm orifice is achieved in clinical practice by implanting multiple devices in a coaxial or telescopic fashion. Although there are no published results on the increased effectiveness of this technique, it is usually performed to amplify the flow-modifying effects of the flow diverter construct [18]. Implanting multiple devices implies an elevated technical complication risk and increased costs. Therefore, a more elegant way would be to augment the flow-diverting properties of a single device.

In vitro and in vivo studies demonstrated that the flow modification power of a flow diverter device is defined by both *low-* and *high-pore density* (defined as the number of pores per area) [19–21]. A certain porosity of the device is also required for persisting patency of the jailed side branches. Decreasing porosity while maintaining or increasing pore density will necessarily increase the amount of material in the construct. This will result in a higher profile of the squeezed device, reduced flexibility and the need for a larger delivery microcatheter. These features may markedly reduce the feasibility of such devices to be delivered to the cerebral arteries and to treat cerebral aneurysms.

The Silk 96 has double the wire count of the commercially available Silk and of the PED, both with the 48-strand braided structure. The resulting porosity and permeability are markedly reduced and the pore density increased. Despite the doubled number of wires, the device exhibits only a slightly higher profile, requiring the use of a 0.025″ ID microcatheter, and could be delivered and deployed at the target site without technical difficulties (for comparison, microcatheter IDs used: 0.021″ for Silk, 0.027″ for the PED and 0.032–0.040″ for Surpass FD delivery). The new device did not induce intimal hyperplasia or parent artery occlusion in any of the cases. It proved to be more effective at inducing aneurysm occlusion.

One interesting finding of our current study was the two different, either "layered" or "homogeneous" thrombus structures at 4 weeks. The layered thrombus has alternative "red" and "white" layers, whereas the "homogeneous" thrombus shows no such distinct layering pattern. Microscopically, a

layered thrombus exhibits laminations known as "lines of Zahn". Two primary prerequisites of a "layered thrombus" are that it is formed at a site of constant blood flow and that its formation is episodic. The formation process signifies the delicate balance between the thrombotic and thrombolytic factors, influenced by the shear rate of the flowing blood [22]. The pale portion of the thrombus consists of platelets mixed with fibrin, whereas the darker layer consists of entrapped red cells. Along the same context, "non-layered" homogeneous thrombus is formed rather instantly owing to the stagnation of blood. The close interaction between the intra-luminal thrombus and the aneurysm wall has already been demonstrated [23]. The quality and volume of intra-aneurysmal thrombus play key roles in inducing aneurysm healing or driving the aneurysm towards the so-called delayed rupture phenomenon, seen in about 1–2 % of cases treated with flow diversion alone [5–7]. The inflammatory reaction and the oxidative stress induced by a large volume of cell-rich clots may be overwhelming to the aneurysm wall, leading to decellularisation and destruction, and finally to rupture [6]. We hypothesise, that a gradually developing thrombus, as shown by the layered pattern, may have a less deleterious effect on the aneurysm wall, by inducing a less important or at least slower acting inflammatory reaction and oxidative stress to the vessel aneurysm wall, eventually also allowing for repair mechanisms. Owing to the applied histological methodology, the thrombus aneurysm wall could not been evaluated in this study.

Our study has several limitations. The relatively low number of animals treated did not allow for assessing significant differences in induction of thrombosis and in the quality of intra-aneurysmal thrombus between the two different devices. Second, the aneurysms treated in this series were relatively small lesions, not necessarily reflecting the aneurysms treated by flow diversion in the clinical practice. This limitation is related to the animal model itself. The results should therefore be interpreted accordingly.

In conclusion, in this elastase-induced rabbit aneurysm model, the 96-strand braided flow diverter device, the Silk 96, proved to be safe and effective in parent artery reconstruction and aneurysm healing. This new-generation device with reduced porosity and permeability induced stable occlusions and remodelling of the treated aneurysms, without signs of neointimal hyperplasia, and without inducing occlusion of the jailed side branches. This new design may be a promising tool for treating cerebral aneurysms more effectively and safely.

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