Temporary surgical clipping of flow-diverted arteries in an experimental aneurysm model

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OBJECTIVE Surgical management of recurrent aneurysms following failed flow diversion may pose difficulties in securing vascular control with temporary clips. The authors tested the efficacy and impact of different types of aneurysm clips on flow-diverted arteries.

METHODS Six wide-necked experimental aneurysms were created in canines and treated with Pipeline flow diverters. In 4 aneurysms, occlusion of the artery at the level of the proximal and distal landing zones ($n = 2$ per aneurysm) was attempted, using temporary, fenestrated, single, and double permanent aneurysm clips. Two aneurysms served as unclipped controls. Serial angiography was performed to investigate the efficacy of clip occlusion, flow diverter deformation, and thrombus formation. After the animals were killed, the flow-diverted aneurysm constructs were opened and photographed to determine neointimal or device damage as a result of clip placement.

RESULTS Angiography-confirmed clip occlusion was only possible for 4 of 8 of the tested flow-diverted arterial segments. Clip application attempts led to filling defects consistent with thrombus formation in 2 of 4 flow-diverted constructs, and to minor damage of the flow diverter with neointimal fracture in 1 of 4 cases.

CONCLUSIONS Aneurysm clips placed on canine parent arteries bearing a Pipeline flow diverter were unable to reliably stop blood flow. Application of aneurysm clips can cause mild damage to the device and neointima, which might translate into thromboembolic risks. If possible, vascular control should be sought beyond the terminal ends of the implanted device.

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KEY WORDS aneurysm clip; closing forces; experimental model; flow diverter; vascular disorders

As flow diversion increases in popularity, neurosurgeons may be faced with persistent or recurring aneurysms following endovascular treatment.^{1,5,8} In narrow surgical corridors, or when the flow diverter spans a long arterial segment, it may be difficult to gain access to a normal artery proximal or distal to the device to place an aneurysm clip, and temporarily clipping the segment of artery containing the flow diverter may become necessary.^{4,9} Clipping of a flow-diverted arterial segment, to our knowledge, has not been reported in the literature. It

is currently unknown whether an aneurysm clip placed on a flow diverter can effectively stop blood flow, or whether clip placement will damage the flow diverter or the vessel bearing the device. We addressed these questions using an in vivo experimental aneurysm model.

Methods

Surgical Aneurysm Creation

Protocols for animal experimentation were approved by

ABBREVIATIONS PED = Pipeline Embolization Device.

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the Institutional Animal Care Committee in accordance with guidelines of the Canadian Council on Animal Care. All procedures were performed in 7–15 kg canines under general anesthesia. Briefly, 6 aneurysms in 4 animals were surgically constructed. Bilateral lingual artery bifurcation aneurysms (n = 2) were made in 2 animals, and curved sidewall carotid aneurysms (n = 1) in 2 animals. Details regarding surgical aneurysm creation can be found elsewhere.^{6,11}

Endovascular Treatment

Aneurysms were treated with flow diverters at least 4 weeks following surgical construction. Animals were treated with 325 mg daily of acetylsalicylic acid and 75 mg of clopidogrel for 4 days prior to flow diversion.

Endovascular treatment was performed with a coaxial microcatheter system inserted through a percutaneous femoral approach. A Marksman microcatheter (Medtronic) was placed distal to the aneurysm, and used to deploy a single Pipeline Embolization Device (PED) flow diverter of nominal dimensions (3.75 × 30 mm) in all cases (flow diverters gifts from Medtronic). The size of flow diverter was selected according to the diameter of the proximal landing zone of the recipient vessel (3.5–4 mm in this model). Clopidogrel therapy was discontinued 10 days after PED implantation, while 325 mg per day of acetylsalicylic acid was continued until the animals were killed at 3 months.

Surgical Clipping of Parent Vessel Containing the Flow Diverter

At 3 months, transfemoral angiography was performed to document the patency of the arteries bearing flow diverters and the degree of aneurysm occlusion. The flow-diverted aneurysm constructs and the proximal and distal device landing zones of the arteries were surgically exposed to permit unobstructed placement of the aneurysm clips (Aesculap AG). Aneurysm clips were new, commercially available clips that are currently in use at our institution. Clip characteristics, including closing forces, are provided in Table 1. Systolic blood pressure was maintained above 110 mm Hg throughout the procedure to ensure reliability of the results of clip placement.

Starting with the temporary aneurysm clip (lowest closing force), an attempt was made to place the clip across the proximal flow diversion. The incidence of clip slippage from the flow-diverted artery was recorded. Clip slippage³ was adjudicated when 3 successive attempts all resulted in the clip slipping off the artery. When the clip was successfully applied to the artery, angiography was repeated to assess for arterial occlusion. If the clip failed to occlude

the artery, it was removed, and angiography repeated to examine for deformation of the flow diverter and to look for thrombus formation. The clip with the next greatest closing force was then tried, and the above sequence repeated with clips of progressively increasing closing force until the clip closing force required to occlude the flow-diverted artery was identified. The sequence of aneurysm clip applications was as follows: temporary clip (closing force 90 g), fenestrated clip (closing force 150 g), and permanent clip (closing force 200 g). When a permanent clip failed to successfully occlude the flow-diverted artery, an additional identical permanent clip was placed in an attempt to occlude blood flow. For an arterial segment to be therefore judged “not occludable” would imply that 3 different attempts to clip the artery with clips of increasing closing force had failed, as had the simultaneous application of 2 permanent clips. At the completion of the experiments on the proximal portion of the flow diversion, the same procedure was repeated on the distal end of the flow diversion. When both terminal ends of the flow diversion had been tested, angiography and 3D angiography with Dyna CT was performed to investigate device deformation, thrombus formation, or angiographic flow disturbances as a result of clip placement.

Photography and Pathology

Animals were killed by barbiturate overdose, and the flow-diverted aneurysm constructs harvested and placed in 10% formalin for pathological analysis. The constructs were opened longitudinally and photographed using a computerized imaging system (Vision PE, Clemex Technologies). The presence or absence of neointimal disruption, intraluminal thrombus, and device deformation were documented.

Results

Three months following flow diversion, 5 treated aneurysms had large saccular remnants, while in the sixth case a small remnant filled only through small channels (Table 2). Untreated aneurysms and parent vessels were patent, without stenosis.

Incidence of Clip Slippage With Flow Diverted Arteries

Clip slippage occurred frequently (in 4 of 8 attempted temporary clip applications, including 2 of 8 fenestrated clip applications and 2 of 8 permanent clip applications). Clips were more likely to slip when the clip was applied to an axially compacted segment of the flow diverter (segments with a higher metallic density). Each device segment was eventually clipped with a different number of

TABLE 1. Yasargil aneurysm clip characteristics

Characteristic	Temporary Clips	Fenestrated Clips	Permanent Clips
Description	Gold, curved phynox clips	3.5-mm fenestration	Side angle
Serial number	FE795K	FE610K	FT761
Blade length (mm)	16.8	9	8
Closing force (g)	90	150	200

clips due to clip slippage, and because when successful angiographic occlusion was achieved, no further clips were applied. Occasionally, the landing zones were of insufficient length to permit placement of multiple clips. The total number of clips applied to each flow diverter construct ranged from 4 to 8 clips (Table 2).

Efficacy of Attempted Arterial Occlusion

The results of the attempts to gain vascular control of a flow-diverted artery using aneurysm clips are presented in Table 2 and Fig. 1. Temporary clips placed on arterial segments beyond the segment bearing the flow diverter were able to temporarily occlude blood flow in all cases. Vascular control by clipping the proximal or distal landing zone of the flow diverter of the same artery was possible in only 1 of 4 cases. For the 3 other cases, either the proximal or distal end, and occasionally neither end, could be occluded by any combination of clips. There was no difference in rates of clip occlusion of proximal compared with distal ends of the flow diverters.

A fenestrated clip was sufficient to occlude 1 proximal flow-diverted arterial segment, a single permanent clip proved effective for 2 segments, and in 1 case, 2 permanent clips were required to stop blood flow. Clips were more likely to be effective when they were applied to segments of the flow diverter that were not axially compacted (where metallic density is less).

Device Deformation and Thrombus Formation Following Clip Removal

Three of the 4 clipped flow diverters immediately returned to their baseline state when clips were removed (Fig. 2). One flow diverter was slightly deformed by clip placement, with a minor stenosis. Three clips had been successfully applied to the proximal portion of this flow diversion, along with 1 permanent clip on the distal end of the flow diversion, in addition to multiple clips slipping off the device. In 2 cases, filling defects consistent with thrombus formation were observed at final angiography when clips were removed.

Pathological Analysis

Three specimens showed no evidence of having been

compressed or damaged despite multiple (4–8) successful clip applications (Fig. 3). One clipped flow-diverted specimen was found to have fractured neointima, with the flow diverter struts slightly deformed and pulled away from the arterial wall. The 2 control aneurysms showed good apposition of the flow diverter to the arterial wall, without evidence of endoleaks. No thrombus was found at pathological examination.

Discussion

The salient feature of this work is that although vascular control can occasionally be obtained with aneurysm clips placed on arteries containing a flow diverter, it remains an unreliable means to stop blood flow. Partial or complete occlusions were reversible but attempts carried a risk of damaging the flow diverter and the neointimal lining that had formed over the device. If it is not possible to expose a normal segment of artery proximal and distal to the flow diverter, and it is judged necessary to place aneurysm clips on a flow-diverted artery, temporary clips may not suffice, and a clip with a closing force of at least 200 g may be necessary. Confirmation of the occlusion with ultrasonography or fluorescence angiography would appear desirable prior to manipulating the aneurysm.

When a flow diversion strategy with a single flow diverter fails, additional devices may be deployed prior to considering a surgical option. The difficulties encountered here, of gaining vascular control over an arterial segment with a single flow diverter, makes it appear unlikely that currently available aneurysm clips would be of sufficient closing force to occlude an arterial segment containing multiple overlapping layers of flow diverter, although this was not studied.

Failure of flow diversion may be associated with improper sizing of the device diameter, inadequate wall apposition, and endoleaks.^{2,12} Temporary clipping of arterial segments in these circumstances was not studied in the present work.

The few cases in which clip application was able to completely occlude the devices occurred when the clip was applied to a relatively noncompacted segment of the flow diverters. The structure of a flow diverter can be modified depending on deployment technique,¹⁰ and more

TABLE 2. Residual aneurysm characteristics, with impact of clip application

Aneurysm No.	Length × Width of Residual Aneurysm (mm)	Proximal Flow Diverter Occlusion	Distal Flow Diverter Occlusion	Total No. of Clips Applied to Flow Diverter	Resumed Pre-Clipping State When Clips Removed	Thrombus Formation	Neointimal Damage
1	6 × 4	Unable to occlude*	Permanent clip	8	Yes	No	No
2	17 × 10	Unable to occlude†	Unable to occlude*	4	Yes	No	No
3	14 × 7	Fenestrated clip	2 permanent clips	7	Yes	Yes	No
4	Crescentic filling only	Permanent clip	Unable to occlude†	4	No, minor deformation	Yes	Yes
5‡	15 × 7	NA	NA	0	NA	No	No
6‡	12 × 6	NA	NA	0	NA	No	No

NA = not applicable.

* With 1 temporary clip (closing force 90 g), 1 fenestrated clip (closing force 150 g), a single permanent clip (closing force 200 g), or 2 permanent clips (closing force 200 g).

† Due to clip slippage.

‡ Control aneurysms.

FIG. 1. Angiograms of attempts to gain vascular control of a flow-diverted artery using aneurysm clips. Black lines denote the terminal ends of the flow diverters. **A1–A4:** Residual flow-diverted aneurysm (*asterisk*, A1), showing the effects of flow diverter clipping with a single permanent clip (A2). There was unimpeded blood flow beyond the clip (A3). Failure of proximal vascular control with 2 permanent aneurysm clips is shown (A4; *arrow* shows continued blood flow). **B1–B4:** Unimpeded flow with a temporary clip (B1), but successful proximal occlusion with a fenestrated clip (B2). Distal control of the same flow diverter was not possible with a permanent clip (B3; *arrow* shows continued blood flow); there was evidence of distal thrombus formation (*arrow*) when all clips were removed (B4).

FIG. 2. **A and B:** Unsubtracted angiographic images demonstrating complete clipping of flow-diverted arteries (A1, B1), with full return to preclipping state when clips were removed (A2, B2). **C:** Demonstration that clipping can damage a flow-diverted artery. The flow diverter before clipping (C1), after proximal (C2) and distal (C3) clipping, with a mild stenotic deformation (*arrow*, C4), and new contrast leakage outside the flow-diverter confines (*arrow*, C5).

FIG. 3. Microscopic photography of clipped ends of 2 different flow-diverted arteries (**A and B**), showing no evidence of neointimal or device damage. **C and D:** Damage due to aneurysm clip application can occur (**C**, magnified in **D**). Note the gap created as the neointima was fractured away from the arterial wall (asterisk), and the deformed flow-diverter struts (arrows). Figure is available in color online only.

compacted segments of the devices were found to be more difficult to occlude. Clip slippage also occurred more frequently when the segment of flow diversion was compacted. Careful study of the extent of device compaction across the zones of interest might help predict the efficacy of clip application.

Damage to the flow diverter and neointima occurred in 1 case, and filling defects were noted at angiography after clip removal in 2 cases, illustrating that surgically clipping a flow diverter likely carries some thromboembolic risk. Although no thrombus was found on the specimens at the time of pathological examination, fresh thrombus, if any, could have been lost during sample preparation. Endothelial damage after temporary clipping of normal animal vessels has previously been documented by electron microscopy,⁷ but we did not assess the intima or neointima of flow-diverted specimens with this method.

Although in vitro or bench-top studies readily showed that flow diversions regain their preclipped form when clips are removed (data not presented), these experiments cannot predict the effects of clipping when the flow diverter is implanted in vivo and covered with neointima.

Limitations of the Study

A small number of animals were included in this work. Surgical aneurysm creation may promote fibrosis around an arterial segment, making it more difficult to successfully occlude blood flow with clips. We do not think this would have significantly influenced the results found here, as temporary clips were readily able to occlude arterial segments beyond the flow diverters. Canine arteries tested in this work remain different from human arteries, and any extrapolation of these results to clinical care should be cautious. We only tested the effects of aneurysm clips on single flow diverters, and arteries containing multiple overlapping devices may be more difficult to occlude.

The aneurysm clips used were new at the beginning of our experiment, but due to repeat clip applications, closing forces exerted by each clip may have been diminished as the study progressed.

We only tested the Pipeline flow diverter, which has a homogeneous construction; flow diverters with different constructions may respond differently to clip application. All aneurysm clips tested were from 1 manufacturer (Aesculap AG), and the length of time of clip application was not measured in this work.

Conclusions

Securing vascular control with aneurysm clips on arteries containing a single Pipeline flow diverter proved unreliable but not impossible in this canine model. Although most flow-diverted arteries could be repeatedly clipped with no consequence, clip application occasionally resulted in thrombus formation, as well as damage to the device and neointima.

References

1. Abila AA, Zaidi HA, Crowley RW, Britz GW, McDougall CG, Albuquerque FC, et al: Optic chiasm compression from mass effect and thrombus formation following unsuccessful treatment of a giant supraclinoid ICA aneurysm with the Pipeline device: open surgical bailout with STA-MCA bypass and parent vessel occlusion. *J Neurosurg Pediatr* **14**:31–37, 2014
2. Carneiro A, Rane N, Küker W, Cellerini M, Corkill R, Byrne JV: Volume changes of extremely large and giant intracranial aneurysms after treatment with flow diverter stents. *Neuroradiology* **56**:51–58, 2014
3. Carvi y Nievas MN, Höllerhage HG: Risk of intraoperative aneurysm clip slippage: a new experience with titanium clips. *J Neurosurg* **92**:478–480, 2000
4. Charbel FT, Ausman JI, Diaz FG, Malik GM, Dujovny M, Sanders J: Temporary clipping in aneurysm surgery: technique and results. *Surg Neurol* **36**:83–90, 1991
5. Chung J, Lim YC, Kim BS, Lee D, Lee KS, Shin YS: Early and late microsurgical clipping for initially coiled intracranial aneurysms. *Neuroradiology* **52**:1143–1151, 2010
6. Darsaut TE, Bing F, Salazkin I, Gevry G, Raymond J: Flow diverters failing to occlude experimental bifurcation or curved sidewall aneurysms: an in vivo study in canines. *J Neurosurg* **117**:37–44, 2012
7. Gertz SD, Rennels ML, Forbes MS, Kawamura J, Sunaga T, Nelson E: Endothelial cell damage by temporary arterial occlusion with surgical clips. Study of the clip site by scanning and transmission electron microscopy. *J Neurosurg* **45**:514–519, 1976
8. Klein O, Colnat-Coulbois S, Civit T, Auque J, Bracard S, Pinelli C, et al: Aneurysm clipping after endovascular treatment with coils: a report of 13 cases. *Neurosurg Rev* **31**:403–411, 2008
9. Ljunggren B, Brandt L, Säveland H, Nilsson PE: Ruptured intracranial aneurysms. *Surg Neurol* **19**:393, 1983 (Letter)
10. Makoyeva A, Bing F, Darsaut TE, Salazkin I, Raymond J: The varying porosity of braided self-expanding stents and flow diverters: an experimental study. *AJNR Am J Neuroradiol* **34**:596–602, 2013
11. Raymond J, Salazkin I, Metcalfe A, Robledo O, Gevry G, Roy D, et al: Lingual artery bifurcation aneurysms for training and evaluation of neurovascular devices. *AJNR Am J Neuroradiol* **25**:1387–1390, 2004
12. Shapiro M, Raz E, Becske T, Nelson PK: Variable porosity of

the pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy. **AJNR Am J Neuroradiol** 35:727–733, 2014

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

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