Flow diverter stents in the treatment of intracranial aneurysms: Where are we?

Flow diverters dans le traitement des anévrismes intracrâniens : où en sommes-nous?

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Summary Flow diverter stents are devices designed to treat complex aneurysms. According to preliminary series published in the literature, treatment of aneurysms with flow diverters is highly efficacious with acceptable morbidity and mortality. Delayed aneurysm ruptures have been reported but mechanisms are actually not completely elucidated. In-stent thrombosis or stenosis was also observed. Indications of flow diverters are complex aneurysms (fusiform, large and giant, wide neck, small aneurysms untreatable by conventional coiling) as well as recurrences. Several randomized studies and registries are actually in progress and will contribute to a more precise knowledge of the place of the flow diverters in the treatment of intracranial aneurysms.

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For several years, endovascular treatment has been the first-line treatment in the management of both ruptured and unruptured aneurysms [1,2]. After standard coiling, several techniques have been successively developed to make the endovascular treatment of anatomically complex aneurysms feasible, notably the remodelling technique and stenting [3–6].

Despite these technical developments, the endovascular treatment of intracranial aneurysms still has some limitations. First of all, it is not always applicable to complex aneurysms such as fusiform aneurysms or very large neck aneurysms. Secondly, even if the endovascular treatment of some complex aneurysms is now feasible using the remodelling technique or regular stenting, the long-term stability of aneurysm occlusion is not guaranteed in all aneurysms. Thus, large and giant aneurysms, as well as large neck aneurysms, are candidates for aneurysm recanalization.

For the last 20 years, endovascular treatment has been focused on filling the aneurysm with coils. However, another approach is possible and theoretically more physiological: parent vessel reconstruction. Flow diverters are dedicated to this type of approach.

Conceptual basis

The goal is primarily to reconstruct the diseased vascular segment harboring the saccular or fusiform aneurysm pouch. The device used for parent vessel reconstruction produces hemodynamic and biological effects:

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- flow redirection: the flow diverter crosses the aneurysm neck and diverts the blood flow from the aneurysm sac, thus reducing shear stress on the aneurysm wall and promoting intra-aneurysm flow stasis and thrombosis. This phenomenon is affected by the amount of metal surface area coverage provided by the stent. The pore density of flow diverters, rather than porosity, seems to be a critical factor modulating device efficacy [7];
- tissue overgrowth: the flow diverter provides a scaffolding for the development of endothelial and neointimal tissue across the aneurysm neck. As with flow direction, the magnitude of this effect is proportional to the amount of metal surface area coverage. It also depends on the structure and composition of the stent material.

Preclinical studies in animals have shown the efficacy and safety of flow diverters in the treatment of aneurysms [8].

Devices

Two devices are currently included in the flow diverter group:

- Pipeline embolization device ([PED], EV3-MTI, Irvine, CA) is a self-expanding, flexible, cylindrical mesh-like device, composed of 25% platinum tungsten and 75% cobalt chromium, made from 48 strands interwoven in a standard pattern (Figs. 1 and 2). The PED has a diameter between 2.5 and 5 mm and a length between 10 and 35 mm;
- Silk (Balt, Montmorency, France) is a self-expanding stent made of 48 braided nitinol strands (Figs. 1–3). Many diameters (2 to 5 mm) and lengths (15 to 40 mm) are available.

Several practitioners were using multiple regular stents deployed within each other to create a "home made" flow diverter.

Feasibility of aneurysm treatment with flow diverters

Preliminary clinical experience with flow diverters for treating intracranial aneurysms was reported in case reports and patient series [9–16]. Our analysis is focused on the series reporting mono- or multicenter results with PED or Silk [9–12]. In Lylyk et al. [9] monocenter series of 53 patients with 63 aneurysms, no failure was reported using the PED. Treatment was achieved with a single PED in 44 aneurysms but with two or three PEDs in 19 aneurysms. In four aneurysms, treated with a single PED, embolization

Figure 1  A. Pipeline embolization device and (B) Silk stent.

Figure 2  Large aneurysm of the carotid bifurcation. A. Preoperative DSA. B. Postoperative DSA, nonsubstracted view showing the flow diverter stent (Pipeline), and (C) postoperative substracted view showing stagnation of contrast media into the aneurysm.
coins were also used. In another monocenter series, Szikora et al. [10] treated 18 patients with 19 aneurysms: treatment with PED was also always possible. In this series, one or several PED were used in 10 aneurysms and a combination of PED and coils were used in nine cases.

Byrne et al. [11] recently reported the results of a multicenter (18 centers), international, prospective study using Silk that included 70 patients with 70 aneurysms. In three cases (4%), the Silk could not be deployed due to technical reasons and the procedure was abandoned. Fifty-seven aneurysms (81%) were treated with a single Silk and 10 (14%) with a combination of Silk and coils. In the series of Lubicz et al. [12] comprising 29 patients with 34 aneurysms, treatment was feasible in 26 patients (90%).

Finally, in these preliminary series, aneurysm treatment with flow diverters was feasible in a high percentage of cases (90% to 100%).

Safety of flow diverters

No major complications were reported in the series of Lylyk et al. [9] Three patients (5%) experienced transient exacerbations of preexisting cranial neuropathies and headache. Giant aneurysms were treated in all cases and symptoms resolved within 1 month using corticosteroids treatment. Szikora et al. [10] observed clinical complications in four cases:

- mild hemiparesis for 2 days due to contrast overload;
- small visual field defect due to occlusion of a retinal artery branch;
- transient hemiparesis due to in-stent thrombosis in a patient not taking his antiplatelet medication;
- death due to massive SAH probably due to the rupture of a small coexisting ICA aneurysm.

Byrne et al. [11] noted a low procedural morbidity: one case (1.4%) was observed related to thromboembolism. Delayed morbidity and mortality were more frequent: an overall morbidity (including procedural) in two patients upon 50 (4%) having follow-up and a mortality in four patients upon 50 (8%). Mortality was due to pneumonia in two cases: both patients had untoward procedural events, an increased brainstem compression in one case and a delayed SAH in the other (see below).
Flow diverter stents in the treatment of intracranial aneurysms: Where are we? 43

Figure 4  Intracavernous aneurysm. A, B. Preoperative DSA. C. Postoperative nonsubtracted DSA showing the flow-diverter (Pipeline) in the carotid siphon. D. DSA performed 15 days after the aneurysm treatment and appearance of ophthalmic signs showing rupture of the aneurysm with direct carotid-cavernous fistula. The fistula was successfully treated via an endovascular approach (not shown).

In the series of Lubicz et al. [12], mortality and morbidity rates were 4% (1/26) and 15% (4/26), respectively. One patient died from delayed aneurysm rupture related to stent migration, three patients experienced a thromboembolic event, and one patient developed progressive visual disturbances related to an increased mass effect.

One important issue concerning the treatment of intracranial aneurysms using flow diverters is the patency of the perforating arteries and side branches covered by the device. In the series of Kulcsar et al. [15] dealing with basilar artery aneurysms (12 patients), all but one of the angiographically visible vessels covered by the device were patent at the end of the procedure. One P1 segment that was covered by the flow diverter was no longer opacified immediately after device implantation, but the PCA was vascularized via the posterior communicating artery. In the follow-up of this series, two patients had small symptomatic lesions (one in the thalamus and one in the pons) probably due to the occlusion of perforator arteries.

Very late thrombosis of the flow diverter is possible and long-term follow-up of treated patients is certainly required [17].

The safety of flow diverters is difficult to precisely evaluate due to the small series of patients currently published in the literature. The results are heterogeneous from one series to another; series are dealing with complex aneurysms making comparison with series with regular aneurysms difficult; finally, these first series are describing preliminary experience during the ascending phase of the learning curve. Accordingly, larger series are certainly needed to assess precisely the safety of aneurysm treatment with flow diverters.

Efficacy of flow diverters

According to the current series published in the literature, the treatment of intracranial aneurysms with flow diverters is associated with a high rate of complete aneurysm occlusion.

Since endovascular treatment using flow diverters is not performed by filling the aneurysm with devices but by covering the neck, the Montreal scale is probably not completely appropriate to evaluate anatomic results. A new grading schema has recently been designed to audit outcomes of patients treated with flow diverters. It is
designated for both saccular and fusiform aneurysms and documents the degree of aneurysm occlusion using a five-point scale and parent artery patency using a three-point scale [18]. This schema was not used in the series already published in the literature since it is very recent. In the series of Szikora et al. [10], a grading system was also proposed. Flow modification after flow diverter implantation was classified as complete stasis (if no contrast media entered the aneurysm following deployment of the flow diverter); significant flow reduction (if contrast stagnation remained); or slow flow (if the contrast circulation within the aneurysm became slower but without contrast stagnation in the late venous phase images). Aneurysm occlusion was rated as complete (if no contrast media entered the aneurysm by the end of the procedure) or incomplete (if any contrast filling of the aneurysm was seen on the last angiogram).

In the series of Lylyk et al. [9], complete angiographic occlusion was achieved in 56%, 93%, and 95% at 3, 6 and 12 months, respectively. Interestingly, the rate of complete occlusion is lower at 3 months compared to 6 and 12 months probably in relation to antiplatelet medications administered postoperatively to prevent in-stent thrombosis. In the series of Szikora et al. [10], after placement of the PED, complete stasis was observed in three cases upon 19, significant flow reduction in 13/19 cases, and slow flow in three cases upon 19 (using the previously mentioned grading system). Complete occlusion was seen in three aneurysms treated with PED and coils and in one case treated with PED only. At 6 months, all but one aneurysm was completely occluded. Occlusion at 6 months does not seem to be affected by additional coil packing.

In the series of Byrne et al. [11], at the end of treatment, complete aneurysm occlusion was observed in seven aneurysms upon 68 (10%), neck remnant in four upon 68 (6%), and residual sac filling in 57/68 (84%). At follow-up, complete occlusion was observed in 24/49 aneurysms (49%), neck remnant in 13/49 (26%) and residual aneurysm filling in 12/49 (25%). Parent artery occlusion was observed in seven cases upon 49 (14%) and arterial narrowing in three cases upon 49 (6%). In the series of Lubicz et al., [12] immediate anatomic results were complete stasis in four aneurysms upon 31 (13%), significant flow reduction in 13/31 (42%), slow flow in 13/31 (42%), and unchanged flow in one upon 31 (3%). At follow-up (3 to 6 months), angiographic control showed complete occlusion in 20/29 aneurysms (69%), neck remnant in one upon 29 (3.5%), and incomplete occlusion in eight upon 29 (27.5%). Parent artery stenosis was observed in eight cases upon 29 (27.5%).

It is quite important to note that the evolution of aneurysm occlusion is quite different between flow diverters and coils. When an aneurysm is treated by selective occlusion using coils, a thrombus will rapidly occur in the aneurysm sac and protection against bleeding or rebleeding is rapidly obtained except in the case of incomplete occlusion. On the contrary, with a flow diverter, a complete occlusion is rarely obtained at the end of the procedure but is frequently observed during the follow-up after 3 to 6 months (49 to 95%). The process of aneurysm occlusion after flow diverter treatment is certainly linked in part to the administered antiplatelet regimen.

### Perioperative medications

Perioperative medications are quite important in the management of intracranial aneurysms with flow diverters since there are competing risks of thromboembolic complications, including in-stent thrombosis and delayed aneurysm rupture (see below).

In all series, patients were treated with heparin during the procedure, heparin anticoagulation being discontinued at the end of the procedure.

The antiplatelet regimen was heterogeneous from one series to another. Several types of pre-medication were administered: single or more frequently double antiplatelet therapy was given for 1 to 5 days before the endovascular intervention. The most frequent pre-treatment was based on an association of aspirin (100 to 325 mg) and clopidogrel (75 to 300 mg). Higher medication doses (320 mg aspirin and 300 mg clopidogrel) were used when the pre-treatment period was short (1 day). Clopidogrel was sometimes replaced by dipyridamole.

Post-treatment antiplatelet regimen was also heterogeneous. In most cases, a double antiplatelet treatment (either aspirin + clopidogrel or aspirin + dipyridamole) was given for 6 weeks to 6 months after the procedure followed by a single antiplatelet, mainly aspirin. The duration of aspirin treatment is not reported in the series.

### Delayed aneurysm rupture after flow diversion treatment

Several papers have recently documented the occurrence of delayed aneurysm rupture after flow diversion treatment [19–21] (Fig. 4). Kulcsar et al. [20] reported 13 delayed ruptures after Silk treatment. Patients were separated into two groups with early (< 3 months) and late (≥ 3 months) ruptures. Early rupture was more frequent (10/13 patients) and occurred 2 to 48 days after the treatment (mean time to rupture: 16 days), and was encountered in patients still receiving aspirin and clopidogrel treatment. Late rupture occurred in three patients upon 13 receiving aspirin alone, at 110 to 150 days (mean: 132 days) after flow diversion treatment.

As suggested by Kulcsar et al. [20], delayed rupture is frequently observed in symptomatic aneurysms (11/13 in Kulcsar’s series), large and giant aneurysms (13/13 in Kulcsar’s series), and aneurysms with a high Aspect Ratio.

Mechanisms of delayed rupture are actually not completely elucidated. A hemodynamic mechanism can play a role, the sudden change in flow pattern leading to increased stress in aneurysm areas that were not previously exposed to strain [22]. In their recent publication, Cebral et al. have outlined that placement of a flow diversion device can increase the intra-aneurysmal pressure due to flow diversion into the higher resistance parent artery pathway in combination with cerebral autoregulation leading to higher pressure gradients and to change in the parent artery configuration [22]. Another potential mechanism involves intra-aneurysmal thrombosis created by flow diversion which can be associated with an inflammatory reaction and the weakening of the aneurysm wall. As suggested by Turowski et al. [19], flow diverter treatment
can be associated with the formation of a nonorganized red thrombus which is not stable and has a high content of proteolytic enzymes that can weaken the wall of the aneurysm. Antiaggregation may also play a role, thus preventing platelet aggregation before and during aneurysm rupture.

According to the potential mechanisms of delayed rupture, several methods have been proposed to prevent delayed aneurysm rupture after flow diversion: aneurysm filling with coils; increase of the flow diverting effect of the implants; and the use of steroid administration just after aneurysm treatment.

Present indications of flow diverters

The precise indications of flow diversion are not yet precisely established. In the series published in the literature, flow diverters were mainly used in the series already published in the literature in large and giant aneurysms, wide neck aneurysms, and recurrent aneurysms. A small series has suggested the value of flow diversion treatment in very small aneurysms untreatable by standard coiling technique [23].

Studies in progress

Several studies, including randomized trials, are currently underway. They will provide more precise information regarding safety and efficacy of flow diversion for treating intracranial aneurysms with respect to standard endovascular techniques (balloon-assisted or stent-assisted coiling). Well-conducted clinical investigations will also provide information concerning the treatment indication for difficult-to-treat complex aneurysms, as well as noncomplex aneurysms.

Conclusion

The treatment of intracranial aneurysms with flow diverters seems to be highly efficacious. According to preliminary series, safety of this treatment seems to be satisfactory, specifically in the context of treating complex aneurysms with these devices. However, the frequency and the mechanism of delayed rupture after flow diversion must be analyzed in order to precisely define the indications of this technique, the appropriate perioperative medications, and the way the treatment is performed (additional coiling or not). The current indications for the use of flow diverters are complex aneurysms, including large and giant aneurysms, wide neck aneurysms, and aneurysm recurrences. Flow diverters have also been proposed for use in very small ruptured aneurysms that are untreatable using standard endovascular techniques.

Several studies including randomized trials are actually underway and will contribute to a more precise knowledge regarding indications and results of the flow diversion technique.

Conflicts of interest statement

Laurent Pierot is consultant for Balt, Boston Scientific, EV3 and Microvention.

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