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p64 flow diverter: Results in 108 patients from a single center

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Abstract

Background and purpose: Flow diverters are increasingly used to treat intracranial aneurysms. We report the safety and efficacy of the p64 flow diverter, a resheathable and detachable device for intracranial aneurysms.

Materials and methods: We retrospectively reviewed 108 patients with 109 aneurysms treated with the p64 between March 2014 and July 2019. There were 87 women and 21 men, mean age 57 years. Of 109 aneurysms, 74 were discovered incidentally, 12 were symptomatic, 18 were previously treated, and five were ruptured dissection aneurysms. A total of 10 aneurysms were located in the posterior circulation. The mean aneurysm or remnant size was 8.1 mm.

Results: Hemorrhage by perforation with the distal guidewire occurred in two patients with permanent neurological deficits in one. In one patient, acute in-stent occlusion caused infarction with a permanent deficit. Permanent morbidity was 1.9% (2 of 108, 95%CI 0.1–6.9%); there was no mortality. During follow-up, three in-stent occlusions occurred, all asymptomatic. There were no delayed hemorrhagic complications. At six months, 77 of 96 aneurysms (80.2%) were completely occluded, and at last follow-up, this increased to 93 of 96 aneurysms (96.9%). In-stent stenosis at any degree occurred in 11 patients, progressing to asymptomatic complete occlusion in one. In the other patients, stenosis resolved or improved at further follow-up.

Conclusion: The p64 offers an effective and safe treatment option. Aneurysm occlusion rate was 97% at last follow-up, mostly achieved with a single device. There were no delayed hemorrhagic complications. Delayed in-stent stenosis infrequently progresses to occlusion but remains a matter of concern.

Keywords

Flow diversion, flow diverter, intracranial aneurysm, interventional radiology

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Introduction

The endovascular treatment of intracranial aneurysms has substantially progressed since the introduction of the Guglielmi detachable coils system in the 1990s.[1] The International Subarachnoid Aneurysm Trial[2] and the California Unruptured Aneurysm Study[3] have shown better outcomes for endovascular treatment than surgical clipping for both ruptured and unruptured aneurysms. Effective treatment of more complex and wide-necked aneurysms with coils alone is often not technically possible. For these aneurysms, balloon remodeling and stent-assisted coiling techniques have developed with proven safety and efficacy.[4] Endoluminal flow diverting stents create an initial flow diversion effect that induces aneurysm thrombosis, followed by definitive parent artery remodeling and resorption of intra-aneurysmal thrombus, which mostly results in durable and complete occlusion.[5,6] The principle of flow diversion is the redirection of blood flow away from the aneurysm along the longitudinal axis of the parent artery. This is accomplished by the endoluminal placement of the flow diverter across the aneurysm neck. The hemodynamic effect depends mainly on the porosity of the mesh at the ostium of the aneurysm.[7,8] The effectiveness of aneurysm occlusion and potential complications are partly related to the specifications of the device.[9] An understanding of the technical features and functions of different flow

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diverters may help proper patient selection and procedure performance.

The initially reported results of aneurysm treatment with the p64 flow diverter (Phenox, Bochum, Germany) are favorable.[8,9] In this study, we present our experiences with the p64 flow diverter in a single center.

Materials and methods

p64 flow diverter

The p64 is a braided tubular device consisting of 64 nitinol wires. It is available with nominal diameters from 2.5 to 5 mm with 0.5 mm increments. The nominal length ranges from 9 to 30 mm with 3-mm increments. The P64 has two platinum wires wrapped around the braided shaft for fluoroscopic visibility. The 64 wires of the implant are grouped into eight bundles of eight individual wires. The end of each bundle carries a 0.5 mm radiopaque marker. The eight bundles are attached to a slotted crown on the distal end of a stainless steel delivery wire. The device can be mechanically detached by pulling a hypotube that covers the slotted crown. Once deployed, the p64 can be fully recovered by advancing the microcatheter while pulling back on the delivery wire.[10,11]

The metal coverage of the implanted flow diverter depends on the size of the device in relation to the diameter of the target vessel. Under standard conditions, coverage varies between 35%–49%. Undersizing increases and oversizing decreases the coverage.[5]

Patients and aneurysms

Each patient was discussed in a multidisciplinary neurovascular team. Patients were informed about the nature of their disease, the intended treatment and potential alternatives, with informed consent obtained at least 24 h before the procedure. General indications for treatment were unruptured intradural wide-necked or fusiform aneurysms and aneurysm remnants or recurrences after previous endovascular or surgical treatment. Ruptured supraclinoid carotid or vertebrobasilar dissection aneurysms were considered for p64 treatment if alternative treatment (for example, vertebral occlusion) was not possible.

A retrospective review was performed on medical records and radiographic studies of all patients treated with the p64 between March 2014 and July 2019. In this period, 108 patients with 109 aneurysms were treated with the p64 and included in this analysis. There were 87 women and 21 men with a mean age of 57 years (median 59, range 30–89 years).

Aneurysm and patient characteristics are summarized in Table 1. Of 109 aneurysms, 74 had been discovered incidentally, 12 were symptomatic by mass effect ($n = 9$), stroke ($n = 1$), or headache ($n = 2$), 18 had reopened after previous endovascular ($n = 17$), or surgical ($n = 1$) treatment, and five were ruptured dissection aneurysms. Of 109 aneurysms, 99 (91%) were located in the anterior circulation (carotid ophthalmic artery 39, carotid-cavernous segment 23, carotid posterior communicating artery 22, carotid hypophyseal artery 7, carotid supraclinoid segment 4, carotid anterior choroidal artery 1, anterior cerebral artery 2, middle cerebral artery 1) and 10 (9%) in the posterior circulation (basilar trunk 2, posterior inferior cerebellar artery 2, superior cerebellar artery 2, vertebral junction 1, vertebral artery 3). There were seven dissection aneurysms, of which five had ruptured.

Table 1. Aneurysm and patient characteristics of 109 aneurysms treated with the p64 flow diverter.

	Anterior circulation ($n = 99$)	Posterior circulation ($n = 10$)
Incidental finding	73	1
Symptomatic		
Mass effect	8	1
Stroke	0	1
Headache	2	0
Posttreatment: coiling	13	4
Posttreatment: clipping	0	1
Blister aneurysm	5	2
Mean size in mm (range)	7.9 (2–25)	8.6 (2–28)
Subarachnoid hemorrhage	3	2

Aneurysm size was defined as fundus size or lumen size in reopened aneurysms. The mean size was 8.1 mm (median 6, range 2–28 mm).

Endovascular procedure

Procedures were performed with the patient under general anesthesia on a biplane or a single plane Philips Allura angiographic system (Philips Healthcare, Best, the Netherlands). A femoral approach was preferred in all patients, and access was made without the use of ultrasound guidance. Either a 6F guide catheter alone or triaxial access was used. A 0.027-inch microcatheter was placed over a 0.014- or 0.016-inch micro guidewire in a straight segment of the parent artery distal to the aneurysm neck. After a suitable working projection was identified from 3D angiographic imaging, the target vessel diameter was measured. The selection of diameter and length of the p64 was made with the aid of computer simulation on the 3D workstation. Slight undersizing was allowed since the diameter of the unconstrained device is approximately 0.3 mm larger than the nominal diameter. Since undersizing results in shortening and a denser metal coverage of the implant, this was avoided if side branches were covered.[5] The device was then advanced to the desired position via the microcatheter. Deployment was performed by a combination of slow withdrawal of the microcatheter, with a

continuous counterpressure on the delivery wire. After the distal end of the device was deployed and anchored in the target vessel, the microcatheter was no longer pulled back. Pushing the delivery wire of the p64 resulted in a progressive deployment of the device with a passive proximal movement of the microcatheter. Once the proximal markers of the device were unsheathed, a single x-ray image or a flat panel CT was performed to confirm the complete opening of the device. If the opening was incomplete, the device was resheathed and redeployed until its full expansion. The fully opened device was mechanically detached by retraction of the hypotube. If the wall apposition of the detached p64 was not as desired, a compliant micro balloon was inserted and gently inflated to obtain complete wall apposition.

Additional coils were used in 12 aneurysms, and in three aneurysms, two flow diverters were placed.

Anticoagulation protocol

Patients were preloaded with 600 mg clopidogrel and 100 mg acetylsalicylic acid at least one day before the procedure. Platelet aggregation inhibition was tested before the procedure with the VerifyNow P2Y12 assay (Accriva, San Diego, CA). In patients with clopidogrel resistance, medication was changed to ticagrelor or prasugrel. The dual antiplatelet medication was continued for six months, followed by acetylsalicylic acid only for life. Periprocedural medication included systemic heparinization with ACT values aimed at 250.

Follow-up

Patients were scheduled for clinical and angiographic follow-up at six months and two and five years. Clinical assessment was performed according to the modified Rankin Scale. Angiographic results were graded as complete occlusion, neck remnant, or persistent flow. Also, aneurysm occlusion was graded according to a modified Raymond-Roy Occlusion (RRO) scale as proposed by Cekirge[9] (Table 2). In-stent stenosis was graded as absent, mild, major, and occlusion. If in-stent stenosis was present, on later angiographic follow-up, this was qualified as unchanged, decreased, or increased. Distal tapering of the p64 was scored as absent or present, and if present, this was followed on later angiographic studies. When tapering or intimal hyperplasia was diagnosed at the first control angiogram, dual antiplatelet medication was continued.

Table 2. Angiographic follow-up classification according to the modified Raymond-Roy Occlusion scale.[9]

Classification
Class 1: Complete occlusion of the aneurysm sac.
1A: Complete occlusion with the full patency of the integrated branch
1B: Complete occlusion with the branch reduced in caliber
1C: Complete occlusion with no antegrade filling of the branch
Class 2: Neck filling
Class 3: Incomplete occlusion with aneurysm filling
Class 4: This class is for the immediate postoperative result (not used in this series)
Class 5: Stable remodeling with flow modification.

Results

Procedural technical aspects and difficulties

Balloon expansion of the p64 after incomplete deployment was performed in four patients and was successful in all attempted cases. In three patients, placement of a second p64 was necessary for complete coverage of the aneurysmal neck.

In one patient, perforation of the right common iliac artery occurred for which placement of a covered stent was required.

Procedural complications

Two patients had minor ischemic lesions with transient neurologic deficits. Two patients had subarachnoid hemorrhage caused by perforation by the distal micro guidewire. In one of these patients, there were no clinical sequelae; in the other patient, the ruptured distal MCA branch was occluded with coils and glue, resulting in ischemia and permanent neurological deficit (mRS 2).

One patient with correct placement of the p64 for a recurrence of a posterior communicating artery aneurysm experienced hemiparesis in the recovery room. Immediate repeat angiography showed complete occlusion of the internal carotid artery and deformation of the p64. With thrombolysis and balloon expansion, flow restored entirely. However, a massive infarction developed with mRS four at the latest follow-up. One patient with a para-ophthalmic aneurysm experienced transient paresthesia in the contralateral arm and hand several days after flow diverter placement. Angiography after 14 days demonstrated a 50% stenosis of the internal carotid artery. At six months' angiography, the caliber of the carotid artery was normal again with complete occlusion of the aneurysm (Figure 1).

Permanent morbidity was 1.9% (2 of 108, 95%CI 0.1–6.9%) and mortality was 0% (0 of 108, 97.5%CI 0.0–4.1%).

Angiographic follow-up

Two patients with ruptured dissection aneurysms died during the admission of the sequelae of Subarchnoid hemorrhage (SAH). Two patients died of unrelated causes (lung cancer, Posterior cerebellar artery (PCA) infarction) before the six months interval. Of the remaining 104 patients with 105 aneurysms, 96

(92.3%) had six months follow-up angiography ($n = 94$) or MR angiography (MRA) ($n = 2$).

In one patient treated with p64 for a recurrent posterior communicating artery aneurysm, six months angiography demonstrated complete occlusion of the internal carotid artery, but the patient was asymptomatic. In this patient, dual antiplatelet medication was prematurely stopped preceding prostatic surgery. In one patient with a ruptured A1 dissection aneurysm, the A1 appeared completely occluded on follow-up MRI without ischemic lesions.

At six months, 77 of 96 aneurysms (80.2%) were completely occluded, 10 aneurysms (10.4%) had a neck remnant, and 9 aneurysms (9.4%) were still open. Of nine patients with nine aneurysms that were still open at six months, eight had two years follow-up angiography. Two aneurysms were still open, five had a neck remnant, and one was completely occluded. Five years follow-up angiography was available for six patients, all with completely occluded aneurysms. Altogether, at last follow-up angiography, 3 of 96 aneurysms (3.1%) were still open.

Occlusion grades according to the modified RRO scale during follow-up are displayed in Tables 3 and 4. Intimal hyperplasia was apparent at first control angiogram in 29 of 99 patients (29%), of which five patients had a significant stenosis with a luminal reduction of more than 50%. (Figure 1)

This returned to normal at later angiography in all five. Distal tapering of the p64 was noted in six cases (five mild, one severe) at the six months' angiographic follow-up. In four patients, the distal narrowing was resolved at two to three years of angiographic follow-up. In one patient with persistent distal tapering, a second p64 was placed at 18 months. However, the mild tapering persisted at two years. In another

Table 3. Results of follow-up angiography according to the modified Raymond-Roy Occlusion scale for 99 aneurysms in the anterior circulation.

Anterior circulation ($n = 99$)	6 months	2 years	5 years
RRO 1	73	58	6
1A	5	3	
1B			
1C	5	2	
RRO 2	7	4	
RRO 3	8	0	
RRO 5	NA	2	
No follow-up at interval	11	35	93
Cumulative total occlusion	73	83	88

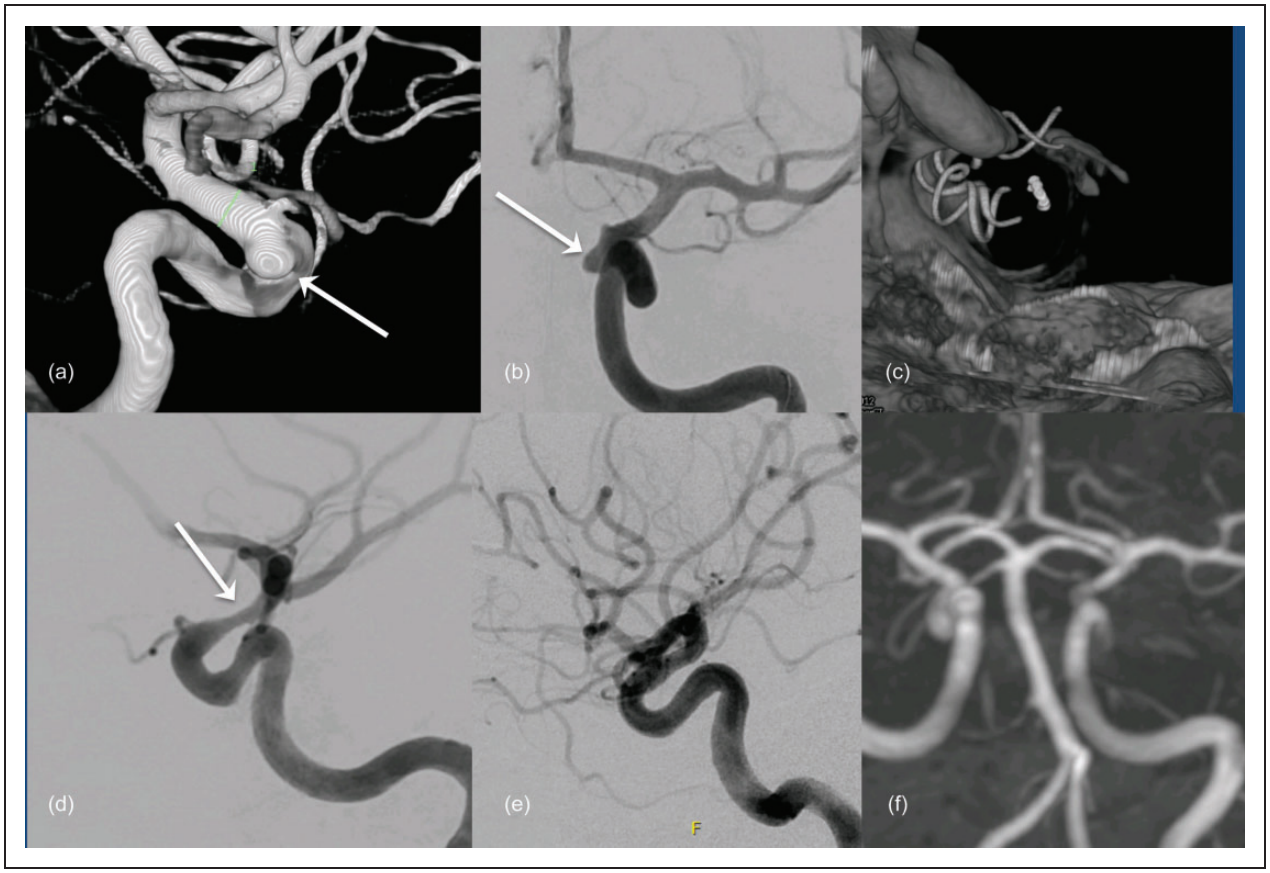

Figure 1. A 37-year-old woman with an incidental para-ophthalmic aneurysm. 3D (a) and 2D (b) angiogram showing small para-ophthalmic aneurysm. (c) The position of the p64 flow diverter. (d) Angiogram at two weeks made because of intermittent sensibility disturbances shows 50% stenosis at the distal end of the p64. (e) Angiogram at six months demonstrates a normal caliber of the carotid artery. The aneurysm is occluded. (f) MRA at two years is unchanged with six months angiogram.

patient, the severe tapering aggravated to complete asymptomatic occlusion of the Internal Carotid Artery (ICA) (Figure 2). There were no early or late parenchymal hemorrhages. Illustrative cases are displayed in Figures 3 and 4.

Table 4. Results of follow-up angiography according to the modified Raymond-Roy Occlusion scale for 10 aneurysms in the posterior circulation.

Posterior circulation ($n = 10$)	6 months	2 years	5 years
RRO 1	4	2	
1A	1		
1B			
1C			
RRO 2	3	2	
RRO 3	1	0	
RRO 5	NA	1	
No follow-up at interval	2	5	10
Cumulative total occlusion	4	5	5

Discussion

Our results confirm the effectiveness and safety of the p64 flow diverter for the treatment of unruptured aneurysms and selected ruptured dissection aneurysms. At six months, over 80% of aneurysms were completely occluded, and at last angiographic follow-up ranging from six months to five years, only 3 of 96 aneurysms showed persistent filling. Permanent procedural complications occurred in two patients. Occlusion of the flow diverter and parent vessel at follow-up was evident in three patients, in all three without neurological deficits. In one of these patients, antiplatelet medication was stopped prematurely. Mild distal tapering was noted in five patients at six months follow-up. In all patients, the vessel caliber returned to normal at later angiographic follow-up. No recurrent bleeding happened in the five ruptured dissection aneurysms and no first bleeding in the 104 unruptured aneurysms during the follow-up period.

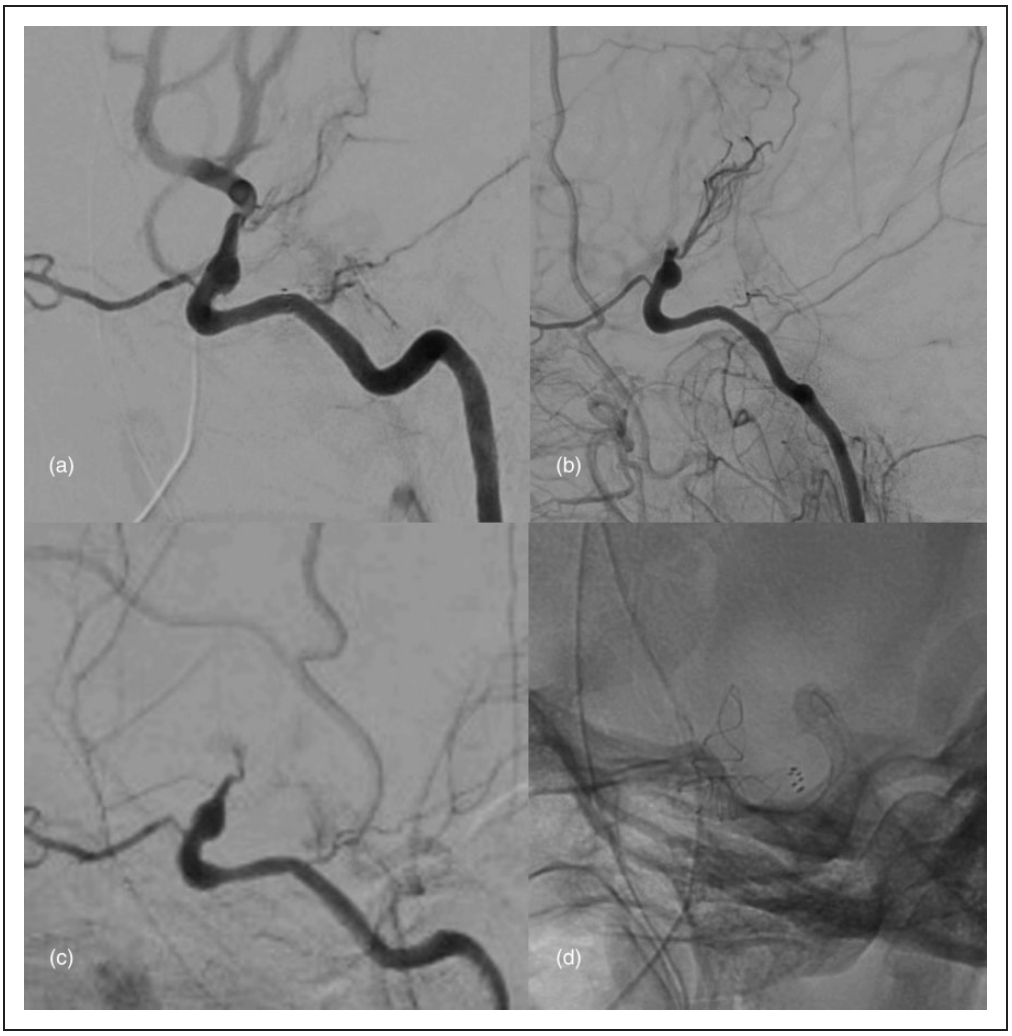

Figure 2. A 38-year-old woman with an incidental supraclinoid aneurysm treated with a p64 flow diverter and progressive stenosis and occlusion at follow-up. Initial images of the procedure are lost. The patient remained asymptomatic with good collateral flow. (a) Follow-up angiogram at six months shows severe stenosis at the distal end of the p64. (b) Angiogram at 12 months shows progressive distal stenosis. (c) Angiogram at two years demonstrates complete occlusion. (d) Position of the p64 with deformation at both ends.

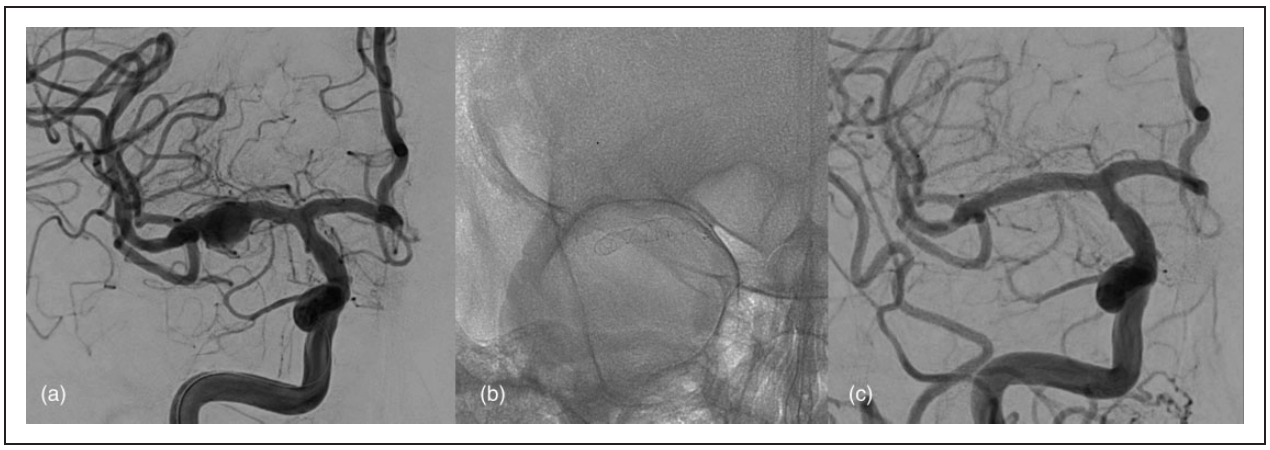

Figure 3. A 72-year-old man with an incidentally found fusiform middle cerebral artery aneurysm. (a) AP carotid angiogram shows a fusiform aneurysm on M1. (b) Position of the p64 flow diverter. (c) Angiogram after six months demonstrates complete occlusion of the aneurysm.

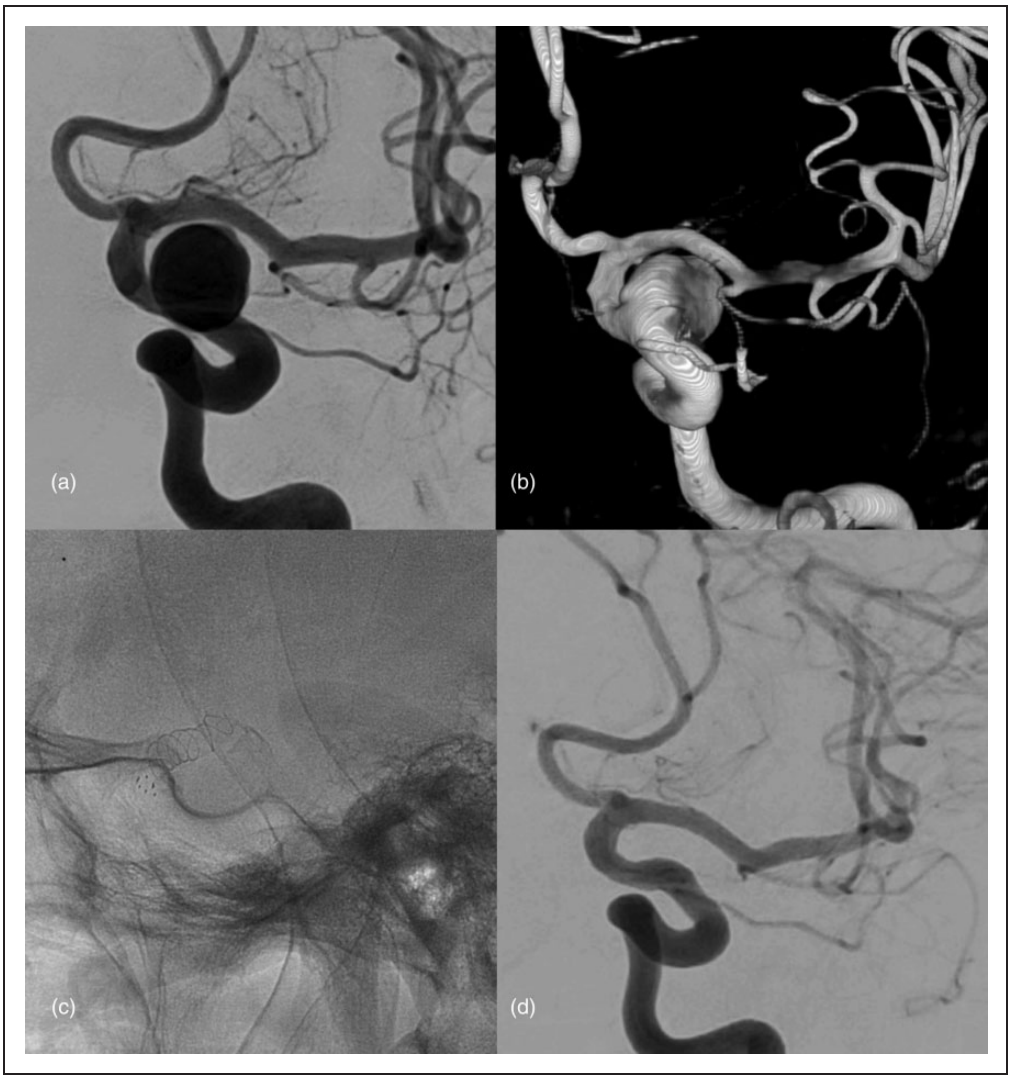

Figure 4. A 74-year-old man with an incidentally found carotid-ophthalmic aneurysm. Carotid angiogram (a) and 3D angiogram (b) reveals a wide-necked ophthalmic aneurysm. (c) Lateral radiograph shows the position of p64 flow diverter. (d) Complete aneurysm occlusion on 6 months follow-up angiogram.

Clinical and imaging results in our study are in line with five previous studies with the use of p64.[10–14] Our results compare favorably with series using different flow diverters.[15–22] In a meta-analysis comprising 2614 patients treated with other flow diverters,[22] the occlusion rate was 75% at 12 months, and the permanent event rate was 7.8%. Our occlusion rate was with 80% better at a shorter interval of six months, and our complication rate was with less than 2% remarkably lower.

The p64 consists of a braid of 64 nitinol wires, which results in a dense metal coverage across the aneurysm neck. It features a controlled mechanical detachment mechanism, which allows repositioning or withdrawal of the device even after complete deployment. The technical properties with the option to withdraw and redeploy the device enhance the safety in comparison with other flow diverters. In our series, it was only occasionally necessary to correct a suboptimal opening of the p64 with a compliant balloon, and in all cases, this was straightforward and effective.

In all but three aneurysms placement of a single p64 was sufficient to cover the aneurysm neck completely. This figure compares favorably with other series. For example, Fischer et al.[10] used more than one p64 in 13 of 127 aneurysms (10.2%), and in 101 cases treated with the Pipeline Embolization Device, more than one device was used in 67 (67%) with an average of 3.2 devices per procedure. Some authors argue that the amount of braid material of one device might be insufficient to enable complete endothelial growth and hence occlusion of the aneurysm.[10] Our results indicate that a single device is sufficient in the vast majority of aneurysms.

In-stent stenosis by intimal hyperplasia and distal tapering is a clinical concern with flow diversion.[23–25] In one study, neo-intimal hyperplasia was positively correlated with smoking, dyslipidemia, and high blood pressure, but not with aneurysm characteristics. Although early follow-up hyperplasia was more frequently associated with the use of the SILK stent rather than the Pipeline Embolization Device, at long-term follow-up, the neo-intimal hyperplasia rate in the total population dropped from 55% to 26% with no more significant difference between the two stents. Before treatment patients should be recommended best medical management of their cardiovascular risk factors to prevent an excessive neo-intimal reaction.[23] In a study by Aguilar Pérez[26] concerning this issue for the p64 in over 200 patients, almost a third had some degree of in-stent stenosis during any time at follow-up. Most stenoses were mild, and no progression to occlusion occurred. More importantly, in-stent stenosis did not cause any neurological deficit, and most stenosis improved or resolved at further follow-up. Also, in our series, in-stent stenosis occurred in several patients leading to complete occlusion in three of them. Although all three patients remained asymptomatic because of adequate collateral circulation, in-stent stenosis is a potential hazard during follow-up. When in-stent stenosis occurs, further angiographic follow-up is mandatory to confirm improvement or worsening. When in-stent stenosis becomes severe, balloon angioplasty might be considered.

Neo-intimal hyperplasia is believed to be an essential phenomenon in the pathophysiology of aneurysm healing after flow diversion.[27,28] The initial event following flow diversion treatment is the adherence of clusters of inflammatory cells across the aneurysm neck. Endothelialization is relatively delayed and derived exclusively from cells in the adjacent parent artery. This might indicate that optimal wall apposition is a key modulator of the healing of the device. Aneurysm closure was noted only when complete or nearly complete endothelialization over the device struts was present.[28]

Another concern with flow diversion is the occurrence of delayed aneurysm rupture. The mechanism is not fully understood. Some suggest that altered hemodynamics induced by the flow diverter increases the wall stress to the aneurysm.[29] Others favor the theory that thrombus formed in the aneurysm releases enzymes that cause lysis of the aneurysm wall.

A meta-analysis showed that the incidence of subarachnoid hemorrhage after flow-diverter placement was 4.0%, with a higher incidence in patients with large or giant aneurysms.[21] In our series, we did not encounter any delayed aneurysm during follow-up, and almost all aneurysms were occluded at last follow-up.

Parenchymal hemorrhage distal to the target vessel, mostly occurring several days after treatment, is another possible hemorrhagic complication after flow-diverter treatment. The mechanism of this complication is unclear. The incidence of delayed parenchymal hemorrhages in a retrospective analysis was 1.9%.[30] In our series, we observed no delayed parenchymal hemorrhages.

In conclusion, the p64 offers an effective treatment option for intracranial aneurysms, both as primary treatment and secondary treatment after incomplete coiling or clipping. Complication rates are low, and over 80% of aneurysms were occluded at six months, mostly achieved with a single device. There were no delayed hemorrhagic complications. Delayed in-stent stenosis infrequently progresses to occlusion but remains a matter of concern. The ability to reposition and remove the device in cases of poor deployment is a significant advantage. Safety margins are within expected limits, with device-related complications being infrequent.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This retrospective study is in compliance with national law with a waiver for ethical approval.

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