

Review Article

Research progress on complications of intracranial aneurysms with flow-diverting stents

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Abstract: The flow-diverting stent (FDS) has been recognized as an effective treatment for intractable and complex aneurysms. However, after implantation, FDSs have been associated with a higher incidence of complications such as aneurysm ruptures, distal brain hemorrhages, ischemic events, stent migration or shortening, brain tissue embolisms and in-stent stenosis. In this study, a review of the literature on the complications of FDS applications was conducted to improve the understanding of these complications. In this review, FDS-related articles were identified using PubMed, and the ones relating to complications were reviewed. As a result of the systematic literature review, it is believed that although it is not possible to avoid complications when using FDSs, selecting appropriate patients could reduce them. When implanting an FDS, avoiding complex operations such as deploying more than one stent, deploying a stent at a blood vessel location that is too tortuous or deploying a stent in an artery with intensive perforator vessels and inadequate perioperative antiplatelet therapy is recommended to reduce the incidence of complications. When implementing an FDS in posterior circulation, one should be very wary because that application has a higher incidence of complications than implementing an FDS in anterior circulation. Furthermore, an FDS of a suitable size should be chosen to avoid delayed stent migration or shortening caused by a stent that is too small.

Keywords: Flow-diverting stent (FDS), intracranial aneurysm, complications

Introduction

A flow-diverting stent (FDS) is a self-expanding stent apparatus with a high metal surface area coverage that is mainly used in conventional arterial embolization and with complex aneurysms that cannot be treated, such as fusiform aneurysms, dissecting aneurysms, giant aneurysms and recurrent aneurysms [1]. After covering the neck of the aneurysm, the FDS induces aneurysm thrombosis and thereby cures the aneurysm; generally a single FDS is deployed [2, 3]. In some cases, when the neck of an aneurysm is covered by an FDS, coils are used to fill the body of the aneurysm to protect the top of the aneurysm and promote thrombosis [4, 5].

An FDS generally includes a Silk flow diverter and Pipeline embolization device, a flow redirection endoluminal device system, a surpass flow diverter and other new products that have similar mechanisms and are similarly effective at treating aneurysms. After years of clinical

applications, a consensus has been reached: using FDSs to treat complex intracranial aneurysms and other aneurysms that are impossible to treat using conventional methods is feasible and safe [6, 7]. However, compared with the interventional treatment of aneurysms using conventional stent-assisted embolization, the biggest problem with the use of FDSs is the higher incidence of complications after their deployment [8].

Therefore, when using FDSs to treat aneurysms, the relative efficacy and morbidity of this treatment must be considered [9]. These complications include aneurysm ruptures, distal brain hemorrhages, perforator vessel occlusions, stent migration or shortening, brain tissue embolisms and in-stent stenosis, which have been always associated with FDS implantation. Currently, the understanding of these complications is very limited. We review the literature. “Flow diverter” or “flow diversion” or “flow diverting stent” and “intracranial aneurysm” were entered into PubMed as search

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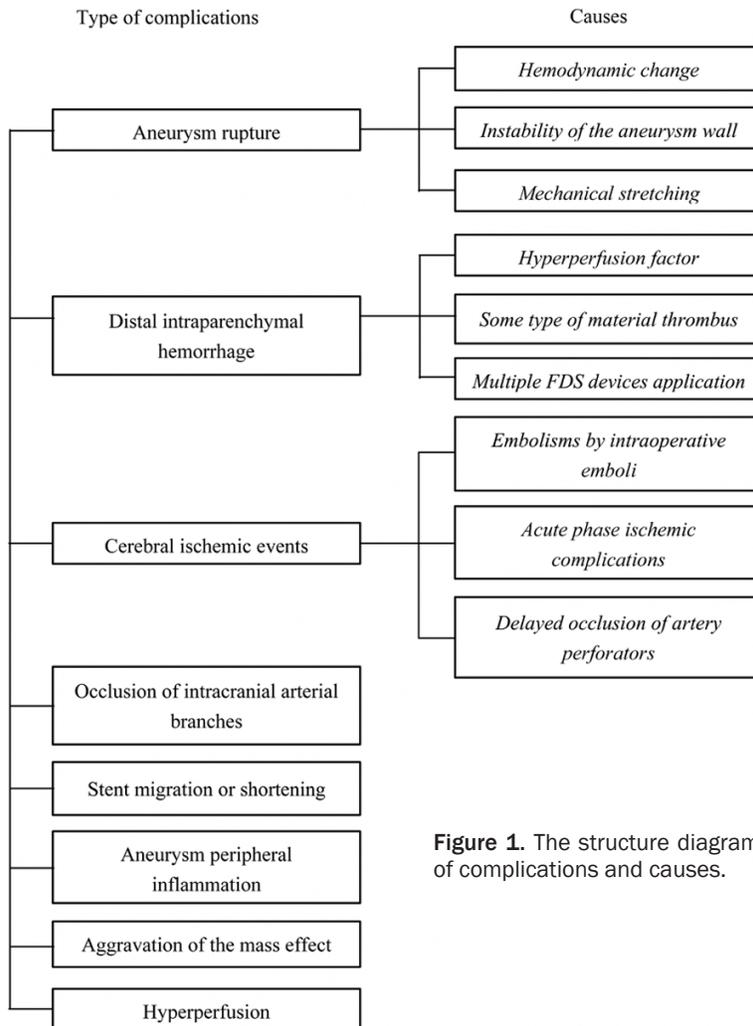


Figure 1. The structure diagram of complications and causes.

terms to identify English-language literature. The literature associated with the complications was also reviewed.

Aneurysm rupture after FDS implantation

Delayed postoperative aneurysm rupture is the most serious complication; it often has disastrous consequences. Even for unruptured aneurysms, delayed aneurysm rupture may occur after the FDS has been implanted. For instance Siddiqui et al. in 2012 reported 2 cases of unruptured giant vertebrobasilar aneurysms that ruptured after FDS treatment, causing the patient's death [10]. In the literature, it is reported that the risk of unruptured aneurysms rupturing after FDS embolization is very low, approximately 0-6.6%, and that rupture is more likely to occur with the Silk device than the Pipeline device [11]. In addition to the delayed ruptures, there were some rare cases in which an aneurysm ruptured rapidly after an FDS

was implanted; for example, Chitale et al. reported 1 case of a posterior paraclinoid aneurysm in which rupture hemorrhage occurred 20 minutes after the operation [12]. Therefore, it was suggested that the risk of an aneurysm re-rupturing was higher after the FDS treatment of a ruptured aneurysm [13]. What makes the FDS's coverage of the neck of an aneurysm fail to play a protective role and, instead, induce a rupture of the aneurysm is still unclear. There has been speculation that it might be related to the following factors.

Hemodynamic factors

Once an FDS has covered the neck of the aneurysm, the flow velocity, inflow rate, and shear rate within the aneurysm's body change; these are all related to the fast closure of the aneurysm [14]. After FDS implantation, sometimes, no thrombus forms in the aneurysm or delayed thrombosis occurs, and the pressure inside the aneurysm does not decrease, leading to

a higher risk of aneurysm rupture after the operation [15, 16]. Even though the FDS induces aneurysm thrombosis, aggressive thrombus-associated autolysis soon follows and the blood stream re-enters, inducing aneurysm rupture [17]. In addition, after FDS implantation, the pressure within the aneurysm does not decrease but rather increases because the implanted FDS changes the parent artery's shape and curvature and lifts its proximal stenosis, which leads to a decreased resistance to blood flow in the proximal end of the aneurysm and an increased pressure gradient within the aneurysm and, thereby, induces a postoperative aneurysm rupture [18, 19].

Unfortunately, our current understanding of the hemodynamic changes in an aneurysm after FDS implantation is very limited; therefore, after the deployment of an FDS, complete aneurysm occlusion is unpredictable [20]. At

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present, it is believed that the occurrence of thrombosis in an aneurysm after FDS implantation is key to healing the aneurysm [21]. Therefore, it is necessary to conduct more in-depth investigations of how the hemodynamic properties of the aneurysm change after FDS implantation and how to control these hemodynamic changes.

Instability of the aneurysm wall

The delayed rupture that occurs after intracranial FDS implantation is related to the instability of the aneurysm wall. The treatment of aneurysms with incorporated branch vessels may perpetuate intra-aneurysmal flow and predispose lesions toward delayed mural instability [22]. In addition, an evolving intra-aneurysmal thrombus may not protect an aneurysm from rupturing. On the contrary, an evolving thrombosis may actually cause a transient destabilization of the aneurysm wall, increasing rather than decreasing its propensity to rupture [23].

Mechanical stretching

The morphological changes in the parent artery that occur after FDS implantation may lead to mechanical stretching, which can cause postoperative aneurysm rupture. Fox et al. in 2014 reported a case of a vertebrobasilar aneurysm that ruptured after FDS treatment; in the autopsy, observing the FDS and aneurysm revealed mechanical stretching shifts in the aneurysm and the basilar artery, which were thought to have caused the aneurysm rupture [24].

Measures to reduce the incidence of delayed aneurysm rupture after FDS application

Using a slightly larger stent is recommended because it provides greater metal coverage and reduces the flow velocity, flow rate and shear stress of the blood stream within the aneurysm, which is conducive to the formation of a thrombus within the aneurysm, thus leading to a lower risk of aneurysm rupture [25]. However, a patient with an aneurysm that promotes continued flow into the neck after flow-diversion may not be an optimal candidate for the flow-diversion treatment strategy [23]. Because ruptures generally occur at the tops of aneurysms covered by FDSs, protecting the top of a large or giant aneurysm with an FDS using,

e.g., coil filling, is recommended; however, robust packing is to be avoided because it can lead to acute FDS thrombotic or compressive occlusion [5, 26].

In any case, one should be vigilant about the emergence of adverse events during aneurysm thrombosis; close postoperative observation is critical. Because an MRI allows observation of the aneurysm wall and aneurysm thrombosis, it provides some valuable information [27]. Meanwhile, the new generation of products, including small pipeline stents and P64 stents, may be worth considering because, in clinical studies of this new generation of FDS products, reports of aneurysm rupture are rare, which is probably due to the shorter time they have been in use and the limited number of cases [28-30].

Distal intraparenchymal hemorrhage after FDS application

The incidence of distal hemorrhage is reportedly 0.8-8.5%, and an incidence of 3% was revealed by a meta-analysis [31]. Distal intracerebral hemorrhage is more common after a Pipeline FDS is used to treat an intracranial aneurysm; the rate of incidence is approximately 2.5% [32]. Recently, Brinjikji et al. analyzed 906 cases of aneurysms treated using FDSs and found that in 20 of them, distal brain hemorrhage occurred (an incidence rate of 2.2%), generally within 6 months of the operation [32]. Reviewing the literature revealed that distal intracerebral hemorrhages have generally occurred in cases of anterior circulation aneurysms treated using FDSs and have only rarely occurred in cases of posterior circulation aneurysms [11].

The amount of bleeding was often quite large, and coupled with dual antiplatelet therapy after FDS application, it made the treatment more difficult. Cruz et al. in 2012 reported 47 cases in which FDS therapy was applied to an anterior circulation aneurysm. In 4 of these cases, a distal intracerebral hematoma appeared 1-6 days after the operation, and even with aggressive therapy, the prognosis remained poor [33]. The cause of these distal intracerebral hemorrhages remains unclear. It might be related to the following factors.

Hyperperfusion factors

Presumably, hemodynamic factors are related to the morphological changes of the parent artery of an aneurysm after FDS implantation because an FDS reduces the local compliance of that vascular segment by altering the “Windkessel effect” and changing the blood pressure waveform transmitted to the distal cerebrovasculature [33]. In cases of intracerebral hemorrhages following the use of an FDS to treat an aneurysm, this generally occurred in larger aneurysms in which the parent artery at the neck of the aneurysm formed a sharper angle. The improvement of the blood flow in the distal brain tissue caused the rupture of blood vessels and, thus, the hemorrhage. Conversely, in reports on the FDS treatment of small aneurysms, the incidence of such distal intracerebral hemorrhages is rather low, which is probably because the FDS treatment of an aneurysm has little effect on the parent artery [34, 35]. The improved blood flow could lead to hyperperfusion in the distal brain tissue of the aneurysm; it was found that hyperperfusion can occur in the parent artery after FDS implantation [36].

Other factors

In addition to hemodynamic factors, intracerebral hemorrhages after FDS implantation may be associated with other factors. Becske et al. retrospectively examined 108 cases of FDS-treated aneurysms and believed that distal intracranial hemorrhage was intraprocedural embolization due to some type of material thrombus, air bubbles, a catheter coating that resulted in microvascular damage, a transient occlusion with microinfarction or hemorrhagic reperfusion [37]. A study by Hu et al. also supported the notion that an intracerebral hemorrhage after FDS treatment was related to intraprocedural foreign body emboli [38]. At the same time, a hemorrhage may be related to the hemorrhagic transformation of small ischemic strokes in the setting of dual antiplatelet therapy [7]. Brinjikji et al. found that using multiple FDS devices and treating ruptured aneurysms with FDSs are risk factors for distal cerebral hemorrhage, although an association with dual antiplatelet therapy cannot be excluded [32]. Presumably because the overlapping of multiple FDS devices changes the morphology of the parent artery more profoundly and improves the blood flow.

Cerebral ischemic events after FDS application

The FDS treatment of aneurysms can cause ischemic events such as the shedding of intraoperative emboli, acute ischemic complications, delayed cerebral infarction caused by the occlusion of perforating branches, and delayed in-stent stenosis. Their incidence is higher for posterior circulation aneurysms than anterior circulation aneurysms (5.6% versus 3.5%) and for large or giant aneurysms than for small aneurysms (6.2% versus 2.8%) [39].

Embolisms caused by the shedding of intraoperative emboli

In conventional stent-assisted aneurysm embolization, ischemic events caused by emboli shedding are rather common [40]. Because FDS operations are far more complex than conventional stent operations, it is estimated that the incidence of cerebral embolism is much higher [41]. The larger the aneurysm was, the more complex the operation was and the more emboli were shed; therefore, aneurysm size is a risk factor for the ischemic complication of brain tissue caused by the shedding of emboli [42]. These studies all involved MRIs captured before and after the FDS was implanted, and the embolisms included both quiet and symptomatic embolisms. Following the latest meta-analysis of the FDS treatment of intracranial aneurysms, it is believed that the incidence rate of symptomatic embolism due to emboli shedding is 4.1% [40].

Although in most cases, this type of embolization poses little harm, results in no clinical symptoms and does not affect refractory aneurysms via FDS embolization, a postoperative MRI examination to observe the extent of brain tissue infarction is still recommended [43]. The treatment of this type of embolism is identical to that of a conventional cerebral infarction, and the prognosis is good.

Acute phase ischemic complications after FDS implantation

These complications mainly include acute stent thrombosis and the acute arterial occlusion of perforating branches. It has been speculated that acute ischemic complications may be associated with inadequate preoperative antiplatelet therapy. The acute occlusion of perfo-

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rating branches occurs at the perforator-intensive vessels, mainly including the basilar and middle cerebral arteries; for example, Kulcsár et al. in 2010 reported 12 cases of FDS therapy for aneurysms, 1 of which developed acute thrombosis in the distal cerebral and superior cerebellar arteries after a Silk FDS was deployed in the superior segment of the basilar artery, and recanalization was achieved after the administration of a glycoprotein IIb/IIIa antagonist, indicating that timely treatment was critical. One case of basilar aneurysm, at the proximal end of which it was difficult for the Silk FDS to distract, was also reported. The stent was distracted with the assistance of balloon dilation and overlapped with a Silk FDS and an Enterprise stent; 12 hours after the operation, symptoms emerged, digital subtraction angiography suggested that the basilar artery was occluded, and the prognosis was poor in spite of aggressive treatment [44].

Therefore, FDS treatment requires adequate preoperative antiplatelet therapy; at the same time, one should strive to reduce the complexity of the operation because deploying an excessive number of stents and having a parent artery that is too tortuous result in difficulty distracting the FDS and an increase in vascular injuries as well as hemodynamic changes that induce in-stent thrombus [45]. It should be noted that the extrusion of an FDS due to coils that are too densely packed may induce stent thrombosis. For example, Siddiqui et al. in 2012 reported a case of cerebral aneurysm that was treated by deploying 2 overlapping PEDs after dense coil embolization, and acute thrombosis occurred in the PED 6 hours after the operation; however, a satisfactory recovery was achieved after thrombolysis [26]. Therefore, it is necessary to minimize the operations performed during surgery and to adopt simple techniques, and when complex techniques are involved, one should watch for complications.

Delayed occlusion of artery perforators

FDS with a high degree of metal coverage can cause perforator occlusion due to the reduced blood flow through the fine perforator vessels. Lubicz et al. in 2010 treated 26 cases with 34 aneurysms using FDS therapy; 3 of these cases developed delayed perforator occlusions, of which 1 occurred in the posterior circulation and 1 occurred in the middle cerebral artery 2

weeks to 4 months after the surgery [46]. This delayed artery perforator occlusion had a high incidence of complications in the posterior circulation in the basilar artery, which was probably related to the intensive perforator vessels in the basilar artery. Recently, Ahmed et al. in 2015 used FDSs to treat fusiform aneurysms in posterior circulation and had 4 cases of delayed ischemia; based on a systematic review of the literature, they believed that treating vertebro-basilar artery fusiform aneurysms with FDSs had a rather high risk [47]. This shows that an FDS can cause reduced blood flow in the perforator vessels of the basilar artery; i.e., there is a possibility of delayed occlusion in the perforator vessels after FDS implantation.

In addition to the basilar artery, arteries with intensive perforator vessels, such as the middle cerebral artery, have the risk of perforator occlusion after FDS implantation. Nelson et al. in 2011 studied 1 case of a giant aneurysm in the M1 segment of the middle cerebral artery, which was treated with Neuroform stent-assisted embolization and for which 2 overlapping Pipeline stents were deployed; 2 days after the operation, deep perforator vessel occlusion occurred [48]. Therefore, it is believed that the deployment of an excessive number of stents and complex operations can induce perforator occlusion.

In-stent stenosis

This FDS-derived stenosis is a primarily vascular response to an FDS and relatively common event because it occurs in approximately 16% of patients. This is significantly higher than the rate of construct stenosis reported for the Neuroform and Enterprise stents (2.5%-5.8%) [49]. This FDS-derived parent artery stenosis often has no clinical symptoms and can be self-relieved. For instance Gascou et al. in 2015 reported that when 66 aneurysms in 59 patients were treated with 96 Pipeline embolization devices, the incidence of in-stent stenosis was 16.2%, with the majority undergoing spontaneous remission [50].

Therefore, it is unnecessary to treat patients with FDS-derived parent artery stenosis who do not have any clinical symptoms; however, close follow-up is required [51]. Watchfulness is necessary for some FDS-induced stenosis because the stenosis caused by thrombosis within an

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FDS can sometimes lead to adverse effects. For example, Tahtinen et al. in 2012 reported that in 24 consecutive patients with 29 stents, follow-up imaging revealed 1 case of delayed in-stent thrombosis that permanently disabled the patient [52]. Antiplatelet therapy after an FDS is installed is crucial for preventing stenosis derived from in-stent thrombosis, especially in patients with multiple overlapping FDSs. Among the vertebrobasilar aneurysm cases treated using FDSs reported by Meckel et al. in 2013, 1 case of delayed in-stent thrombosis occurred in 1 giant fusiform aneurysm treated with 9 overlapping PEDs 11 months after the procedure, and the patient had a history of disabling clopidogrel 2 weeks prior to the onset of thrombosis [11].

Even with regular medication, some patients may develop stenosis caused by in-stent thrombosis during the long-term follow-up period. Fiorella et al. in 2010 reported that 1 case treated using an FDS had thrombosis-induced in-stent stenosis 23 months after the operation even though the patient had been using antiplatelet therapy [53]. Therefore, although antiplatelet therapy is critical, there may be other causes. Given the critical role of inflammation in the pathogenesis of in-stent stenosis, due to the suggestions of some studies, we believe that the ability of aspirin to protect against in-stent stenosis is probably related to its anti-inflammatory properties [54].

Effect on intracranial arterial branches

Once it covers the basilar artery or the middle cerebral artery, an FDS can cause acute or delayed occlusion of the perforating branches because these perforating branches are intensive and fine and lack abundant blood flow. However, the current study found that when an FDS covers thicker arteries, occlusion does not occur after FDS implantation because the branches are thick and have abundant blood flow, and the vascular endothelium is unable to cover the opening of the artery due to the strong impact of the blood flow [4]. This has already been confirmed in clinical applications of FDSs. Vedantam et al. in 2014 summarized 42 cases in which FDSs were used and noted that the incidence of major supraclinoid ICA branch occlusion after treatment with PEDs was low; these events were not associated with new neurological deficits [55].

Although these results are encouraging, the reduction or occlusion of the arteries in some parts may actually generate clinical symptoms. Rouchaud et al. in 2015 followed 28 cases of ophthalmic aneurysms treated with FDS therapy and found that 11 of the cases (39.3%) exhibited eye symptoms; therefore, they believed that patients whose ophthalmic artery originated in the aneurysm sac were at high risk for retinal emboli. Patients whose ophthalmic artery originated in the inner curve of the carotid siphon were at high risk for optic nerve ischemic atrophy, and avoiding covering the ophthalmic artery opening as much as possible is recommended [56]. Furthermore, whether occlusion in the branches of the carotid artery cause any clinical symptoms or not depend on the distal arterial blood supply on collateral circulation [57].

Stent migration or shortening

FDS applications are rather complicated, primarily because FDSs are designed to achieve higher metal coverage; an FDS is mostly a woven stent, and its deployment requires a combination of pushing and pulling [58]. Complex operations render an FDS susceptible to migration or dislocation if there is even a small mistake. Even if an FDS is deployed in position and in full distraction with good adherence to the aneurysm wall, it could slowly migrate like a spring, i.e., undergo delayed stent migration or shortening, which is the so-called "spring effect". This is similar to the stent migration that occurs after a conventional aneurysm embolization assisted with intracranial stent [59]. As for delayed FDS migration or shortening, Chalouhi et al. in 2013 reported 5 cases of FDS migration or shortening, 4 of which involved migration toward the proximal end and 1 toward the distal end; spontaneous delayed migration or shortening of the PED was a serious and potentially fatal complication, and of these 5 cases, 1 case led to death from aneurysm rupture and another led to parent artery occlusion [60].

Therefore, one should be wary of the possibility of delayed FDS migration after implantation. To prevent FDS migration or shortening after implantation, ensuring complete expansion of the PED by using a longer PED, increasing the vessel coverage, using adjunctive aneurysm coiling, and avoiding dragging and stretching of

the PED are important preventive measures. At the same time, close postoperative follow-up imaging should be planned. The position of the FDS needs to be observed via VasoCT immediately after the operation to facilitate later comparisons [61]. A postoperative follow-up examination can be performed using computed tomography angiography (CTA) to observe the position of the stent [62]. In addition, magnetic resonance angiography (MRA) is a good alternative [63].

Other rare complications

Aneurysm peripheral inflammation

After the FDS treatment of intracranial aorta aneurysms, peripheral inflammation may sometimes appear, manifesting as cerebral edema with corresponding clinical symptoms. Berge et al. in 2011 reported 17 cases of unruptured aneurysms treated using FDSs; 7 showed delayed clinical symptoms, such as headaches and aggravation of the mass effect, and MRIs revealed the presence of vasogenic edemas induced by blood-brain barrier damage peripheral to the aneurysm, which was considered a temporary inflammatory response that would be relieved in 3-30 days. Especially in the cases that the aneurysm and the surrounding brain tissue were closely adhered, it was more prone to inflammation [64]. After conventional aneurysm embolization, there could have been an inflammation response peripheral to the aneurysm, not the limited one that appears in the presence of an FDS [65].

Aggravation of the mass effect

After the FDS embolism of an aneurysm, a thrombosis forms within the aneurysm, the volume of the aneurysm gradually decreases, and the original mass effect disappears [66]. For instance Kelkar et al. in 2014 found that bilateral ophthalmic aneurysms compressed the olfactory nerve, leading to hyposmia, and resolution of the diminished olfactory sensation was achieved by treating bilateral ophthalmic segment aneurysms with flow diversion [67]. For another example Patel et al. in 2015 reported that the return of visual function after bilateral loss of vision following the flow diversion embolization of a giant ophthalmic aneurysm was due to reductions in both the mass effect and aneurysm pulsation [68]. However, in some

cases, the volume of the aneurysm increased after FDS implantation and the emerging mass effect introduced clinical symptoms. Among the 10 cases of FDS-treated vertebral basilar artery aneurysm reported by Meckel et al. in 2013, there were 2 cases that had experienced the mass effect preoperatively, 1 of which developed an aggravated mass effect after FDS implantation; the symptoms improved after symptomatic hormone therapy, and the mass effect disappeared in 18 months. In the other case, the symptoms worsened 5 months after FDS implantation, and the patient died 7 months after the implantation in spite of hormone therapy [11]. This might be attributed to thrombosis of the aneurysm after flow diversion leading to secondary swelling and compression of adjacent structures.

Hyperperfusion

Covering the neck of an aneurysm with an FDS is equivalent to reconstructing the parent artery mainly by reducing its curvature and expanding it; therefore, theoretically, hyperperfusion can occur in the brain tissue at the side of an aneurysm. Chiu et al. in 2013 reported that 1 52-year-old patient developed a conscious disturbance and hemiplegia 11 days after FDS implantation, which was confirmed by computed tomography perfusion showing increased blood flow on the FDS side, i.e., hyperperfusion; 6 months later, the patient had recovered well and had normal radiological images [36]. Gascou et al. in 2015 reported that 66 aneurysms in 59 patients were treated with 96 Pipeline embolization devices, and the incidence of hyperperfusion was 3.4% [50].

Therefore, for some patients, the possibility of hyperperfusion needs to be considered after FDS implantation, antihypertensive therapy needs to be carefully executed, and if necessary, blood pressure needs to be controlled to prevent intracranial hemorrhage.

Summary

Currently, as an effective treatment for refractory and complex aneurysms, FDSs have been recognized. However, the high incidence of complications after FDS implantation should not be ignored. The complications include aneurysm ruptures, distal brain hemorrhages, the occlusion of perforator vessels, stent migra-

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tion and shortening, brain tissue embolisms and in-stent stenosis. Because the pathology of the above-listed complications is not clear, these complications have been associated with treatments that use FDSs. Selecting appropriate patients, e.g., patients with smaller aneurysms and patients without tortuous parent arteries, can reduce the incidence of these complications. When an FDS is implanted, complex operations, such as the deployment of more than one stent, deploying a stent in a location that is too tortuous or in an artery with intensive perforator vessels, and inadequate perioperative antiplatelet therapy should be avoided because they are all risk factors for these complications. When an FDS is implanted in posterior circulation, extra care must be taken because posterior circulation has a higher incidence of complications than anterior circulation. Moreover, an FDS of an appropriate size should be selected to avoid delayed stent migration or shortening due to a stent that is too small. The structure diagram of complications and causes was shown in **Figure 1**.

Disclosure of conflict of interest

None.

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