Mechanism of Action and Biology of Flow Diverters in the Treatment of Intracranial Aneurysms

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Flow diverters have drastically changed the landscape of intracranial aneurysm treatment and are now considered first-line therapy for select lesions. Their mechanism of action relies on intrinsic alteration in hemodynamic parameters, both at the parent artery and within the aneurysm sac. Moreover, the device struts act as a nidus for endothelial cell growth across the aneurysm neck ultimately leading to aneurysm exclusion from the circulation. In silico computational analyses and investigations in preclinical animal models have provided valuable insights into the underlying biological basis for flow diverter therapy. Here, we review the present understanding pertaining to flow diverter biology and mechanisms of action, focusing on stent design, induction of intra-aneurysmal thrombosis, endothelialization, and alterations in hemodynamics.

KEY WORDS: Endothelialization, Healing, Thrombosis, Pipeline embolization device, Endovascular

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Flow diversion has emerged as a safe and efficacious first-line therapy for select intracranial aneurysms, revolutionizing treatment; indeed, in some centers up to one-third of aneurysms are treated with flow diverters. Although originally approved for treatment of large or giant, wide-necked aneurysms of the internal carotid artery (ICA), recent years have seen expansion of their scope to several "off-label" uses, including treatment of ruptured aneurysms.[1,2] Despite an exponential increase in their use in recent years, the biological mechanisms underpinning the mode of action of flow diverters have not been precisely elucidated. Indeed, given the strongly promising initial clinical effectiveness of flow diverters, comparatively less literature focused on underlying biological phenomena explaining this effectiveness in the earlier years of implementation. The introduction of newer-generation surface-modified flow diverters (eg, Pipeline with Shield Technology [PED Shield; Medtronic Inc]) has thus represented a reassessment of the biological basis of action of flow diverters.[3] An improved understanding of the mechanisms of action of flow diverters will thus contribute to further improvement of this technology, aiming to improve device safety profiles and potentially expand indications.

ABBREVIATIONS: Ang1, angiopoietin-1; **CFD,** computational fluid dynamics; **FD,** flow diverter; **FRED,** flow re-directing endoluminal device; **ICA,** internal carotid artery; **IPH,** intraparenchymal haemorrhage; **PED,** Pipeline embolization device

Aneurysm occlusion via flow diversion has traditionally been proposed to occur via 2 predominant processes: (1) intra-aneurysmal thrombosis following device-related alteration of blood flow and (2) provision of a scaffold for endothelial cell growth at the aneurysmal neck, by the device itself (Figure 1).[4,5] Unlike surgical treatment and other endovascular modalities, the aneurysm is not immediately occluded from the circulation—treatment efficacy thereby relies on interaction between flow diverter, parent artery, and aneurysm at cellular and molecular levels to allow subsequent aneurysm occlusion. In this article, we provide an overview of the current understanding of the flow diversion mechanism of aneurysm occlusion, highlighting the biological and mechanical effects of device design, hemodynamics, and deployment.

THROMBUS FORMATION

Upon flow diverter deployment, flow disruption and subsequent stable thrombus formation within the aneurysm are primary events that play a critical role in aneurysm occlusion. The innate flow-altering capability

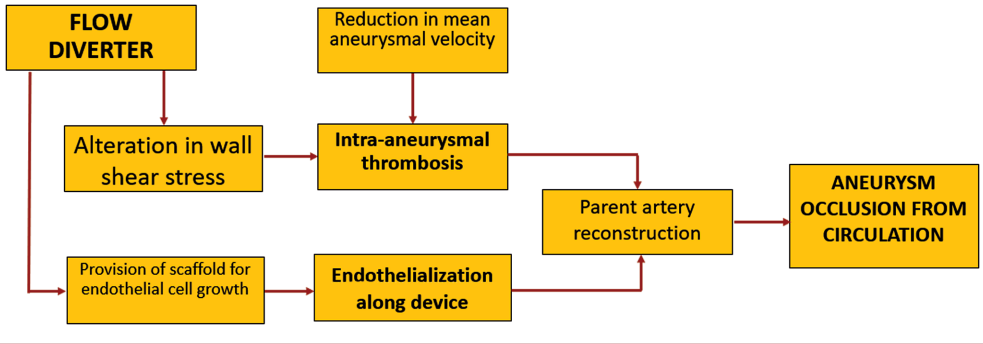

FIGURE 1. *Global mechanism of action of flow diverters, illustrating role of intra-aneurysmal thrombosis and endothelialization.*

of flow diverters is a direct function of device porosity, defined as the fraction of metal-free area per total stent surface area coverage,[6] and pore density, the number of pores per unit area along the device-neck interface. Device porosity and pore density both directly determine resistance to flow through pores into the aneurysmal sac. Devices with lower porosity result in higher resistances to flow into the aneurysmal sac, thereby theoretically stagnating flow into the aneurysm and resulting in intra-aneurysmal stasis.[7] As per Virchow's triad, thrombosis within the aneurysmal sac subsequently ensues. Lower porosity (leading to concomitantly greater flow reduction within the aneurysmal sac) has thus been considered a key driver of aneurysm thrombosis.[8] Numerical simulations of patient-specific aneurysm morphology have revealed that the device struts slow blood flow velocity within the aneurysm sac during systole, resulting in intra-aneurysmal stasis. Importantly, velocity magnitude profiles within the parent artery remain similar to magnitudes without flow diverter in situ.[9,10] Independent of device porosity, this effect is more pronounced in smaller arteries vs larger arteries, likely owing to vessel resistance.[7] The effect of pore density is less established; in silico computational studies suggest high pore density to result in decreased intra-aneurysmal flow as the devices have more changes of disrupting inflow jets, but these results have not been recapitulated in preclinical animal models.[11,12] Metal coverage and porosity may evolve with time after implantation because of parent vessel remodeling until the flow diverter (FD) reaches its nominal dimensions.[13] Novel thin-film nitinol flow diverters have been tested preclinically with promising results; these devices are constructed from patterned sheets, as opposed to braids thus enabling substantially higher pore density than more conventional braided wire flow diverters.[14] Although a linear correlation has not been demonstrated, achieving low-flow velocity (<0.025 m/s) and the use of a device with porosity around 65% to 70% seems to provide optimal conditions for sac thrombosis.[9] In a recent numerical simulation study by Zhang and colleagues,[9] using patient-specific aneurysm geometries, greatest intra-aneurysmal velocity reduction was achieved at a porosity threshold of 65%. Intriguingly, a threshold of 75% was found to be the upper limit of efficacy for larger aneurysms (Table). Porosity requires a tradeoff in expandability and thus affects potential deployment ability. Prioritization of device manipulation in potentially tortuous distal ICA vessels has thus resulted in lower porosities in order to compensate for potential tradeoffs in pore density and deployment ease. Indeed, it has been suggested that higher post-treatment flow velocities are associated with failed aneurysm occlusion.[15] However, other factors such as aneurysm location, neck geometry, flow velocity, and platelet function may also influence stable thrombus formation. Device porosity must also be balanced with chances of parent branch vessel occlusion, which increases with lower porosity. Additionally, stent flexibility is compromised at lower porosities making endovascular manipulation limited. Flow diverters inducing a shear driven flow as opposed to pressure-driven flow have also shown a more efficacious reduction of blood flow.[8,16] These data reinforce the principle of flow diverters leading to effective disconnection of intra-aneurysmal flow from the parent artery.

By contrast to flow diverters, endovascular coils act as direct obstacles to flow, dependent on coil packing density. Indeed, coils could thus be purported to represent a form of endosaccular flow diverter. The temporal nature of healing following coil embolization of cerebral aneurysms has been well characterized. Within 7 d of coiling, histopathological studies demonstrate

TABLE. Currently Used Flow Diverters and Associated Porosity Values

Device	Porosity	No. of braids
PED	65%-70%	48
Surpass	70%	48-96
P64	51%-60%	64
Silk	45%-60%	48
FRED	Low-porosity inner mesh, higher porosity outer mesh	48

presence of fibrin-rich thrombus within aneurysmal sac, followed by macrophage and fibroblast invasion and coverage of coils with a fibrin layer within 1-mo post-treatment.[17-20] Histopathological analysis of acute to subacute thrombus formation after flow diversion remains scant, and largely limited to preclinical data or case reports from studies at autopsy. Following flow diversion, histological evaluation of aneurysms treated with the Pipeline embolization device (PED) in patients at autopsy has demonstrated presence of intra-aneurysmal thrombus.[21] Presence of unorganized thrombus has also been shown at autopsy as acutely as 7 d postflow diverter treatment, but also at up to 12 mo post-treatment despite angiographic evidence of complete occlusion.[14,22,23] Unlike flow diverters, coils induce minimal to no parent artery reconstruction given their endosaccular location and thus intra-aneurysmal thrombosis remains the prominent mechanism of action for endovascular coils.

Flow Diverter Hemodynamics

Computational fluid dynamics (CFD) analyses have provided valuable, though at times controversial, preliminary insights into the hemodynamic alterations induced by flow diverter implantation.[24-26] CFD analyses of elastase-induced aneurysms in rabbits treated with flow diversion have suggested that a reduction of flow velocity with secondary induction of thrombosis is the foremost mechanism of aneurysm exclusion.[26] At least at the aneurysmal dome, diminished flow velocity may thus serve as the key driver of aneurysm healing. Following flow diverter placement, computational analysis shows that intra-aneurysm flow becomes restricted to the aneurysm neck.[12,27] Dhlokia and colleagues[12] recently conducted the first detailed CFD analysis of intra-aneurysmal hemodynamics based on micro-computed tomography imaging of the devices; in their study, both Pipeline and Flow Re-directing Endoluminal Device (FRED) devices were shown to induce reversal in the direction of intra-aneurysmal flow. Changes in inflow zone from distal to proximal were also observable. Contrastingly, with higher porosity intracranial stents (LVIS, Enterprise, and Neuroform) a large counterclockwise flow vortex was observed inside the aneurysm dome, most pronounced in peak systole. This vortex was not present in spatial CFD maps of the low-porosity flow diverters. Moreover, both the PED and FRED resulted in the highest reductions in intra-aneurysmal kinetic energy profiles. However, the use of an in Vivo pressure sensing wire system in human patients has notably shown no difference in intra-aneurysmal pressure with flow diverter implantation.[28] Taken together, these results suggest that flow diverter-induced changes in the aneurysm inflow vector may contribute to thrombosis, though maintaining minimal pressure gradients across device-neck interface.

Diminished wall shear stress has been proposed as a critical component in the process of aneurysmal thrombosis and is independently postulated to contribute to rupture risk.[29,30] Intracranial aneurysms treated with flow diversion with shorter times to occlusion have also been reported to exhibit different hemodynamic conditions than those with longer occlusion times, with significantly lower mean aneurysmal velocity, inflow rate, and shear rate observed in this former group.[31] Flow diverter-mediated reductions in aneurysmal inflow and wall shear stress thus provide an environment for promoting parent vessel remodeling.[32]

Of note, though providing a platform from device design and optimization, data from CFD analyses must be interpreted judiciously. These analyses incorporate several key simplifying assumptions, particularly application of boundary conditions based on ideal fluid flow and assumption of vessel wall rigidity, that have been deemed remote from actual in Vivo conditions.[24] Moreover, varying methods of defining the wall shear stress term make comparison across aneurysmal phenotypes difficult.

CELLULAR AND MOLECULAR MECHANISMS OF FLOW DIVERSION

Previous work from our group evaluating gene expression following flow diverter treatment using RNA sequencing technology has shown substantial differences in gene expression profiles in coiled vs flow diverter-treated aneurysms.[33] Compared with untreated aneurysms, key genes involved in endothelial function including apelin and CXCL-8 were upregulated in flow diverter-treated aneurysms. Additionally, a large number of upregulated gene expression in flow diverter are oriented toward mitogenic activity and cell cycle progression (cyclin B2 cyclin-dependent kinase 1 [cyclin B1] among others). Moreover, upregulation of ICAM2, which has a key role in angiogenesis and leukocyte transmigration,[34] was observed only in flow diverted aneurysms. This tendency in gene expression supports the hypothesis that flow diverter technology intrinsically facilitates endothelization. Further work from our group has shown increased expression of tumor necrosis factor alpha and monocyte chemoattractant protein 1 in flow diverter-treated aneurysms compared with coil embolized aneurysms.[35] These observations suggest that inflammatory infiltrates, particularly macrophages, may underpin healing following flow diversion. Production of matrix metalloproteinase and transforming growth factor beta by invading fibroblasts and myofibroblasts during aneurysm healing results in an inflammatory niche that leads to activation of local vascular endothelium.[4] A fundamental difference in observed gene profile is presence of local inflammatory cells in the flow diverter group, likely chemoattracted from the circulation. Direct contact with the parent vessel intima and induction of remodeling by flow diverters may contribute to this difference in part. At the flow diverter-artery interface, local inflammation is initially stimulated. Over the process of aneurysm healing, the activated vascular endothelium further propagates an inflammatory milieu through chemoattractant secretion. The interaction of the flow diverter at the aneurysm neck specifically promotes paracrine interaction of vascular endothelium and smooth muscle cells that may lead to the observed fibroblastic response in the parent

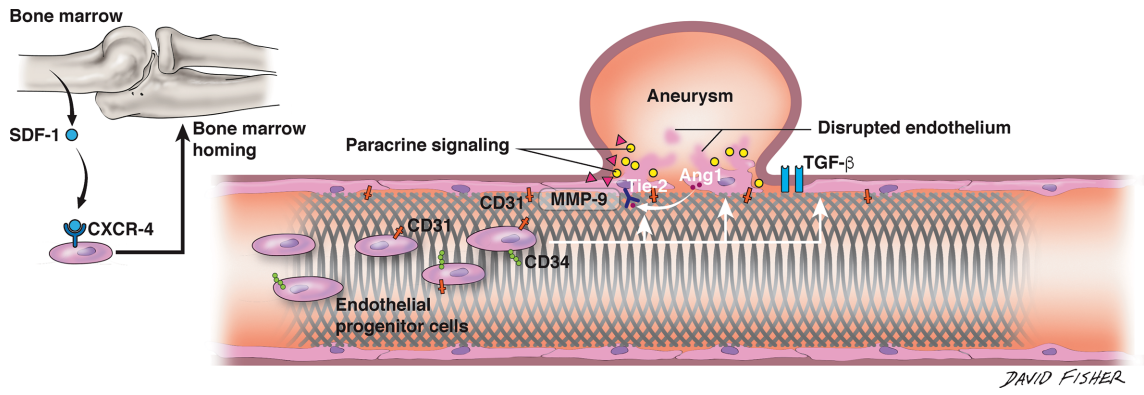

FIGURE 2. *Cellular and molecular mechanisms underpinning device endothelialization follow flow diversion treatment of cerebral aneurysms. Depicted are the contributing roles of local endothelial cells, activated by paracrine factors at site of flow diverter deployment, and circulating endothelial progenitor cells origination from the bone marrow. Artist: David Fisher, Department of Neurosurgery, University of Alabama-Birmingham. Published with permission.*

vessel and in the aneurysm dome. Within the aneurysm dome, the endothelium is minimally present, and thus, no activation takes place with endosaccular coil placement to allow migration of circulating monocytes and local macrophages. In particular, angiopoietin-1 (Ang1), a growth factor secreted by smooth muscle cells, acts on the Tie2 receptor expressed at the surface of endothelial cells, and the subsequent Ang1-Tie2 complex regulates matrix adhesion as well as cell (Figure 2). Leukocyte adhesion here may thus represent initial steps in the cascade of healing. Interestingly, similar interactions have been described in the setting of coronary stent restenosis because of neointimal growth, albeit in a vascular bed with substantially different hemodynamics.[36,37]

ENDOTHELIZATION

Although initial stable thrombus formation is the initial step in the healing process, formation of a nonpermeable symmetric endothelial tissue is an integral step in aneurysm occlusion. The endothelization process starts from the first day of flow diverter deployment through adhesion of undifferentiated cells at random sites of the stent.[38,39] Within 1 d of flow diverter placement, scattered clusters of inflammatory cells are formed across the aneurysm neck. Endothelialization begins from the site of device contact within the parent artery and eventually reaches the aneurysm neck. Progressive adhesion of differentiated smooth muscle cells takes place, resulting in an initial neointima layer, which is visible histologically by day 7. At around week 8, the neointimal layer appears to have CD31+ endothelial cells over smooth muscle antigen-positive smooth muscle cells.[38] This appears to suggest that endothelialization following PED placement occurs in 2 phases: rapidly, at the parent artery and slowly at the aneurysmal neck, with the latter requiring an underlying scaffold of smooth muscle cells. The endothelium that covers the FD is contiguous, and the time to formation appears to be correlated with the length of vessel.[40] A recent study using optical coherence tomography intravascular imaging compared the PE Flex vs PED Shield and Solitaire device in terms of endothelial formation and reported a complete intima formation on day 21 for all 3 devices.[39] Whether endothelial cells originate from adjacent vessel endothelium or from circulating bone marrow progenitors remains unclear.[4] Modulation of the bone marrow homing axis influences endothelial cell coverage, whereas infusion of autologous fluorescently labeled bone marrow progenitor cells demonstrates a degree of localization to the flow diverter struts.[41] Other studies, however, support mainly adjacent smooth cell components in newly endothelial tissue which is confirmed by the absence of CD34-positive cells, a surface marker of endothelial progenitor cells.[38,42]

Hemodynamics also play an important role in neointima formation. The process of endothelization is mainly dependent of optimal blood flow reduction,[43] and degree of wall integrity, direct contact of struts with the adjacent parent artery, or aforementioned decreased wall shear stress.[44]

Shear stress leads to cascade of intracellular events in vascular endothelium, including the adoption of a proinflammatory phenotype. Increasing shear stress is known to inhibit vascular endothelial cell proliferation in Vitro, via inducing cell cycle arrest, with further in Vivo work validating significant proliferation of endothelial cells following shear stress reduction.[45,46] Shear stress has been shown to be inversely related to neointimal coverage in coronary stents.[47] After flow diverter implantation, endothelial proliferation is promoted when wall shear stress is low in both in the reconstructed parent artery and in the free segments of the flow diverter at the aneurysm neck.[48] Increased residual blood flow across the aneurysm neck has also been shown to delay neointimal formation.[43] Endothelialization hinges on contiguous

contact of the flow diverter against vessel wall and thus may theoretically optimized by changes in device strut thickness. Few studies have directly assessed the role of flow diverter engineering, such as difference in endothelialization efficacy with larger total braid numbers or braid angles. Braid angle may contribute to shear stress reduction, but the effect of braid number is less clear.[27] Strut thickness is a determinant of wall apposition, which is known to be an important driver of effective endothelialization.[38] Increasing strut thickness reduces the probability of malapposition, improving contact with the parent artery wall and therefore optimizing cellular reconstruction.

The endothelization process is also influenced by the thrombogenic potential of these devices, which is ultimately a common clinical concern. In a recent study using cellular and acellular blood, the PED Shield demonstrated decreased thrombin generation and platelet activation with subsequent surface thrombus formation when compared with its counterpart Pipeline Flex Embolization (Medtronic) under single antiplatelet therapy.[49] In addition, patients under single antiplatelet therapy and Pipeline Shield Stent (Medtronic) showed higher endothelization than patients under dual anti-platelet therapy and Pipeline Flex.[49] Other approaches that are currently being assessed for circumventing the need for dual antiplatelet therapy include trial of novel single monotherapy regimens. Particularly in the acute setting of subarachnoid hemorrhage, single-platelet regimens may pave the way for increasing flow diversion use for ruptured aneurysms. Surface modification, however, likely represents the most promising of techniques for avoiding need for dual antiplatelet therapy.

Peak systolic flow velocity values are known to be higher (30-50%) in anterior rather than in posterior circulation; however, the specific effect on shear stress is yet to be clarified, in light of increasing use of flow diversion in the posterior circulation.[50,51] It seems intuitive that aneurysm location and not only the decreased flow induced by the flow diverter play a major role in wall shear stress and as consequence in endothelization. Indeed, increased wall shear stress was more frequently observed in unsuccessful patients treated with flow diverters.[15] Variation in the degree of endothelization may thus potentially be expected among aneurysms in different locations.

WALL APPOSITION

Wall apposition of flow diverter plays a decisive role in robust endothelization process. In the rabbit model, aneurysms with histologically graded good wall apposition following PED treatment had higher angiographic occlusion rates than those with poor wall apposition treatment.[52] In a rat model, number of poorly opposed struts was significantly lower in aneurysms that went onto occlusion; notably, in this study, no difference was found in aneurysm occlusion between low- and high-pore density flow diverters.[53] It is believed that direct stent contact with the wall is necessary to provide a scaffold for contiguous endothelial cell growth from the parent vessel, and thus, strut thickness may represent an important engineering variable for optimization.

DEVICE COMPLICATIONS

Delayed Intraparenchymal Hemorrhage

Meta-analysis has estimated the overall rate of periprocedural thromboembolic events after flow diversion to be 7.5% with a postprocedural hemorrhage rate of 4.7%.[54] Distal intracerebral hemorrhage is a specific complication of flow diverters that is not encountered with standard coiling. Its incidence is not precisely known, with the largest study reporting a rate of 2.5%.[55] In almost 20% of cases, this hemorrhage occurs distal to the aneurysm, often contralateral to the treated side.[56] The 2 leading explanations for intraparenchymal hemorrhage (IPH) include (1) deranged downstream hemodynamics resulting from FD implantation and (2) hemorrhagic transformation of small ischemic infarcts associated with the procedure.[55,56] The hemodynamic hypothesis involves a reduction in the "windkessel effect," which refers to a decrease in blood vessel elasticity that leads to an increase in distal pulse pressure, subsequently leading to IPH.[57] A recent study from our group demonstrated that elevated pulse wave velocity and vascular contractility in the distal aortic regions follow FD implantation in the rabbit model.[58] However, this study failed to show any cellular and structural changes in the distal segments. The ischemic hypothesis suggests that small thromboembolic infarcts, especially in the setting of dual antiplatelet therapy, subsequently undergo hemorrhagic transformation.

THROMBOEMBOLISM

As with any intraluminal device, the risk of thromboembolism with FDs remains high relative to intrasaccular devices.[59] Rates upward of 5% of this complication have been noted with FDs, even in patients treated with adequate dual antiplatelet therapy.[60] Elevated risk of thromboembolism likely results from endothelial injury as well as the thrombogenic nature of the devices themselves. It also remains possible that malapposition to the vessel wall results in localized areas of stagnation and disordered flow, and that endothelialization is impeded, all of which may predispose patients to thromboembolic stroke. Advances in this line of research may diminish risk not only of thromboembolic stroke but also of delayed hemorrhage.

SPONTANEOUS ANEURYSM RUPTURE

There appears to be a concerning risk for spontaneous rupture of previously unruptured aneurysms following FD treatment.[21,61,62] The mechanism for this event is unknown, and is especially puzzling because, in some instances, aneurysms that ruptured spontaneously appeared to have been nearly

completely occluded at the time of rupture.[21] For giant or fusiform aneurysms, the risk of delayed hemorrhages may even increase because of FD treatment.[22] Importantly, until thrombus formation in the aneurysm and neck neointimal formation along the stent is complete, there is still flow in and out of the aneurysm, and thus, thrombus embolization from the aneurysm sac remains a possibility. In abdominal aortic aneurysms, proteases originating from intra-aneurysmal thrombus have been implicated as potential causes of wall degradation and subsequent rupture.[63,64]

FUTURE DIRECTIONS

Current translational research aims to improve design of current stents so as to expand the scope of flow diverters. The introduction of new-generation-coated devices is aimed to eliminate the need for dual antiplatelet therapy, thereby opening avenues flow diverter usage in the context of ruptured aneurysms. Newer devices such as the Woven EndoBridge embolization device (Sequent Medical) are also beginning to be introduced clinically for use in bifurcation aneurysms. Advances in endovascular microcatheters and delivery systems allow for device deployment in smaller parent vessels, including use distal to the circle of Willis. Further mechanistic insight into key molecular and cellular pathways involved in aneurysm healing after flow diversion may lead to identification of a potential biomarker of successful aneurysm healing. An improved understanding of involved molecules identifies potential targets that may be used to optimize device effectiveness.

CONCLUSION

Flow diverting stents result in aneurysm occlusion via stagnation of intraneurysmal thrombus formation, and stimulation of contiguous endothelial cell growth along device struts and aneurysm neck. Both of these phenomena act in concert to allow exclusion of the aneurysm from the circulation over time. As indicated by computational analyses, the vascular environment at the aneurysm neck is substantially different from the nascent arterial wall. Stable thrombus formation seems to be promoted by very low-flow velocities, which are secondary influenced by an optimal device porosity of 65% to 70%. However, anatomic factors have ultimately a high influence in obtaining optimal blood flow velocity. Flow diverters induce the upregulation of multiple genes, many of which are involved in mitogen cell activity and endothelization. Optimal wall apposition is crucial in the endothelization process, as it facilitates migration of endothelial cell precursors from parent artery. Lastly, although a nonlinear correlation exists, ensuring a decreased wall shear stress following stent deployment seems to be contributing to successful aneurysm occlusion.

Disclosures

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