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Cerebral Arteriovenous Malformation Venous Stenosis is Associated with Hemodynamic Changes at the Draining Vein-Venous Sinus Junction

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Abstract

Cerebral arteriovenous malformations (AVMs) are an uncommon vascular anomaly that carry the risk of rupture and hemorrhage. Several factors have been implicated in the propensity of an AVM to bleed. One such factor is stenosis of AVM draining veins, as impairment of the AVM venous drainage system is associated with increased risk of intracranial hemorrhage. Currently, our understanding of the pathogenesis of AVM venous outflow stenosis is limited, as there is insufficient data on the blood flow patterns and local hemodynamic parameters of these draining veins.

The angioarchitecture of AVMs features a nidus lacking a high resistance capillary network. Accordingly, our previous studies on AVM arterial feeders have demonstrated an abnormally high flow volume rate along with low pulsatility and resistance indices on quantitative magnetic resonance angiography. As such, AVM vessels endure high, non-physiologic levels of flow that may partially contribute to ectasia or stenosis depending on whether wall shear stress (WSS) is high or low, respectively.

We hypothesize that AVM venous outflow stenosis occurs most commonly near the junction of the draining vein and the dural venous sinus. Increased flow volume rate through the AVM circuit coupled with the variation in compliance and rigidity between the walls of the draining vein and the dural venous sinus likely create turbulence of blood flow. The resulting flow separation, low WSS, and departure from axially aligned, unidirectional flow may create atherogenic conditions that can be implicated in venous intimal hyperplasia and outflow stenosis. We have previously found there to be a significant association between intimal hyperplasia risk factors and venous

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outflow stenosis. Additionally, we have found a significant association between age and likelihood as well as degree of stenosis, suggesting a progressive disease process.

Similar conditions have been demonstrated in the pathophysiology of stenosis of the carotid artery and dialysis arteriovenous fistulas. In both of these conditions, the use of computational fluid dynamics (CFD) has been employed to characterize the local hemodynamic features that contribute to the pathogenesis of intimal hyperplasia and stenosis. We recommend the utilization of CFD to characterize the anatomic and hemodynamic features of AVM venous outflow stenosis. An improved understanding of the possible causative features of venous outflow stenosis may impact how clinicians choose to manage the treatment of patients with AVMs.

INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are an uncommon type of central nervous system vascular anomaly that have the potential to rupture and cause intracranial hemorrhage (ICH). Because they are uncommon, only occurring in 0.1 percent of the population, AVMs had not been extensively researched until recent years.¹ Much of the widely accepted anecdotal understanding of these vascular malformations has now begun to be clarified by a wide array of studies that are generally multidisciplinary in their approaches—often relying on more recent technological advances to either characterize or to treat them. While the pathogenesis of AVMs is not well understood, it is thought that they are prenatal in origin and generally become clinically relevant in the context of ICH, seizure, progressive neurological deficit, or chronic headache.² It has been consistently shown over the past 50 years that approximately 50% of cerebral AVMs present with ICH.¹ Classically, literature has placed the annual rupture rate of cerebral AVMs at 4%, while the more recent ARUBA trial reported a 2% annual rupture rate.^{3,4} As such, identification of AVM characteristics that increase the propensity of an AVM to rupture is imperative.

Several factors have been implicated in the propensity of an AVM to cause ICH. These include age, associated aneurysm, venous outflow stenosis, AVM size, AVM location, and deep venous drainage.^{1,5,6} The latter 3 of these parameters are used to calculate surgical risk of removing an AVM using the Spetzler-Martin Grading scale.^{3,5,6,7} *Impairment of venous drainage of an AVM has been shown to be significantly associated with risk of hemorrhage.*^{8,9} *Moreover, venous stenosis has been implicated by multiple studies to be associated with increased likelihood of AVM rupture.*^{10,11,12,13,14} Conversely, arterial feeder stenosis has been demonstrated to have a protective effect with a decreased likelihood of intracranial hemorrhage.¹³ This suggests that increased resistance in the venous drainage system influences the likelihood of AVM pressurization and rupture.⁹ The focus of our investigation will be on the association of the hemodynamic parameters of venous outflow stenosis with the risk of AVM rupture and ICH.

The angioarchitecture of an AVM involves an abnormal connection between one or multiple feeding arteries and draining veins.¹⁵ This connection is constituted by a tangle of blood vessels, known as the nidus, that lack an intervening high resistance capillary network and are a site of high-flow shunting of blood from the feeding arteries to the draining veins.^{15,16} Our previous studies on AVM arterial feeders demonstrated an abnormally high flow volume

rate along with low pulsatility and resistance indices based on quantitative magnetic resonance angiography (qMRA).^{17,18} As such, AVM arterial feeders endure high, non-physiologic levels of flow that subsequently increase wall shear stress (WSS).¹⁷ Following embolization of arterial feeders, AVM flow rates and vessel luminal diameter as measured by qMRA were found to be decreased, suggesting a dynamic process, a remodeling related to lower WSS.^{7,18,19,20} It has been demonstrated that there is a dynamic compensatory dilatory response in arteries exposed to chronically high levels of WSS in an attempt to normalize the WSS, and this is likely what occurs post-embolization.^{7,19,21,22,23} As the AVM nidus lacks a high resistance capillary bed, it is nearly certain that the same phenomenon would occur within the venous drainage system. The veins would ultimately become *ectatic* as they are exposed to an abnormally high flow volume rate and increased WSS. High levels of WSS have been shown to have an inverse relationship with intimal hyperplasia.²⁴

HYPOTHESIS

Contrary to the presumed mechanism of venous ectasia secondary to high WSS, we are proposing a different hemodynamic mechanism underlying venous *stenosis*, that involves a decrease in WSS at a more distal part of the AVM venous drainage system. Until now, no study has characterized the hemodynamic parameters that contribute to the pathogenesis of venous outflow stenosis. *We hypothesize that AVM venous outflow stenosis in the setting of higher flows most commonly occurs near the junction of the draining vein and the dural venous sinus.* There are several anatomic and hemodynamic features at these junctions that deviate from normal parameters of physiologic flow. Coupled with increased volumetric flow rate through the circuit, it is likely that the proximity of the more distensible draining vein to the rigid and less compliant dural venous sinus creates turbulence of blood flow. The resulting flow separation, low wall shear stress (WSS), and departure from axially aligned, laminar flow may create conditions that can be implicated in venous intimal hyperplasia and outflow stenosis. The WSS is exceptionally high in the draining veins of the AVMs because of higher relative higher flows in those veins. Yet the pathophysiology of the venous stenosis would be on the opposite spectrum of the disease where a lower WSS would be related to the venous stenosis. Similar conditions have been implicated in the pathogenesis of intimal hyperplasia and stenosis of the carotid artery and dialysis arteriovenous fistulas.^{25,26,27}

In a previous study, we demonstrated a statistically significant relationship between intranidal maximum vein wall thickness and total AVM flow, AVM flow through each draining vein, and mean intranidal vessel diameter.^{28,29} *This study was the first to link high AVM flow to venous intimal hyperplasia and venous outflow stenosis, suggesting that there is a relationship between the abnormal hemodynamic features found in AVMs and the development of stenosis.*^{28,29,30} In another recently published study, we demonstrated a statistically significant association between age and the prevalence of AVM venous outflow stenosis.³¹ Venous stenosis was present in a significantly higher proportion of patients 50 years versus patients <50 years of age ($P = 0.03$). Additionally, the mean percentage stenosis was significantly higher in patients 50 years (32%) versus patients <50 years of age (22%, $P = 0.001$). AVMs are considered to be congenital in nature.² *That prevalence and degree of outflow stenosis of cerebral AVMs is associated with older age suggests that the stenosis is a*

*progressive disease process.*³¹ In a 26 year (1990-2016) retrospective chart review, we also demonstrated a statistically significant association between intimal hyperplasia risk factors and AVM venous outflow stenosis.³² Intimal hyperplasia risk factors included age >50 years, sex, race, hypertension, type 2 diabetes mellitus, hyperlipidemia, coronary artery disease, chronic kidney disease stage III, and cigarette smoking. Univariate analysis demonstrated a statistically significant association between several of these risk factors and venous stenosis.³² Multivariate analysis demonstrated that hyperlipidemia is predictive of AVM venous outflow stenosis.³² *That hyperlipidemia is predictive of outflow venous stenosis—which may be a progressive disease process—suggests that intimal hyperplasia may be a contributing factor in its pathogenesis.* Despite the fact that we propose that the majority of venous stenosis in AVM draining veins would be in close proximity to the sinus, there would be a subset of patients where draining veins stenosis are not in close proximity to the sinus. This would be explained by relative changes in the veins diameter and tortuosity, resulting in areas where WSS would be relatively lower and theoretically leading venous stenosis. A similar comparison would be to that aneurysm formation on the arterial tree, where a relative changes in the WSS at vessel curvatures does provide the explanation to aneurysm formation.

In the setting of carotid artery atherosclerosis, intimal thickening and atherosclerosis are most likely to occur in the setting of decreased WSS, increased flow separation, and overall departure from axially-aligned laminar flow.²⁵ In a previous study utilizing qMRA, we found that increased WSS and flow led to aneurysm formation in collateral vessels in the setting of carotid artery occlusion.³³ Assessment of blood flow patterns and local hemodynamic parameters associated with carotid artery atherosclerosis has been performed noninvasively through the utilization of cine phase-contrast (PC) magnetic resonance imaging (MRI).^{26,34,35} In studying the carotid artery, PC-MRI has proven to be a valuable tool in velocity measurement and the quantification of different parameters of shear stress; however, its inability to properly outline the vessel wall boundaries coupled with its low spatial resolution and low velocity magnitude limit its accuracy.^{26,35}

In recent years, the advent of 3D reconstruction of medical imaging has given way to the rise of the use of model-based computational fluid dynamics (CFD) calculation as a modality to investigate blood flow patterns.^{26,35,36,37,38} One such hemodynamic parameter that CFD has shown superior fidelity in measuring is the distribution of time averaged wall shear stress (TAWSS) throughout flow.^{26,34,35,39} CFD more accurately demonstrates that as flow approaches the carotid bifurcation, flow separation creates a recirculation zone in the carotid bulb and ultimately lowers TAWSS, creating optimal conditions for atherogenesis.^{25,26,34}

Just as CFD has been used to characterize the hemodynamic parameters of carotid artery stenosis, it has also been exploited to inspect blood flow patterns that contribute to the eventual failure of hemodialysis vascular access fistulae.^{27,39} The employment of CFD in analyzing these shunts demonstrated non-homeostatic measures of WSS and high-fidelity characterization of deformation modes of the venous system enduring these non-physiologic hemodynamic parameters.^{27,39} The hemodynamic and anatomic features of these shunts are similar to those of AVMs in that there is a change in compliance and rigidity between the artery and the venous conduit.^{24,27} The variation in vessel wall parameters coupled with the

high flow through the artificial arterial-venous connection that lacks a capillary bed increases turbulence, introduces flow separation, and decreases WSS—creating optimal conditions for intimal hyperplasia to occur.^{24,27} In dialysis arteriovenous fistulae, stenosis was most commonly found to occur near the arteriovenous junction, where there is significant different in flow and WSS between the two conduits, further exemplifying it as a model for our hypothesis of stenosis most commonly occurring near the venous-sinus junction.²⁴ In order to investigate our hypothesis and characterize the anatomic and hemodynamic features of AVM venous outflow stenosis, we recommend the utilization of CFD in a future study. Any proposed validation study with CFD models has to incorporate a patient specific reconstruction of the real anatomical details from high resolution angiographic data (3DRA, or MRA), along with blood flow measurement within the draining veins and sinuses. A patient specific (anatomical and physiological) CFD model would be critical to prove our hypothesis.

CONCLUSION

Venous outflow stenosis of AVM draining veins poses serious implications in the potential of AVM rupture and intracranial hemorrhage. We currently have a limited understanding of the hemodynamic and anatomic features of venous outflow stenosis, as no study has examined these features. The finding that stenosis of AVM draining veins occurs most commonly near the venous-dural sinus junction as a consequence of non-physiologic parameters of flow may impact how clinicians choose to manage the treatment of patients with cerebral AVMs.

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