Cerebral arteriovenous malformations. Part 2: physiology

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Object. The scientific understanding of the nature of arteriovenous malformations (AVMs) in the brain is evolving. It is clear from current work that AVMs can undergo a variety of phenomena, including growth, remodeling, and/or regression—and the responsible processes are both molecular and physiological. A review of these complex processes is critical to directing future therapeutic approaches. The authors performed a comprehensive review of the literature to evaluate current information regarding the genetics, pathophysiology, and behavior of AVMs.

Methods. A comprehensive literature review was conducted using PubMed to reveal the angioarchitecture and cerebral hemodynamics of AVMs as they relate to lesion development.

Results. Feeding artery pressures, brain AVM compartmentalization, venous drainage, flow phenomena, and vascular steal are discussed.

Conclusions. The dynamic nature of brain AVMs is at least in part attributable to hemodynamic and flow-related phenomena. These forces acting on an evolving structure are critical to understanding the challenges in endovascular and surgical therapy. As knowledge in this field continues to progress, the natural history and predicted behavior of these AVMs will become more clearly elucidated. (DOI: 10.3171/2009.2.FOCUS09317)

Key Words • arteriovenous malformation • physiology • cerebral hemodynamics

While the molecular mechanisms of AVM formation and remodeling are integral to understanding the lesion’s clinical behavior in vivo, it is equally important to recognize the physical forces at work as blood flow causes mechanical stress. It has been well established in the literature that features such as intranidal aneurysms, high pressure in feeding vessels, and obstruction of venous outflow increase the risk of hemorrhage.6,11,42,66 These factors may also be responsible for changes in AVM morphology. Other theories regarding the factors that increase the risk of hemorrhage, such as occlusive hyperemia, impaired AVM autoregulation, and arteriovenous thoroughfare channels, are still elusive and need further validation.

Feeding Artery Pressures

In a prospective analysis of 31 consecutive patients who underwent diagnostic angiography for cerebral AVMs, Norris et al.49 used contrast dilution curves to look at parameters of AVMs that may correlate with their clinical presentation. In patients who had presented with seizures, the AVMs demonstrated the shortest time to peak contrast density in the feeding vessels, insinuating higher flow in these vessels. These AVMs also tended toward shorter times for the arterial contrast density to decrease. On the other hand, in patients who had presented with hemorrhage, the AVMs exhibited the longest time to both peak and nadir contrast density in the feeding arteries (again, only a trend). This finding indicates an increase in resistance (increased feeding artery pressures compared with systolic pressures) or capacitance to blood flow. Slow movement of contrast through the nidus also indicates high transnidal pressures, which when combined with high feeding artery pressures would increase the predisposition to hemorrhage.

Many authors over time have noted that smaller AVMs are more prone to rupture than larger ones.8,11,12,18,25,26,38,54,66,74 In a clinical in vivo study, Spetzler and colleagues66 simultaneously recorded the intraoperative perfusion pressure of AVM feeding arteries and systolic mean arterial blood pressure in 24 patients with brain AVMs. Smaller malformations (< 3 cm) had a significantly higher rate of hemorrhage. When the lesions did bleed, there was an inverse relationship between the size of the hematoma and that of the AVM. Feeding artery pressures were significantly higher in AVMs that had ruptured (90.4% of mean arterial blood pressure for ruptured lesions compared with 47% of mean arterial blood pressure for unruptured AVMs). As one could infer, the AVM size was inversely related to the feeding artery pressure. Data collected by Norris et al.49 support this relationship; that is, smaller AVMs were found to have higher resistance compared with larger lesions. Likewise, Spetzler and col-

Abbreviations used in this paper: AVM = arteriovenous malformation; CBF = cerebral blood flow; CVM = cerebral venous malformation; CVR = cerebrovascular reactivity; HIF = hypoxia-inducible factor; VEGF = vascular endothelial growth factor.
leagues noted that partial embolization of AVMs resulted in higher feeding artery pressures. This observation has been confirmed by a more recent study in which a direct relationship was found between the degree of embolization and the feeding artery pressure.19

Venous Elements

Disturbances in the venous drainage system are thought to contribute to the pathogenesis of brain AVMs. From a structural standpoint, these malformations resemble primitive venous channels found during embryogenesis. The endothelial cells lining these lesions are very similar to cells of the fetal venous channels, and the configuration of the arterialized draining veins of AVMs follows an embryonal pattern. Although the veins retain their embryonic morphology, the arteries undergo normal developmental maturation.9,45,46

There have been no consistent reports in the literature of “mature” AVMs in the brains of newborns, although there have been numerous documented cases of venous malformations in this age group.5,21,23,25,60,73 Some believe that venous anomalies are the predecessors of brain AVMs; it is hypothesized that during embryogenesis, anomalies of the venous cerebrovascular system manifest in the form of venous occlusion, stenosis, or agenesis.4,20,30,69,70 Throughout childhood and into adulthood, certain factors, such as venous hypertension, then transform these venous anomalies into brain AVMs. As mentioned in Al-Rodhan et al.1 Nornes and Grip, while measuring the intraluminal pressure of the cortical draining veins of AVMs, noticed that pressures normalized after resecting a brain AVM. The role that venous hypertension plays in the growth of AVMs is still indeterminate.

Chronic venous hypertension that increases intraluminal pressure may lead to reduced tissue perfusion with resultant tissue hypoxia,75 which in turn may act as a stimulus for HIF and the angiogenic cascade. Disturbed venous drainage and venous hypertension lead to ischemia, stimulating angiogenesis and promoting the development of arteriovenous fistulas of venous origin. Such a direct fistula between an artery and a vein further increases pressure in the venous branch, resulting in a cycle that maintains and promotes the development of brain AVMs (Fig. 1).57 Additionally, diapedetic hemorrhages resulting from venous overload may further potentiate angiogenic factors such as VEGF.75

Alternatively, venous outflow obstruction may open preexisting arteriovenous connections (arteriovenous thoroughfare channels) that then evolve into pathological vascular malformations.75 Investigations in healthy animals have suggested that cerebral arteriovenous shunting may be a physiological phenomenon,14,51,61,62 and this line of thought has been supported by the existence of “red cerebral veins.” Preliminary work by Drs. Moftakhar and Martin has revisited this concept through PET. Initial data suggest that native arteriovenous connections may temporarily open up under certain stressors, such as cerebral infarction, focal seizure, and traumatic brain injury.43,44,75

Studies of the venous angioarchitecture of brain AVMs have promoted the belief that these malformations are fistulized CVMs or developmental venous anomalies. Mullan45 and colleagues46,47 have postulated that the CVM is a template for an AVM or at the very least that both of these lesions are transition forms of each other, originating from failure in the development of the cortical venous mantle. Some AVMs share the classical triad of CVMs: abnormal surface venous drainage, a “star clas-
ter" system of deep collecting veins, and a deep draining vein. Numerous other studies have documented AVMs with abnormal patterns in venous drainage. Yaşargil has reported that 30% of brain AVMs studied had abnormal venous drainage and that 100% of the large AVMs had abnormal venous drainage. Furthermore, the finding of de novo AVMs in proximity to and draining into developmental venous anomalies or CVMs suggests that these venous anomalies can induce the formation of new malformations or the progression of small, previously present AVMs. Under these circumstances, it is thought that venous hypertension transforms venous anomalies into AVMs.

Studying the venous angioarchitecture and hemodynamics also elucidates the potential reasons behind AVM rupture and hemorrhage. Venous elements such as exclusively deep drainage, venous stenosis, and venous reflux increase the risk of hemorrhage. Multiple studies have supported this association. Venous stenosis in combination with angiogenesis positively correlates with intracranial hemorrhage. Arterial angioarchitectural features (arterial stenosis or arterial angiectasia), however, have not been found to be associated with higher rates of hemorrhage.

Flow Regulation

Studies of flow regulation in and around brain AVMs have been controversial. Several theories, such as the normal perfusion pressure breakthrough theory of...
Spetzler and colleagues,67 have focused on the possibility that autoregulation may be impaired with these vascular malformations. Their theory implies that AVMs cause a loss of autoregulation. Others believe that a loss of autoregulation might actually be the root cause of AVM development and growth.59 In computer simulations in which local control of blood flow is impaired, the vascular model degenerates into an AVM-like structure; however, simulated models cannot mimic all of the 3D properties of in vivo brain AVMs.58

Several forces acting on and within brain AVMs, including vascular injury, abnormal endothelial signaling, and microshunt formation in early development, have all been identified as potential mechanisms of impaired autoregulation (Fig. 2).16,29,56 Furthermore, flow regulation can be impaired when perfusion pressures are above or below the limits of autoregulation. With venous hypertension, for example, the perfusion pressure may fall below the lower limit of autoregulation and thus cause impaired flow regulation and stimulate AVM development and growth.59 Venous hypertension, venous thrombosis, and venous derangement can all stimulate AVM growth, and the loss of autoregulation may be the mediator of the growth and remodeling of AVMs.

It is feasible that AVMs are a compensatory response to abnormal hemodynamics.59 Brain AVMs develop, grow, regress, and reappear to accommodate hemodynamic abnormalities such as high flow, arterial hypotension, venous hypertension, and impaired or nonexistent flow regulation. Normal vessels physiologically degenerate to minimize the number of redundant vessels and decrease the total volume of blood; this resultant vascular adaptation and pruning can lead to vascular instability and shunt formation.59 Individual vessels then compensate, adjusting their radii to bring shear stress back within acceptable limits. The resultant architecture of the arterial tree manifests as a brain AVM.

Although shunting, arterial hypotension, and venous hypertension have become mainstream theories for AVM physiology, the idea of autoregulatory dysfunction in brain AVMs is not universally accepted. Preserved vasomotor responsiveness to CO₂ before and after the treatment of an AVM has been demonstrated.70 In adaptive autoregulatory displacement, vascular territories adjacent to AVMs have a lower limit of the autoregulation curve that appears to be shifted to the left.22 This adaptive shift to the left places the lower pressure limit at a level considerably lower than that postulated for the normal brain (50 or 60 mm Hg). Consequently, hemodynamic disturbances such as chronic hypotension or the steal phenomenon do not necessarily result in vasoparalysis.17 Impaired autoregulation may exist along a spectrum in brain AVMs.

**Hidden Compartments**

The multicompartmental nature of brain AVMs was first described by Yaşargil (Figs. 3 and 4a and b).78 These lesions can be very simple, with a single compact nidus of 1 feeder and ≥ 1 draining vein (monocompartmental). The eliminative of the single feeder leads to a collapse of the entire malformation. In a multicompartamental AVM, several feeders and draining veins can be separated into compartments that are confluent or separated by small nonfunctional or even functional brain parenchyma.

The notion of “hidden compartments” refers to unfilled compartments on angiography, which cause AVMs to appear to grow by serial filling of small or large hidden compartments over time or after therapy (Fig. 5).55 Abrupt filling of a hidden compartment could have deleterious effects such as deep hemorrhage and postoperative edema. Hidden compartments can be unveiled with serial superselective digital subtraction angiography or serial high-resolution MR angiography.15,24 Compartamental visualization can help to guide tailored surgical and endovascular treatments. Using a combination of angiography and color Doppler ultrasonography, Yamada et al.77 have devised a preliminary method of outlining compartments so they can be isolated and dissected individually without causing any damage to surrounding brain tissue.

**Perinidal Vessels**

“Reserve nidus” refers to angiographic evidence of abnormal vascular groups proximal to the nidus that may subsequently become part of the nidus.63 These vessels have been termed the “perinidal dilated capillary network.”64 These perinidal capillaries connect to the nidus, feeding arteries, and draining veins via arterioles and venules; they also connect to normal capillaries, arterioles, and venules. It is possible that this capillary network contributes not only to postoperative bleeding, but also to nidal recurrence after excision.

“Modja-modja” (shaggy hair) vessels is a term used to describe the perinidal hypervascular network.71 These dilated, fragile red vessels result from a hemodynamic overload state. Subsequently, the obliteration of the arteriovenous shunt increases the intravascular pressure of
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the feeding arteries, which leads to a condition in which these fragile, shaggy perinidal vessels rupture, resulting in intraoperative and/or postoperative bleeding. Some clinicians have thus concluded that it may be important to coagulate these abnormal vessels at the base of the resection bed by performing meticulous intraoperative cauterization, to induce postoperative hypotensive therapy to reduce bleeding and edema, and to decrease the chance of recurrence.64 These modja-modja, perinidal dilated capillary network, or reserve niduses are thought to be physically connected to the nidus and even mimic tiny brain AVMs, with the potential to stimulate AVM regrowth (Fig. 4a and b).

Vascular Steal Phenomenon

The idea of vascular steal through high-flow shunting within brain AVMs is not a new concept. From a practical perspective, this phenomenon may be the source of clinical symptoms in patients who present with cerebral AVMs and neurological deficits. There is, however, debate about whether the vascular steal phenomenon indeed exists empirically.

Single-photon emission CT studies have demonstrated that brain AVMs cause a decrease in flow in areas surrounding and distant to the malformation, leading to the propensity for seizures and cognitive impairment.24 Local CBF, as measured on Xe-CT, has also been shown to be impaired in areas surrounding AVMs; after excision, these values increased significantly up to normal levels, resulting in clinical improvement of neurological deficits.52 Biomathematical models of hemodynamic alterations within cerebral AVMs have demonstrated that the degree of vascular steal is inversely proportional to the resistance within the AVM itself. Furthermore, complications resulting from posttreatment hyperemia are most likely to occur in AVMs that are high flow and demonstrate the steal phenomenon.31

In a study focused on vascular reserve in patients with cerebral AVMs (utilizing acetazolamide augmentation and perfusion CT methods), decreased hemodynamic reserve was noted in 27% of parenchymal regions of interest close to the AVM and in 17% of parenchymal regions of interest far from the AVM. Ten of 13 patients studied had parenchyma exhibiting low baseline CBF that failed to increase with the administration of acetazolamide.72 These alterations surrounding the AVM are thought to account for the creation of cortical ischemia.

The idea of cerebrovascular steal both local and distant to the lesion has been clinically supported by neuropsychological studies that demonstrate deficits in verbal and visuospatial processing regardless of whether the AVM is located in the dominant or nondominant hemisphere.32 Marks et al.34 have noted that AVM size, angiomatic change (the development of abnormal cortical feeding vessels to the AVM, viewed as recruitment due to chronic cerebral cortical hypoxia), and peripheral venous drainage correlated with the history of vascular steal phenomenon. Furthermore, in the radiographic literature, it is thought that the dystrophic cerebral calcifications in the watershed areas noted in some patients with brain AVMs may be attributable to vascular steal from these areas.80

It is known that AVM endothelial and adjacent glial cells demonstrate the upregulation of VEGF. Vascular endothelial growth factor is essential to endothelial development, survival, and vascular fenestrations. The fenestrations, in particular, are critical to aqueous diffusion and may play a role in hyperperfusion syndrome. If a brain AVM creates a steal phenomenon, the surrounding tissue has less perfusion. On resection of a high-flow AVM, the surrounding cerebral vascularity will face an elevated flow. Given an increased CBF to normal brain tissue in conjunction with increased VEGF and an associated increase in vascular endothelial fenestrations, edema can result. Therefore, beyond the theoretical discussion involving autoregulation and hyperperfusion syndrome, molecular factors may also play a role.

Note, however, that there is controversy regarding the existence of vascular steal. Transcranial Doppler ultrasonography studies measuring flow velocities around medium and large AVMs have provided no evidence to support the cerebral steal hypothesis.37 No relationship has been found between feeding artery pressures or flow velocities and focal neurological deficits, calling into question the idea of steal and brain tissue hypoxia.56

In a study originating at the University of Bonn,40 capillary O2 saturation measured by spectrophotometry demonstrated that in a majority of brain AVM cases, capillary recruitment at the cortical level allows CBF to be maintained at near-normal levels. Conversely, in other cases capillary reserve was exhausted and chronic hypoperfusion developed (which the authors claimed is equivalent to a steal phenomenon). Noticeably, in most patients, the cortex adjacent to an AVM was not hypoxic. In patients in whom the cortex was hypoxic, however, reperfusion into unprotected capillaries appeared to be the underlying mechanism of the breakthrough phenomenon.39 This breakthrough phenomenon in chronically hypoxic perinidal cortex supports the theory of hypoxia-stimulated HIF release and subsequent VEGF upregulation, resulting in increased capillary fenestrations. This molecular response may partially explain the hyperperfusion syndrome. Additionally, this mechanism of HIF release and VEGF upregulation may also account for neovascularization of AVMs following partial embolization. In this case, VEGF release may contribute to remodeling and proliferation of the underlying vascular network.

Moreover, while CVR can suggest a microvascular steal phenomenon before the resection of brain AVMs, this reactivity is no different from the normal variability of CVR in healthy control cortex. Furthermore, after surgery, the same CVR patterns are noted in both brain AVMs and controls. This finding has led some to conclude that there is no conclusive evidence of a CVR pattern specific for brain AVM vascular steal.65

More recent work utilizing imaging modalities with greater spatial resolution has also demonstrated abnormal blood flow regulation in regions surrounding brain AVMs. Using MR perfusion imaging, Guo et al.13 have shown high transnidal blood flow and perinidal perfusion abnormalities within AVMs that gradually reversed following radiosurgery. Newer techniques, such as continuous arterial spin-labeled (CASL) perfusion MR imaging,
have revealed that the degree of arteriovenous shunting is related to contralateral white matter and thalamic CBF, with the latter possibly exhibiting vascular steal. Clearly, more work needs to be done using these imaging procedures to look at intranidal and perinidal physiology.

It is unclear whether vascular steal exists in vivo, since there is a level of discordance between various modalities used to investigate this phenomenon. Further investigations with modern imaging technologies will likely offer greater insight into this controversy. It does appear clear, however, that at least in a subset of patients brain tissue hypoxia does indeed exist and may have a role in the proliferation and dynamic remodeling of brain AVMs.

Conclusions

In addition to a variety of growth factors and extracellular proteins that may inhibit or stimulate the growth and remodeling of brain AVMs, it is clear that the structural and hemodynamic properties of these lesions have an effect on their natural history. There is interplay between the genetics of vasculogenesis and the physiology of flow through these abnormal vessels that causes growth, remodeling, regression, and hemorrhage. No model of brain AVMs would be complete without taking these physical and biological factors into consideration, and thus they must be considered in future therapeutic endeavors.

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