Brain arteriovenous malformations (BAVMs) are an important cause of intracerebral hemorrhage (ICH) in young adults. Biological predictors of future ICH risk are lacking, and controversy exists over previous studies of natural history risk among predominantly ruptured BAVM cohorts. Recent studies have suggested that the majority of BAVMs are now diagnosed as unruptured lesions, and that the risk according to natural history among these lesions may be less than previously assumed. In the first part of this review, the authors discuss available data on the natural history of BAVMs and highlight the need for future studies that aim to develop surrogate biomarkers of disease progression that accurately predict future risk of ICH in BAVMs.

The etiology of BAVM remains unknown. Recent studies have suggested a role for genetic factors in the pathogenesis of sporadic BAVM, which is further supported by reports of familial occurrence of BAVM and association with known systemic genetic disorders (such as Osler-Weber-Rendu disease, Sturge-Weber disease, and Wyburn-Mason syndrome). Molecular characterization of BAVM tissue demonstrates a highly angiogenic milieu with evidence of increased endothelial cell turnover. Taken together with a number of reports of de novo BAVM formation, radiographic growth after initial BAVM diagnosis, and regrowth after successful treatment of BAVM, these findings challenge the long-held assumption that BAVMs are static lesions of congenital origin. In the second part of this review, the authors discuss available data on the origins of BAVM and offer insights into future investigations into genetics and endothelial progenitor cell involvement in the pathogenesis of BAVM.

Current treatment options for BAVM focus on removal or obliteration of the lesion in an attempt to protect against future ICH risk, including microsurgical resection, endovascular embolization, and stereotactic radiosurgery (SRS). In the third part of this review, the authors discuss available data on SRS in BAVMs and highlight the need for future studies on the radiobiology of BAVMs, especially in regard to biomarker detection for tracking SRS response during the latency period.

Insights from future investigations in BAVM may not only prove important for the development of novel therapies and relevant biomarkers for BAVM, but could also potentially benefit a variety of other disorders involving new vessel formation in the CNS, including stroke, tumors, moyamoya disease, and other cerebrovascular malformations. (DOI: 10.3171/2009.2.FOCUS0926)

**Key Words** • arteriovenous malformation • angiogenesis • radiosurgery • stroke • pathogenesis • genetics

In this review, we discuss current concepts and progress in the literature regarding BAVM epidemiology, clinical management, and pathogenesis. In particular, we highlight areas of ongoing molecular and genetic research with the potential to address key issues within these areas. Insights from these investigations may not only prove important for the development of novel therapies and biomarkers specific to BAVMs, but they could also potentially benefit a wide variety of other disorders involving new vessel formation in the CNS, including stroke, tumors, moyamoya disease, and other cerebrovascular malformations.

**Clinical Characteristics and Natural History: A Need for Biofeedback**

Brain AVMs can present with ICH or they can be...
unruptured, that is, with symptoms resulting from mass effect, inflammation, altered hemodynamics from direct shunting, or recruitment of dilated perinidal capillary networks (for example, progressive neurological deficits, seizures, recurrent headaches, and congestive heart failure in neonates).5,21,27,31,32,51,63,72,80,98

Following the advent of noninvasive imaging techniques, including the widespread availability of CT and MR imaging, there has been a significant increase in the incidental detection of unruptured BAVMs,59 which until now represented only a minority of BAVM diagnoses in previous studies.21,72 In most recent studies, however, unruptured BAVMs now account for the majority of cases.51,80

Some investigators have expressed concerns over the optimal management strategies for the growing number of patients harboring unruptured lesions,60 and the role of prophylactic intervention in unruptured BAVMs is the subject of ARUBA.69 These investigators pointed to the classic study of Ondra et al.72 as an example of insufficient evidence to support treatment of unruptured BAVMs.80 This study reported annual hemorrhage rates of 2–4% in patients with untreated BAVMs (major morbidity 1.7%, mortality 1%, and combined morbidity and mortality 2.7% per year); however, the vast majority (71%) of these BAVMs had ruptured at initial presentation. As such, some investigators argue that these data actually blend estimates of recurrent hemorrhage risk from a majority of ruptured BAVMs with estimates of new ICH risk from a minority of unruptured BAVMs. These investigators hypothesized that, as a result, classic data likely overestimate new ICH risk among unruptured BAVMs and underestimate recurrent stroke risk among ruptured BAVMs. Similar issues have been raised regarding the classic analysis by Crawford et al.21 of 343 patients with BAVMs treated without surgery; they found to have experienced a 42% risk of hemorrhage, a 29% risk of death, and a 27% risk of neurological morbidity by 20 years after diagnosis, as the majority of this cohort (64%) had ruptured BAVMs at initial presentation.

Nevertheless, data are lacking to support the hypothesis that differences exist between classic AVM cohorts and modern-day cohorts in terms of overall annual ICH risk estimates or that increasing numbers of unruptured BAVMs are implicated in changing trends across studies over time. Two large, modern North American cohorts51,89 encompassing 2086 patients with BAVMs and reflecting a preponderance of unruptured lesions (53–55%) have independently estimated the annual ICH risk to be 2.1–2.8% overall (1.3–1.4% for unruptured lesions, 3.7–5.9% for ruptured lesions at initial presentation).21,89 This yields overall 20-year cumulative ICH estimates of 43–56%—that is, identical to or greater than what was observed in the study by Crawford et al.21 despite a 24% decrease in the proportion of hemorrhagic presentations over time. This would seem to argue against the hypothesis that previous studies overestimated the annual risk due to a larger proportion of ruptured lesions.21,72 With a mean age of 36 years among patients with BAVM in these 2 modern studies,51,89 and assuming a life expectancy of 44 years by 2004 Social Security Actuarial Publications as previously described,20 the cumulative lifetime ICH risk from unruptured BAVMs in the patients in these studies is estimated to be 59%, with a 5-year stroke risk of 6.8%.

In one of these cohorts, 33% of patients who suffered new ICH demonstrated poor neurological outcome on 30-day modified Rankin Scale assessment (score > 2), and 18% of these individuals went on to suffer recurrent hemorrhage, leaving 47% with poor neurological outcomes.89 Therefore, these data suggest that unruptured BAVMs carry a significant risk of future ICH and associated morbidity, albeit less dramatic than in ruptured BAVMs.

Given that patients with BAVMs are at lifelong cumulative risk of future ICH and typically receive the diagnosis at a young age, it is the subject of much controversy whether conclusions drawn from a 5-year study period like that of the ARUBA trial will generate accurate data of all risks and benefits comparing surgical prophylaxis against a lifetime of natural history risk from an untreated, unruptured BAVM.20,64 In the estimates above, it is clear that a 5-year cumulative stroke risk of 6.8% would appear at best to show no surgical benefit when weighed in the short term against acute surgical morbidity associated with invasive therapy. However, this would be ignoring the feared lifetime cumulative stroke risk of 59% that forms the true motivation for surgical intervention.

More recently, the AVM database of Helsinki University in Finland has provided compelling new data on the natural history of BAVM.43,56 Reviewing > 60 years of experience, these authors identified 631 consecutive patients with BAVMs.43 The majority of these patients, however, were excluded from the natural history analysis, which was limited to patients with at least 1 month of hemorrhage- and treatment-free follow-up.43 Nevertheless, the resulting group of 238 patients followed up for a mean duration of 13.5 years provides important data on rupture rate of untreated AVMs, even though the majority of these lesions were previously ruptured (58.4%).43 These authors confirmed that the annual hemorrhage risk from an AVM was 2.4%, noting that the rate was highest during the first 5 years after diagnosis (4.7%) compared with > 5 years after diagnosis (1.6%).43 This effect was largely driven by the majority of previously ruptured lesions in this cohort, which had a 6.2% annual hemorrhage risk during the first 5 years compared with 2.3% for unruptured lesions.43 Importantly, these authors have also demonstrated that excess mortality from BAVM compared with the normal population was highest if the BAVM was treated conservatively, intermediate if the BAVM was partially occluded, and lowest if the BAVM was completely occluded.46 Once the BAVM was occluded, there was no ongoing excess death after the 1st year.46 These authors noted that these benefits were seen 5–7 years after treatment46 and, therefore, shorter-term studies such as the ARUBA study may not be adequate to show such a benefit.

For these reasons, it is unclear whether a consensus can emerge from current clinical trials and epidemiological studies alone. This is especially true in light of the complexity of BAVM covariates that can each contribute uniquely to ICH risk in a specific patient, including age, ethnicity, traditional cardiovascular risk factors (smoking,
hypertension, hypercholesterolemia, and diabetes), AVM size, location, venous drainage, and presence of associated aneurysms. The complexity of the disease makes it unlikely that a generalized rule, such as to offer surgery or not, can be applied on the basis of a single clinical variable alone, for example, unruptured BAVM status.

On the other hand, research efforts focusing on biofeedback have the potential to uncover disease markers that overcome the limitations of population-based research in informing treatment decisions at a patient-specific level. Proteomic analyses of sera from patients with BAVM are a promising research tool to identify biological patient-specific markers of vascular remodeling and inflammation that may signal the presence of vascular instability in a patient before the onset of a hemorrhagic event. Two-dimensional polyacrylamide gel electrophoresis sorts proteins by isoelectric focusing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis separates proteins by molecular weight. These techniques can be coupled with mass spectrometers, including matrix-assisted laser desorption ionization time of flight mass spectrometers (MALDI-TOF-MS) and electrospray ionization tandem mass spectrometers (ESI-tandem-MS) to detect differentially expressed proteins in sera. Protein biomarkers of interest identified by these techniques can then be validated using Western blot and immunohistochemical analysis.

In addition to proteomic approaches for serum biomarker detection, gene expression profiling of peripheral blood mononuclear cells represents another promising approach to detect patient-specific biological signals of vascular instability and inflammation by profiling immune signatures and circulating EPC expression patterns.

These proteomic and gene expression profiling techniques may provide patient-specific data on circulating immune and endothelial progenitor cell activity that can provide clinicians early insight into the inflammation and abnormal vascular remodeling characteristic of unstable BAVMs. Such research efforts, focusing on patient-specific biofeedback as a means to stratify patients, may hold the greatest potential to address current controversies over the treatment of patients with BAVMs by offering new methods of risk stratification and treatment selection that overcome conclusions generalized from population-based studies.

**Pathogenesis of BAVM**

The etiology of BAVM remains unknown. Recent studies have suggested a role for genetic factors in the pathogenesis of sporadic BAVM, which is further supported by reports of familial occurrence of BAVM and the association of BAVM with known systemic genetic disorders (such as Osler-Weber-Rendu disease, Sturge-Weber disease, and Wyburn-Mason syndrome). Molecular characterization of BAVM tissue demonstrates a highly angiogenic milieu with evidence of increased endothelial cell turnover and inflammatory cell-mediated vascular remodeling. Taken together with a number of reports of de novo BAVM formation, radiographic growth after initial BAVM diagnosis, and regrowth after successful treatment of BAVM, these findings challenge the long-held assumption that BAVMs are static lesions of congenital origin. As such, future studies are needed that explore new paradigms in BAVM pathogenesis, including the possibility that BAVMs might represent benign slow-growing vascular tumors (not just static congenital lesions), could result from acquired somatic mutations (not just congenital/germ line mutations), and may represent aberrant adult vasculogenesis (not just persistent neonatal angiogenesis).

**Genetic Considerations**

Genetic analyses have the potential to uncover underlying pathogenic mechanisms of BAVM that could enhance our understanding of vascular disease and identify novel targets for therapeutic intervention. Identification of genetic markers such as SNPs could improve the understanding of BAVM physiology and may be useful in the clinical treatment of patients with BAVMs.

It is likely that the growth and clinical behavior of BAVMs are under genetic influences from multiple modifying pathways that control vascular remodeling and vasculogenesis. For example, HHT is an autosomal dominant genetic disorder with a high prevalence of BAVM, representing an interesting example of genetic influences in the development of BAVM. Whereas the incidence of sporadic BAVM in the normal population is estimated to be 0.01%, incidence in HHT2 is 1%, and in HHT1 it is 10%, highlighting the fact that genetic dysfunction in HHT represents a "hyper-risk factor" for development of BAVM. The gene involved in HHT1 codes for endoglin, an accessory protein of transforming growth factor- receptor complexes, whereas HHT2 involves the gene for ALK1, a transmembrane kinase. The highly elevated risk of BAVM development among HHT patients suggests that germline variants of genes relating to these pathways could exert influence over risk for development of sporadic BAVMs. In fact, a common polymorphism in ALK1, thought to result in alternative splicing, has been associated with sporadic BAVM susceptibility, suggesting that genetic variation in genes mutated in heritable BAVM syndromes may play a role in sporadic BAVMs. Furthermore, recent evidence suggests that ALK1 is associated with vascular remodeling and arterialization in response to hemodynamic changes, and loss of function of this gene results in loss of distinct arterial and venous boundaries in mice.

Consistent with increasing evidence implicating inflammation in the pathophysiology of BAVM, recent studies of promoter polymorphisms in inflammatory cytokine genes have included the following: 1) association of promoter polymorphisms in IL-1 with BAVM susceptibility; 2) association of a promoter polymorphism in IL-6 with clinical presentation of ICH in BAVM and correlation of IL-6 mRNA and protein levels in resected AVM tissue with genotype; and 3) association of promoter polymorphisms in tumor necrosis factor- and apolipoprotein E2 with new ICH after diagnosis as well as risk of posttreatment hemorrhage. These results implicate inflammatory cytokines in pathologic angiogenesis and AVM formation as well as risk of ICH in pa-
patients harboring BAVMs and highlight the role of genetic screening in elucidating biomechanisms of disease.

Future studies involving genetic analyses in BAVM will include the use of GWAs and high-density SNP arrays. This approach was recently applied to the study of intracranial aneurysms to identify genetic variants that showed significant association with intracranial aneurysms, with odds ratios of 1.24–1.36. The GWAS approaches are now being applied in BAVM with the hope of uncovering underlying pathogenic mechanisms in this important disease.

Endothelial Progenitor Cells and Aberrant Vasculogenesis

Most BAVM research has focused on abnormal angiogenesis, that is, endothelial cell sprouting from existing vessels, in the underlying pathogenesis of a BAVM. However, adult vasculogenesis is increasingly being understood as the pathway for adult neovascularization. Vasculogenesis differs from angiogenesis in that new blood vessels arise from circulating bone marrow–derived EPCs rather than from sprouting of local endothelial cells. During tissue ischemia, vasculogenesis is initiated via increased expression of the transcription factor HIF-1, which promotes local production of SDF-1 and VEGF-A by hypoxic endothelial cells. It is hypothesized that release of SDF-1 ligand results in reversal of a marrow/periphery gradient that normally inhibits EPCs by cleavage of membrane-bound kit ligand in the bone marrow. Consistent with aberrant vasculogenesis as a factor in the etiology of BAVM, increased expression of HIF-1, VEGF, and VEGF receptors are detected in BAVM tissue. Expression of matrix metalloproteinase–9 is also increased in BAVM tissue and has been shown to be hypoxia responsive and may result in release of EPCs by cleavage of membrane-bound kit ligand in the bone marrow.

Recently, aberrant vasculogenesis and EPC trafficking have been recently implicated in the development of other vascular abnormalities, including infantile hemangioma and moyamoya disease. Children with proliferating infantile hemangioma demonstrate increased levels of mobilized EPCs and surgical specimens of infantile hemangioma are positive for progenitor-specific markers including CD34, AC133, and VEGF.

Consistent with aberrant vasculogenesis as a factor in the etiology of BAVM, increased expression of HIF-1, VEGF, and VEGF receptors are detected in BAVM tissue. Expression of matrix metalloproteinase–9 is also increased in BAVM tissue and has been shown to be hypoxia responsive and may result in release of EPCs by cleavage of membrane-bound kit ligand in the bone marrow.

Stereotactic Radiosurgery and Radiobiology of BAVMs

Current treatment options for BAVM focus on removal or obliteration of the lesion in an attempt to protect against future ICH risk. These options include microsurgical resection, endovascular embolization, and SRS. While microsurgical resection physically removes the nidus and endovascular embolization selectively occludes feeding arteries, neither treatment is mediated by the intrinsic vascular biology of the patient in its therapeutic effect. As such, SRS represents the only biological therapy for BAVM that avoids the need for invasive treatment. Obliteration is the hallmark of successful radiosurgical treatment of BAVM, and is defined by “complete absence of pathological vessels forming the AVM nidus, disappearance or normalization of veins draining the AVM, appearance of normal circulatory kinetics, and absence of visible arteriovenous shunt.”

Despite the widespread use of SRS in the management of BAVMs, the exact mechanism of radiosurgical obliteration remains poorly understood. Available data regarding the biology of radiation-induced vascular obliteration result from observations in BAVM tissue resected after radiosurgical treatment and in irradiated arteries in animal models.

Observations from BAVM tissue have suggested that damaged endothelial cells shrink, detach from neighboring endothelial cells and basement membrane, and permit platelet infiltration with deposition of fibrin and hyaline. As these endothelial cells slough off over time, inhibition of smooth muscle cell proliferation is lost, and smooth muscle cell migration into the subintimal layer results in collagen deposition that thickens the subintima and adventitia, progressively narrowing the lumen and eventually occluding it.

Study of irradiated arteries in animal models has suggested that the radiosensitivity of BAVMs originates in endothelial cells. Failed mitosis of irradiated endothelial cells, damaged by direct interactions with irradiating electrons and indirect free-radical byproducts, results in eventual apoptosis and initiation of radiation-induced arteriopathy. As such, it is believed that the latency period of BAVM obliteration after SRS is dependent on the turnover rate of endothelial cells, which typically ranges on the order of a couple of months to a couple of years, since initiation of the arteriopathy only manifests once endothelial cells attempt mitosis. Currently, the major disadvantage of SRS is the latency period before a BAVM might successfully become obliterated, during which time the patient remains unprotected against risk of new ICH. Widespread variation in patient response to SRS treatment of BAVMs may be the result of varying degrees of endothelial cell turnover, which is known to be abnormal in BAVMs.

Important progress has recently been made in animal models of SRS-induced arteriopathy, and it provides the basis for future studies in transgenic mice as to the role of genetic variation in modulating response to SRS. Future studies in patients with BAVMs will include proteomic analyses and gene expression profiling.
of peripheral blood cell populations, which may reflect indirect interactions from circulating through diseased tissue as well as direct interactions in the pathophysiology of BAVM. These peripheral blood cells could provide important biofeedback as to progression toward tissue damage and direct interactions in the pathophysiology of BAVM.15–17,33,71 These peripheral blood cells could from the Child Health Research Program at Stanford (RG). Further support comes from the Russell and Elizabeth Siegelman (GKS), Bernard and Ronni Lacroute (GKS), and the William Randolph Hearst Foundation (GKS). This work was supported in part by Russell and Elizabeth Siegelman (GKS), Bernard and Ronni Lacroute (GKS), and the William Randolph Hearst Foundation (GKS). This work was supported in part by Russell and Elizabeth Siegelman (GKS), Bernard and Ronni Lacroute (GKS), and the William Randolph Hearst Foundation (GKS). Further support comes from the Child Health Research Program at Stanford (RG).

References

26. Fuks Z, Persaud RS, Aliferi A, McLoughlin M, Ehleiter D,
Pathogenesis and radiobiology of BAVMs

64. Mathiesen T: Arguments against the proposed randomised trial (ARUBA). Neuroangiography 50:469–471, 2008

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