What Should We Do About Asymptomatic AVMs?

A neurosurgeon explains his approach to clinical decision-making for this at-risk patient population.

By Kevin M. Cockroft, MD

Treatment of asymptomatic cerebral arteriovenous malformations (AVM) presents a significant clinical dilemma. The medical literature is replete with various studies suggesting a wide variety of different natural history profiles and treatment risks. While the latter are often carefully assessed by "independent neurological examination," rarely is such a rigorous approach used in the examination of the consequences of natural history events. Yet, in the end the decision to treat must be based on a careful weighing of the natural history risks versus the risks of treatment, tailored as specifically as possible to the individual patient. For cerebral AVM, this risk calculation must be performed without the benefit of a large prospective, randomized controlled trial.

For many years, intracranial AVMs were generally considered to carry a bleed risk of about two percent per year for asymptomatic cases and around four percent per year for symptomatic lesions, with each hemorrhage having an associated neurological morbidity of 20-30 percent and a mortality of 10-30 percent.[1-6] Based on a combination of retrospective and prospective studies—sometimes performed without a clear distinction between symptomatic and asymptomatic AVM, and with some studies performed in the pre-MRI or pre-CT era—these numbers are by no means set in stone. However, although some recent studies have reported a dramatically lower mortality rate with AVM hemorrhage, the yearly hemorrhage rate and rate of morbidity have not been found to be dramatically different.

In a 2006 report using prospective data from the Columbia AVM Databank, Stapf et al., with a median follow-up of only 102 days, reported a 1.3 percent yearly rate of hemorrhage in unruptured AVM (5.9 percent for those that presented with hemorrhage).[7] Of course, it is not really the yearly rupture rate that is important; rather, the essential calculation is the *cumulative* risk of rupture—and thereby the cumulative risk of morbidity or mortality. Cumulative risk may be calculated by the formula $1-(1-R)^L$, where R represents the yearly risk of rupture as a fraction and L equals life expectancy in years. If one takes the aver-

Table 1. Spetzler-Martin Surgical AVM Grading Scale[9]

AVM receives a score of 1-5 based on points assigned from the characteristics listed below.

Characteristic	Score
Size (Maximal dimension)	
<3cm	1
3-6cm	2
>6cm	3
Venous Drainage	
Superficial	0
Deep	1
Eloquence	
Yes	1
No	0

Table 2. Cumulative Risk of Hemorrhage and Significant Neurological Morbidity by Age

Age (years)	Life Expectancy (years)*	Cumulative Hemorrhage Risk (%)**		Cumulative Risk of Significant Neurological Morbidity (%)***	
		1.3%/yr	2.0%/yr	1.3%/yr	2.0%/yr
35	41	41	56	41	56
55	24	27	42	27	42
65	16	19	28	19	28
75	10	12	18	12	18

** From United States Social Security Administration Periodic Life Table http://www.ssa.gov/OACT/STATS/table4c6.html*

*** Based on two commonly used estimates of yearly hemorrhage risk in patients with asymptomatic AVM (see references 1,7).*

**** Based on 33 percent rate of significant neurological morbidity from Choi et al8 and either of two potential yearly hemorrhage rates.*

age age of the AVM population from the Stapf et al. study of 34 years of age and uses a life expectancy of 44 additional years (42.25 years male, 46.75 years female, according to the Period Life Table, Actuarial Publications, available at www.ssa.gov/OACT/STATS/table4c6.html), the cumulative risk of hemorrhage from an asymptomatic AVM is 44 percent. In terms of outcome, again using the Columbia AVM Databank, the same group recently published clinical outcomes after first and recurrent AVM hemorrhages and reported a 30-day rate of moderate to severe disability (Rankin Score 3-5) of 33 percent.[8]

Obviously the "flip-side" to natural history risk is treatment risk, and here interpretation of published data becomes even more complex. There are three major treatment options for cerebral AVM: microsurgical resection, stereotactic radiosurgery and endovascular embolization. Each one may be used alone or in combination, depending on the location and complexity of the malformation. Unfortunately, the variation in lesion complexity as well as treatment combinations does not lend itself to a straightforward assessment of the risks and benefits of treatment for a specific lesion. However, a brief review of the various modalities is useful in understanding some complexities involved.

Microsurgical Resection

Microsurgical resection can provide an immediate cure and elimination of the future risk of hemorrhage. However, surgical resection may be limited by the size of the lesion or by the AVM's location within deep or eloquent brain. In a retrospective series of 100 surgically cured AVMs, Spetzler and Martin reported minor postoperative deficits in 5-19 percent of patients and major deficits in 4-12 percent.[9] The incidence of postoperative deficits depended on the location, size and type of venous drainage of the AVM. Based on their results, the authors proposed an AVM grading system, which remains in widespread use (see Table 1).

Subsequent surgical series have reported rates of significant permanent complications ranging from less than two to approximately 18 percent,[10-15] depending on various AVM factors, the most important of which appears to be size and location. Rates of non-disabling permanent complications have been reported as high as 32 percent.[11] The incidence of death in these series also varies widely, from zero to approximately seven percent, depending on the size of the case series as well as the complexity and the presentation of the AVMs being reported.

Unfortunately for the clinician trying to sort out the particular surgical treatment risks of an asymptomatic AVM, most studies combine both symptomatic and asymptomatic lesions and many later studies include patients that have undergone endovascular embolization. As for cure rates, the majority of the primarily surgical series report high rates of angiographic cure. For small AVMs (<3cm), in a purely surgical series Sisti et al. reported an overall cure rate of 94 percent, with the rate increasing to 100 percent in hemispheric lesions.[13] For larger AVMs in more eloquent locations, reported cure rates are also high, but rates of concomitant neurological morbidity also rise precipitously.

Case Example #1

A 34-year-old man with a complaint of chronic headaches was evaluated with an MRI (Figure 1a) which revealed an abnormal collection of flow voids (arrow) suspicious for AVM in the periventricular region posterior to the left lateral ventricle. A subsequent cerebral arteriogram (Figure 1b) confirmed an AVM with a nidus (vertical arrow) measuring approximately 17mm by 18mm and superficial venous drainage (horizontal arrow). Given the patient's age and expected cumulative risk of hemorrhage and neurological morbidity, treatment was recommended. Based on the size and deep location within the dominant hemisphere, the decision was made to treat the lesion with Gamma Knife stereotactic radiosurgery. The patient received 24 Gy to the 50 percent isodose line. After three years of serial follow-up with MRI, a cerebral arteriogram (Figure 1c) was performed which confirmed complete obliteration of the AVM.

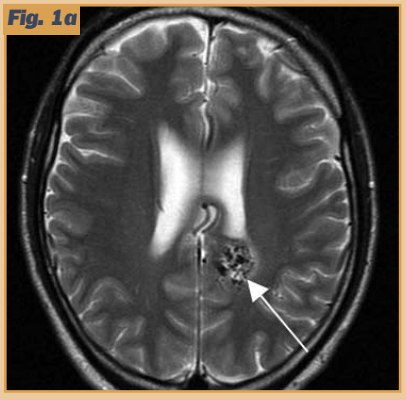


Fig. 1a

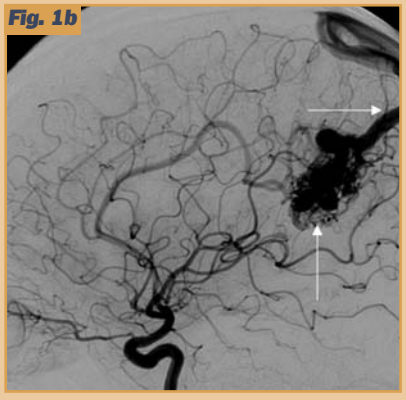


Fig. 1b

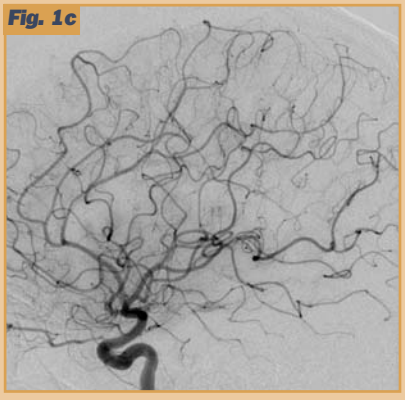


Fig. 1c

Stereotactic Radiosurgery

Stereotactic radiosurgery is often used to treat AVMs in deep locations or those situated within eloquent brain. There are three major delivery systems for focused beam radiosurgery, linear accelerator based (LINAC) programs, gamma radiation units (gamma knife) and heavy particle (helium ion or proton beam) systems. Various clinical series have demonstrated efficacy for all of these techniques, with 80-95 percent cure rates at three years post-treatment for lesions under 3cm (<14ml) receiving 20-25 Gy or GyE.[16-23]

These series also report low complication rates of 2.5 to 4.5 percent for permanent neurological deficits and two to five percent for transient deficits. Most complications arose from radiation toxicity and necrosis in the surrounding brain. Although, radiosurgery is primarily efficacious in smaller lesions, several series have reported the use of staged gamma knife, fractionated radiotherapy and heavy particle radiosurgery for larger lesions (>14ml).[19,24,25] Obliteration rates ranged from 50 percent to just over 80 percent depending on the size of the lesion and the dose used. Aside from toxicity issues, the major disadvantage of radiosurgery is that during the time it takes for AVM obliteration, the risk of hemorrhage persists and may even be increased.[2,4,6,26]

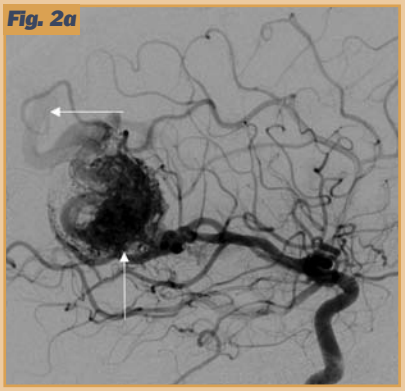
Endovascular Embolization

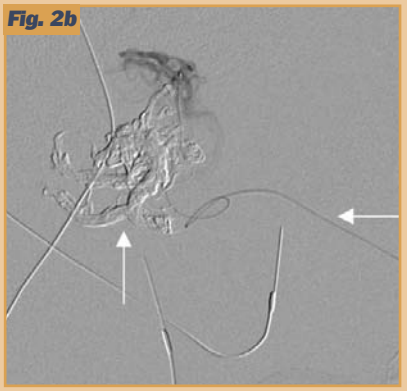
For the most part, endovascular embolization is employed as an adjunctive therapy in the treatment of CNS vascular malformations. While microsurgical removal may provide an immediate cure for accessible lesions, resection of malformations with a large nidus, deep feeding vessels, and/or high-flow shunts may carry a relatively high risk of morbidity. Likewise, endovascular embolization is also commonly used as an adjunct to stereotactic radiosurgery. In patients with AVMs located in eloquent cortex or deep structures, stereotactic radiosurgery may be a preferable alternative to microsurgical resection where the risk of morbidity and mortality may be unacceptably high. Since cure with radiosurgery is highly dependent on treatment volume, in such patients with larger lesions (greater than 3cm in maximal dimension or 14ml in volume), endovascular embolization may be employed to reduce the size of the AVM prior to radiosurgery. In addition, embolization can eliminate certain angiographic features, such as intranidal aneurysms, that may provide for elevated risk while the patient is awaiting AVM obliteration after radiosurgery.

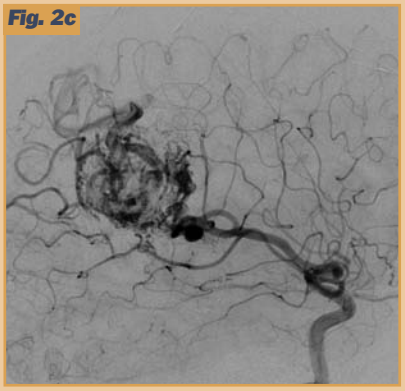
Understanding the risks and efficacy associated with embolization can be difficult due to the various agents/techniques employed as well as the heterogeneity of the lesions and presen-

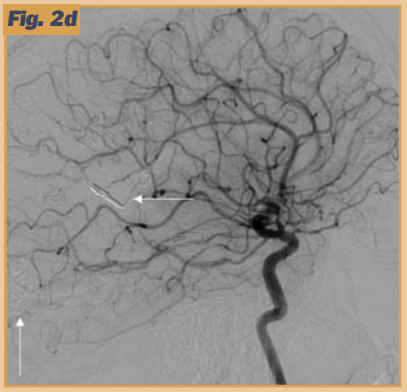
Case Example #2

A 19-year-old female complained of persistent headaches after being involved in a recent motor vehicle accident. Initially an MRI was performed which demonstrated a lesion concerning for a right parietal AVM. The patient was referred for a cerebral arteriogram (Figure 2a), which revealed an AVM (vertical arrow) with arterial supply primarily from hypertrophied middle cerebral artery (MCA) branches and superficial venous drainage (horizontal arrow). In light of the patient's young age the decision was made to treat the AVM. Given the superficial location with prominent deep arterial supply, multimodality treatment in the form of endovascular embolization with Onyx-18 Liquid Embolic System, followed by microsurgical resection was chosen. A roadmap image (Figure 2b) shows glue casts from embolization of the first pedicle (horizontal arrows), with the microcatheter (vertical arrow) in position in a second MCA pedicle and fresh Onyx visible as a black cast in the remaining nidus. A post-embolization angiogram (Figure 2c) demonstrates decreased flow through the AVM nidus. The day immediately following the embolization the patient was taken to the operating room and the remaining AVM was microsurgically resected. A postoperative angiogram (Figure 2c) reveals complete obliteration of the AVM, subtraction shadows from surgical clips (horizontal arrow) and cranial fixation hardware (vertical arrow) are visible.









tations included in most series. Nevertheless, a variety of non-randomized, mostly retrospective case series have shown improved outcomes, shortened operative time and reduced blood loss in patients with preop embolization as compared to patients with microsurgical resection alone.[27-35]

The largest prospective, randomized, controlled trial to assess endovascular embolization of AVMs was actually an industry sponsored equivalency trial designed to support FDA approval for N-butyl-cyanoacrylate (NBCA) in the treatment of intracranial AVMs. Published in 2002, the study compared NBCA with the then "standard of care" polyvinyl alcohol (PVA) particles for the preoperative embolization of cerebral AVMs. The study demonstrated equivalence for both agents, at least in terms of the percentage of nidus reduction and number of pedicles embolized.[36] The most common complication in this series was seizures, occurring in 9.3 and 9.6 percent of the NBCA and PVA groups, respectively. One patient died after embolization in each group (1.9 percent) and new ischemic strokes occurred in 3.7 and 5.8 percent of the NBCA and PVA groups, respectively. Subsequently Ledezma et al.[37] in a series of 168 patients (295 procedures) reported a 1.2 percent mortality rate with clinically significant complications in 6.5 percent of patients. A Hartmann et al.[38] publication of 233 patients undergoing 545 embolization procedures reported a one percent mortality rate and 14 percent incidence of treatment related neurological deficits, with two percent being persistent and disabling. Complications in these studies were related to increasing age, number of embolizations and the complexity of the AVM.

AVM "cure" rates after endovascular embolization are particularly difficult to assess. Since embolization evolved primarily as

a therapeutic adjunct, many published series suffer from considerable referral bias, whereby only "large" AVMs incapable of being treated with radiosurgery or open microsurgery alone are referred for embolization and smaller lesions are treated without endovascular intervention. In general, most studies of intracranial AVMs, not specifically selected for endovascular treatment alone, report cure rates with embolization of 5-11 percent.[30,33,39-41]

Much higher rates of cure with endovascular therapy may be seen when patients were selected specifically for embolization as a primary modality. In such a subset of patients, Valavanis and Yasargil[42] noted a cure rate with embolization alone of 74 percent (or 35 percent of their overall series). More recent series using Onyx (micronized tantalum powder suspended in a mixture of ethylene vinyl alcholol and dimethyl sulfoxide), a new cohesive rather than adhesive liquid embolic agent have also reported higher obliteration rates and lower complication rates, with improved intraoperative handling properties,[43-45] suggesting a more prominent future role for embolization as a primary treatment modality in specifically selected patients.

Multimodality Treatment

Practically speaking, a large percentage of AVMs treated today undergo some combination of therapies, otherwise known as multimodality treatment. Such combinations only serve to further complicate the understanding of treatment risks and outcomes. However, it is worth considering some of the published outcome data from these management paradigms.

From the Columbia AVM Databank, in 2005 Hartmann et al.[46] published prospective outcome data from 119 consecutive patients with a mixture of symptomatic and asymptomatic AVM that had undergone staged endovascular and surgical treatment. There were no treatment related deaths and overall significant morbidity was nine percent (RS 3-5). Among the 78 patients who had not experienced a hemorrhage before treatment, the rate of significant morbidity was only six percent. In a multimodality series from the Barrow Neurological Institute, Lawton et al.47 reported a nine percent treatment related morbidity in the treatment of deep AVMs of the thalamus, basal ganglia and brainstem.

The treatment of very large or giant AVMs almost always requires a multidisciplinary approach. Management decisions are particularly controversial, with some groups advocating no treatment at all.[48] In mixed group of asymptomatic and symptomatic giant AVMs (average size 6.8cm, range 6-15cm) Chang

et al.[49] from Stanford University reported a long-term treatment related morbidity rate of 15 percent. However, only 36 percent of patients were completely cured of their AVM despite many patients undergoing treatment with all three major modalities.

Decision Making

Clearly, the decision to treat a patient with an asymptomatic AVM, and if so how to treat that patient, must be based on a variety of factors. The patient's clinical situation and the natural history of the lesion are perhaps the most important considerations when deciding whether or not to treat. The exact method of treatment should be planned after a careful analysis of the AVMs radiographic characteristics. The overall goal must be to treat only the patient/AVM in which the perceived risks of treatment are less than the presumed natural history risk. For many asymptomatic AVM this risk-benefit calculation still favors treatment (see Table 2).

Table 3. Suggested Treatment Algorithm for cerebral AVM

Small Size (<3cm)	
superficial, non-eloquent	*microsurgical resection*
deep, or superficial & eloquent	*stereotactic radiosurgery*
Intermediate Size (3-6cm)	
superficial, non-eloquent	*microsurgical resection with possible adjuvant endovascular embolization*
superficial, eloquent	*consider embolization plus adjuvant stereotactic radiosurgery (may require staged radiosurgical treatment)*
deep	*consider embolization plus adjuvant stereotactic radiosurgery (may require staged radiosurgical treatment)*
Large Size (>6cm)	
(Assess risk factors for hemorrhage, consider expectant management, consider treatment when high cumulative risk of hemorrhage.)	
superficial, non-eloquent	*microsurgical resection after adjuvant endovascular embolization*
superficial, eloquent	*consider embolization plus adjuvant stereotactic radiosurgery (may require staged radiosurgical treatment)*
deep	*consider embolization plus adjuvant stereotactic radiosurgery (may require staged radiosurgical treatment)*

By way of example, a hypothetical 34-year-old (the average age of the patients in previously mentioned Stapf et al's study from the Columbia AVM Databank) with an asymptomatic AVM of approximately 4cm in maximal dimension that would require multimodality treatment with endovascular embolization and surgical resection would carry an estimated lifetime risk of significant morbidity of approximately 14 percent assuming only one hemorrhage (cumulative rupture rate of 44 percent multiplied by a 33 percent risk of moderate to severe disability with each hemorrhage). With a treatment risk estimated at six percent for multimodality intervention,[46] this translates into a greater than 50 percent reduction in the relative risk of significant morbidity. As an alternative example, consider a 60 year-old male with small (<3cm) AVM that carries the same optimistic yearly rupture risk of 1.3 percent. This patient has a cumulative rupture risk of 23 percent based on an actuarial life expectancy of 20 years (actuarial tables are available at www.ssa.gov/OACT/STATS/table4c6.html), which translates into a cumulative risk of significant morbidity of 7.6 percent. Granted, this risk does not seem particularly high, but if one assumes a 3.5 percent rate of significant morbidity for radiosurgical treatment of this lesion (about midrange for the published literature) this still represents a greater than 50 percent reduction relative risk reduction for treatment.

Obviously, the above examples do not account for the many variations in natural history and treatment risk known to exist related to both patient and AVM factors. The fact that such a plethora of potentially significant variables exists only serves to further complicate treatment decisions and makes the extrapolation of data from published trials to individual patients exceedingly difficult. However, these illustration do serve to emphasize the point that the fact that a short-term risk may be low does not necessarily mean that the cumulative risk is equally low or that a treatment, even with some risk of its own, will not be beneficial.

Conclusions

The uncertainty presently inherent in the clinical treatment of cerebral AVM, particularly the unruptured variety, has led some to conclude that a prospective randomized trial (PRCT) will provide definitive conclusions as to the management of these complex lesions. Such a study, "A Randomized Trial of Unruptured Brain AVMs" (ARUBA), is presently in the process of enrolling centers. Unfortunately, as designed, ARUBA is subject to many of the same methodological problems common to most PRCTs. Selection bias remains a major challenge and in a disease such as cerebral AVM with a long history of established treatment patterns, the randomization of an adequate number of representative lesions with various risk profiles and multimodality treatment patterns will be difficult. Without such representation, the trial's external validity will be limited.

The trial also uses a five-year endpoint, which is typical of PRCTs of this type. However, such a short time period is unlikely to provide relevant information for clinical decision-making in a disease that may play out over a lifetime. In addition, adequately controlling for the myriad of necessary covariates will probably render the study underpowered to detect a significant difference at only five-years. In the end, ARUBA will undoubtedly provide clinicians with new information, but the scope and applicability of this information will likely be much more limited than first anticipated.

Except for very small AVMs, optimal treatment today often utilizes a combination of modalities, with the best results being achieved at specialized centers where all three major treatment modalities are available (see Table 3). Regardless of the modality used, complete obliteration of the AVM as documented by angiography, must be obtained in order to eliminate any future risk of hemorrhage. Partial treatment is not an effective means of preventing future hemorrhage. Ultimately, as with any disease, and most certainly with one in which the patient is asymptomatic and future morbidity is uncertain, whenever intervention is contemplated the risks and benefits of treatment must be carefully weighed against those of observation alone. For cerebral AVM a considerable body of evidence continues to support treatment in many asymptomatic patients. **PN**

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