Curing arteriovenous malformations using embolization

MATTHEW B. POTTS, M.D.,1,2 DANIEL W. ZUMOFEN, M.D.,1,2 EYTAN RAZ, M.D.,2 PETER K. NELSON, M.D.,1,2 AND HOWARD A. RIINA, M.D.1,2

Departments of 1Neurological Surgery and 2Radiology, New York University School of Medicine, and Bernard and Irene Schwartz Neurointerventional Radiology Section, NYU Langone Medical Center, New York, New York

Endovascular embolization is typically reserved as an adjuvant therapy in the management of cerebral arteriovenous malformations (AVMs), either for preoperative devascularization or preradiosurgical volume reduction. Curative embolization plays a limited role in AVM treatment but several studies have shown that it is possible, especially with later-generation liquid embolic agents. Given the complexity of AVM anatomy and the recent controversies over the role of any intervention in AVM management, it is critical that the cerebrovascular community better define the indications of each treatment modality to provide quality AVM management. In this review, the authors evaluate the role of curative AVM embolization. Important considerations in the feasibility of curative AVM embolization include whether it can be performed reliably and safely, and whether it is a durable cure. Studies over the past 20 years have begun to define the anatomical factors that are amenable to complete endovascular occlusion, including size, feeding artery anatomy, AVM morphology, and endovascular accessibility. More recent studies have shown that highly selected patients with AVMs can be treated with curative intent, leading to occlusion rates as high as 100% of such prospectively identified lesions with minimal morbidity. Advances in endovascular technology and techniques that support the efficacy and safety of curative embolization are discussed, as is the importance of superselective diagnostic angiography. Finally, the durability of curative embolization is analyzed. Overall, while still unproven, endovascular embolization has the potential to be a safe, effective, and durable curative treatment for select AVMs, broadening the armamentarium with which one can treat this disease.

Endovascular Embolization in AVM Management

Endovascular embolization of an AVM was first described by Luessenhop and Spence in 1960 when they reported treating a large left-frontal AVM with 4 methyl methacrylate pellets, ranging in size from 2.5 to 4.2 mm.
that were directly placed into the carotid artery. These pellets were carried with blood flow through the enlarged middle cerebral artery branch feeding the AVM and resulted in significant reduction in flow to the AVM. Since that time, neurointerventionalists have used silk sutures, ethyl alcohol, balloons, metal coils, polyvinyl alcohol particles, and most recently, various liquid embolic agents for embolization of AVMs. Today, embolization plays a significant role in AVM management with 5 main uses: 1) preoperative flow reduction; 2) preradiosurgical volume reduction; 3) targeting of specific angioarchitectural features; 4) palliative flow reduction; and 5) complete curative occlusion.

The most common, and perhaps most important, role for embolization in AVM management is as a preoperative adjunct to either reduce blood flow within the nidus or to embolize deep, surgically inaccessible feeder arteries. Both N-butyl cyanoacrylate (NBCA) and ethylene vinyl alcohol (EVOH) copolymer gained FDA approval specifically for this use and several case series have demonstrated benefits, especially with larger AVMs. Despite its widespread use, there are no randomized studies to prove the benefit of preoperative embolization. In fact, a recent literature review by Morgan et al. even suggested that preoperative embolization does not reduce the overall morbidity of surgical treatment, especially in low-grade AVMs. The benefits of preradiosurgical embolization to reduce nidal volume are even less clear. While early studies demonstrated reasonable efficacy of preradiosurgical embolization, more modern series have shown this technique to be of no benefit and even possibly associated with worsened outcomes compared with radiosurgery alone. Again, randomized trials are lacking but the use of preradiosurgical embolization is waning. Occasionally, embolization is also used to treat specific, high-risk angioarchitectural characteristics such as nidal aneurysms to prevent hemorrhage, or for palliative flow reduction, as with large, high-flow AVMs causing venous congestion or arterial steal syndromes.

The final role of AVM embolization, and the main topic of this review, is curative embolization. Many series of endovascular AVM treatments report on subsets of patients in whom complete occlusion was achieved with embolization (Table 1). Immediate angiographic cure rates range from approximately 5% to more than 94% (excluding those studies that only investigated cured AVMs). Such wide variability is likely dependent upon many factors, particularly selection biases (differences in size, location, and others) and goals of embolization (curative vs preoperative devascularization). It is therefore difficult to make direct comparisons between various studies. It is even more difficult to understand how curative intent was implemented or accounted for in various studies. Oftentimes, cure is achieved during the course of planned presurgical or radiosurgical embolization. Other studies adopt a general approach of attempting endovascular cure with all or most AVMs without stating specific guiding principles and then refer the failures for surgery or radiosurgery. Still other studies report broad guidelines used to select AVMs for curative embolization but do not specifically report outcomes for that subset. In general, these studies confirm that complete occlusion using embolization is possible and they begin to define the AVM characteristics most predictive of endovascular cure. The most important question, however, is whether embolization can reliably cure select AVMs, and this is best demonstrated in series that report unique subgroups of patients chosen specifically for curative embolization. These latter studies suggest the importance of prospectively identifying specific target subsets of patients with AVMs, the true population of patients for which the success of embolization monotherapy in curing AVMs should be compared with, and further demonstrating that with proper selection, occlusion rates between 60% and 100% can be achieved in targeted lesions.

Factors Associated with AVM Cure

AVM Size

Several studies have identified factors associated with achieving complete AVM obliteration with embolization. The most commonly reported AVM characteristic is size. Among the 8 patients reported by Cronqvist et al., who attained complete AVM obliteration with embolization, 75% had a nidal volume < 6 ml. Similarly, Pierot et al. found that AVMs < 3 cm in maximal diameter were nearly 5 times as likely to be completely embolized compared with AVMs ≥ 3 cm in diameter. Series reporting subgroups with curative intent of embolization have used small AVM size as a selection criteria. Sahlein et al. reported a mean AVM size of 21.8 mm (maximum diameter) for their curative intent group while Yu et al. only selected AVMs with a maximal diameter of 3 cm or less for curative intent. Similarly, studies reporting embolization of micro-AVMs (defined as nidal diameter < 1 cm) have also shown excellent cure rates. Anatomically, small AVM size may equate to a less complex AVM with fewer feeders. Small size, however, is not universally acknowledged as a positive predictive factor for the success of AVM embolization. Valavanis and Yaşargil believed that size (as well as number of feeders) chiefly affected the complexity of the endovascular embolization and not necessarily the angiographic outcome.

Feeding Arteries

Several features of the pedicles supplying AVMs have been associated with complete obliteration using embolization. A low number of feeding pedicles has been a prerequisite for curative embolization in multiple studies of AVMs. Fournier et al. found that the 4 AVMs they cured with embolization all had only 1 or 2 pedicles. Yu et al. only included AVMs with ≤ 3 pedicles in their curative intent group while Sahlein et al. found a mean of 2.2 pedicles in their curative intent group (compared with a mean of 5 pedicles in AVMs that they treated for preoperative or preradiosurgical devascularization). Strauss et al. also found that large pedicles (defined as twice the normal diameter) had an odds ratio of 4.6 of complete obliteration compared with small pedicles. Feeding artery location is likewise associated with complete obliteration, with superficial arteries positively associated
<table>
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<th>Authors &amp; Year</th>
<th>No. of Patients†</th>
<th>% Spetzler-Martin Grades (I/II/III/IV/V)</th>
<th>Primary Liquid Embolic Agent</th>
<th>Mean Embolization Sessions per Patient</th>
<th>Immediate Complete Occlusion (%)†</th>
<th>Mortality/Morbidity (%)‡</th>
<th>Recurrences in Occluded AVMs (%)</th>
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<td>1/6.8/12.8 NR</td>
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<td>median 2</td>
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(continued)
with cure while feeders arising from lenticulostriate and thalamoperforating arteries were associated with an inability to achieve complete occlusion. Importantly, the presence of en passage arteries was found to be negatively associated with complete embolization. Arteriovenous malformation size and number of feeders are typically closely related and, as with size, Valavanis and Yaşargil believed that the number of feeders was not a significant factor. Instead, they believed that AVM location as it applies to arterial feeders is a more critical concept, with AVMs fed by direct, “dominant” feeders being much easier to catheterize and therefore embolize than those fed by less direct, “supplementary” feeders. They describe a topographical classification of AVMs, with sulcal AVMs that occupy the sulci fed by pial arteries while gyral AVMs that are covered by cortex are more often supplied by cortical or medullary arteries that may be deeper. The former are therefore more amenable to safe and effective embolization.

**AVM Location**

Superficial AVMs and those in noneloquent locations have proven easier to achieve complete embolization than deeper and eloquent lesions. These associations likely involve technical considerations, as superficial AVMs tend to be fed by larger, more superficial feeding arteries such as the middle and anterior cerebral arteries. Eloquence is significant because ischemic or hemorrhagic complications of eloquent AVMs will be more clinically apparent than in noneloquent lesions. The interventionalist’s aversion to risk is therefore lower with noneloquent AVMs.

**Spetzler-Martin Grade**

While the Spetzler-Martin AVM grading scale was designed and validated to predict surgical outcomes, its ubiquitous use in characterizing AVMs has made it an easy factor to associate with embolization results. Both Fournier et al. and Strauss et al. have associated low Spetzler-Martin grades with complete embolization. This finding is consistent with the fact that both small size and noneloquent location have also been associated with complete AVM embolization.

**AVM Morphology**

Valavanis and Yaşargil found that AVM morphology was also associated with endovascular occlusion of AVMs. Predominately fistulous type AVMs were, in their hands, easier to embolize than the pure plexiform type. These authors postulated that fistulous AVMs were associated with more direct feeding arteries than plexiform AVMs, making it technically easier to embolize fistulous lesions. They also found that single-compartment AVMs were more amenable to complete embolization than multicompartmental AVMs (88% complete occlusion vs 28%, respectively). They observed that there may be intercommunication between individual AVM compartments that facilitates the embolization of multicompartmental niduses.
Arteriovenous malformation embolization

Ruptured Status

Interestingly, in a recent prospective study of Onyx (Covidien) embolization of AVMs, Pierot et al. found that ruptured AVMs were nearly twice as likely to be completely embolized than were unruptured AVMs. Multivariate analysis was not performed, so it is not clear how ruptured AVMs compared with unruptured lesions in terms of other AVM characteristics.

Technical Considerations

Perhaps one of the most important aspects of endovascular AVM embolization is accessibility of the lesion to endovascular treatment. This factor encompasses several of the aforementioned variables, including size and location of feeding pedicles and noneloquent AVM location. Safe and complete occlusion of a nidus cannot be achieved without superselective access to feeding pedicles. In addition, Reig et al. found that a complete glue cast of the AVM nidus was essential for a durable cure. In their series, 2 of 18 patients with complete occlusion were found to have AVM recanalization on follow-up angiography. These 2 patients were also the only 2 in that subgroup in which a complete casting of the nidus was not achieved.

Superselective Diagnostic Angiography

Superselective catheterization of feeding arteries is required for successful embolization of AVMs, but this technique should arguably also be used during the diagnostic workup of an AVM to fully appreciate the anatomy and better plan management. For example, superselective microcatheterization has been shown to be more sensitive to the presence of nidal aneurysms than conventional diagnostic studies. In addition, superselective catheterization can accurately define the number and nature of feeding arteries, identify multiple compartments within the nidus, and prove accessibility of an AVM nidus, all factors important in the successful complete embolization of an AVM. The theoretical risks of superselective catheterization for diagnosis compared with a standard 3- or 4-vessel diagnostic angiogram include vessel injury leading to hemorrhage or ischemia. In a series of 130 patients for whom superselective diagnostic angiograms were performed at a separate session prior to AVM embolization, only a single patient (0.8%) experienced a permanent neurological deficit due to the diagnostic angiogram.

Embolic Agents

The success of modern endovascular embolization is in large part attributable to the development of liquid embolic agents. Prior to that, polyvinyl alcohol particles were most commonly used to thrombose AVMs but had a high recanalization rate. Cyanoacrylate agents—first isobutyl-2-cyanoacrylate (IBCA) and then NBCA—are adhesive agents that not only occlude supplying pedicles to an AVM, but incite an inflammatory reaction and fibrosis, leading to more permanent occlusion. N-butyl cyanoacrylate was approved for preoperative embolization of AVMs in 2000 after a randomized trial comparing NBCA to polyvinyl alcohol embolization showed no differences in efficacy or safety and it quickly became the mainstay of AVM embolization. More recently, the nonadhesive liquid embolic agent EVOH (Onyx, and the newer Squid [Emboflu]) has gained popularity. Unlike NBCA, this agent can be injected slowly for long periods, allowing for a more controlled injection. Flow through a nidus can be somewhat redirected by pausing flow to allow injected EVOH to harden, creating new low-resistance pathways. While the advantages of EVOH have undoubtedly expanded the practice of AVM embolization, successful treatment of AVMs can be accomplished with both NBCA and EVOH (Table 1).

Advanced Embolization Techniques

In addition to advances in liquid embolic agents, new embolization strategies hold promise for increasing the curative potential of AVM embolization.

Transvenous Embolization

Transvenous embolization of arteriovenous fistulas is a developing strategy. Such an approach to AVMs, however, has traditionally been avoided for fear of compromising venous outflow without a concomitant reduction in arterial inflow, a situation that could lead to AVM rupture. This concept was first described in detail in 1999 by Massoud and Hademenos who proposed that systemic hypotension or balloon occlusion of arterial feeders could prevent hemorrhagic risks. The theoretical advantages of a transvenous approach include: 1) easier access through larger, less tortuous veins; 2) prevention of potential ischemic complications caused by arterial embolization; and 3) improved penetration of the AVM nidus. More recently, several groups have demonstrated the safe application of this approach for the endovascular treatment of deep AVMs or AVMs with en passage feeders. Pereira et al. used this method to treat a 2-cm deep temporooccipital AVM fed by branches of the posterior cerebral artery with deep venous drainage. These investigators performed balloon occlusion of the posterior cerebral artery and then injected a liquid embolic agent transvenously and retrogradely into the nidus. This procedure resulted in complete occlusion that was stable on 2-month follow-up. Consoli et al. subsequently demonstrated successful complete occlusion of 5 deep AVMs using transvenous or combined transvenous/transarterial methods. Nguyen et al. successfully used transvenous embolization to occlude a small Sylvian AVM whose en passage feeding artery precluded safe transarterial embolization. Massoud has also since studied this technique in large animal experiments.

Balloon-Assisted Embolization

The ability to gain flow control during embolization with liquid embolic agents is critical for safe and effective delivery, especially with high-flow shunts. This flow control is often completed by wedging a microcatheter into a distal arterial feeder or, in the case of EVOH, by building a cast of glue around the microcatheter tip. This latter technique is a necessary but often time-consuming
first step when using EVOH for embolization. The recent development of EVOH-compatible balloons (HyperForm and HyperGlide [ev3], and Scepter C and Scepter XC [MicroVention]) provides improved flow control when using EVOH, allowing for more rapid and aggressive embolization. Balloon catheters also minimize reflux around the microcatheter, thereby theoretically minimizing the risk of catheter retention. This technology has been mostly reported for the treatment of dural arteriovenous fistulas, but has also been used successfully for the embolization of cerebral AVMs.

**Detachable-Tip Microcatheters**

An inherent risk when using liquid embolic agents is that the delivery microcatheter can become “glued” in place. The adhesive nature of NBCA and other cyanoacrylates requires that the delivery catheter be rapidly removed after injection. While the nonadhesive nature of Onyx allows for longer injection times and even long waiting periods between injections, an extensive retrograde cast of Onyx around the catheter can also hold tight to the catheter, leading to possible vessel injury as the catheter is retrieved. This risk may limit a neurointerventionalist’s tolerance for buildup of a cast around the catheter tip, which is sometimes necessary to achieve a successful, deeply permeating embolization of the AVM nidus. The efficacy of detachable-tip microcatheters, such as the SONIC (Balt) and APOLLO (ev3), has been demonstrated with both NBCA and EVOH and will potentially allow for longer, higher volume injections of liquid embolic agents without the associated risk of retained catheters.

**Double Arterial Catheterization**

A major challenge in curative AVM embolization is to fill the entire nidus before occluding the draining vein. While microcatheters can be positioned as close as possible to the nidus, neurointerventionalists have little control over where liquid embolic agents flow within the nidus. With EVOH, slow injections followed by short pauses allow the embolic agent to redirect through the various channels within a nidus; however, casting of the draining vein prior to complete obliteration of the nidus is a real danger that, at its worst, can lead to hemorrhage, but otherwise invariably means the embolization procedure must be stopped. In an attempt to improve nidal penetration, Abud et al. have adopted a double arterial catheterization method for AVMs with more than 1 feeding pedicle. Through bifemoral access, these authors advance 2 separate microcatheters into 2 separate pedicles and then perform simultaneous EVOH injections. In a series of 17 patients treated using this method, they achieved complete AVM occlusion in 16 patients, with 2 procedural complications leading to permanent deficits in 1 patient.

**Complications Associated With Endovascular Cure**

An exhaustive analysis of the complications associated with AVM embolization is beyond the scope of this review. In brief, however, the mortality incidence for the series reviewed in Table 1 ranged from 0% to 4.3% while significant morbidity (permanent neurological deficits or clinically confirmed hemorrhages) ranged from 0% to 22%. Most of these series included only a small subset of patients for whom complete embolization was achieved and included high-grade AVMs with significant surgical or radiosurgical risks. Kim et al. specifically assessed the risk profile of AVM embolization based on the Spetzler-Martin scale and found permanent morbidities of 0% and 5% in Grade I and II AVMs, respectively. Ledezma et al. similarly identified Spetzler-Martin Grades I and II to be favorable factors in terms of embolization-associated complications. This is important because, as discussed above, low-grade AVMs are associated with complete embolization. In fact, the 2 studies reporting a subgroup of patients who were specifically selected for curative embolization based on AVM characteristics (including small size, few pedicles, and accessibility of the nidus) showed no mortality and no permanent morbidity in these highly selected patients. Interestingly, Starke et al. performed a multivariate analysis to identify several variables associated with new neurological deficits after AVM embolization and found both small (< 3 cm) and large (> 6 cm) size to be negative prognostic factors. Other factors included the need for more than 1 embolization session and, in keeping with the components of the Spetzler-Martin score, eloquent location and deep venous drainage. Starke et al. combined these factors to form a scale to predict new deficits immediately after AVM embolization (Table 2). The concept of normal perfusion pressure breakthrough is often discussed in association with complete endovascular occlusion of AVMs, and the theoretical risks of hemorrhagic complications after complete occlusion have led some neurointerventionalists to stage endovascular treatments. Several experienced neurointerventionalists, however, report that they have not observed this phenomenon.

As we further refine the indications for curative AVM embolization, choosing only highly selected patients with a high probability of cure, more studies will be needed to better define the risks involved in such curative embolization.

**Durability of Complete AVM Embolization**

An important consideration in the curative treatment of AVMs with endovascular embolization is the durability of complete AVM occlusion. While angiography at the end of the embolization session and, in keeping with the components of the Spetzler-Martin score, eloquent location and deep venous drainage. Starke et al. combined these factors to form a scale to predict new deficits immediately after AVM embolization (Table 2). The concept of normal perfusion pressure breakthrough is often discussed in association with complete endovascular occlusion of AVMs, and the theoretical risks of hemorrhagic complications after complete occlusion have led some neurointerventionalists to stage endovascular treatments. Several experienced neurointerventionalists, however, report that they have not observed this phenomenon.

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<table>
<thead>
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<th>Factor</th>
<th>Points</th>
<th>Score</th>
<th>Risk of Any Deficit (%)</th>
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<tr>
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<tr>
<td>size &gt;6 cm</td>
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<td>need for &gt;1 embolization session</td>
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<td>4</td>
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* Developed by Starke et al.
Arteriovenous malformation embolization

The conclusion of an embolization case may show complete occlusion, AVM recurrence has been reported (Table 1). Possible reasons for AVM recurrence after complete embolization include: 1) recanalization through incompletely embolized channels; 2) revascularization of an unpermeated, transiently thrombosed compartment of the AVM nidus through recruitment of nearby arteries; and 3) incomplete embolization due to a nidal compartment not visualized during the initial embolization.52 The last situation is possible in ruptured AVMs in which a hematoma is exerting mass effect on the nidus. Among the series reviewed in Table 1 that included long-term angiographic follow-up,5,11,17,19,21,24,44,45,49,51,53,62,63,65,66,68–72 there were a total of 668 patients with immediate angiographic cure with embolization. Of these, only 4.5% had reported recurrence on follow-up angiography. The length of angiographic follow-up varied among these studies but some recurrent AVMs were detected as early as 3 months after embolization. Importantly, however, not a single AVM rupture or other major adverse event was reported among these patients due to recurrence of their AVMs, and most were subsequently treated using resection or radiosurgery. These results suggest that complete angiographic occlusion of an AVM is, in fact, a durable cure but that angiographic follow-up is still warranted.

Conclusions

Arteriovenous malformation treatment must be definitive, with the goal of complete obliteration in all but the most complex lesions. Surgery and radiosurgery are currently the mainstays of curative AVM treatment but neither is 100% effective nor 100% risk free, even in selected populations. To date, curative embolization has played a very limited role in AVM management but we believe that its true potential has yet to be fully realized, especially as endovascular technologies continue to advance. Still, the AVMs that are most amenable to curative embolization overlap with those most amenable to resection or radiosurgical ablation. With the risks and indications of surgery and radiosurgery fairly well established, we do not propose that curative embolization be used to replace these other modalities. Instead, we believe that neurointerventionalists must work to identify the population that would benefit most from curative embolization—perhaps patients with contraindications to surgery, those in whom the hemorrhagic risk of the radiosurgical latency period is too high, or those whose personal preference is for endovascular treatment. Overall, the more options we have to treat AVMs, the better we can tailor our management to these complex lesions. While still unproven, endovascular embolization has the potential to be a safe, effective, and durable curative treatment for select AVMs, broadening the armamentarium with which we can treat this disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparationinclude the following. Conception and design: Potts. Acquisition of data: Potts. Analysis and interpretation of data: Potts. Drafting the article: Potts. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Study supervision: Riina.

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