TARGETING CEREBRAL ARTERIOVENOUS MALFORMATIONS FOR MINIMALLY INVASIVE THERAPY

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OBJECTIVE: Cerebral arteriovenous malformation (AVM) embolization has been performed for nearly 40 years to reduce the risk of hemorrhage, to reduce symptomatic arteriovenous shunting, and to pretreat patients for surgical excision or radiosurgery. In some cases, embolization alone may be able to angiographically cure an AVM, although this is a small percentage of all AVMs.

METHODS: This report reviews the current limitations of embolic therapy of cerebral AVMs from the standpoint of AVM angioarchitecture and the physical limitations of current embolic materials. In addition, it seeks to identify the areas in which embolization therapy may make advancements both as a pretreatment and as a sole therapy.

RESULTS: Currently, liquid embolic agents, ethylene vinyl alcohol, and *n*-butylcyanoacrylate seem to provide the greatest resistance to recanalization in AVM embolization. These agents, however, elicit only a weak, nonspecific, bioactive inflammatory response by histopathology.

CONCLUSION: The further evaluation and understanding of the vascular biology of AVM vessels and the endothelium cell wall biology will help us devise more bioactive material solutions to AVM nidus obliteration. Targeting specific receptors in AVMs with the embolic material delivered may additionally enhance the effects of radiosurgery in these patients.

KEY WORDS: Cerebral arteriovenous malformation, Embolization, Vascular endothelial growth factor, Vascular markers

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The prevalence of cerebral arteriovenous malformations (AVMs) in the population has been estimated between 0.14 and 0.52% of adults (20, 22). Patients may present with cerebral hemorrhage (subarachnoid, intraventricular, intraparenchymal, or subdural), seizures, headaches, or progressive neurological deficit from ischemia seen in vascular steal created by arteriovenous shunting. Patients may also have an incidental diagnosis.

The options for cerebral AVM management include medical management only, surgical excision, radiosurgery, and embolization therapy. For large or complex AVMs or for AVMs with associated cerebral aneurysms, a multidisciplinary approach is often the best strategy (5). In the early 1960s, Luessenhop and Presper (18) and Luessenhop and Spence (19) at Georgetown University first reported the transcatheter embolization of cerebral AVMs, which were thought to be inoperable, in efforts to reduce arteriovenous shunting and cerebrovascular steal. Although the microcatheter tools and techniques have advanced considerably since then, there are still technical limitations to transarterial embolization and other minimally invasive technology, such as stereotactic radiosurgery. Our growing understanding of the biology of AVMs is also evolving with the analysis of the developmental characteristics and cytokine interactions distinct for these vascular malformations (1, 4). This report evaluates the current targeting strategies for minimally invasive therapy of cerebral AVMs and speculates on advances for future therapies.

EMBOLIZATION STRATEGY

The strategy for cerebral AVM embolization is based on the goal of the embolization.

For select small AVMs with few feeding pedicles, complete angiographic obliteration of the AVM by embolization may be the goal (*Fig. 1*). In our experience, this represents fewer than 10% of cases referred at our institution. Others have reported higher angiographic cure rates of approximately 40% with more aggressive techniques (8, 30, 31). More aggressive embolization, however, may result in higher neurological complication rates. Do et al. (8) and Yakes et al. (31) reported a 47% overall neurological complication rate in a series of patients embolized via a transarterial route with absolute alcohol. Some interventionalists have advocated the use of coils to segmentally occlude a feeding artery pedicle distal to *en passage* feeders to subsequently embolize the branch with *n*-butylcyanoacrylate (NBCA). Curiously, others have proposed transvenous embolization. The long-term follow-up period in these series is lacking, bringing into question whether or not the angiographic obliteration at the time of embolization represents a long-term cure.

Embolization may be performed in preparation for surgical excision. Depending on the size of the AVM, this may require multiple sessions. Embolization of larger AVMs is usually staged because aggressive embolization of a large AVM in a single session is thought to have a higher periprocedural bleed rate. The goals of presurgical embolization may be to generally reduce the degree of arteriovenous shunting and total blood flow through the nidus, in efforts to reduce blood loss during surgical excision. Or, the goal may be more directed, such as embolizing the deep feeders to obliterate the more difficult section of the AVM to resect. A gradual change in the hemodynamics in and around an AVM are less likely to result in hemorrhage secondary to the embolization procedure itself.

For deep AVMs, embolization can help reduce the target size of the nidus for radiosurgery or radiotherapy. In such cases, we prefer liquid polymer embolization compared with polyvinyl alcohol particles (PVA) because the former is more durable, and the latter may have recanalization (28) (*Table 1*) in the 2-year period of optimal radiosurgery effect.

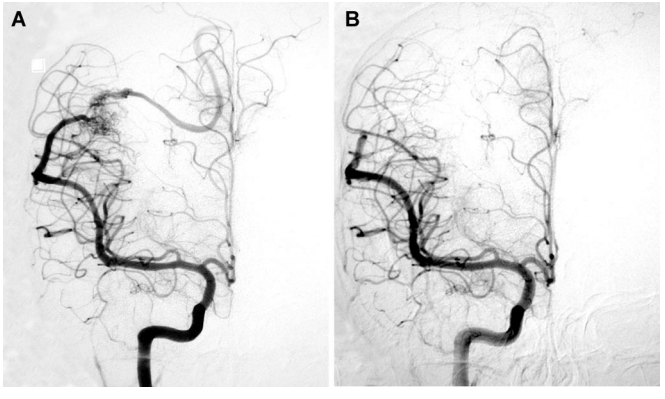

FIGURE 1. *Pre- and postembolization anteroposterior angiograms of a small parietal AVM in a 15-year-old child who presented with a hemorrhage. Two separate branches off of the posterior parietal middle cerebral artery trunk were embolized with n-butylcyanoacrylate, resulting in angiographic obliteration of the AVM.*

Palliative treatment of cerebral AVMs may be a goal in some patients, particularly those with very large AVMs, in whom subsequent surgery or radiosurgery is not planned. In these patients, headaches or ischemic symptoms may be ameliorated by decreasing the degree of arteriovenous shunting, particularly if there is a fistulous component to the AVM. Flow-related headaches seen most prominently in the parietal-occipital region seem to respond well to embolization. It is unclear from the literature whether or not palliative embolization changes the risk of AVM hemorrhage. Valavanis and Yaşargil (30) have suggested that appropriately targeted AVM embolization in otherwise untreatable AVMs may actually reduce the risk of hemorrhage, particularly if nidal aneurysms are embolized.

Limitations of Current Embolic Agents

Liquid Polymers

Liquid polymers have the advantage of being injected through small, flow-guided microcatheters, which may be positioned directly adjacent to or within cerebral AVMs. By injecting a quickly polymerizing agent directly into the nidus, a section of the nidus may be obliterated, even if there are multiple feeders to that segment. Two liquid embolic agents are currently approved by the Food and Drug Administration for AVM embolization: TruFill NBCA (Cordis Neurovascular, Miami, FL) and Onyx ethylene vinyl alcohol (EVOH) (EV3 Neurovascular, Irvine, CA).

The limitation of polymer embolization is that *en passage* feeders from a normal cortical artery cannot be effectively accessed for embolization without occluding the main artery, which may supply eloquent cortex. Likewise, feeder arteries less than 1.5–French (0.5 mm in diameter) generally cannot be accessed, and that portion of the AVM is left untreated. Similarly, if the NBCA or EVOH does not polymerize at the desired rate, it may occlude the feeding pedicle too proximally, resulting in no nidus penetration, or too distally, resulting in venous phase polymerization, compromised venous drainage from the AVM, or pulmonary emboli.

The introduction of Onyx EVOH for AVM embolization has allowed for more prolonged embolization injections and, therefore, better nidus penetration of the liquid embolic agent compared with TruFill NBCA. However, the dimethyl sulfoxide-compatible microcatheters necessary for EVOH embolization are currently stiffer and less trackable than traditional flow-guided microcatheters.

Particle Embolization

Embolization of AVMs with PVAs (Contour Embolization Particles; Boston Scientific, Cork, Ireland) of preset sizes emulates the original embolization strategy of Luessenhop, who used varying sizes of diameter beads or pellets to occlude feeding artery pedicles (18, 19). Before the availability of Food and Drug Administration-approved liquid polymer embolics, PVA was the primary embolic agent for cerebral AVMs (23). Its advantages included ease of manipulation at surgery, con-

TABLE 1. Properties of embolic agents for cerebral arteriovenous malformations[a]

Embolic agent	Ability to penetrate cerebral arteriovenous malformation nidus	Resistance to recanalization	Bioactivity
NBCA (23)	++	+++	+
EVOH (12)	+++	+++	+
PVA particles (28)	+++	+	+
Embospheres (17)	+++	+	+
Silk suture (27)	+	++	+++

[a] NBCA, *n*-butylcyanoacrylate; EVOH, ethylene vinyl alcohol; PVA, polyvinyl alcohol particles. Qualitative evaluation of embolic material properties: +, mild; ++, moderate; +++, strong.

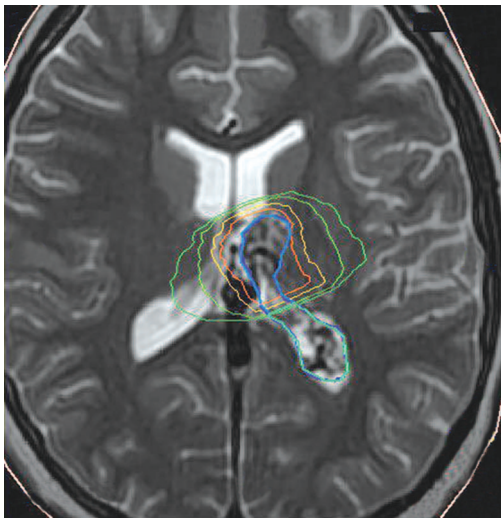

FIGURE 2. *Planning magnetic resonance imaging scan for stereotactic radiosurgery of a 13-year-old girl who presented with intraventicular hemorrhage. Note that the 1500-cGy isodose line extends significantly into the thalamus despite conformal target planning with multileaf collimators, primarily because of the irregular shape of the AVM.*

trolled embolization of a pedicle without worrying about inadvertently gluing the delivery microcatheter in place, and variety of particle sizes. Long-term evaluation of particle embolization, however, has brought into question the durability of the embolization because long-term recanalizations have been reported (28). Therefore, in its current form, PVA is used primarily as a preoperative embolic agent.

Embospheres (EmboGold Microspheres; BioSphere Medical, Inc., Rockland, MA) work on the same principle as PVA embolization in that various sizes of embospheres may be used to occlude differently sized branches. No significant documentation is available on any bioactive component of Embospheres.

Other Agents

Silk sutures may be used to embolize larger branch feeders to cerebral AVMs. Typically 6–0 silk sutures are cut in lengths measuring 1 to 3 cm and delivered through the microcatheter (27). Braided silk is a highly thrombotic agent and also elicits an inflammatory response. Because the ability of silk suture to penetrate the small vessels deep in the nidus is limited, and the silk has nearly nonexistent radiopacity, it has practical use limitations. However, from the standpoint of bioactivity, it has one of the most bioactive profiles of the embolic agents currently available.

LIMITATIONS OF RADIOSURGERY

The primary method of AVM treatment by radiosurgery is radiation-induced intimal injury or radiation arteritis, which results in vessel thrombosis. Regardless of the type of unit and radiation source used (gamma knife, linear accelerator, proton beam), radiosurgery is limited in cerebral AVMs by size criteria. In general, AVMs less than 10 cm^3 have a 2-year cure rate of 65 to 80% at the 2-year follow-up examination (10, 25, 32). Additionally, irregularly shaped AVMs may pose a targeting problem for radiosurgery because of "hot spots" in the surrounding parenchyma or undesirable extension of high-isodose lines in eloquent areas (*Fig. 2*).

Linear accelerator modality stereotactic radiosurgery uses noncoplanar beams constricted by micromultileaf collimators to conform to the AVM target. However, even with the benefit of jaws to focus on an irregularly shaped target, the isodose lines for planned treatment demonstrate higher radiation doses to the surrounding brain in irregularly shaped AVM targets. Therefore, the ability to reduce the target dose with the aid of radiation sensitizers would potentially help reduce the incidence of edema and radiation necrosis seen adjacent to the treated AVM. AVM embolization before stereotactic radiosurgery may help reduce the target volume for more effective radiation-dose planning; however, this is true only if specific anatomic compartments of the AVM nidus can be obliterated with embolization. Occluding the feeder arteries proximally or embolizing the nidus diffusely does not reduce the volume of the radiosurgery target.

FUTURE APPLICATIONS

Bioactive Materials

The ideal embolic agent would be an agent that could penetrate the AVM nidus; in the event that the AVM was not obliterated by the embolization itself, the embolic agent would have incorporated a bioactive or radiosensitive compound, which would induce a controlled cell-mediated or thrombotic response in the residual AVM and would not affect surround brain parenchyma or microvasculature. The restriction on this

technology is that differentiation between normal and pathological arteries may be difficult to achieve unless a differential expression of endothelial receptors, such as vascular endothelial growth factor (VEGF) or angiogenesis factors, are demonstrated in the AVM. A nonselective inflammatory reaction to the embolic material would also cause potentially harmful inflammation in the surrounding brain parenchyma.

NBCA promotes a mild inflammatory reaction within AVM vessels. The embolization of AVM vessels is usually durable, with improved long-term results compared with isobutyl cyanoacrylate. Delayed giant cell reactions have already been seen in cyanoacrylate embolization, particularly with the use of adjunctive tantalum powder (9). The combined effects of NBCA embolization and radiation have brought into question an increased risk of cerebral edema in sequential therapies during a short period of time. Therefore, we will normally delay the radiosurgery therapy for a short while (a few weeks) after embolization therapy to avoid an increase of periprocedural edema.

EVOH copolymer is typically delivered in dimethyl sulfoxide diluant and mixed with tantalum for radiopacity. Histological studies of this embolic combination in humans (12) show that blood vessels 80 μm to 1 mm may be filled and occluded. No associated infiltrate or reaction is seen in the vessels if the AVM is resected the same day as the embolization. At 1 day after embolization, a mild inflammatory reaction with polymorphonuclear leukocytes is seen, but little angionecrosis is observed. By a few days after embolization with EVOH, angionecrosis can be seen, with loss and fragmentation of nuclei of cells in the vessel walls, particularly smooth muscle cells. No significant evidence of recanalization has been seen.

Calcium alginate is a gel that has been evaluated in an animal model of cerebral arteriovenous malformations. Alginate and the reactive component calcium chloride are injected concomitantly. Both acute and 6-month follow-up evaluations have shown that the calcium alginate can penetrate the AVM nidus and have shown persistent occlusion in embolized vessels. In the swine rete mirabile model, histological evaluation has shown a minor bioactive response to the embolic material. Evidence of a reactive encapsulation with fibrinous tissue surrounding the alginate polymer promotes stability of the embolic material, deterring recanalization (2, 3).

Unfortunately, the bioactivity of all of the agents described is a nonspecific inflammatory response. Uncontrolled, this cellular response could lead to increased edema in surrounding brain parenchyma after embolization. The use of targeted bioactive therapy based on differential AVM markers would focus the therapeutic effect on the AVM itself and potentially minimize any harmful bystander effect to the surrounding brain parenchyma.

AVM Markers

Cerebral AVMs have abnormal vessels, angioarchitecture, and flow hemodynamics. To target these vessels for treatment via immunological, cellular, chemotherapeutic, or radiation therapies, differences in surface receptors and cellular cytokine expression may be exploited for future embolic therapies. Therefore, understanding the cellular biology of the endothelium and other cell populations of AVMs may help guide us in embolic agent development. The basic studies detailed below are summarized in *Table 2*.

Hatva et al. (11) have analyzed surgically resected AVMs by in situ hybridization and immunohistochemistry and have found that AVM endothelium and surrounding brain cells demonstrate significantly elevated levels of Tie messenger ribonucleic acid protein as well as VEGF messenger ribonucleic acid protein, whereas normal brain demonstrated little or no Tie or VEGF expression. Tie is a tyrosine kinase-dependent VEGF receptor. This suggested ongoing angiogenesis or AVM maintenance functions.

Kılıc et al. (14) evaluated 34 surgically resected AVMs, 10 cavernous malformations, and two venous angiomas, and also found increased expression of VEGF within the endothelium and subendothelium of AVMs and cavernous malformations. Transforming growth factor α elevations were also seen in the endothelial and perivascular layers. These elevations were not seen in normal brain specimens or venous angiomas. Unlike the AVMs, surrounding glial cells adjacent to cavernous malformations did not demonstrate elevated levels of VEGF, suggesting the cavernous malformations do not demonstrate all

TABLE 2. Receptors/markers for vascular pathologies[a]

Tissue type	VEGF (11, 14, 15, 29)	Tie (11)	bFGF (14, 24)	Laminin (24)	Fibronectin (24)	TGFα (14)
Cerebral arteriovenous malformation	+	+	−/+	−/+	−	+
Brain surrounding cerebral arteriovenous malformation	+	+	ND	−	−	ND
Cavernous malformation	+	ND	+	−	+	+
Brain surrounding cavernous malformation	−	ND	−	−	−	−
Venous angioma	−	−	−	ND	ND	−
Brain parenchyma	−	−	−	−	−	−

[a] VEGF, vascular endothelial growth factor; TGFα, transforming growth factor α; bFGF, basic fibroblastic growth factor; ND, no data. Qualitative immunohistochemical analysis: −, no significant elevation in expression; −/+, demonstrated in some cases, but absent in others; +, expression seen in the majority of specimens.

of the same angiogenic factors as AVMs. Likewise, in this study, AVMs did not demonstrate upregulation of basic fibroblastic growth factor, but cavernous malformations did.

In contrast, Rothbart et al. (24) showed faint expression of basic fibroblastic growth factor in four out of seven AVMs analyzed. However, both this study and the Kılıc study concur that AVMs show increased laminin expression not seen in cavernous malformations, and cavernous malformations showed increased fibronectin expression. Collagen Type 4 and α smooth muscle actin were seen both in AVMs and cavernous malformations.

Koizumi et al. (15) specifically analyzed the VEGF subtypes (VEGF-A–D) and their receptors (Flt-1, Flk-1, and Flt-4) on 31 resected AVMs and found that VEGF-A expression was the most universal in the samples (96.8%), with lesser expression of VEGF-C (54.5%), VEGF-D (51.6%), and VEGF-B (9.7%). Immunohistochemistry studies of the VEGF receptors showed equivalent positivities for Flt-1 and Flt-4 (61.3% each), with lesser expression of Flk-1 (19.4%). Interestingly, the nidus size and age of the patient did show differential expression, indicating that AVM angiogenesis is an evolving process with patient age and is not restricted to development in utero. This correlates to our previous report of a de novo AVM in a patient with angiographic documentation of no previous AVM (1) and also with previous reports of recurrent AVMs, particularly in children, who have complete angiographic resection of their AVMs.

Sure et al. (29) have implied that presurgical AVM embolization itself may promote neoangiogenesis by eliciting regional hypoxia. In their series, 17 out of 22 (77%) of the AVMs demonstrated high VEGF expression, but only two out of eight (25%) patients without preoperative embolization demonstrated elevated VEGF in their AVMs. They did perform immunohistochemical analysis that demonstrated proliferative and growth signals evident in these AVMs. Positive endothelial staining for proliferating cell nuclear antigen (87%) and MIB-1 (20%) was seen in these specimens.

Radiosensitizers

The use of radiation sensitizers in the treatment of cerebral tumors has achieved a higher dose distribution in select tumors based on sensitizer uptake. This principle also has potential applications in the AVM population. The incorporation of a radiation sensitizer in embolic material for AVM embolization is attractive because it might make the combined therapy of embolization and radiosurgery more effective. The potential deficit of this technology's application to AVMs compared with cerebral tumors is that the sensitizers would most likely be concentrated in areas of embolization, with perhaps no enhanced radiation to nonembolized sectors of the AVM nidus—the areas of the AVM that would need it the most.

In tumors, certain drugs act as adjuvants to radiotherapy or photodynamic therapy by selectively sensitizing hypoxic cells in areas of tumor that have outgrown their vascular supply or by selectively protecting well-oxygenated cells (6). The use of radiation sensitizers to selectively target deoxyribonucleic acid (DNA) and non-DNA targets seen in aberrant tumor cells has been evaluated (16). By using select DNA targeting in the radiation sensitizer, drug toxicity factors may be reduced as well (7). Finally, targeting tumor angiogenesis has proven to be an innovative strategy (13) because tumor angiogenesis differs from normal angiogenesis in that tumor vessels are generally more tortuous and hyperpermeable than normal vessels. Neovascularization and angiogenesis can also be targeted for photodynamic therapy using benzoporphyrin derivatives to enhance laser therapy (26) or hematoporphyrin esters to sensitize for photodynamic therapy in a time-dependent fashion (21).

In contrast to radiation sensitizers for tumors, however, the use of these agents for AVM therapy must take different approaches. We cannot target AVMs on the basis of hypoxia or hyperemia because normal brain-surrounding AVMs may represent either of these conditions. With current available knowledge, it would be difficult to target DNA aberrations in AVMs because these may not be as definable as in tumors. However, inroads may be made by targeting angiogenic growth factors, protein or ribonucleic acid profiles, and vascular endothelium or subendothelium receptor expression. Microcatheter delivery of liganded compounds directed to bind with these upregulated vascular receptors directly in the AVM nidus may help provide the basis for radiation sensitization in targeted radiosurgery.

Alternatively, it has been speculated that radiation-bearing microspheres may be used to directly deliver a prescribed radiation dose to the AVM directly via catheter-directed therapy. Lee and Reece (17) calculated virtual doses of radiation based on a putative model of 142 Pr-enhanced microspheres within an AVM model. Although not currently used, it is another example of targeting cerebral AVMs nonspecifically or specifically with catheter-directed therapy.

CONCLUSION

The progress of AVM therapy by embolization or combined therapies is based on an understanding of the cellular and vascular biology of the AVM vessels, particularly the arterial endothelium. By understanding the endothelial receptor characteristics, sheer stress effects, and biological differences of the AVM vessels, we can target our therapies in a more effective manner.

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