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MR Evaluation of Brain Perfusion after Radiosurgery of Cerebral Arteriovenous Malformations: A Neuroradiologist's Perspective

Arteriovenous malformations (AVMs) of the brain are fascinating lesions that produce a variety of anatomic and physiologic changes. Many of these features are detectable by MR imaging techniques. The neuroradiologist's toolbox includes cross-sectional imaging, time-of-flight MR angiography (MRA), phase contrast flow measurements, functional MR imaging, diffusion tensor imaging, and perfusion imaging. An emerging technology is the combination of 3D MRA vascular models with computational fluid dynamics. This approach generates computer simulations of flow for a specific patient's vascular geometry.

Stereotactic radiosurgery is a widely accepted treatment for AVMs that cannot be removed by microsurgical techniques. Radiosurgery has a 2-year obliteration rate of approximately 87% for AVMs less the 4 cm^3 in volume. Larger AVMs may be successfully treated by a combination of embolization and radiosurgery.

In this issue of the *AJNR,* Guo et al describe the perfusion characteristics of brain tissue adjacent to AVMs before and after radiosurgery. The authors present examples of reversible perfusion defects and conclude that the regions of hypoperfusion on pretreatment studies are due to a steal phenomenon. Elegant evaluations of AVMs by using positron emission tomography (1) and in vivo measurements of arterial pressure (2) only weakly substantiate the widely held opinion that alterations in regional perfusion are the result of hemodynamic failure and loss of autoregulation.

In addition to altered hemodynamics, AVMs affect neighboring brain tissue by diachisis-like cortical depression from neuronal deafferentation. The result is reduced perfusion to the depressed cortex. Other causes of reduced perfusion include venous hypertension, mass effect, radiation injury, and edema. Slow-growing AVMs also allow the brain to reorganize with translocation of eloquent brain functions to other cortical regions, thus reducing the metabolic demand for flow near the AVM (3). Regional perfusion may increase because of alterations in nitric oxide signaling, the release of angiogenesis factors, or prolonged seizure activity.

The authors clearly demonstrate that brain perfusion is highly variable in regions surrounding AVMs. Brain tissue adjacent to AVMs may have 1) normal perfusion, normal autoregulation; 2) normal perfusion, maximized vasodilatation, increased cerebral blood volume (CBV), and exhausted flow reserve; or 3) chronic reduced perfusion with blunted autoregulation.

The authors report that a fourth condition exits in which flow is increased in brain tissue adjacent to the AVM. In their Table 1, the authors list five patients of 19 with type I patterns (increase perfusion in both immediate and remote surroundings) and nine patients with type II patterns (increased perfusion in immediate surroundings and decreased perfusion in remote surroundings). This observation is truly interesting. What is the underlying biology of this increase in flow adjacent to the AVM nidus in 14 of the 19 reported cases? Is this a manifestation of increased capillary density due to the release of vascular endothelial growth factor A, which is know to be elevated in patients with AVMs? Or is this increase in perfusion an effect of excess angiogenesis gene expression such as the proangiogenesis Hox D3 gene, resulting in poor regulation of capillary proliferation? It would very valuable if CBV could be used as a surrogate for angiogenesis. There is some evidence that this may be the case. For example, CBV is often markedly elevated in high-grade gliomas. These neoplasms also have highly activated angiogenesis systems with prominent neovascularity.

One final thought. Does increased perfusion adjacent to the AVMs have any relation to the phenomenon of post-AVM resection normal perfusion pressure breakthrough (also termed "arterial-capillary-venous hypertension syndrome")? This poorly understood condition appears to be a combination of increased permeability of endothelial cells, friable vascular malformation remnants at the edge of the resection, or propagation of venous occlusive syndromes (4). Is it possible that the regions of increased perfusion as reported by Guo et al represent a transition zone wherein the metabolic effects of angiogenesis renders the brain vulnerable to postresection edema and hemorrhage?

The report contains several interesting observations regarding the complex nature of perfusion alterations related to AVMs. I would encourage the reader to consider the multitude of events that occur in the vicinity of an AVM and to not attribute the findings entirely to a steal phenomenon. In addition, a more complete characterization of the perinidal perfusion will be needed to determine whether the perfusion increase is a valuable new observation or an epiphenomenon of limited clinical importance.

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MR Evaluation of Brain Perfusion after Radiosurgery of Cerebral Arteriovenous Malformations: A Surgeon's View

In this issue of the *AJNR,* Guo et al use MR imaging independent component analysis to show the effects of radiosurgery on the perfusion of cerebral arteriovenous malformations (AVMs). Their analysis shows varied perfusion disturbances involving AVMs and surrounding brain tissue and the gradual changes toward normal perfusion after radiosurgery.

Although the thrust of this study was to demonstrate changes in vascular steal phenomena, the prime objective of stereotactic radiosurgery of AVMs is to prevent hemorrhage (1). Nevertheless, such MR techniques may be of clinical utility. The biggest question raised by this study is whether employing this technique routinely would add significantly to the simple visual inspection of routine MR imaging sections.

The effects of radiosurgery on AVMs occur over a prolonged period as the radiated vessels develop endothelial changes, smooth muscle cell proliferation, and hyalinization and eventually become occluded (2). In general, 1–2 years are required for obliteration of the entire AVM. On occasion, significant change in the lesion may be seen as early as 6 months after treatment, and obliteration may occur as long as 3 years after treatment. Routine follow-up MR imaging of AVMs that respond to radiosurgery shows reduction in nidus size and associated abnormal vasculature, areas of elevated T2 signal intensity surrounding the lesion, and variable degrees of contrast enhancement in and around the lesion. MR imaging may eventually strongly suggest obliteration of the AVM, but usually conventional angiography is used to confirm obliteration. Very small residual lesions may occasionally be seen on follow-up angiograms, particularly signaled by persistent early draining veins that are not well delineated on MR images.

The additional characterization of perfusion of the AVM and surrounding brain might be helpful in early prediction of ultimate obliteration. Collection of additional patient data with long-term follow-up and angiographic correlation might show that this technique can supply data that would help one predict whether an AVM would eventually show a good response to radiosurgery. This might allow a significant degree of reassurance to the patient who is waiting for that response to provide protection from hemorrhage. In terms of risk assessment, perhaps changes in the perfusion data, such as the rate of change of perfusion, might predict the risk of development of significant edema during the follow-up period.

Contrary to what might be inferred from advertising sometimes directed at the lay public, radiosurgery of AVMs is not a uniformly successful enterprise (3, 4). Radiographic follow-up is crucial, and at times radiosurgery of an AVM is repeated if the lesion is not totally obliterated after an appropriate duration of follow-up (5). Conceivably, an AVM might appear obliterated on follow-up MR images, but a residual abnormality on the perfusion study might predict that a small remaining defect may well be present, thus drawing closer attention to detailed follow-up conventional angiography. A lack of change of perfusion data at some relatively early point in follow-up might help one predict eventual inadequate response and raise the possibility of earlier radiosurgical retreatment.

Most neurosurgeons accept the dictum that the patient is not protected from hemorrhage unless the AVM is totally obliterated. Some hold the view that partial obliteration may be somewhat protective and better than no treatment, and there has been some suggestion that radiosurgery affords some reduction in hemorrhage rate even if the lesion is not seen to be obliterated. On the other hand, others hold the view that reducing the size of the AVM without completely obliterating it may increase the risk of hemorrhage because of changes in hemodynamics, with the smaller lesion still subjected to a similar pressure gradient. In cases of incomplete obliteration, follow-up MR perfusion data might separate subgroups with some protective effect of partial obliteration from groups with no protective effect or increased risks of hemorrhage.

Like all studies of stereotactic radiosurgery of nonmalignant disease, determination of the utility of this technique will require extended follow-up of many patients. The patients in this study have been followed up for a relatively limited period. None of them have reached the point at which postradiosurgery angiography is needed. The longest follow-up was 25 months, with only seven of the 19 patients followed for at least 18 months. Only two AVMs were shown to be obliterated on the basis of MR imaging criteria. The AVMs in this study are relatively larger targets; certainly none of them can be called small. The smallest was 10 mL in volume. Application of this perfusion MR imaging technique to small AVMs would also be of interest.

It would be of great interest to correlate the changes visualized by use of MR perfusion imaging with seizure frequency in patients with epilepsy caused by their AVM. Perhaps changes in perfusion short of complete obliteration might affect seizure frequency. Nine of the patients presented with seizures alone as symptomatology; no discussion of response of their seizures to treatment exists.

There is considerable discussion in the article regarding development of radiation-induced edema surrounding the lesion. Some of the signal intensity change around the lesion may reflect gliosis rather than edema. Long-term follow-up will be necessary to differentiate the two, because edema should eventually resolve, and residual long-term T2 signal intensity changes should reflect mainly gliosis. There is no discussion as to whether the edema was symptomatic. The authors state that there was reduced perfusion

caused by the radiation-induced edema. An alternative explanation for reduced perfusion in those areas would be actual occlusion of small blood vessels in the brain due to the irradiation.

The authors describe increased perfusion of the ipsilateral hemisphere relative to the normal hemisphere and implicate a steal phenomenon to explain this ratio. Although there is a relative difference, there is not clear proof that the elevated blood flow in the nidus hemisphere is coming at the expense of the contralateral hemisphere. It may be extra flow delivered only at the expense of extra work by the heart.

The authors have presented a technique for additional MR imaging characterization of the effects of stereotactic radiosurgery on brain AVMs and the surrounding parenchyma, and they appropriately speculate about the possible applications of this MR imaging technique for the assessment of endovascular and surgical treatment of AVMs. Further long-term follow-up of more patients with this perfusion technique would be of great interest and would be most useful if accompanied by clinical correlation with the neurologic manifestations of radiation-induced edema, seizure control, and ultimate angiographic and neurologic outcome.

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Guest Editorialist

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Low-Flow Vascular Malformations of the Orbit: A New Approach to a Therapeutic Dilemma

Low-flow vascular malformations of the head and neck present many challenges for the treating physician. Surgical intervention is often fraught with difficulty, with a high potential for bleeding complications, difficult anatomic dissection, and ultimately a high recurrence rate. These drawbacks have restricted the use of a surgical approach alone to a limited subset of small and well-defined lesions. The highest degree of success has been found when low-flow vascular malformations are treated in a multidisciplinary setting. A key element of this collaborative approach has been image-guided sclerotherapy through the percutaneous injection of ethanol or other sclerosing agents. Image-guided sclerotherapy has proved highly effective, with good to excellent results possible in 75–90% of patients (1). As experts in imaging and percutaneous needle placement, radiologists have taken a central role in the multidisciplinary teams at many institutions, and often drive decisions regarding the type of image guidance, sclerosing agent, and staging of therapy. As the range of modalities within the imaging armamentarium has increased, successful sclerotherapy has been performed with fluoroscopy, duplex sonography, CT, and MR image guidance, with the choice of technique based on the location of the malformation, experience of the radiologist, and availability of technology.

Within the spectrum of head and neck low-vascular malformations, which represent a challenging entity at best, treatment of orbital venolymphatic malformations, as described by Ernemann et al in this issue of the *AJNR,* presents a distinct challenge due to the severity of potential complications. In particular, the consequences of inadvertent ophthalmic vein thrombosis may be catastrophic and can lead to orbital compartment syndrome, cavernous sinus thrombosis, and loss of vision. While accurate needle insertion and careful monitoring of sclerosant injection is always important, the margin for error in treatment of orbital and periorbital disease is small, and meticulous care is necessary.

Treatment with sclerotherapy can be broken down into several discrete steps, and each may be best performed with a specific imaging technique. One of the most important stages of the sclerotherapy procedure is the preprocedural evaluation of the patient, requiring careful planning of the safest percutaneous approach to the malformation, definition of the anatomic extent of the lesion, identification of critical adjacent neurovascular structures, and when possible, delineation of venous drainage pathways. MR imaging has become the primary technique for therapy planning. Numerous authors have demonstrated the ability of MR imaging to characterize and delineate vascular malformations of the head and neck (2), and specific aspects of the MR imaging appearance have been shown to have prognostic value with regard to percutaneous sclerotherapy (3). Percutaneous puncture of the malformation can be successfully performed with X-ray fluoroscopy, CT, duplex sonography, or MR imaging. The best puncture-guidance technique for an individual lesion depends on the complexity, depth, and size of the malformation, along with the availability of an acoustic window. The next step in sclerotherapy is estimation of the volume of sclerosing agent required for effective treatment,

often performed through the monitored injection of contrast agent until the malformation is filled. The final and most critical step in the sclerotherapy procedure is real-time monitoring of the distribution of the sclerosing agent during injection. In particular, in orbital and periorbital malformations such as those described by Dr. Ernemann et al, drainage via the ophthalmic vein must be carefully assessed, and the treating physician must be ready to stop injection quickly should this avenue for venous egress of sclerosant be identified.

The puncture-guidance phase of the procedure can be difficult for orbital lesions, and the use of image fusion and frameless stereotactic guidance for needle placement along with X-ray fluoroscopic monitoring of the injection procedure, as described in the article in this issue of the *AJNR*, represents a novel solution to the particular challenges of orbital low-flow malformations. Duplex sonography combined with fluoroscopy, a highly successful combination for many head and neck malformations, can be particularly challenging with the complexity, location, and adjacency to bone noted with orbital and periorbital lesions. Dr. Ernemann et al have taken a relatively straightforward technical solution from the operating room and have applied it to one of the more challenging steps in the sclerotherapy procedure in this anatomic location. The spatial accuracy of frameless stereotactic systems, typically around one to two millimeters, is also well suited to the size of the lesion treated. It is possible that the procedure could have been further simplified with the use of MR image data alone, since the size of the lateral orbital wall defect was sufficient to allow easy visualization on the MR images, possibly obviating the need for CT fusion. However, the CT information would likely contribute to the safety and ease of needle placement in lesions with smaller bony defects. The ability of the authors to bring the advantages of MR and CT into the X-ray fluoroscopic suite allowed full advantage of the temporal and spatial resolution of X-ray fluoroscopy for monitoring of potential ophthalmic vein filling, the most critical step in the treatment session.

In contrast to the combination of modalities demonstrated in this current article, recent advances in sclerotherapy have included the modification of a single technique to provide each of these procedural steps. Most notably has been the recent description of MR imaging as a technique for, not only the diagnosis, but also the treatment phase of the sclerotherapy procedure. MR imaging developments have allowed the accurate imaging characteristics typically used for diagnosis and characterization of low-flow vascular malformations to be directly applied for needle puncture, sclerosant volume determination, and sclerosing agent injection monitoring (4), and more recently has been shown to document that a sufficient concentration of sclerosing agent has been attained within the treated malformation during the therapeutic procedure (5). MR imaging has also been shown to monitor temperature within the lesion during treatment, a feature that can be useful when thermal methods of therapy are used for low-flow vascular malformations as an alternative to chemical sclerotherapy (6). However, although real time imaging has steadily been improving with MR imaging and may make a "single-technique" approach feasible for many anatomic sites, the temporal and spatial resolution of these real time MR techniques is still limited as compared with that of X-ray fluoroscopy, and the size and critical nature of ophthalmic vein filling makes this technology less applicable to orbital malformations. The lack of general availability of open MR imaging systems equipped with interventional accessories also provides a barrier to the use of this technology as a stand alone treatment-guidance technique.

In summary, the necessary steps for safe performance of sclerotherapy include precise preprocedural lesion visualization and characterization, accurate needle placement, determination of the correct volume of sclerosing agent for injection, and real time monitoring of venous egress during the injection procedure. In this issue of the *AJNR*, Dr. Ernemann et al have described a novel method that combines the advantages of MR imaging and CT for accurate needle placement with the unsurpassed temporal and spatial resolution of X-ray fluoroscopy for the monitoring of sclerosant injection, and this strategy should be considered for vascular malformation at various anatomic locations that are difficult to approach with ultrasonography or MR imaging guidance alone. Image fusion, frameless stereotaxy, and computer-assisted device guidance are central to the future of image-guided minimally invasive therapy, and the authors are to be commended for bringing this combination into the realm of low-flow vascular malformation therapy.

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Training, Experience, and Evidence Matter

When all is said and done, more is usually said than done.

Winston Churchill

Knowing is not enough; we must apply.
Willing is not enough; we must do.

Johann Wolfgang von Goethe

This issue includes a consensus statement from a coalition of seven professional societies—the American Academy of Neurology, the American Association of Neurologic Surgeons (AANS), the American Society of Interventional and Therapeutic Neuroradiology, the American Society of Neuroradiology, the Congress of Neurologic Surgeons (CNS), the AANS/CNS Cerebrovascular Section, and the Society of Interventional Radiology—representing most of the physicians in North America who specialize in the diagnosis and treatment of diseases of the brain and spinal cord. In this statement, the societies propose standards for training, competency, and credentialing in the performance of diagnostic cervicocerebral angiography, carotid stent placement, and cerebrovascular interventions. Based on a concern for patient safety, this statement is an attempt to address what seems likely to become the rampant performance of some of these procedures by physicians who, because they are not properly trained, cannot be considered competent in this area.

At no time in the history of medicine has growth in knowledge and technologies been so great. As one whose early practice in neuroradiology included pneumoencephalography, gas myelography, and plain-film angiography to monitor the positioning and detachment of balloons manually tied on the end of a catheter, I am awed by both the power of the diagnostic and therapeutic tools that I now use daily and by the potential harm and cost that the improper application of these tools can bring to patients and their families. To use these appropriately and safely, specialized training and expertise are required.

This consensus statement is not a demand for a utopia, but rather, a realistic and reasoned call to physicians wishing to do these procedures that they obtain and then maintain the proper skills to protect their patients from undue harm. Reports from the Institute of Medicine have documented frequent and unnecessary injury to patients, as well as a failure of the healthcare system to deliver the quality of care that patients deserve and expect (1, 2). The statement published in this issue is one attempt to improve and ultimately eliminate this deficiency. While no injury is acceptable, damage to the nervous system is especially serious. In the face of strong evidence that training matters in preventing adverse events and also in minimizing injury when it does occur, it is unacceptable for individuals to take or institutions to offer "shortcuts" to aid physicians in obtaining skill in these procedures.

Those having proper training are obligated to be certain that the potential benefits of the procedures they perform outweigh the potential risks. In large part, this entails using and understanding the concepts of evidence-based practice. Fundamental to such practice is the integration of the best research evidence with clinical expertise and patient values (1). In this definition, clinical expertise means "the ability to use clinical skills and past experience to rapidly identify each patient's unique health state and diagnosis, individual risks and benefits of potential interventions, and personal values and expectations" (1). Such skills cannot be acquired quickly, easily, or informally. Maintenance of these skills demands ongoing education.

Finally, it is emphasized that this call is not one that seeks to carve out or protect "turf." Healthcare will increasingly be delivered by teams that work in complex and novel arrangements. The concept of physicians with varied training and experiences working together should be welcomed and adopted, as traditional alliances are shown to be no longer productive or rational. An amalgamation of specialties with different skills and experiences offers the potential for huge improvements, as it is often on the edge of disciplines where the really significant advances occur. These alliances should, however, be focused on patient well-being and not on efficiencies of personnel or on economic gain.

I applaud the effort of these societies to ensure that all patients receive the quality of care and protection that they deserve.

CHARLES M. STROTHER
Senior Editor

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