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The Carotid Artery Through a Keyhole

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Assessing Effective Transvascular Particle Delivery to the Brain Parenchyma: A Challenge to Neuroradiology

With the increased discussion over issues surrounding genetic manipulation of cells, neurotissue regeneration, and potential therapeutic models designed to alter cell growth and lines, a timely article by Muldoon et al appears in this issue of the *American Journal of Neuroradiology* (page 217). Questions basic to the future of neuroradiology and its role in the cellular treatment and imaging of a variety of CNS diseases are twofold. Will the transvascular delivery of minute, viral-sized particles effectively cross *all* cellular barriers within the brain, and will imaging protocols be developed that can help one accurately assess the efficacy of transvascular delivery of such particles to their desired cellular locations?

Muldoon et al have demonstrated with their rodent model that current MR imaging techniques cannot adequately reveal the precise particle distribution of therapeutic agents after transvascular delivery to the brain. Signal changes on MR images revealing iron-containing compound leakage through an intentionally disrupted blood-brain barrier (BBB) only gives gross anatomic information. These signal changes give little indication of what is happening where it counts, i.e. at the microscopic cellular level. The authors indicate that two physiologic barriers impede even distribution across the BBB: the well known tight vascular endothelial junctions of the BBB, and a basal membrane barrier. An important premise of this article asserts that when an agent crosses the BBB, it may not permeate the entire brain because of this second level of impairment to free diffusion. Because the two experimental materials, Feridex and MION, are of similar size, the authors discount particle size as a major factor for their observation of unequal particle distribution within the brain. Rather, they theorize that differences either in opsonization (susceptibility to phagocytosis) or in the electrostatic charge caused by dextran coating could account for their findings. Whatever the explanation, the implications these results have for the means of particle delivery and the subsequent imaging assessment of its effect are significant.

To develop imaging methods that can help one discriminate between effective and ineffective agents (‘‘stealth’’ and ‘‘non-stealth,’’ as the authors put it) will be a difficult challenge for neuroradiology; however, possible strategies could be developed. The use of MR systems with field strengths far greater than currently employed high-field magnets might allow a better understanding of the distribution of particles by achieving high spatial resolution (i.e., 20–40 micron in-plane resolution). This, in concert with appropriate contrast-labeled particles and rapid time-resolved high-resolution MR, might help determine whether particles are distributed evenly throughout the brain parenchyma or have accumulated heterogeneously at or near brain capillaries. Regardless of the outcome, this article not only challenges the ‘‘conventional wisdom’’ relative to the BBB, but offers a distinct challenge for highly detailed MR imaging.

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The Carotid Artery Through a Keyhole

Universal acceptance of an MR angiographic method for imaging the carotid arteries has been elusive. Despite numerous improvements in data acquisition and processing for 2D and 3D time-of-flight (TOF) techniques, the limitations imposed by spin dephasing caused by disordered flow, spin saturation, or both adversely affect the accurate measurement of stenosis on source and maximum intensity projection (MIP) images in many patients. Because of these flow effects, MR angiography is sometimes relegated to the role of ‘‘road map’’ in the noninvasive examination of neurologically symptomatic patients considered for carotid endarterectomy, with Doppler sonography (or even CT angiography) providing the stenosis measurement.

To overcome the limitations of TOF studies of the carotids, some radiologists have turned to ultrafast 3D gadolinium-enhanced methods. These methods, however, require strategies to ensure that the central lines of k-space are acquired during the first passage of the intravenous bolus of gadolinium through the carotid arteries, prior to gadolinium arrival in the jugular veins. Protocols that involve a timed injection (mechanical or manual) and a linear phase-encoding profile for filling k-space are commonly used. These protocols often incorporate a ‘‘test dose’’ or automatic bolus detection technique with scan triggering, if available, to determine the optimal time delay between contrast infusion and 3D data acquisition. Unfortunately, such protocols can be time-intensive for the radiologist, and may not temporally resolve carotid and jugular enhancement. In those cases, carotid stenosis can be obscured on reformatted source or targeted maximum intensity projection (MIP) images by a closely adjacent jugular vein.

To achieve better temporal resolution in a series of images without markedly compromising spatial

resolution, two approaches can be identified. The first is to accelerate acquisition of the full space matrix with ultra-short echo and repetition (TE/TR) times that require more powerful gradient sets. The second is to restrict the size of the acquired k-space data and to use one of several methods of ''constrained reconstruction'' to generate the images in the time series. In this issue of the *American Journal of Neuroradiology* (page 263), Melhem et al have used one of the earliest and simplest of the constrained reconstruction methods, keyhole imaging. In their study, the acquisition of a complete (102 phase x 256 read) k-space reference matrix was followed by reduced acquisition of only the central 46 phase-encoding steps. While this decreased imaging time by a factor of 102/46, intrinsic spatial resolution of the update images along the phase-encoding direction would also be decreased by the same factor. With the keyhole method, the missing outer k-space rows of the update matrices are filled with the corresponding rows of the reference matrix prior to image reconstruction. Optimally, the result is a series of images with apparent high resolution.

Melhem et al observed that MIP projections generated from subtracted images had superior vessel-to-background contrast compared to MIP projections from unsubtracted images. The subtracted images, however, show only the changes between the updated and reference data sets, and thus have low spatial resolution along the phase-encoding direction (1). This limitation, with the relatively large partition thickness (5 mm), conspires to undermine the spatial resolution of their gadolinium-enhanced images, making them less impressive compared to standard TOF images. An alternative method, the so-called 3D-TRICKS (3D time-resolved imaging of contrast kinetics) proposed by Korosec and colleagues (2) produces images with slightly lower temporal resolution (4.5 sec/3D volume versus 3.6 sec/3D volume reported by Melhem et al) yet much higher spatial resolution. The 3D-TRICKS method includes intermittent acquisition of full k-space update images, shared data among update images, and temporal interpolation between acquired data sets. These capabilities improve the high spatial frequency information in the gadolinium-enhanced time series compared to the basic keyhole method.

Despite the claim by Melhem et al that their keyhole method can be implemented on clinical scanners with average gradient performance, the probability that most manufacturers will be ready and willing to do this is low. It is more likely that a sophisticated constrained reconstruction method, with minor variations among manufacturers, will become available commercially once the efficacy of gadolinium-enhanced carotid MR angiography, which can be performed by a technologist, has been demonstrated in clinical trials. Many questions remain, though. What will be the role of unenhanced TOF angiography? Which MR angiographic method will be used to examine the carotid siphon and common carotid origin for possible tandem stenosis? How well can an x-ray angiographic ''string sign'' of the cervical carotid be detected? Until these and related questions are answered, we will not know whether time-resolved, contrast-enhanced MR angiography will become the universally accepted MR method for assessing carotid disease.

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Technical Advances and Clinical Progress in Carotid Diagnosis

In this issue of the *American Journal of Neuroradiology*, Hara et al (page 267) nicely describe a practical technique (extended field-of-view imaging [FOV]) for seamlessly integrating successive long-axis B-mode images to produce a single ''panoramic'' representation of the cervical common and internal carotid arteries, similar to that obtained with transfemoral arteriography, spiral computed tomographic arteriography (sCTA), or magnetic resonance angiography (MRA). The authors successfully examined 68 arteries in 34 patients. They found intimal thickening or luminal stenosis in 19 (28%) of 68 vessels, only two of which had a stenosis greater than 40%. In two other patients with carotid occlusion, movement artifact obviated extended-FOV imaging. In six (32%) of the 19 successfully studied vessels that had wall disease, extended-FOV imaging indicated a more topographically extensive lesion than was evident on conventional B-mode imaging. The authors conclude that the extended-FOV technique provides ''more interpretable images'' than does conventional real-time B-mode scanning, and is therefore ''clinically useful.''

Theoretically, the authors' technique may be useful for clarifying the sites of multiple lesions found during conventional B-mode imaging, for facilitating interpretation of follow-up studies of such lesions and for dissecting out the course of highly tortuous vessels. The authors did not test these hypotheses, nor do they present convincing evidence that extended-FOV imaging is clinically useful. In

report our ultrasound findings in terms of estimated residual lumen diameter, giving decrements of 0.25 mm when the lumen is less than 2.5 mm.

Whether measuring a precise residual lumen diameter serves a useful purpose is questionable to those individuals who believe that signal drop-out revealed by MR angiography is all that is required to identify a surgical lesion. In our opinion this criterion is imprecise. Signal drop-out may occur frequently with 65–70% stenosis (12), but has been reported also with 40–60% stenosis (12,13). Once signal drop-out occurs, no current conventional MR angiographic data can help characterize reliably the actual degree of stenosis until the distal internal carotid artery is seen to narrow compared to the opposite (more normal) side. In our experience this distal narrowing is apparent on MR angiograms when the residual lumen diameter is 0.9 mm or less (85–90% stenosis). With spiral CT angiography and transfemoral arteriography, distal constriction of the vessel occurs when the residual lumen diameter is 0.5–0.7 mm (11). MR angiography probably simulates this change earlier because of slow, unenhanced flow along the edges of the vessel. Spiral CT angiography cannot help one determine residual lumen diameter reliably because the thickness of the contrast column is dependent upon window settings, and extensive calcification can obscure the intraluminal contrast.

Carotid Doppler ultrasound gives the most precise noninvasive data on residual lumen diameter, although it can be misleading when the lesion is so tight (0.5–0.7mm, in our experience) that blood flow falls and frequencies and velocities begin to drop to lower values that ordinarily are used to characterize less severe disease. Otherwise, it can reliably differentiate, for example, between a 2-mm and 1-mm residual lumen diameter, which is important. Our clinical experience indicates that a 2-mm residual lumen diameter (65–70% stenosis) is a relatively benign lesion that can be followed, whereas a 1-mm residual lumen diameter (85–90% stenosis) represents a high risk for stroke (11). Further, our data suggest that a 2-mm residual lumen diameter does not necessarily progress to a tighter stenosis. If both these latter observations are correct, surgery on a 2-mm residual lumen diameter may be unnecessary in some patients.

In sum, major issues in carotid disease remain unsettled. If advances in carotid ultrasound imaging are to help resolve them, the new techniques need to characterize meaningful physiologic and anatomic details that elucidate ischemic mechanisms, reflect the prevelance of stroke risk factors, and anticipate clinical events. Extended-FOV permits B-mode images to mimic the ''panoramic'' vascular profile provided by spiral CT angiography, MR angiography, and transfemoral arteriography. This adds convenience to the interpretative process, which might be more important for communicating findings to the referring physician than for providing diagnostic insights.

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