How Can We Make BOLD Contrast Bolder?

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The Potential Value of Iron Oxide Nanoparticles in Brain Tumor Treatment

Dr Neuwelt and his coworkers have continued their efforts to define the biological activity and possible clinical utility of dextran-coated iron oxide nanoparticles in imaging and therapy. Previous investigators have focused on use of these particles in imaging and quantitating the transport across a disrupted blood-brain barrier and in studying the distribution of convection-delivered fluid in the brain interstitium. The use of iron nanoparticles has also been considered in MR angiography; lymph node imaging; and target-specific imaging, in which they are conjugates to antibodies.

In the article in this issue of the *AJNR*, Neuwelt et al (see article by Varallyay et al) eliminated the use of Feridex, in its currently allowed doses, as an agent in the clinical imaging of brain tumors because of its inability to breach an disrupted blood-brain barrier. Ferumoxtran-10 (Combidex), likely because of its smaller and more uniform particle size and its more complete dextran coat, passes the incompetent blood-brain barrier and is trapped intracellularly. Therefore, ferumoxtran-10 can serve as a contrast agent for MR imaging; but the evidence reported here does not support its replacement of gadolinium as the contrast agent of choice in brain tumor imaging; ferumoxtran-10 enhancement appears to be far more inconsistent and variable than gadolinium enhancement.

Ferumoxtran-10 has a prolonged enhancement timeline, with sharp delineation of tumor margins at 24 hours after injection. These characteristics might make this contrast agent better than gadolinium-based media when surgery with intraoperative MR imaging is planned; gadolinium-based agents have the unfortunate quality of leaking from the blood or across the blood-brain barrier into the surgical cavity and interfering with the image when it is administered intraoperatively. An increasing number of dedicated MR imaging units are being placed in operating rooms worldwide, and they are intermittently used during the frequently prolonged course of brain tumor resection. The use of long-lived agents such as ferumoxtran-10 might be appropriate in protracted operations if the preoperative administration and the clearance of the agent from the blood before intraoperative imaging can be timed correctly. Because intraoperative MR imaging is proving to be useful in evaluating the extent of the resection of gliomas (particularly) and pituitary tumors, the spotty and unpredictable enhancement with the iron oxide particles with these tumors is disappointing.

As the authors point out, gene therapy has potential in the treatment of brain tumors and other disorders. The ability to predictably deliver the virus into the brain has been one of major clinical obstacles. The authors have concluded from previous studies in rodents that iron oxide nanoparticles seem to have a similar volume of distribution after direct injection into the brain as adenoviruses and a similar ability to get into the intracellular compartment as adenovirus and herpesvirus through a blood-brain barrier. Because, in this study in humans, the iron oxide particles accumulated in tumor and normal brain in both the interstitial space and intracellular compartment, the authors postulate that the iron oxide particles might be a valuable tracer for the transvascular or interstitial delivery of viral vectors.

However, the animal data that are used to compare the movement of iron oxide particles to that of viruses to and through the brain is far from conclusive. The proteins on the surface of viruses make their movement past cell-surface receptors exceedingly complex. As a result, the distribution of viruses through brain tissue is somewhat unpredictable compared with that of inert iron particles. Recently, several groups, studying the potential of delivery of adeno-associated viruses for gene therapy by using convection-enhanced delivery at slow infusion rates, have indirectly shown the interaction of viruses with cells in the brain interstitium. In these studies, the coinfusion of either mannitol or heparin reduced the binding of viruses to cells near the infusion site and allowed the viruses to move further afield to improve the volume of distribution and gene transduction.

The growing interest in gene therapy for brain tumors and the poor viral gene expression in brain tumor trials to date has made the study of convection-enhanced delivery and other methods of optimizing the distribution of viruses in the brain imperative. To be successful in these pursuits, the tracking of viruses and/or imaging of gene transduction is essential. In a promising approach developed at our center, a marker gene for herpes thymidine kinase (HSV1-tk), is included in the viral genome and co-expressed in the target cell. Then, a radiolabeled marker substrate, 2′-fluoro-2′-deoxy-1-beta-d-arabinofuranosyl-5-[(124)I]iodouracil (FIAU), is delivered. This substrate is metabolized by HSV1-tk, trapped within the transduced cell, and detected with positron emission tomography. Because this approach is used to directly image an expressed gene, it should be superior to tracking the movement of iron particles, which can only model the movement of the viruses without assessing their ability to express their genes intracellularly.

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Subcortical Low-Intensity Areas on T2-Weighted Images: An Uncommon Finding with a Common Explanation?

In this issue of the *AJNR*, Lee and colleagues describe a finding, referred to as a subcortical low-intensity (SCLI), on T2-weighted fast-spin-echo and fluid-attenuated inversion recovery (FLAIR) images in patients with meningitis, viral encephalitis, or leptomeningeal metastases. For these clinical diagnoses, the frequencies of observation of the finding on retrospective review of the MR images were 8.6% (five of 58 patients with meningitis), 23.7% (nine of 38 patients with viral encephalitis), and 23.8% (five of 21 patients with leptomeningeal metastases). Interestingly, cortical hyperintensity was observed in most patients (73.9%) and leptomeningeal enhancement was observed in all of the 19 patients with SCLI areas; the percentages were approximately double those obtained in the cohort of patients without SCLI areas.

The striking features of SCLI lesions are the following: 1) focal-to-diffuse involvement of the subcortical white matter (unilateral, frontal and parietal lobes), 2) reversibility in patients with meningitis or encephalitis, 3) isointense-to-hypointense signal on isotropic diffusion-weighted images (DWI), and 4) decreased apparent diffusion coefficients (ADCs) (compared with values obtained from the contralateral normal white matter) in half of the lesions evaluated with DWI (mean decrease of approximately 9%). On the basis of these observations, the results of a single biopsy that showed focal myelin pallor, and the results of studies by other investigators that have revealed the uncommon occurrence of SCLI-like areas in a variety of other pathologic conditions (eg, early cortical ischemia, multiple sclerosis, Sturge-Weber syndrome), the authors conclude that SCLI is a nonspecific sign of meningeal and cortical disease (although encephalitis is not an exclusively cortical disease) and that SCLI may be caused by a transient increase in the amount of free radicals.

Why free radicals? Free radicals, which are principally reactive oxygen intermediates (eg, superoxide radical, hydrogen peroxide, hydroxyl radical) are transient and have been implicated in numerous pathologic processes, including brain edema, ischemia and infarction, meningitis, encephalitis, and malignancy. The last includes the processes that Lee and colleagues reported. Furthermore, the oxygen free radicals are paramagnetic because of their unpaired electrons, and paramagnetic species can shorten the T2 relaxation time, resulting in SCLI. The flaw in this reasoning, of course, is that no cause and effect has been demonstrated. The implication of oxygen free radicals seems to be based on "guilt by association," and the conclusion becomes problematic when the authors attempt to explain why no cortical low-intensity areas are present and how the temporal expression of short-lived oxygen free radicals is related to the time course of SCLI, which may be observed for days to weeks after the onset of symptoms.

What about other potential causes of SCLI? The authors consider two causes in detail and reject both: the accumulation of nonheme iron and a structural change in the subcortical white matter. Abnormal iron accumulation in the extrapyramidal system is generally accepted as the cause of excessive T2 shortening in the deep gray matter nuclei in several neurodegenerative diseases such as Parkinson disease and the Parkinson-Plus syndromes. T2 shortening in the subcortical white matter of patients with cerebral ischemia and infarction has also been attributed to iron deposition (secondary to disruption of axonal transport of iron); however, the link between T2 shortening and iron accumulation in the subcortical white matter is unproven, as Lee and colleagues note. Although iron accumulation is an intriguing possibility from the standpoint of the DWI findings, Lee and colleagues reject it as a cause of SCLI, primarily on the basis of conflicting reports in the literature, the transient nature of SCLI, and the lack of detectable iron on Perls staining of the biopsy sample obtained from the cortex and subcortical white matter in a patient with viral encephalitis.

The second postulated cause of SCLI that the authors rejected may not be so easily dismissed without additional histochemical and ultrastructural information. The statement that "no obvious evidence of structural abnormality" is present on histologic examination is not exactly true because myelin pallor was observed in the only biopsy specimen obtained. Although no histopathologic evidence of myelin catabolism (as it occurs in Wallerian degeneration) was reported, could subtle ultrastructural changes in myelin be occurring in SCLI areas? It is curious that the subcortical white matter signal intensity changes on T2-weighted images in conditions as disparate as Wallerian degeneration and Sturge-Weber syndrome pass through a stage of hypointensity that is attributable to myelin metabolism. These conditions and the SCLI reported here differ, though in the time course of signal intensity changes (longer in Wallerian degeneration and Sturge-Weber syndrome) and in the eventual white matter destruction that occurs in Wallerian degeneration.

With their study, Lee and colleagues raised more questions than they answered. This is often the case in science. The answer to the question of whether the relatively uncommon finding of SCLI in various pathologic conditions can be explained by a common mechanism must await more thorough and hypothesis-driven investigation. Certainly, more tissue specimens should be obtained and analyzed, and conceivably, an animal model may need to be developed to

cytochemically demonstrate negative oxygen intermediates by using published techniques. The results of such laboratory investigations are more likely to answer the questions raised in this article than additional clinical MR measurements of parameters such as magnetization transfer ratios, T2 relaxation times, or metabolite concentrations from in vivo proton spectroscopy. Before embarking on extensive investigations, though, one should also ask whether this nonspecific MR sign is of sufficient clinical benefit to be worth the effort.

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Functional magnetic resonance imaging (fMRI) based on blood oxygenation level–dependent (BOLD) contrast is a noninvasive technique that offers an unprecedented opportunity to explore the neuronal basis of human cognition, perception, and behavior. Despite extensive studies over the last decade, we still have only a rudimentary understanding of the relationship between the BOLD fMRI signal and the underlying neuronal activity. Understanding this relationship is important if we are to discover methods to increase the sensitivity of what is now a technique with relatively low sensitivity, which has particularly limited the application of fMRI in the evaluation of cognitive and psychiatric disorders.

It is now generally accepted that the BOLD fMRI signal changes in response to activation stimuli are related to the increase of regional cerebral blood flow (rCBF), which alters the relative local concentrations of oxyhemoglobin and deoxyhemoglobin. However, little is known about the process by which focal neuronal activity triggers the increase in rCBF. A complex system involving vasoactive substances, nitric oxide, neurotransmitters, and intrinsic factors has been postulated. In addition to this local coupling of rCBF with neuronal activation, CBF is also sensitive to factors acting globally; these include perfusion pressure, the partial pressures of CO_2 and O_2 in the cerebral circulation, and other biologic and pharmacologic variables.

In view of these global perfusion regulatory systems, the question of whether the increase in rCBF during neuronal activity is linked to the baseline cerebral blood flow arises. The clarification of the relationship between the baseline cerebral blood flow at rest and the increase in rCBF as a result of focal neuronal activity may lead to a better understanding of the processes underlying the BOLD response. It also has substantial practical relevance for the intersubject comparison of BOLD signal intensity during task activation. The dependency of the rCBF associated with a neural activation on the prevailing cerebral blood flow has been the focus of many functional neuroimaging investigations.

For BOLD fMRI, changes in global cerebral blood flow and rCBF are indirectly related to changes in cerebrovascular oxygenation, but this fact accounts only for a small fraction of the measured signal intensity on T2*-weighted images. Therefore, the physiologic basis for the current analytical models of the BOLD signal is incomplete. This lack is reflected by the often-inconsistent reports on the dependence of local activation–related BOLD signal changes on the baseline BOLD signal modulated by various approaches such as hypercapnia, hypocapnia, and vasoconstrictive or vasodilatory drugs. The report of the animal study by Morton et al (1) in this issue of the *AJNR* represents another effort to clarify the relationship between the local activation–induced BOLD signal changes and globally modulated baseline BOLD signal amplitude.

In brief, the results from previous research are complex and sometimes confusing. The effect of global cerebral modulation (either vasodilation or vasoconstriction) on the local activation–induced BOLD response can be either up- or down-regulating, depending on the experimental setting. On the basis of the current understanding of the BOLD effect, the activation-induced BOLD signal changes are dependent on both the rCBF response and the cerebral metabolic rate of oxygen. If the activation-related rCBF response is assumed to be independent of the prevailing CBF level, as the direct perfusion results from arterial spin-labeling fMRI studies (2) implicate, the observed variations in the BOLD response under conditions of global cerebral vasodilation and vasoconstriction can only be attributed to changes in the oxygen consumption. Quite possibly, CO_2-, O_2-, and drug-induced global modulations of vasomotor tone may lead to different functional-metabolic couplings of tissue during task activation. However, the precise mechanisms underlying the effect of each agent on the BOLD response is not yet well understood.

In this study, Morton et al (1) found that the systemic administration of theophylline markedly increases the BOLD response in rats. The findings from this study are similar to the recent results of a study about the use of caffeine as a contrast booster for BOLD fMRI studies in human subjects (3). Given the fact that caffeine and theophylline belong to the same methylxanthine family of drugs and that both drugs act as vasoconstrictors in the brain, the two drugs are likely to have the same mechanism regarding the booster effect on BOLD contrast. It was suggested that the enhanced BOLD sensitivity was possibly due to the increased concentration of deoxyhemoglobin at the resting state that results from the reduced CBF during vasoconstriction. This interpretation is conceivable, but it fails to explain why vaso-

constriction induced by indomethacin (4), for example, attenuates the BOLD response. The neuroexcitability effect of these drugs offers another plausible explanation for the resetting of the coupling between cerebral blood flow and energy metabolism.

A full understanding of why and how BOLD fMRI signal is related to the underlying neuronal activity requires a great deal of further research. However, this issue is very important because the ultimate success of fMRI depends on the establishment of a specific relationship between the fMRI signal and neuronal firing activity. The characterization of the relationship between local BOLD response and the prevailing cerebral blood flow level modulated by chemical agents is a promising approach that can potentially elucidate the cascade of processes that trigger rCBF change in response to task activation. Despite an incomplete understanding of the underlying mechanisms, the study by Morton et al reveals a significant increase in the BOLD response in rats by using systemically administered theophylline. This finding indicates that the development of BOLD contrast boosters to overcome the low sensitivity of fMRI technique might be possible; this improvement may make fMRI more applicable in clinical medicine.

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Intraosseous Venography during Percutaneous Vertebroplasty: Is It Needed?

In the last 15 years, neuroradiologists in Europe and America have pioneered the technique of percutaneous vertebroplasty for the treatment of pain and decreased mobility associated with osteoporotic and pathologic vertebral-body compression fractures. Multiple reports in the medical literature detail the clinical experience and technique of percutaneous vertebroplasty. In this issue of the *AJNR*, Kaufmann et al (pages 601–604) address a particular conundrum concerning the technique and performance of vertebroplasty by investigating the relevance of antecedent venography in percutaneous vertebroplasty for treatment of osteoporotic compression fractures. Opinions differ, and the utility of antecedent venography in determining improved clinical outcomes or decreased complications during vertebroplasty is controversial. The authors retrospectively reviewed results in consecutive patients treated with percutaneous vertebroplasty for vertebral-body compression fractures. The first group of patients underwent antecedent venography, whereas the second group was treated without venography. The clinical outcomes were assessed by means of quantitative measurements of pain and mobility. The intraosseous venograms and postvertebroplasty radiographs were evaluated for extravertebral polymethylmethacrylate (PMMA) deposition, amount of extravasation at each treated level, and correlation between results with venography and results with vertebroplasty. The authors found that improvements in pain and mobility did not differ between the two treated groups. Similarly, the demonstrated extravasation of PMMA cement was not significantly different between the two groups. Interestingly, in 14 (64%) of 22 patients in the group who underwent antecedent venography, correlative extravasation was shown with venography. The authors concluded that antecedent venography did not significantly augment the effectiveness or safety of percutaneous vertebroplasty procedures performed by this group of experienced interventional neuroradiologists.

When percutaneous vertebroplasty was initially evaluated and performed in North America at the University of Virginia beginning in 1993, antecedent venography was an integral part of this procedure and performed in every patient. In the initial report about the technique and the early clinical outcomes with this technique in the treatment of painful osteoporotic compression fractures, Jensen et al (1) advocated the use of antecedent venography to decrease potential complications associated with incorrect or suboptimal needle placement in the basivertebral venous plexus or in direct connection with a paravertebral vein. The purpose is to delineate a potentially dangerous route by which PMMA cement might escape the confines of the vertebral body. PMMA cement can escape posteriorly into the spinal canal, causing spinal canal stenosis or cord compression; to the intervertebral foramina, causing nerve root compression; or to the vena cava and pulmonary arteries, causing pulmonary embolism. With a right-to-left cardiac shunt, such as that in patent foramen ovale or ductus arteriosus, a potential stroke may occur, although it may never be reported. This event may necessitate needle readjustment or, as the authors

suggest, it may require the use of maneuvers to prevent potential cement extravasation. Such maneuvers include 1) the placement of Gelfoam pledgets prior to injection of PMMA or 2) an initial deposition of PMMA and a period of waiting to allow the cement to harden and obliterate the direct venous connection(s) and then the use of a second needle to inject the cement into the vertebral body. However, some authors (2–4) disagree with this approach and state that, due to differences in the viscosity and flow characteristics of contrast material and cement, venographic findings are not predictive of the actual flow of PMMA cement and path of extravasation. Additionally, the persistence of intravertebral opacification could obscure visualization of cement, for example, during an injection into necrotic cavities in cases of vertebral osteonecrosis or Kümmell disease (5) or during an injection through the endplates to the intervertebral discs. Preoperative imaging with demonstration of intravertebral gas or a fluid collection should alert one to the possibility of vertebral osteonecrosis; therefore, the venographic procedure should be modified by injecting contrast material gently and by using the minimal volume of contrast agent (1–2 mL).

Although venography may not augment the safety of vertebroplasty when it is performed by experienced operators, it may guide novice or inexperienced operators and help them to perform vertebroplasty in a safer manner. In addition, although venographic findings may not be absolutely correlated (64% in Kaufmann et al's series) with the actual extravasation of cement, the additional information that the delineation of the venous anatomy around the vertebral body may potentially be of benefit. Percutaneous vertebroplasty is an intravascular procedure because the vertebral bony trabeculae is a large venous space with eventual connections to the draining veins. PMMA cement should be considered to be a liquid embolic agent, and it should be treated and used with caution and full knowledge of its possible adverse effects. When the venograms are shown on separate monitors, these reference images may provide guidance in the detection of early-appearing and small quantities of extravasated cement. Although cement extravasation does occurs, the volume and amount of extravasation causes potential clinical complications. Therefore, the early detection and knowledge of cement extravasation is the key to the safe performance of vertebroplasty. Other important factors in the safe performance of vertebroplasty include correct patient selection; good knowledge of vertebral bony and vascular anatomy; adequate opacification of PMMA cement; and high-quality fluoroscopy, preferably with biplane types. Although the authors mention the issue of excessive radiation exposure and the cost of contrast material in the performance of venography, these are likely to have no clinical importance. To my knowledge, no report of the adverse effects of venography exists in the literature. The amount of contrast agent used per venogram is approximately 3–5 mL; therefore, the risk to patients with renal failure is minimal. The authors correctly point out that, in those adept at the performance of vertebroplasty, venography may represent a superfluous step. Venography, however, may be extremely beneficial for less experienced physicians. The use of intraosseous venography should still be advocated during training courses, and its clinical value should be pointed out to the trainees.

The results of this study are valuable and thought provoking. As the authors acknowledge, the study is limited by its retrospective nature, and the sample size may result in a lack of statistical power. Prospective randomized trials to evaluate the effectiveness of vertebroplasty compared with that of sham-vertebroplasty and conservative medical treatment are underway. If possible, an evaluation of the value of antecedent venography in these studies may provide interesting results.

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