MRI and the Evaluation of the Blood–Spinal Cord Barrier following Injury

Much of the published work on the use of MR imaging in experimental models seems to fall into two categories. The first are articles that focus on the use of MR imaging to visualize the known histologic effects of a pathologic process and its treatment. This research is extremely important in translation to the bedside, because clinical trials are often dependent on imaging findings. In addition, the use of MR imaging to evaluate an animal model serially saves time and money, because large numbers of animals need not be sacrificed at multiple time points to obtain significant results. The second are articles that focus on presenting new imaging techniques and/or pulse sequences, with the application to an experimental model used to confirm underlying hypotheses of the imaging physics, not necessarily the pathologic process. These new imaging techniques may then be tested with a variety of diseases and subsequently find their way into the clinic as an improved method of diagnosis. Less frequently seen, however, is a third category of research in which MR imaging is used as a tool to support hypotheses regarding pathophysiologic mechanisms.

In this issue of *AJNR,* the article by Berens et al appears to fall into both the first and third categories. They have used MR imaging both to visualize the known histologic effects in an animal model of posttraumatic cavity formation and as a research tool to determine whether blood–spinal cord barrier (BSCB) disruption may play an important role in this pathologic process. Their experimental model is an intraspinal injection of quisqualic acid (QUIS), which simulates injury-induced elevations of excitatory amino acids (EAAs). There were differing effects of the QUIS, depending on injection depth in white matter, with deeper injections resulting in spinal cord cavities that have histologic features similar to those seen following traumatic spinal cord injury. The known histologic findings of this model, such as cysts and hemorrhage, are clearly seen on their in vivo MR images, a finding that supports the utility of MR imaging in following the pathologic progression of these lesions. More interesting, however, is the use of dynamic contrast-enhanced MR imaging to determine whether there was disruption of the BSCB, which could potentially contribute to cyst formation.

Disruption of the BSCB following traumatic spinal cord injury may be an important cause of propagating injury following spinal cord trauma and is therefore a potential target for therapy (1). Loss of BSCB integrity appears to be biphasic. There is primary mechanical disruption of the spinal vasculature at the time of traumatic injury resulting in hemorrhage and ischemia. There is then a cascade of secondary events, including toxicity from blood products, as well as EAAs, which are the focus of the experimental model in this article. The secondary injury, however, is due to not just the sequelae of mechanical disruption; there is a second phase of BSCB permeability that begins 3–4 days following initial injury (2) and may last up to 28 days. This second phase of BSCB disruption may result in more injury to the spinal cord, allowing entry of inflammatory cells and small toxic molecules into the extracellular space. Subsequently, there is increased tissue damage, including areas of intact spinal cord adjacent to the central hemorrhagic core. Because protection of $<10\%$ of axons in spinal cord white matter may result in significant functional recovery (3), this penumbra of tissue surrounding the central hemorrhagic core may be a promising target for therapy.

In the current article, the authors imaged the spinal cords at 17–24 days following injury and they found no evidence of BSCB disruption. This finding may not be surprising, in view of research indicating that the BSCB is no longer permeable to large molecules at 21–28 days postinjury. It will be interesting to see whether there is leakage of the BSCB soon after QUIS injection and whether the degree and duration of BSCB leakage predicts or quantifies future cavity formation. Perhaps intrinsic differences in neuronal response to QUIS injections, and the subsequent effect on vascular integrity, will help explain the lack of cavity formation in the shallower QUIS injections.

Although the vascular events following spinal cord injury are complex, it is clear that the integrity and permeability of the BSCB is an important factor and a potential therapeutic target. The issue of BSCB integrity and its relation to secondary injury is being addressed in the neuroscience literature. One line of research has involved matrix metalloproteinases (MMPs), which are excessively expressed by inflammatory cells following spinal cord injury. MMPs are thought to increase BSCB permeability, thus resulting in an influx of inflammatory cells and EAAs that are toxic to the spinal cord. Mice that do not express these proteinases, as well as mice administered an MMP inhibitor, show improved recovery to spinal cord injury (4, 5). These articles utilized histologic techniques for evaluating the BSCB, such as staining for immunoglobulin G leakage or measuring leakage of intravenously injected macromolecules through the BSCB. All these methods, however, are performed postmortem and thus at only one time point. Although the feasibility of serially evaluating the disruption, and subsequent restoration, of the BSCB in vivo following injury has been demonstrated for years (6, 7), the use of MR imaging as a neuroscience tool has not been fully exploited. Perhaps we need to educate our basic science colleagues about the utility of MR

imaging as a primary research tool, above and beyond the translational aspect.

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References

1. Mautes AE, Weinzierl MR, Donovan F, Noble LJ. **Vascular events after spinal cord injury: contribution to secondary pathogenesis.** *Phys Ther* 2000;80:673–687
2. Pan W, Kastin AJ, Gera L, Stewart JM. **Bradykinin antagonist decreases early disruption of the blood-spinal cord barrier after spinal cord injury in mice.** *Neurosci Lett* 2001;307:25–28
3. Kakulas BA. **A review of the neuropathology of human spinal cord injury with emphasis on special features.** *J Spinal Cord Med* 1999;22:119–124
4. Noble LJ, Donovan F, Igarashi T, et al. **Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events.** *J Neurosci* 2002;22:7526–7535
5. Wells JE, Rice TK, Nuttall RK, et al. **An adverse role for matrix metalloproteinase 12 after spinal cord injury in mice.** *J Neurosci* 2003;23:10107–10115
6. Bilgen M, Abbe R, Narayana PA. **Dynamic contrast-enhanced MRI of experimental spinal cord injury: in vivo serial studies.** *Magn Reson Med* 2001;45:614–622
7. Runge VM, Wells JW, Baldwin SA, et al. **Evaluation of the temporal evolution of acute spinal cord injury.** *Invest Radiol* 1997;32:105–110

Vertebroplasty and the Randomized Study: Where Science and Ethics Collide

Vertebroplasty, which was first performed in the early 1990s, has become widely available in the United States, primarily for the treatment of osteoporotic and malignant compression fractures. Although initially described by Deramond, the first major study describing the effectiveness of vertebroplasty in osteoporotic vertebral compression fractures (OVCFs) was by Jensen et al (1) in 1997. They reported on 29 patients with painful vertebral fractures, with a 90% success rate, and the flag was dropped. With an estimated 700,000 vertebral compression fractures (VCFs) a year, resulting in 150,000 hospital admissions and five million restricted-activity days, the only previous means of treatment (ie, bracing and bed rest) accelerated the disease process. Vertebroplasty was therefore seen as a potential major medical breakthrough, and numerous other studies soon followed. Barr et al (2) found 95% of patients in their retrospective study of 47 had at least moderate relief of pain, and other retrospective studies on groups ranging up to 245 patients have been reported, all of which describe high percentages of success.

The number of prospective studies has been few, and most deal with a small number of patients. In this issue of the *AJNR,* Huy Do et al report on the largest group of vertebroplasty patients yet to be followed prospectively. Although they have run into the difficulties of following a patient population that typically is cognitive– and long-term survival–challenged, their data are strong evidence that further supports the effectiveness of vertebroplasty in the treatment of medically refractive OCVFs. The limitation of this study, which the authors freely admit, is the lack of a control group to compare their results. In fact, when reading most major articles on vertebroplasty, the lack of a double-blind randomized prospective study is lamented as a major obstacle that needs to be overcome before vertebroplasty can be "proved" to be effective. At this point, however, the question should not be "how could such a study be done?" but "should we do it?"—two questions that may sound similar but approach the problem from entirely different points of view.

Purists, of course, would disdain the idea that a randomized controlled study is not necessary when considering a medical treatment. From a pragmatic and ethical standpoint, however, such a study, though appealing in an intellectual sense, would almost assuredly merely confirm the data that we already have. To begin with, OVCF is a disease that, until vertebroplasty came along, had only one means of treatment—namely, conservative therapy, consisting of bed rest, which can accelerate bone loss, bracing, and narcotic anesthesia, In the past, when conservative management failed, the only option was . . . more conservative management. In most practices and studies, and by using Medicare guidelines, vertebroplasty is not typically considered until the patient has already failed conservative management. In other words, one could argue that the need for a control study has been reduced or eliminated, because these patients have already failed the only other treatment option. In light of this fact, as well as the extremely high success rates reported in the numerous studies of vertebroplasty, including the article in this issue of the *AJNR,* is it ethically defensible to deprive half the patients in a study of realistically their only chance for pain relief, especially when a side effect of the alternative therapy is to make the disease process accelerate? Some will argue that it is, for the sake of science and future patients, but others, including myself, would argue that what is already is in the literature is so uniformly positive that there is justification for treating medically refractory VCF with vertebroplasty, despite the absence of a randomized double-blind prospective study.

Where a study is needed, however, is in patients with acute osteoporotic compression fractures, particularly those patients who are hospitalized or bedridden from the pain of such fractures. This subgroup of patients has the highest risk of additional bone loss,

hospital-associated morbidity and mortality, and costly hospital stays, merely for pain control. Minimizing or eliminating hospital stays and bed rest time by performing vertebroplasty in the acute setting might have significant benefits to such patients, although there is no large study on this population. This type of study would greatly benefit from a control group, because these patients would not have had a chance to try conservative management otherwise, and the data without a control group would therefore be much weaker. A randomized double-blind study would be very useful in determining how aggressive we should be in treating these patients.

Ultimately, however, on the basis of the existing data on vertebroplasty in medically refractory OVCF, a true, long-term, randomized double-blind study does not seem necessary or ethically justifiable.

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References

1. Jensen ME, Evans AJ, Mathis JM, et al. **Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects.** *AJNR Am J Neuroradiol* 1997;18:1897–1904
2. Barr JD, Barr MS, Lemley TJ, McCann RM. **Percutaneous vertebroplasty for pain relief and spinal stabilization.** *Spine* 2000;15:25:923–928