◆ EDITORIAL VIEWS

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Sensitive Physiologic Imaging with Contrast-enhanced Magnetic Resonance Imaging

As an anesthesia resident who was moments away from his first neurosurgery case many years ago, I asked a seasoned clinician to give me a quick summary of the essentials of neuroanesthesia. His answer was, "There are two types of brain — good brain and bad brain — and bad brain can cause problems." This answer, although it came after the first observation of NMR spin echos,[1] was delivered before magnetic resonance imaging (MRI) was clinically available. (Yes, many anesthesiologists who remember that era are still in practice.) But MRI is widely available now, and in this issue of ANESTHESIOLOGY, Payen *et al.*[2] describe an animal study that demonstrates the feasibility of using an advanced MRI technique and a new MRI contrast agent to determine cerebrovascular CO_2 reactivity and to display the results *via* physiologic imaging. The MRI images that are shown are not standard anatomic images, with pixel signal intensity simply being proportional to the number of water molecules in the pixel. One of Payen *et al.*'s conclusions is that their methods now seem ready for trials in humans as one means of distinguishing "good brain" from "bad brain." The authors should be commended for undertaking animal studies that aim to rapidly transfer such technology to humans.

In the examination of technologically intense endeavors, however, unfamiliarity sometimes makes it more difficult to recognize and appreciate excellence. Such might be the case for many readers who try to understand the concise work of Payen *et al.*, who commendably, unlike Blaise Pascal[3] and myself, kept their writing short. The advanced MRI technique that they used is called *steady-state magnetic susceptibility contrast imaging,* and the final MRI images derived with their technique are not the conventional MRI images that many anesthesiologists are accustomed to seeing. That is, they are not ordinary T_1-weighted or T_2-weighted images.[4,5] Now, just as there is a difference between great wine and *vin ordinaire,* so is there a difference between the authors' R_2^* images and those produced by conventional spin-echo MRI. In my experience, many anesthesiologists are comfortable with examining T_1-weighted images (water is dark and fat is bright), or T_2-weighted images (water is bright and fat is dark), and even T_1-weighted images after gadolinium contrast injection, usually with Magnevist™ (gadolinium pentetate dimeglumine; Berlex Laboratories Wayne, New Jersey 07470; website URL is http://www.betaseron.com/pis/Magnevist-Pl.html). Magnevist™ is an agent that brightens the intravascular compartment of T_1-weighted images by shortening the T_1 of water protons near the agent. (Magnevist™ also brightens regions where it extravasates across the blood-brain barrier, which is why it provides especially accurate images of acoustic neuromas.) But it is also my experience that few anesthesiologists are likely to know about T_2^* or R_2^* images or about magnetic susceptibility and its ever increasing role in MRI. Although the educational appendix by Payen *et al.* tersely gives much essential basic information, I will digress for one paragraph and present a brief review of some additional details, using the "no-equations" style of "physics for poets."

If one puts a solid, liquid, or gel into a large, external magnetic field of precisely known strength, one can determine the magnetic field inside the material and see that the strength is different. The difference between the external and internal magnetic field strengths defines the *magnetic susceptibility* of the substance, as stated by Payen *et al.* in equation [5] of their Appendix. Although such magnetic field differences in tissue might seem ridiculously small, they are responsible for a substance being either pulled into, or pushed out of, the fringe field of a magnet, where the magnetic field exhibits a gradient, and decreases as one gets further from the magnet. Curiously, the direction — being pulled in or pushed out — depends only on the substance and not on the direction of the magnetic field.[6] Substances

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that are pushed out are said to be *diamagnetic,* and this group includes water, sodium chloride, copper, lead, and graphite. Most substances that are pulled in are called *paramagnetic,* and this group includes sodium, aluminum, and molecular oxygen. Of course, iron and magnetite (Fe_3O_4), being fiercely pulled in, turn out to be *ferromagnetic,* which means that aggregations of iron form interacting domains that can retain a magnetic field after the external magnetic field is turned off, or even spontaneously line up when there is no external field and become a bar magnet. Fringe field forces on ferromagnetic substances are typically more than $\approx 10^5$ times larger (per g) as forces on other substances. Diamagnetic susceptibilities characterize substances that have most of their magnetic dipoles originating from orbital electron currents. Paramagnetic susceptibilities characterize substances that have most of their magnetic dipoles originating from the compass needle property of an unpaired electron. (In diamagnetic substances, the compass needle property of an individual electron is not an issue. Electrons occur in oppositely oriented pairs, and the compass needle property of one is nulled by its "upside-down" partner.) Substances with a dilute iron presence, meaning that one does not have interacting ferromagnetic domains or residual magnetization after removal of an applied field, can end up with susceptibilities that cause them to be called either *paramagnetic* or *superparamagnetic* (susceptibility is a function of the applied field, as stated by Payen *et al.*). Paramagnetic relaxation in MRI studies is commonly caused by intravascular paramagnetic contrast agents, such as Magnevist™, but it can also be caused by deoxyhemoblogin (which, unlike diamagnetic oxyhemoglobin, has an unpaired electron) and even by molecular oxygen. The solution of dextran-coated iron particles that was used by Payen *et al.* as a contrast agent is superparamagnetic. (Advanced Magnetics Inc.'s AMI-227 is marketed as Sinerem™ in Europe and as Combidex® in the U.S.A. AMI has a clinical operations center in Princeton, NJ, and its website URL is www.advancedmagnetics.com).

So, how and why do paramagnetic and superparamagnetic contrast agents affect MR images? First, we must remind ourselves that MRI detects water protons, not the contrast agent. This makes reading MRIs very different from our inspection of radiographic images. X-rays are scattered by charged particles, with the intensity of scattering being greater for particles having more electric charge. X-rays are very efficiently scattered by high Z nuclei like iodine (Z = 53) and xenon (Z = 54). Therefore, when we look at radiographic images from patients injected with radiopaque contrast, we naturally identify increases in image brightness with direct x-ray absorption by the radiopaque contrast agent itself. To understand MRIs where contrast agents were used we must ask: (1) how did the contrast agent affect water protons?, and (2) how do affected water protons behave in the particular imaging technique being used? The answer to (1) initially looks easy. Paramagnetic and superparamagnetic agents decrease relaxation times, typically by a factor of ≈ 10 or more (both T_1 and T_2) in two ways: *via* dipolar relaxation by the unpaired electron, or *via* transfer of the unpaired electron to the atom whose nucleus gets relaxed. The end result depends strongly on the choice of relaxing agent. For example, the lanthanides are excellent paramagnetic relaxation agents, and gadolinium is particularly effective at decreasing T_1, whereas dysprosium is a favorite for decreasing T_2^*. However, besides appreciating that Payen *et al.* made an outstanding choice of agent, it is also crucial to note that they used *gradient echo imaging,* as opposed to standard *spin-echo imaging.* Gradient echo imaging does not refocus spins whose coherence (phase) has been disrupted by small magnetic field inhomogeneities. Standard spin-echo imaging is more forgiving, as it does refocus those spins. The presence of an intravascular contrast agent accentuates magnetic susceptibility differences between the inside and outside of capillaries and causes water molecules near those capillaries to cruise through different magnetic field strengths, as well as associated magnetic field gradients. Consequently, pericapillary water protons dephase more than normal, and gradient echo images, being sensitive to dephasing, suffer enhanced MRI signal loss. The combined technique, use of gradient echo and contrast agent, triumphs by inducing only as much paramagnetic relaxation as is needed for generating relevant image differences. In summary, the effects on water protons observed with steady-state, contrast-enhanced, magnetic-susceptibility gradient-echo MRI arise from microscopic magnetic field differences, expecially near capillaries.

Why did Payen *et al.* need to have a special intravascular contrast agent? Why could they not use Magnevist™, with which we are all familiar? The answer appears to be partly pharmacokinetic. Magnevist™ is eliminated by urinary excretion with an approximately 15-min half-life. In contrast (*excusez-moi!*), AMI-227 has an elimina-

tion half-life of ≈4.5 h (primarily *via* reticuloendothelial phagocytosis in liver, spleen, bone marrow, and lymph nodes—the primary locations targeted for its use as an MRI contrast agent.). Additionally, AMI-227 also has more paramagnetic clout. Does one need a paramagnetic contrast agent at all? Many readers who follow developments in functional MRI know that endogenous deoxyhemoglobin can serve as a contrast agent in healthy brain. Thanks to the coupling of regional cerebral blood flow (rCBF) and regional metabolism, brain neuronal activity is accompanied by increases in rCBF. It turns out that local microvascular oxyhemoglobin/deoxyhemoglobin ratios are increased after such rCBF increases (which occur within 5–10 s after neuronal activity starts). Decreased, local concentrations of paramagnetic deoxyhemoglibin can therefore be detected in fast MRIs as bright spots identifying regions of brain in which all this took place. This method is known as *blood-oxygen-level-dependent* (BOLD) *magnetic susceptibility contrast imaging,*[7] and it has been used in one animal study of brain CO_2 reactivity.[8] But Payen *et al.*'s approach using a superparamagnetic contrast is more comprehensive and practical. Perhaps we can now finally go on to ask: what are R_2^* images, and how did Payen *et al.* make them?

MRI physicists have found it convenient not only to have the symbol, T, for *relaxation time,* but also to have the symbol, R = 1/T, for *relaxation rate.* Corresponding to T_2, the *transverse relaxation time,* is R_2, the *transverse relaxation rate.* If, *via* a radiofrequency pulse, one rotates up-down nuclear magnetization into the transverse plane, one can repeatedly measure the transverse magnetization with an echo technique, with there being several to choose from. The decay of transverse magnetization is seen as a repeated percentage decrease in the amplitudes of successive echos. By plotting echo amplitude *versus* time, one can determine T_2 and R_2, the related parameters that describe transverse relaxation. Because MRI systems in separate labs are each slightly imperfect and also different, the *measured* R_2, which might be slightly faster than the actual R_2 because of magnetic inhomogeneities in the system, is instead called R_2^*, the "*effective transverse relaxation rate.*" The echo imaging technique used by Payen *et al.* was gradient-echo T_2-weighted imaging. The radiofrequency pulse train used for imaging included eight successive echos. For each pixel, the train of echo amplitudes permitted determination of R_2^*. From these values they then constructed the R_2^* and ΔR_2^* images (which are of very high quality) found in figures 1 and 2 of their paper. Because the NMR physics of magnetic susceptibility contrast imaging is complex and partly phenomenologic, readers of this journal will have to make a leap of faith in accepting that ΔR_2^* is linearly proportional to cerebral blood volume (CBV). Knowing that it is true should permit readers to find it plausible. Payen *et al.* have appropriately cited relevant seminal references, on this and on magnetic susceptibility contrast imaging. The leap is also consistent with intuition if one pictures two snapshots: the first one with normal CO_2 after the contrast agent has found an equilibrium concentration in blood; and the second one a few minutes later, after CO_2 has been increased, and there has been vasodilation with a corresponding increase in the number of dextran-coated iron particles in each microvessel. It certainly seems plausible that because pericapillary water molecules will have more iron in their territory, they will experience an increased relaxation rate.

In conclusion, the manuscript of Payen *et al.* not only demonstrates the feasibility of a new type of measurement that is important to anesthesiologists, it also brings, for the very first time, a new kind of MRI to ANESTHESIOLOGY. One now sees more than standard anatomic imaging. One sees a kind of physiochemical imaging, where each pixel intensity represents the quantification of a change in a physiochemical parameter. It should not be offensive that the parameter imaged by Payen *et al.* relates to physiological and chemical interactions of water, which has many important intracellular roles and protein interactions that remain to be fully understood.[9,10] We can definitely expect additional innovations from MRI groups in the way of physiologic and functional imaging. But we should also not lose track of follow-up studies by Payen *et al.* and others. We look forward to the likely emergence of new types of human MRI examinations that will aid in patient care.

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References

1. Hahn E: Spin echoes. Phys Rev 1950; 80:580–94
2. Payen J-F, Vath A, Koenigsberg B, Bourlier V, Decorps M: Regional cerebral plasma volume response to CO_2 using magnetic resonance imaging. ANESTHESIOLOGY 1998; 88:984–92

3. Pascal B: Je n'ai fait celle-ci plus longue que parce que je n'ai pas eu le loisir de la faire plus courte." ("I have made this letter long because I did not have the time to make it short."). In *Lettres Provinciales, Selzième Lettre,* Bartlett's Familiar Quotations, 1980; 15:299

4. Edelman RR, Warach S: Magnetic resonance imaging (1). N Engl J Med 1993; 328:708-16

5. Edelman RR, Warach S: Magnetic resonance imaging (2). N Engl J Med 1993; 328:785-91

6. Purcell EM: Electricity and Magnetism, Berkeley Physics Course, Volume 2. New York, McGraw-Hill, 1965, pp 352-8

7. Ogawa S, Lee TM, Kay AR, Tank DW: Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Nat Acad Sci U S A 1990; 87:9868-72

8. Graham GD, Zhong J, Petroff OA, Constable RT, Prichard JW, Gore JC: BOLD MRI monitoring of changes in cerebral perfusion induced by acetazolamide and hypercarbia in the rat. Magn Reson Med 1994; 31(5):557-60

9. Fulton AB: How crowded is the cytoplasm? Cell 1982; 30: 345-7

10. Assaf Y, Cohen Y: Detection of different water populations in brain tissue using 2H single- and double-quantum-filtered diffusion NMR spectroscopy. J Magn Reson 1996; 112(B):151-9