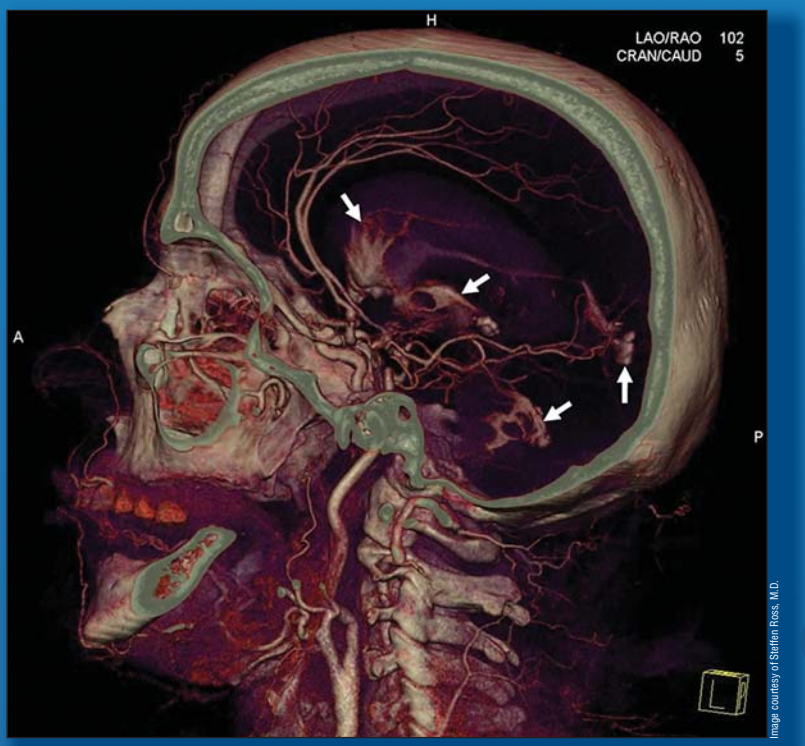
August 2008 • Volume 18, Number 8

RSNA News



Forensic Imaging Bolstered by New Technology, Techniques

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Published monthly by the Radiological Society of North America, Inc., 820 Jorie Blvd., Oak Brook, IL 60523-2251. Printed in the USA.

POSTMASTER: Send address correction "changes" to: *RSNA News*, 820 Jorie Blvd., Oak Brook, IL 60523-2251.

Nonmember subscription rate is $20 per year; $10 of active members' dues is allocated to a subscription of *RSNA News*.

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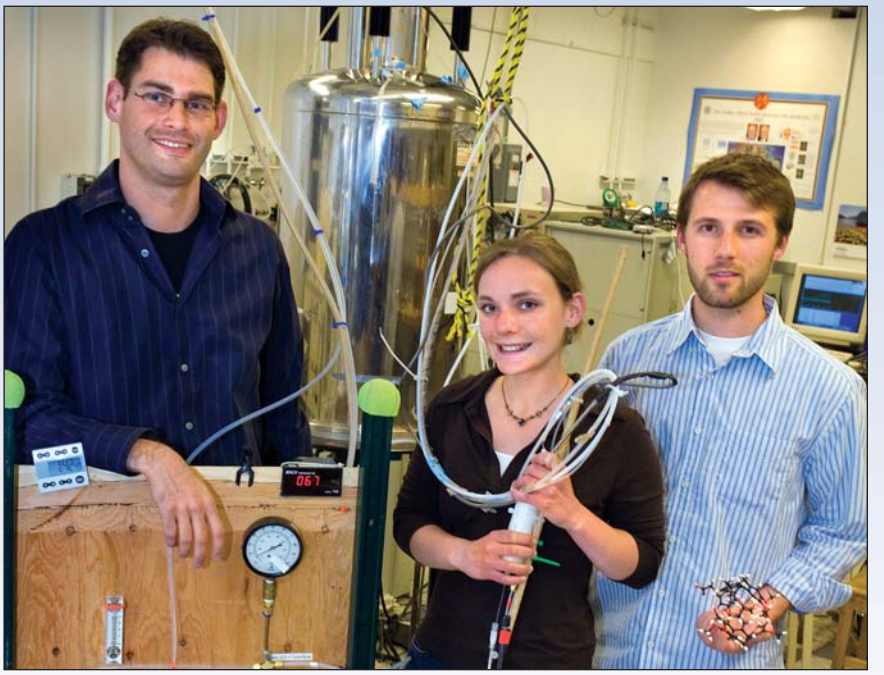
New MR Imaging Method Capitalizes on Temperature to Improve Sensitivity

PUTTING A series of nuclear magnetic resonance (NMR) techniques to use, researchers at the U.S. Department of Energy's Lawrence Berkeley National Laboratory have developed a new MR imaging process. Using something called temperature-controlled molecular depolarization gates, the process quickly creates more selective and sensitive MR images.

Leif Schröder, Ph.D., led the team, that included personnel in the labs of Alexander Pines, Ph.D., and David Wemmer, Ph.D., at Berkeley Lab and the University of California, Berkeley. The research sprung from the use of xenon in NMR to image void spaces such as lung areas. The spin of xenon's nuclei, like other noble gases, is easily polarized, making the gas useful in NMR imaging—when the xenon is depolarized with a burst of radiofrequency energy, the depolarized xenon stands out and enhances contrast.



Leif Schröder, Ph.D. *(left),* and graduate students Monica Smith and Tyler Meldrum at Lawrence Berkeley National Laboratory have developed a new MR imaging process that uses temperature-controlled molecular depolarization gates to quickly create more selective and sensitive MR images.

Since Drs. Pines and Wemmer and colleagues published results of the use of xenon as a biosensor in 2001, xenon lung imaging has made its way into clinical applications. Drs. Pines and Wemmer developed a process of "caging" the xenon atoms in so-called biosensors—constructs containing a targeting unit and molecular cages known as cryptophanes. These biosensors can then be attuned and sent to find specific molecules of interest.

The goal is to make MR imaging more compatible with the sensitivity of PET or SPECT.
Leif Schröder, Ph.D.

In 2006, Dr. Schröder's team found a way to boost the signal from the hyperpolarized xenon atoms inside the biosensor cages. This new technique, called hyperpolarized xenon chemical exchange saturation transfer (HYPER-CEST), allows for a much stronger signal that creates images much more quickly. Meanwhile, the flexible nature of the cryptophane biosensors could allow imagers to "multiplex" and simultaneously seek out and highlight several different types of targets.

"As always, sensitivity is a big issue in NMR/MR imaging," said Dr. Schröder. "If you work with small concentrations of the biosensor as your contrast agent—and this is the case in realistic applications—there is only a small amount of xenon directly associated with the molecular cages. We had to come up with an indirect detection method. The goal is to make MR imaging more compatible with the sensitivity of positron emission tomography (PET) or single photon emission computed tomography (SPECT)—for example, combining molecular information from new contrast agents like the xenon biosensor with all the nice advantages MR imaging has over the other radiotracer methods."

Temperature Shift Has Big Impact

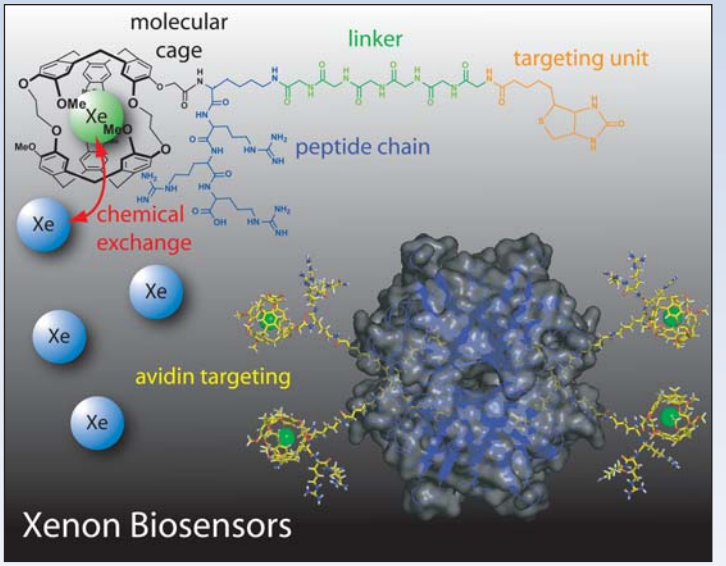
HYPER-CEST MR imaging had only been tested at room temperature until this past year, when the team was able to develop a HYPER-CEST process that also worked at body temperature—an upward temperature shift that drastically changes how the xenon atom reacts with the cryptophane cage.

"Even with HYPER-CEST, we saw the need for further improvement and started studying the impact of increased temperature, which works in our favor," said Dr. Schröder. "It dramatically increases the sensitivity of the HYPER-CEST process and we are optimistic for applications with physiologically relevant temperatures."

The temperature-controlled molecular depolarization acts as "a kind of control mechanism to optimize the contrast generated by HYPER-CEST," said Dr. Schröder. "The temperature effect is useful to improve sensitivity at body temperature, so we are optimistic that this will cancel out some other problems that we might face for in vivo applications," he said. "On the other hand, it might be a promising technique to monitor sites of inflammation with increased body temperature."

The overall result is not just faster, sharper, more specific MR imaging, but the possibility of more closely examining chemical exchanges in nanostructures and other varied applications across different research fields.

"Temperature-controlled molecular depolarization is not going to change the way that MR imaging is used," said team member Monica Smith, a graduate student in the Wemmer lab. "However, the sensitivity to changes in temperature achievable with this method shows promise for clinical applications, such as detecting 'hot' atherosclerotic plaques." Smith went on to note that "HYPER-CEST, and by extension temperature-controlled molecular depolarization, is a method that can either be used as a spectroscopic technique or it can incorporate the encoding mechanisms of MR imaging to provide spatially resolved spectroscopic information."



Leif Schröder, Ph.D., and colleagues use this graphic to illustrate hyperpolarized xenon chemical exchange saturation transfer (HYPER-CEST). Xenon biosensors link a molecular cage to a targeting unit for specific sensing of biochemical target (in this case the biosensor can bind to avidin through biotin). Atomic xenon is trapped temporarily inside the cage and can transfer the information from the biosensor into the pool of free xenon. This process becomes more sensitive at higher temperatures.

Numerous Experiments Under Way

HYPER-CEST will be an additional tool to provide molecular imaging information with a high sensitivity, said Dr. Schröder. "The spatial resolution will probably not be as good as on modern scanners for proton imaging, but it will most likely reach into a new dimension of sensitivity and should close the sensitivity gap between MR imaging and PET/SPECT," he said.

While Dr. Schröder was unwilling to guess at a possible timeline for clinical application of HYPER-CEST MR imaging, his team is moving forward with preliminary animal experiments this year. Smith added that the team plans to conduct more clinically relevant experiments.

Dr. Schröder also noted that, from the chemical side, researchers in the Wemmer group are working on new sensors with more biochemical relevance—for use, for example, in studies addressing heart and vascular disease.

"On the detection side, we are working on implementation of bioreactors into our NMR setup to run experiments on living cells, such as for detection on tissue samples," continued Dr. Schröder. "Other challenges are the limited lifetime of the hyperpolarization. We are currently working on a setup to deliver xenon to so called bioreactors with suspensions of living cells."

MR Imaging at RSNA 2008

"The Categorical Course in Diagnostic Radiology Physics: CT and MR Imaging" includes a session on MR Safety on Wednesday morning. Co-directed by Willi A. Kalender, Ph.D., and Edward F. Jackson, Ph.D., this session will detail the American College of Radiology 2007 White Paper on MR Safety and address MR and implanted devices and high field, radiofrequency and gradient safety. Enrollment is under way for this and all RSNA 2008 courses at *RSNA2008.RSNA.org*.

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