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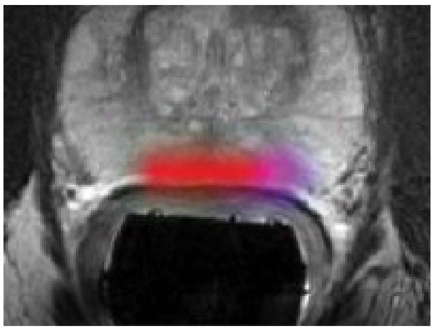
MR in Hyper-drive: Introducing Hyperpolarized MRI & A New Era of Metabolic Imaging



Hyperpolarized MR image of lactate/pyruvate in prostate cancer
Sarah Nelson, PhD, UCSF

Hyperpolarized MRI, also known as hyperpolarized MRSI (or HP-MRSI), is a new technique representing a major development in molecular MR currently making the rounds in the international molecular imaging circuit. The technology offers unheard-of imaging resolution and has already been researched in a human trial for prostate cancer. A number of oncologic applications, most notably the imaging of prostate cancer and cardiovascular disease, are lined up for future research. Scientists, engineers and clinicians at the forefront of this research are being lauded for their contributions by the World Molecular Imaging Society (WMIS) this year. Molecular Imaging Insight discusses the innovative technology, its limitations and potential with three Gold Medal awardees.

Dynamic nuclear spin polarization—this is the feat that researchers in multiple institutions the world over have been working on to bring hyperpolarized MR imaging into being. It is a very complicated technology requiring a lot of physics, materials engineering and precision on the imaging side, but the potential payoff is rich. A few different systems and bioreactors have been in the works and one particular MRI system was unveiled during the International Society of Magnetic Resonance in Medicine (ISMRM) and European Society of Magnetic Resonance in Medicine and Biology (ESMRMB) joint meeting in Milan in May. During the upcoming World Molecular Imaging Congress from Sept 17-20 in Seoul, Korea, the WMIS champions the imaging technique by bestowing Gold Medal awards for science on major players in the engineering, design and clinical research involved.

“While the field of hyperpolarized MRI has exploded over the past decade, and there are numerous worthy nominees, the WMIS Gold Medal winners have led the way in identifying novel biologically relevant compounds that can be exploited by this technology,” says incoming WMIS President Jason S. Lewis, PhD, currently vice chair for research in the department of radiology at Memorial Sloan Kettering Cancer Center in New York City. “There is a great unmet need for more precise and versatile molecular imaging technologies, and the development of such means would have an enormous public-health impact."

Molecular Imaging Insight talked with three of the pioneers: Kevin Brindle, PhD, professor of biochemistry at Cambridge University in the United Kingdom; Jonathan Murray, an electrical engineer and founder of Research Circle Technology; and Daniel B. Vigneron, PhD, a professor and director of the Hyperpolarized MRI Technology Resource Center at the University of California San Francisco (UCSF).

Exponential resolution gains

MRI is an ideal technology for high resolution imaging of soft tissues, but researchers have been hampered at times by semi-static imaging and resolution ceilings. Scientists have been exploring MR metabolic imaging for some time, but low resolution continued to be an issue until hyperpolarization was painstakingly developed for this purpose. In the past decade, the technique has had to make it over several hurdles to ensure that preparation of hyperpolarized agents was not only feasible, but state-of-the-art and reproducible. A prepared agent has gone from a semblance of a solid state in freezing temperatures to a dip in boiling water before it is injected for imaging.

"Essentially you can polarize the spin outside the magnet at almost absolute zero temperature—about one degree kelvin—and then rapidly warm it up without losing the polarization and inject this polarized material intravenously," explains Brindle. "It has been done in humans at UCSF, and now you've got so much signal that you can actually image where this molecule goes in the body. In magnetic resonance that is unprecedented. It's a more than 10,000 fold gain in sensitivity."

Initial studies of hyperpolarized agents came on the scene in the early 2000s but have only just picked up enough momentum to really gain the attention of the molecular imaging community. The first human trial was conducted in 2010, says Murray. He explains that the innovation in hyperpolarized MR is not just in the resolution, but what can now be imaged compared to conventional MRI and other molecular imaging modalities.

"If you take a typical MR machine, for each average image it is working on parts per million and you hear the MR machine go thunk, thunk, thunk, because it's doing a lot of averaging to get to the image," Murray says. "With this technique, we can move that from three parts per million to 300,000 parts per million. That moves you to sub-second resolution and you get enough signal that you can image carbon atoms. PET just tells you where that atom is, but it doesn't tell you which molecule it has gone to."

Agents of change

Initial studies using this particular incarnation of hyperpolarization have been working with carbon-13 agents and more specifically C-13 pyruvate, an intermediary of glycolysis, which is an ideal target for oncologic imaging because researchers are able to track pyruvate as it turns into a lactate pool by way of tumors' hyperactive cellular metabolism.

"The tumors light up because they are full of lactate and we can monitor the kinetics of that process," says Brindle. In the context of treatment monitoring, a patient could be administered a therapy and within 24 hours hyperpolarized MRI can provide proof positive whether the treatment is working. Not all patients respond to therapy due to genetic heterogeneity and other factors. With this technique, clinicians can see that lactate pool collapse within a day after the initiation of a course of treatment. Hyperpolarized MRI is poised for use in both treatment selection and response.

“We’ve been promoting this as a way of tracking treatment response,” Brindle notes. “And it is becoming particularly clear that we need to select patients for particular drugs.”

The collapse of that lactate pool is the sign of a successful therapy because as tumors decrease utilization of pyruvate, a metabolite, researchers then see increases in fumarate, another metabolite, which signals cell death. Another trial is expected to begin this year or next to explore hyperpolarized MR for treatment response in glioma, breast cancer and lymphoma patients. Researchers have already compared hyperpolarized MR with FDG PET imaging and that research will continue (Magn Reson Med. 2013; 70: 1200).

Always a caveat

There are several limitations to working with hyperpolarized MR but researchers are actively working to improve the technology. Firstly, there is the issue of a limited number of agents. However, pyruvate is not the only agent being developed. One of the most recent studies is incorporating hyperpolarized glucose also radiolabeled with carbon-13. It follows the same concept of tracing metabolites in tumor glycolysis (Nature Med. 20: 93-97, 2014).

More substrates can be used to create these agents. A variety of metabolites are on the research bench, but often they have exceedingly short lifespans. “The Achilles heel of this technique is that you have 2 to 3 minutes to do everything,” says Brindle. That means targets have to be working at a very fast pace to go through all the steps of a given metabolic pathway. Glucose is showing a lot of promise and may have a longer lifespan to image all these steps.

The applications of metabolism

Preclinical studies using model tissues and transgenic mouse models have already started evaluating the technique for brain tumor studies, liver and kidney cancer and breast cancer. Other institutions have done some cardiac hyperpolarized MR studies, as well, says Vigneron.

It is important to note that this technique is not just revealing an energy exchange but the language of genetics. Patients with genetic predispositions are going to show an up-regulation of their glycolysis pathway that fuels metabolism and cancerous tumors. The change from pyruvate to lactate creates a frequency change detected by MR. This is, in a way, an advancement beyond PET imaging.

“In a way, for the first time, we are looking at enzymatic changes that reflect genetic changes that molecular biologists have been studying for the last 10 to 20 years since oncogenes were discovered,” adds Vigneron.

Patently hyperpolarized

The dawn of hyperpolarized MRI has required specific plastics to withstand freezing helium and boiling water. Not only that, but prepared agents also are exposed to low-energy microwaves somewhere in the middle. The agent is an approximately one-gram glassy pellet that is then lifted out of the helium bath and flushed with scalding hot water transforming into about 50 grams of warm solution slightly cooler than body temperature all in an enclosed and automated system. This technology is sure to become an excellent addition to MI suite.

Topic Category:
Nuclear Oncology [1]
