MRI Hyperpolarization and Molecular Imaging

Conventional magnetic resonance imaging (MRI) relies on magnetic resonance (MR) signal from proton nuclei of water within the body. The MR signal is encoded with magnetic field gradients for 2D and 3D imaging with no fundamental barriers to spatial resolution as long as sufficient MR signal is available. The latter is an Achilles’ heel limiting MRIs spatial and temporal resolution. Moreover, magnetic resonance spectroscopic imaging (MRSI) potentially offers the fourth dimension of chemical shift reporting on composition of tissue, i.e. imaging of protons of metabolites, in addition to three spatial dimensions. Despite its potential power for reporting on in vivo biochemistry, MRSI methods are even more signal limited than conventional MRI due to low concentration of metabolites, thus resulting in a typical voxel size of 1-10 mL.

Fundamentally, MR signal is linearly proportional to nuclear spin polarization and concentration. The former is linearly proportional to the applied magnetic field \( B_0 \) and is on the order of \( 10^{-3} \) for protons in a 1.5 Tesla (T) magnet. This dependence resulted in the implementation of high-field MRI systems: 3 T clinically used now in addition to 7 T and 9.4 T systems used in clinical research. However, despite clear advantages of high-field MRI scanners, the gains in polarization and consequently MR signal are rather modest.

An alternative approach is to polarize spins by several orders of magnitude using methods of nuclear spin hyperpolarization, i.e. significantly higher polarization than conventional equilibrium polarization endowed by the field of MRI magnet. While these hyperpolarized techniques can, in principle, polarize proton nuclear spins in water, they typically return back to their equilibrium state, i.e. very low polarization, within seconds and are rendered useless in the realm of hyperpolarized MRI. \( ^{13}C, ^{129}Xe, ^3He, ^{15}N \) and other nuclear spins can be hyperpolarized to the order of near unity resulting in signal enhancement by 4-6 orders of magnitude. Moreover, the decay of their hyperpolarized spin state can be as long as several hours (Nikolaou, Proc. Natl. Acad. Sci. USA 2013; 110:14150-14155) characterized by the spin lattice relaxation time constant of exponential decay \( T_1 \) with \( t_{1/2} = \ln(2)/T_1 \). These relatively long-lived nuclear spins of chemical compounds make them useful as hyperpolarized contrast agents. These agents are prepared by physical and/or chemical manipulations followed by administration of these contrast agents in living organisms and their MRI or MRSI imaging. Notably, hyperpolarized contrast agents are similar to radioactive tracers in that their signal-generating capability decays exponentially with time. This feature makes hyperpolarized MRI somewhat similar to SPECT and PET imaging.

SNMMI Mid-Winter Meeting Heads to Palm Springs

In only a few short months, the Society of Nuclear Medicine (SNMMI) will host its 2014 Mid-Winter Meeting, which will be held February 6-9, at the Renaissance Palm Springs Hotel in Palm Springs, Calif. The meeting brings together leading nuclear and molecular imaging physicians, technologists, pharmacists, scientists, and laboratory professionals representing the world’s top medical and academic institutions and centers.

Kicking off the meeting, the SNMMI Center for Molecular Imaging Innovation and Translation and SNMMI Clinical Trials Network will be co-sponsoring and organizing a one-day summit on Thursday, February 6, titled “Response to Therapy.” In the workshop, speakers and participants will discuss the technical factors that impact quantitative results, solid tumor response, response of tumor cells by a heme oxygenase inhibitor, and future trends in therapy.

Also on Thursday, February 6, the American College of Nuclear Medicine (ACNM) will be sponsoring a day-long program for attendees. A plenary session will be held from 8:00 a.m. – 9:00 a.m., followed by resident abstract presentations and several focused

IN THIS ISSUE

CMIIIT Laboratory Professionals Awards 3
CMIIIT Young Investigator Awards 3
Tech Corner: Molecular Breast Imaging 4
MI References 5
MI In the News 7
Calendar 8

Continued on page 2. See MRI

Continued on page 5. See SNMMI Mid-Winter Meeting.
Molecular Ultra-Fast Imaging

Hyperpolarized MRI is a rapidly emerging and developing field of molecular imaging. Hyperpolarized $^{129}$Xe and $^3$He polarizing equipment was pioneered in the 1990s in clinical research. An example of $^{129}$Xe ventilation images of a healthy human lung acquired using an open-source $^{129}$Xe polarizer (Nikolaou, Proc. Natl. Acad. Sci. USA 2013; 110:14150-14155) is shown in Fig. 1. In contrast, the first dynamic nuclear polarization (DNP) polarizer for production of injectable metabolic $^{13}$C and $^{15}$N contrast agents was described in 2003 (Ardenkjaer-Larsen, Proc. Natl. Acad. Sci. USA 2003;100:10158-10163). In less than a decade it transitioned to clinical trials in men (Kurhanewicz, Neoplasia USA 2003;100:10158-10163). During this relatively short period, pre-clinical studies have shown that hyperpolarized MRI and MRSI can be used for molecular imaging for diagnostic purposes, monitoring response to treatment (Day, Nat. Med. 2007, 13:1382-1387), disease grading (Albers, Cancer Res. 2008;68:8607-8615), and ultra-fast imaging speed (Bhattacharya, Magn. Reson. Mat. Phys. Biol. Med. 2005;18:245-256). Hyperpolarized MRI was extended to many contrast agents beyond hyperpolarized $^{129}$Xe/$^3$He gases to $^{13}$C-pyruvate, $^{1-13}$C-lactate, $^{15}$N-choline, $^{13}$C-glutamine, $^{13}$C-bicarbonate, $^{13}$C-fumarate, $^{13}$C-succinate and others (Gallagher, Prog. Nucl. Mag. Res. Sp. 2009;55:285-295). These contrast agents report on different pathways related to metabolism and its dysfunction. For example, hyperpolarized $^{1-13}$C-pyruvate reports on elevated rates of glycolysis, and therefore is similar to fluorodeoxyglucose (FDG) PET. Because FDG PET cannot be used for imaging of prostate cancer, hyperpolarized $^{1-13}$C-pyruvate can be a useful contrast agent for molecular imaging of prostate cancer demonstrating that PET and hyperpolarized MRI contrast agents can be complementary molecular imaging techniques.

Because hyperpolarization of contrast agents is not endowed by the magnetic field of the MRI scanner, hyperpolarized MR signal is not recoverable, i.e. it can only decay during the MRI scan. As a result, the delay referred to as repetition time in MRI can be ignored, and ultra-fast MRI sequences can be used for image acquisition, and sub-second imaging speed can be achieved (Golman, Magn. Reson. Med. 2001;46:1-5).

Hyperpolarized MRI and Other Molecular Imaging Modalities

There are fundamental differences between hyperpolarized MRI and radioactive contrast agents. Hyperpolarized MRI contrast agents do not use ionizing radiation. Moreover, MRSI techniques allow simultaneous imaging of multiple metabolites, e.g. in vivo MRSI of injected hyperpolarized $^{1-13}$C-pyruvate is capable of imaging both injected pyruvate and its daughter metabolite $^{1-13}$C-lactate in addition to others (Golman, Proc. Natl. Acad. Sci. USA 2006;103:11270-11275). This is a clear benefit, because it enables measurements of metabolism rather than tracer uptake typically measured by PET and SPECT.

Despite signal boost by several orders of magnitude, hyperpolarized MRI relies on signal from relatively dilute spins of administered hyperpolarized contrast agents. For example, hyperpolarized $^{13}$C-lactate concentration in vivo is on the order of a few mM, which is several orders of magnitude lower than proton concentration of tissue water. As a result, SPECT and PET are inherently significantly more sensitive (by orders of magnitude) imaging modalities when accounting for contrast agent quantity. Consequently, imaging applications of dilute biomolecules such as receptors using hyperpolarized contrast agents are truly challenging from a signal sensitivity perspective. A potential remedy to this challenge is to use other signal amplification methods. For example, a combination of Super-Paramagnetic Iron Oxide (SPIO) nanoparticles with hyperpolarized contrast agents can potentially bridge the required sensitivity gap by several orders of magnitude (Branca, Proc. Natl. Acad. Sci. USA 2010; 107, 3693–3697), because two signal enhancement methods are used synergistically.

While the main advantage of hyperpolarized MRI is the large sensitivity boost enabled by increased nuclear spin polarization, this increase is not endowed by the magnetic field of the MRI scanner. As a result, it is possible to perform MRI of hyperpolarized contrast agents in very low magnetic fields. For example, 3D images using hyperpolarized $^3$He of human lungs were successfully acquired at 6.5 mT (Tsai, J. Magn. Reson. 2008;193:274-285), which corresponds to ~1/500 of the main field of a 3 T MRI scanner. The possibility of molecular imaging using low magnetic field MRI scanners opens new opportunities for multi-modal imaging.
by potentially combining the power of molecular imaging of hyperpolarized MRI for example, with anatomical power of CT. Moreover, low-field MRI is inherently low cost, because the need for a high-field cryogenic magnet is eliminated. The combination of low cost and sub-second scan speed is a clear advantage, which has not been fully explored and exploited.

When comparing hyperpolarized MRI to PET imaging, it should also be noted that the vast majority of hyperpolarized contrast agents have significantly shorter lifetime on the order, of 0.5-5 minutes in vivo. This double-edged sword limits the use of hyperpolarized contrast agents from the perspective of metabolic pathways penetration, contrast agent in vivo delivery, pharmaceutical preparation and imaging site distribution. On the other hand, it offers an opportunity to perform a repeat scan within minutes after initial hyperpolarized scan, because there is no background signal from the first initially administered dose.

Other Translational Challenges

$^{13}$C, $^{15}$N, $^{129}$Xe and other heteronuclei are used in hyperpolarized MRI because of their relatively long-lived hyperpolarized state. However, using heteronuclei, represents a significant translational challenge, because most clinical MRI scanners can only detect proton nuclei, and therefore hyperpolarized contrast agents utilizing other nuclear spins such as $^{13}$C or $^{129}$Xe cannot be readily imaged. A typical solution is to upgrade the scanner to multi-nuclear capability, which is both costly and non-trivial. A potential long-term solution is the advent of a dedicated hyperpolarized MRI platform optimized for contrast agents and the site of interest, e.g. imaging of prostate using $^{13}$C hyperpolarized 1-13C-pyruvate.

Summary

To summarize, hyperpolarized MRI is an emerging and rapidly developing field in its infancy. It offers clear benefits for in vivo molecular imaging with respect to imaging methods relying on radioactive tracers, but has its limitations. The main challenge is the relatively short-lived nature of hyperpolarized contrast agents. For example, 13C-pyruvate has a T1 of less than 1 minute in vivo. However, new techniques are emerging for extending hyperpolarized lifetimes, e.g. using singlet states (Warren, Science 2009;323:1711-1714), as well as new contrast agents and their preparation techniques (Nikolaou, Proc. Natl. Acad. Sci. USA 2013; 110:14150-14155). Furthermore, new methods for hyperpolarized contrast agents’ imaging including low-field MRI and indirect proton imaging of hyperpolarized contrast agents (Mishkovsky, Magn. Reson. Med. 2012; 68:349-352). These and other new technologies, scientific developments, and innovations will likely reshape hyperpolarized MRI as we know it today.
TROUBLE SHOOTING DIFFICULT CASES WITH MOLECULAR BREAST IMAGING

Molecular breast imaging (MBI) is a recent, but rapidly evolving, nuclear medicine technique that utilizes small semiconductor-based \(\gamma\)-cameras in a mammographic configuration to provide high-resolution functional images of the breast. Current studies with MBI have used Tc-99m sestamibi, which is an approved agent for breast imaging. The procedure is relatively simple, and can be performed within five minutes postinjection, with the breast lightly compressed. Images of each breast are acquired in the craniocaudal and mediolateral oblique projections facilitating comparison with mammography.

Studies using MBI and breast-specific \(\gamma\)-imaging have shown that these methods have comparable sensitivity to breast MRI. A large clinical trial compared MBI with screening mammography in over 1,000 women with mammographically dense breast tissue and increased risk of breast cancer, and showed that MBI detected 2-3 times more cancers than mammography. In addition, MBI appears to have slightly better specificity than mammography in this trial.

MBI provides high-resolution functional images of the breast and its potential applications range from evaluation of the extent of disease to an adjunct screening technique in certain high-risk populations. MBI is highly complementary to existing anatomical techniques, such as mammography, tomosynthesis, and ultrasound. While the reported overall sensitivity of screening mammography is high (ranging from 71 to 96 percent), the sensitivity is significantly reduced in certain subsets of women, particularly in women with radiographically dense breasts and those at increased risk of breast cancer. Estimates of film mammographic sensitivity in women with extremely dense breasts range from 48 to 63 percent. The introduction of digital mammography has led to only modest improvements in sensitivity in the subset of women who are under 50 years of age, pre- or peri-menopausal and have dense breasts. Other modalities for breast imaging, such as ultrasound and MRI, have been extensively evaluated to determine their role in these subsets of women at increased risk. As of yet, MRI can be difficult to get approved without a cancer diagnosis, significant symptom, or BRCA+. MBI has been making headway at our facility because it costs 80 percent less than MRI, and with equivocal sensitivity, we are finding physicians want more ways to utilize this procedure.

In July of 2012, the state of Virginia made the decision to notify patients of their breast density and some problems related to mammography in dense breasts when a patients gets their annual screening results. While mammography is still crucial in these women, nuclear medicine is playing a larger and larger role at our institution, especially in difficult cases. Some examples:

Patient 1 – EB. EB is a 30-year-old female with history of diabetes who presented for diagnostic mammography for evaluation of palpable mass. The patient’s mass localized to the periareolar 12:00 position of the left breast. Mammography revealed dense breasts without evidence of discrete mass. Subsequent directed ultrasound showed a suspicious mass along the areolar edge of the left breast at the 12:00 position. This measured 3.0 x 3.5 cm. Patient underwent molecular breast imaging with a dedicated scintigraphic breast device which showed no abnormal accumulation in either breast particularly in the region of the left breast mass. Because of the suspicious sonographic features and our early inexperience, image-guided biopsy was performed which revealed stromal fibrosis and chronic periductal inflammation consistent with diabetic mastopathy. This patient could have avoided a biopsy.

Patient 2 – TK. TK is a 48-year-old patient with a remote history of benign left breast biopsy who was seen for diagnostic evaluation of developing nipple inversion. She had had a recent digital screening mammography which showed no change from prior exams but with 50-75 percent breast tissue density. At the time of diagnostic evaluation, an ultrasound was performed which revealed a 2.5 cm hypoechoic area with shadowing in the bed of the prior biopsy. The ultrasound was considered inconclusive and MBI was performed. This revealed a large focus of abnormal activity in the far posterior and outer aspect of the left breast. Ultrasound-guided core biopsy of the lesion was performed and revealed invasive carcinoma with lobular features and solid ductal carcinoma in-situ (DCIS). Pre-surgical MRI showed a 9.0 cm spiculated mass at approximately the 2-3:00 position. Final pathology from the left mastectomy specimen showed invasive lobular carcinoma. This patient had a 9 cm (or a golf ball) cancer missed by mammography due to dense breasts and even retrospectively her mammogram had remained stable for years.

Patient 3 – BS. BS is a 62-year-old patient with a known right breast carcinoma. As part of evaluation prior to definitive management, the patient underwent MBI of both breasts to evaluate for multifocal or bilateral disease. The MBI imaging revealed uptake in the known periareolar right breast cancer but also a focus of accumulation in the outer aspect of the left breast. Diagnostic left mammography and directed ultrasound were performed and showed no abnormality in the area of the abnormal MBI activity. Due to cont-
talks. The program will conclude with the ACNM banquet and awards dinner to be held Thursday evening where the ACNM leadership will recognize outstanding leaders in the field, as well as resident abstract winners.

Friday, February 7, begins the three day SNMMI/SNMMI-TS education program, which includes educational sessions designed in collaboration with several of SNMMI's councils. The education sessions cover a wide variety of topics, including simultaneous PET/MRI, MIBG in diagnosis and therapy, emerging radiotracers, lymphoscintigraphy, alpha particle therapy agents, Alpha radin in castration-resistant prostate cancer and clinical SPECT/CT, among others.

Once again, SNMMI and ACNM will offer the ever-popular CT case review course for nuclear physicians. On Friday, February 7, and Saturday, February 8, a total of 100 cases—25 each in head and neck, chest, abdomen and pelvis, and musculoskeletal system—will be reviewed for credit. Additionally, an MRI Case Review session will be held on Saturday, February 8, that include 20 cases on the brain and central nervous system, as well as the body.

The SNMMI Mid-Winter Meeting also offers attendees the opportunity to network with peers and meet new colleagues who share similar interests. In addition to the ACNM banquet, SNMMI will host a social event in the exhibit hall during the evening on Friday, February 7. The exhibit hall will also be open during the day on Friday and Saturday, and attendees will be able to visit with the top nuclear medicine and molecular imaging product and service providers to experience the latest in technology.

In addition to attending the scientific sessions while in Palm Springs, meeting participants will also have the chance to explore the city and all it has to offer. The desert resort town offers activities and attractions for all, including outdoor adventures, spa getaways, museums and a wide array of dining options.

Additional information regarding the meeting, including registration details, can be found at www.snmmi.org/mwm2014.

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### References

Each month, the CMIIT Editorial Board selects the top molecular imaging research papers from all papers indexed by PubMed. Below are recent papers on molecular imaging research.

The links below go to these references, including their abstracts and links to the full paper on PubMed.

- **Feasibility of Vascular Endothelial Growth Factor Imaging in Human Atherosclerotic Plaque Using 89Zr-Bevacizumab Positron Emission Tomography.**

- **Imaging of Integrin αVβ3 Expression Using 68Ga-RGD Positron Emission Tomography in Pediatric Cerebral Infarct.**

- **Visualizing cellular interactions with a generalized proximity reporter.**

- **Dynamic dual-tracer MRI-guided fluorescence tomography to quantify receptor density in vivo.**

- **Imaging DNA with Fluorochrome Bearing Metals.**
  Cho H, Guo Y, Sosnovik DE, Josephson L.

- **In vivo visualization and monitoring of viable neural stem cells using noninvasive bioluminescence imaging in the 6-hydroxydopamine-induced mouse model of Parkinson disease.**

- **Comparison of cyclic RGD peptides for alphavbeta3 integrin detection in a rat model of myocardial infarction.**

- **PET Imaging of Chemokine Receptors in Vascular Injury-Accelerated Atherosclerosis.**
cerns based on the findings with MBI, the patient elected to change the initial surgical plan of a lumpectomy and have bilateral mastectomies. The interpreting pathologist used the MBI findings to help direct the left breast histologic analysis which revealed a 2.5 mm focus of invasive tubular carcinoma. The MBI changed surgical planning and picked up a second cancer that could be a future problem.

In conclusion, these cases demonstrate the benefit and utility of MBI for the management of difficult cases when using conventional imaging techniques, specifically, mammography and sonography. It is well known that lobular carcinoma is very difficult to detect mammographically—especially in the dense breast—because of its growth pattern and characteristics. Very large lesions such as that described in the second case may be mammographically occult. Another very difficult situation is seen in patients with diabetic mastopathy. Mammography and ultrasound may show multiple and widespread abnormalities where the determination between benign and malignant disease is almost impossible. Selection of an appropriate biopsy site among the numerous abnormalities seen with conventional modalities is very problematic without other imaging techniques. Because sestamibi accumulates in areas of high mitochondrial activity and concentration, this agent is not affected by dense breast tissue, extensive scarring or other conditions that limit mammography and sonography. And, as illustrated in the third case example, the MBI technique is extremely sensitive as it allowed detection of very small carcinoma.

James Crowley, CNMT
Jackson Kiser, MD
In the News

Brain Scan Rules Out Alzheimer’s in Ex-NFL Player
http://www.medpagetoday.com/MeetingCoverage/AAlC/40485
A tracer-enhanced PET scan for beta-amyloid plaques helped doctors arrive at a correct diagnosis in a former pro football player with progressive cognitive impairment, a researcher said here.

The unnamed player was finally diagnosed with a form of post-traumatic dementia with possible chronic traumatic encephalopathy (CTE), rather than Alzheimer’s disease, after the PET scan showed no evidence of beta-amyloid plaques in his brain, said Effie Mitsis, MD, of the Mount Sinai School of Medicine in New York City.

FDG-PET Scans May Improve Prostate Cancer Management
Fluorodeoxyglucose positron emission tomography (FDG-PET) findings can help identify prostate cancer (PCa) patients who have high-risk disease prior to radical prostatectomy and are at elevated risk for treatment failure, researchers reported at the Canadian Urological Association’s 68th annual meeting.

Lead investigator Frederic Pouliot, MD, PhD, a urologic oncologist at Laval University in Quebec, and his team found that increased FDG uptake by the prostate is highly correlated with factors indicative of a poor prognosis such as advanced clinical stage, a pathological Gleason score of 8 or higher, and percentage of intraprostatic cancer.

NaF-PET/CT beats scintigraphy, SPECT/CT for bone metastases
Sodium fluoride (NaF) PET/CT provides greater sensitivity and specificity for the detection of bone metastases than planar bone scintigraphy and SPECT/CT, according to a new pilot study from Copenhagen University Hospital.

In the comparison, planar bone scintigraphy also had a relatively high number of equivocal scans compared to NaF-PET/CT, which could reflect uncertainty in reading planar bone scintigraphy due to the modality’s low sensitivity and specificity, the researchers concluded.

PET/MR Detects Prostate Cancer Recurrence
An 11C-choline PET/MR protocol for the restaging of prostate cancer was well tolerated by patients and detected significantly more recurrences than PET/CT, according to new research. PET/MR was particularly good at detecting small local recurrences.

In theory, magnetic resonance imaging is more beneficial than computed tomography for prostate cancer restaging because it provides higher soft-tissue contrast. “In the analysis of recurrent disease, it would potentially have a higher detection rate,” said lead investigator Matthias Eiber, MD, a radiologist from the Technical University Munich in Germany.

Migraine Really Is a Brain Disorder
Positron emission tomography of patients experiencing the premonitory phase of migraine, prior to the headache setting in, shows activation in several areas of the brain, indicating that migraine is a brain disorder and not a response to pain stimuli.

The results are significant in terms of understanding the neurobiology of migraine and could have future implications for drug treatment, said study author Peter James Goadsby, MD, PhD, professor of neurology, and director of the Headache Program at the University of California at San Francisco, and president of the International Headache Society.

FDG PET could predict treatment response for major depressives
Previous studies have pointed to treatment-specific imaging biomarkers for predicting response to therapy for patients with major depressive disorder (MDD), but brain imaging with FDG PET, particularly of the anterior insula, is going a step further to differentiate response to combined treatments, which could improve management of patients with the mood disorder, according to a study published June 12 in JAMA Psychiatry.

18F-FDG PET May Predict Cervical Spinal Cord Compression Outcome
Imaging with 18F-FDG PET may predict outcomes for patients with degenerative cervical myelopathy, according to a study published in The Journal of Nuclear Medicine.

Researchers in Germany prospectively assessed regional changes in glucose metabolism in the cervical spinal cord using 18F-FDG PET in 20 patients with symptomatic degenerative monosegmental cervical stenosis who underwent decompressive surgery.

Chasing the lightning: Molecular epilepsy imaging with PET and SPECT
Recent studies have indicated that epilepsy may be more comprehensively characterized with the help of PET and SPECT, and these modalities could benefit the 1-2 percent of the U.S. population with the neurological disorder, according to a review published online Aug 22 in the Journal of Nuclear Medicine.

Ajay Kumar, MD, PhD, an assistant professor of pediatrics and neurology at Wayne State University of Medicine, and Harry T. Chugani, MD, chief of the division of pediatrics at Children’s Hospital of Michigan in Detroit, weighed in on PET’s potential for mapping epilepsy in the brain, specifically two types called sporadic temporal and extratemporal lobe epilepsy.
Calendar of Events

Quantitative Image Analysis and Application
Specific Imaging - PRIMA IV
http://www.wmicmeeting.org/PRIMA-IV-workshop.php
September 22–26, 2013
Savannah, Georgia

Advanced Molecular Imaging and its Clinical Translation
http://advancedmolecularimaging.org/wp/
October 27–30, 2013
Boston, Massachusetts

First Preclinical Imaging Symposium
November 4, 2013
London, United Kingdom

SNMMI 2014 Mid-Winter Meeting
www.snmmi.org/mwm2014
February 6–9, 2014
Palm Springs, California

SNMMI 2014 Annual Meeting
www.snmmi.org/am
June 7-11, 2013
St. Louis, Missouri

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