Hyperpolarized and Inert Gas MRI and Xenon Biosensor Molecular MRI

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Magnetic resonance imaging (MRI) is a non-invasive imaging modality for assessment of disease within the body. Dr. Mitchell Albert co-invented hyperpolarized gas MRI technology which involves use of a contrast agent coupled with MRI to improve the sensitivity of xenon imaging by up to 100,000 times [1]. Hyperpolarized (HP) xenon-129 (^{129}Xe) and helium-3 (^{3}He) MRI can provide structural and functional information on organs throughout that body that can be useful in staging disease. This breakthrough technology is potentially one of the most significant contributions to the field of medical imaging.

Imaging the lungs is particularly difficult. MRI uses a magnet to align the proton spins of hydrogen molecules that are typically found in water throughout the body, however, the lungs are not hydrogen dense and thus imaging for diagnosis and disease monitoring is limited. HP noble gases and inert fluorinated gases have the potential to address the need for sensitive, functional imaging of the lungs. Dr. Albert has demonstrated the ability of HP ^{129}Xe and ^{3}He to obtain high quality structural and functional images of the lungs. Due to the high costs of the required polarizers and isotopes, Dr. Albert has also developed inert fluorinated gas lung imaging which can be used to obtain structural and functional images of the lungs without an expensive polarizer. Figure 1 shows a comparison of HP ^{3}He and ^{19}F MRI scans in the same healthy volunteer. Although the ^{19}F images appear to have blurred lines, there are no significant differences in lung biomarker measurements between the two techniques [2]. This technology is currently being tested to determine if the quality of ^{19}F images obtained can be used to provide clinical information beyond the capability of current imaging technology. Due to its low-cost and abundance, this technology could be easily implemented in every MRI scanner in the world.

HP gas MRI also has potential application for brain imaging. Dr. Albert first published the first *in vivo* results using the HP ^{129}Xe brain imaging technique for cerebral ischemia and cortical brain function. In a stroke model, his team observed HP ^{129}Xe signal voids in regions of the ischemic core. This technology has progressed to clinical trials and for the first time ever, a participant with Alzheimer's disease was imaged using this HP gas MRI technology. Longer washout times were found in both spectroscopy and imaging, indicating slower perfusion or blood flow in Alzheimer's disease volunteers compared to controls. These preliminary results have shown to be promising for potential early detection of Alzheimer's disease. Further, the findings of this research have potential implications for the discovery of drug treatments and monitoring of disease progression. In addition, in studying healthy volunteers, HP gas functional magnetic resonance imaging (fMRI) showed signal enhancement approximately 10 times larger compared to conventional proton BOLD fMRI. Xenon-129 fMRI has the potential to be the next significant contribution to neuroimaging.

Although HP noble gases do not specifically bind to biological receptors, they can be delivered to a disease target by molecular system biosensors. Dr. Alberts' research team has developed biosensors that target inflammation sites in the body using a hyperCEST MRI pulse sequence to cryptophane-A cages functionalized with a PK11105 ligand. Dr. Albert's team has also successfully obtained the first ever *in vivo* images of a contrast agent, cucurbit[6]uril, for a HP ^{129}Xe biosensor to image the vascular system throughout a living animal model. This work has recently been published in the journal *Scientific Reports* [3]. Cucurbit[6]uril (CB6) is a cage molecule that can be used as a contrast agent for HP ^{129}Xe gas due to its ability to exhibit a hyperpolarized has Chemical Exchange Saturation Transfer (hyperCEST) effect. Following *in vivo* injection of CB6, a radio frequency pulse was applied at the chemical shift of Xe-CB6 to depolarize the xenon within the CB6 cage, effectively reducing the detectable polarized xenon atoms. This enables detection of CB6 cages. In Figure 2, the resulting saturation maps for the rat abdomen (Figure 2A) and the rat brain (Figure 2B) are overlaid on traditional ^{1}H MRI images to show the location of the CB6 molecules. This is an important contribution to the field of molecular imaging in that Dr. Albert's research has shown that hyperCEST imaging is possible *in vivo*

and future work will include an in depth study of how to achieve optimal sensitivity in animal models, as well as the development of a functionalized cage molecule with a high yield for specific disease detection. This technology could potentially revolutionize the field of molecular imaging for disease detection and monitoring.

Figures

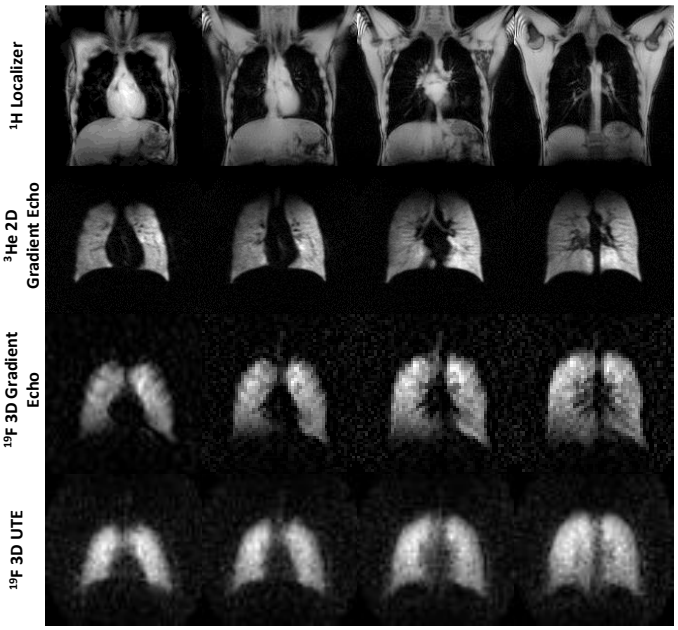

Figure 1: Comparison of representative ^{1}H localizer, ^{3}He 2D gradient echo, ^{19}F 3D gradient echo, and ^{19}F 3D UTE images acquired in the same healthy volunteer.

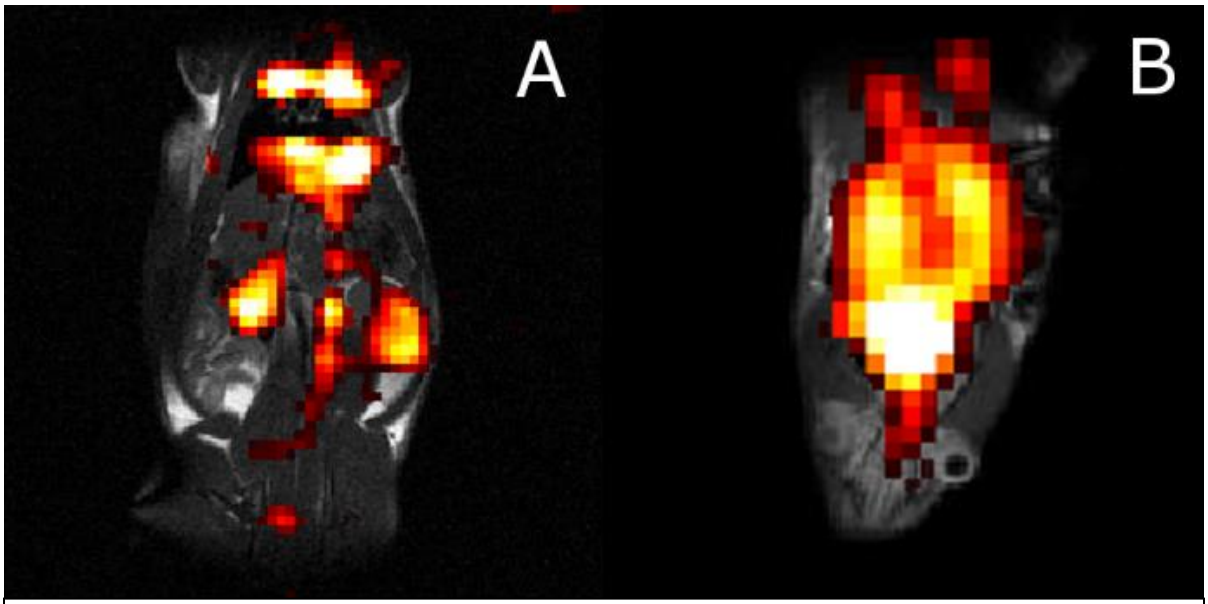

Figure 2. A) HyperCEST saturation map of a rat abdomen. The saturation map is overlaid on a 1H TSE MR image to show accumulation of the CB6 cage contrast agent in the heart, lungs, aorta, kidneys, and bladder.
B) HyperCEST saturation map of rat brain overlaid of a 1H TSE MR image. A strong signal is observed in the brain, and a weaker, albeit detectable, bilateral signal is observed from either the muscle or carotid arteries.

Biography

Dr. Mitchell Albert is a Research Chair in Molecular Imaging and Advanced Diagnostics at Lakehead University and the Thunder Bay Regional Health Research Institute in Thunder Bay, Ontario. Dr. Albert earned his Ph.D. in Physical Chemistry at the State University of New York at Stony Brook. Following completion of his doctorate, Dr. Albert served in faculty positions at Harvard Medical School and the University of Massachusetts Medical School. Dr. Albert has published over 70 peer-reviewed papers, over 120 peer-reviewed conference proceedings, and he has given over 75 invited talks at conferences and workshops. In recognition of his contributions to Medical Imaging, Dr. Albert received the United States Presidential Award from President Clinton and a National Science Foundation CAREER Award.

References

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