Development of High Resolution 3D Hyperpolarized ^{13}C Imaging Techniques

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Purpose: New hyperpolarization (HP) methods have provided unprecedented biological information noninvasively using MRI. Imaging HP substrates with MRI offers a new powerful tool for detecting the metabolic and physiological changes that underlie disease processes. HP pyruvate and lactate provide important metabolic information for the study of cancer and other diseases, while HP urea provides perfusion and urea transporter imaging.[1,2] Spatial resolutions of ~0.05cm^3 or coarser are typically used, but in this project we developed and applied techniques for 3D high resolution (1.5 mm isotropic; 0.003cm^3) ^{13}C images of [1-^{13}C]lactate, [1-^{13}C]pyruvate, and [^{13}C,^{15}N$_2$]urea *in vivo*.

Methods: In the first set of experiments, hyperpolarized [1-^{13}C]lactate T_2 mapping was performed on normal rats.[3] In the second set of experiments, a 3D bSSFP pulse sequence was utilized in normal rats with 1.5 mm isotropic resolution. A 1.6 ms sinc pulse with a flip angle θ =180°, after a θ =90° prep pulse, was used with a TR/TE of 8.5/4.25 ms and 480 phase encoding steps, corresponding to a total sequence time of ~4 s. The ^{13}C images of [1-^{13}C]lactate, [1-^{13}C]pyruvate, and [^{13}C,^{15}N$_2$]urea were acquired independently in 4 s starting at 20 s after beginning of injection. In the third set of experiments, the same 3D bSSFP sequence was used on mice with transgenic breast and prostate tumors (TRAMP), albeit with fewer phase encoding steps needed to achieve the same isotropic resolution, leading to total scan times ranging from 1.6-2.4 s. The experiments were conducted on a 3T GE clinical scanner. DNP experiments used HyperSense and SpinLab polarizers, and 3mL (rat) or 500µL (mouse) of 160mM [1-^{13}C]lactate, 80mM [1-^{13}C]pyruvate, and 110mM [^{13}C,^{15}N$_2$]urea was injected via tail vein catheters in three different animals.

Results and Discussion: The T_2 distribution of [1-^{13}C]lactate can be seen in Figure 1, where the longest T_2 values exist in the vasculature and the renal pelvis of the kidney. Previously acquired T_2 maps of [^{13}C,^{15}N$_2$]urea show a similar distribution within the kidney, but with ~2 fold higher T_2 values compared to [1-^{13}C]lactate.[3] The resulting 3D images in rats of [1-^{13}C]lactate and [1-^{13}C]pyruvate (Figure 2) and [^{13}C,^{15}N$_2$]urea show uptake of these compounds within the kidney, with the image resolution being sufficient to visualize the renal pelvis and cortex of the kidney, as well as the connecting vasculature components. Similarly, the 3D images of the TRAMP and breast cancer mice (Figure 3), which were overlaid on top of the ^{1}H images, show uptake of [1-^{13}C]pyruvate within the kidneys and the tumor. While the mouse anatomy is smaller, the resolution here was also sufficient to image the distribution of [1-^{13}C]pyruvate within vasculature, renal pelvis and cortex, and tumor. With the RF pulse not being spectrally selective, the resulting [1-^{13}C]pyruvate images will contain some signal from metabolic conversion (not an issue when injecting HP [1-^{13}C]lactate).[1]

Conclusion: The development of a specialized 3D sequence provided improved structural and functional assessments at a high (0.003 cm^3) resolution *in vivo* utilizing HP ^{13}C substrates, exploiting their long T_2's. This 1.5mm isotropic resolution is similar to that used for ^{1}H imaging and application of this approach can be extended to future studies of uptake, metabolism, and perfusion in cancer and other disease models and may ultimately be of value for clinical imaging.

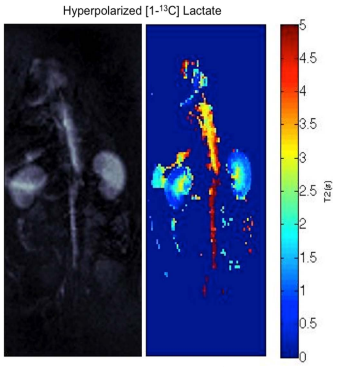

Figure 1: T_2 map of [1-^{13}C]lactate in a normal rat. A T_2 gradient exists from vasculature to cortex of kidney.

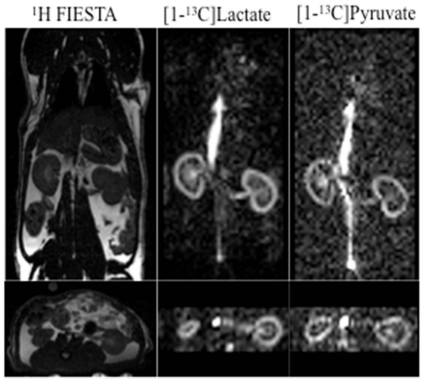

Figure 2: 3D [1-^{13}C]lactate and [1-^{13}C]pyruvate images in a normal rat. The coronal and axial reformats show hyperintense signal from the vasculature and renal pelvis due to the inward T_2 gradient and the heavy T_2-weighting of the sequence.

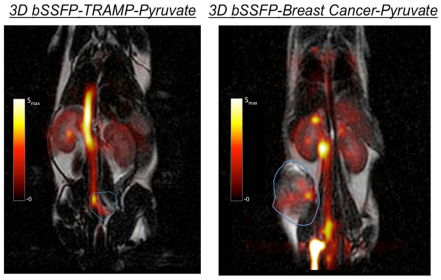

Figure 3: 3D images overlaid on proton images of [1-^{13}C]pyruvate in TRAMP (left) and breast cancer (right) mice. The blue ROIs indicate tumor region. The signal intensity follows that of the normal rat images.

References: 1) Kurhanewicz et al., Neoplasia 2011. 13(2). 2) von Morze et al., Magnetic Resonance Imaging 2012. 30(3). 3) Reed et al., IEEE Transactions on Medical Imaging 2013. 33(2).