RAPID *IN VIVO* ADC MAPPING OF HYPERPOLARIZED ^{13}C METABOLITES ON A CLINICAL 3T MR SCANNER

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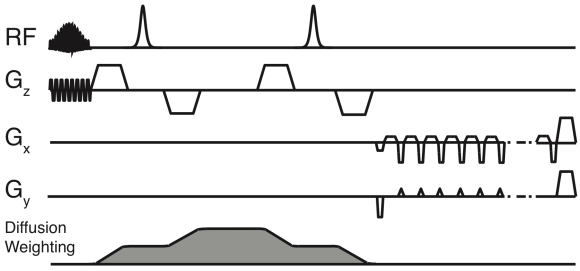
Introduction: Apparent diffusion coefficient (ADC) maps of water have become useful for prostate cancer identification and characterization.[1] Differences in local water mobility create contrast in these images, which in turn give an indication of the local tissue microstructure. The growing field of hyperpolarized ^{13}C has also proven to be useful in identifying tumors by measuring the real-time metabolism of hyperpolarized ^{13}C pyruvate to lactate.[2] Yet, while *in vivo* MRSI and MRI studies spatially localize these hyperpolarized ^{13}C metabolites, they do not give an indication of their distribution within the local tissue microstructure based on their mobility. Understanding this distribution could help elucidate what fraction of hyperpolarized ^{13}C lactate signal is vascular versus within dense tumor tissue. Aggressive tumors, for example, have been shown to transport higher fractions of lactate into the extracellular environment.[3] Recent work has laid the foundation for hyperpolarized ^{13}C diffusion-weighted MR[4-6] and showed improved tumor contrast with diffusion weighting.[7] In this study, we developed a novel diffusion-weighted hyperpolarized ^{13}C EPI sequence on a clinical 3T MR scanner to rapidly obtain ADC maps of hyperpolarized ^{13}C metabolites *in vivo*.

Experimental Methods: All experiments used a 3T clinical MRI scanner (GE) equipped with 4 G/cm peak gradient amplitude (1.5 G/cm/ms peak slew rate) and a dual-tuned mouse birdcage coil. Hyperpolarized ^{13}C diffusion experiments were performed using a pulsed gradient double spin echo sequence with a single-shot flyback echo planar imaging (EPI) readout (**Fig 1**); T_E=175ms, T_R=250ms, FOV=4×8cm (3.3×3.3mm resolution). To efficiently use the entire non-renewable hyperpolarized magnetization, spectral spatial excitation pulses with a specified progressive flip angle scheme (**Fig 1**) provided constant signal in the absence of diffusion gradients. A pair of adiabatic sech/tanh pulses[8] produced the spin echo. Diffusion gradient pairs surrounding the refocusing pulses were given opposite polarity to generate large ^{13}C diffusion b-values, even with clinical gradient strength constraints.

A HyperSense (Oxford Instruments) was used to polarize ^{13}C pyruvate. Upon dissolution, the hyperpolarized sample was either injected into a 60mL phantom or into a transgenic mouse with prostate cancer (TRAMP). Each hyperpolarized ^{13}C metabolite was imaged 4 times within 1s, thus minimizing signal changes due to T_1 or metabolism. After a flip angle correction based on a simultaneously acquired double-angle transmit B_1 map (see below), ADC maps were generated by fitting the diffusion weighted images on a per-voxel basis according to ADC = -ln(S/S$_o$) / b.



Parameters for each HP ^{13}C Metabolite

Scan	1	2	3	4
Start time [s]	0	0.25	0.5	0.75
Flip angle	30	35	45	90
b-value [s/mm^2]	820	256	8	8

Figure 1. The pulsed gradient double spin echo sequence with an echo-planar imaging readout. The table shows the experimental parameters used for each hyperpolarized ^{13}C metabolite acquistion.

Results and Discussion: To validate the sequence, we imaged hyperpolarized ^{13}C pyruvate in room temperature phantoms (n=3) (**Fig 2**). Considering that the progressive flip angle scheme repeatedly samples the non-renewable hyperpolarized signal, flip angle errors propagate through all acquisitions. Our simulations showed that for the experimental parameters used here, flip angle errors of 20% could cause 20% errors in the ADCs. To correct for this source of error and increase the quantitative robustness of the ADC measurements, we generated a hyperpolarized ^{13}C metabolite specific B_1 map. Calculated by comparing the last 2 images with the double angle identity $\sin(2\theta) = 2\sin(\theta)\cos(\theta)$ and accounting for the non-renewable signal, the B_1 map was used for voxel-wise flip angle corrections across all images. The ADC map for hyperpolarized ^{13}C pyruvate, showing a mean ADC = 1.09×10^{-3}mm^2/s ± 0.20×10^{-3}, corresponds with previous solution measurements.[4]

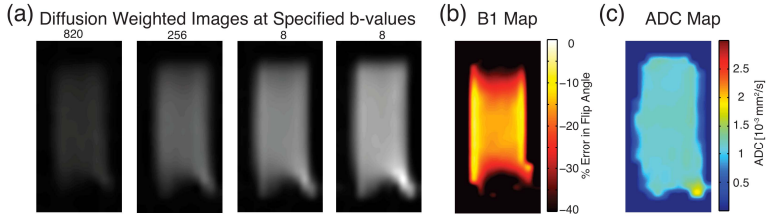


Figure 2. Phantom studies with hyperpolarized ^{13}C pyruvate. (a) The diffusion weighted EPI images of hyperpolarized ^{13}C pyruvate taken at the various b-values. **(b)** The transmit B_1 map created from the difference in signal between the last 2 diffusion-weighted images and the double-angle identity (see text). **(c)** The ADC map of hyperpolarized ^{13}C pyruvate in solution.

Hyperpolarized ^{13}C pyruvate and lactate were imaged in TRAMP mice bearing prostate tumors (n=3) (**Fig 3**). The image overlay of hyperpolarized ^{13}C lactate with minimal diffusion weighting (**Fig 3b**, *left*) shows lactate signal throughout the abdominal area. The same acquisition with a high degree of diffusion weighting (**Fig 3b**, *right*) shows only hyperpolarized ^{13}C lactate from the tumor, thereby increasing tumor contrast. The ADC map shows lower ADCs in the tumor (ADC = 0.35×10^{-3}mm^2/s ± 0.09) than those found higher in the abdomen (ADC = $0.6–1.8\times10^{-3}$mm^2/s depending on location). Further studies will use hyperpolarized ^{13}C lactate ADC maps to improve tumor localization and pathologic grading in prostate cancer.

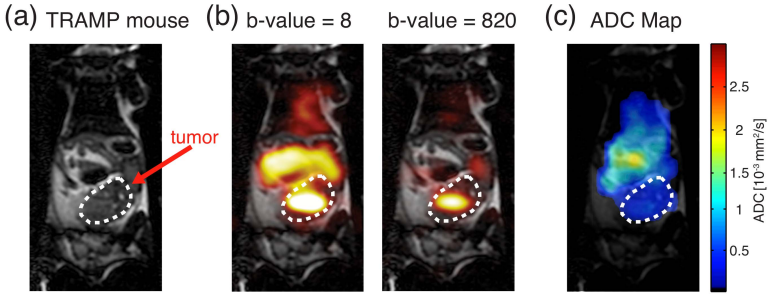


Figure 3. ADC mapping of hyperpolarized ^{13}C lactate in a TRAMP mouse. (a) A fast spin echo proton image with the arrow pointing at the tumor. **(b)** Low and high b-value overlay EPI images of hyperperpolarized ^{13}C lactate. **(c)** The ADC map of hyperpolarized ^{13}C lactate.

Conclusion: This study is the first demonstration of ADC mapping of hyperpolarized ^{13}C metabolites on a clinical 3T MR scanner. The pulsed gradient double spin echo EPI sequence allows us to rapidly acquire diffusion-weighted images and generate ADC maps at clinically translatable SNR and spatial resolution. This is possible despite both gradient amplitude limitations and the lower MR sensitivity of ^{13}C. Clinically, ADC mapping of hyperpolarized ^{13}C lactate could allow for improved classification of tumor grade and metastatic potential by measuring both enhanced metabolic flux and differences in lactate's microenvironment.

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References: [1] Nagarajan *et al. Advances in Urology* **2012,** 1–5 (2012). [2] Albers *et al. Cancer Research* **68,** 8607 (2008). [3] Ganapathy *et al. Pharmacol Therapeut* **121,** 29–40 (2009). [4] Koelsch *et al. Analyst* **138,** 1011 (2013). [5] Schilling *et al. NMR in Biomedicine* **26,** 557–568 (2013). [6] Kettunen *et al. Magn. Reson. Med.* **70,** 1200–1209 (2013). [7] Larson *et al. IEEE Trans Med Imaging* **31,** 265–275 (2012). [8] Cunningham *et al. J Magn Reson* **187,** 357–362 (2007).