Toward a Hyperpolarized C13 Metabolic Imaging of Human Brain at 3T

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Introduction: The first clinical trial using hyperpolarized ^{13}C MR metabolic imaging has been successfully performed in patients with prostate cancer[1]. Pre-clinical studies have indicated the promise of this technique for applications in patients with brain tumors[2,3]. The purpose of this study was to design a hyperpolarized ^{13}C metabolic imaging experiment that can be translated into a clinical trial for patients with brain cancer and to demonstrate its feasibility by acquiring data from pre-clinical model systems. ^{13}C coils and pulse sequences that were designed for use in humans were first tested in phantoms and rats. Dynamic ^{13}C data were then obtained from a healthy non-human primate brain using the optimized ^{13}C coils and pulse sequences. The kinetics of changes for *in vivo* metabolites were estimated.

Methods: All experiments were performed using a whole-body GE 3T MR scanner. The hyperpolarized [1-^{13}C]-pyruvate was produced using either a prototype SpinLab^{TM} (General Electric, Niskayuna, NY)[4] or a Hypersense® (Oxford Instruments, Abingdon, UK) DNP polarizer. Two ^{13}C RF coils were developed in-house for human brain studies (Fig 1): a volume transmit-receive birdcage ^{13}C coil (Fig 1a) or a clamshell volumetric ^{13}C transmit coil with a bi-lateral 8-channel phased array receive coil (Fig 1b,c). ^{13}C spectroscopic imaging data were acquired from an ethylene glycol cylindrical phantom with a 16 cm diameter and from healthy rats in order to optimize the ^{13}C coils and pulse sequences[2]. A 9-year old female cynomolgus monkey (macaca fascicularis, body weight=4.3 kg) was then studied to verify the developed experimental setup for human brain study. The following ^{13}C dynamic spectroscopic data were acquired from a 20 mm slice through the brain: slice-localized data with 10° flip angle (TE/TR=35/3000 ms, 3s temporal resolution, 64 total time points), 2D-localized data with a multiband RF excitation using 20°/4° for lactate/pyruvate flip angle (TE/TR=4.6/130 ms, 3s temporal resolution, 24 total time points)[5] and 2D-localized data with a variable flip angle multiband RF excitation (TE/TR=6.1/130 ms, 3s temporal resolution, 10 total time points)[6]. The 2D-localized data had 10 phase encodes in the AP direction and a symmetric echo-planar readout in the RL direction, providing 10x10mm in-plane resolution. Slice-localized and 2D-localized data were acquired simultaneously during or following a 4s injection of 5.9 mL [1-^{13}C]-pyruvate (250 mM) through the saphenous vein. Apparent rate constants for the conversion of pyruvate to lactate (K_{PL}) were estimated using a two-site exchange model [7].

Results: The two ^{13}C coils provided excellent detection of metabolites from phantoms and rats. The signal-to-noise-ratios (SNR) measured from the middle of the phantom were 25:1 and 82:1 for the birdcage volume coil and the clamshell transmit/8 channel receive coils, respectively. Figure 2 shows 2D-localized data from the brain of a non-human primate, which were obtained using the clamshell ^{13}C transmit/8-channel phased array receive coils with a variable flip angle multiband scheme. The spatially resolved dynamic spectroscopic data demonstrated excellent detection of ^{13}C-labeled pyruvate and lactate resonances in both the normal brain and surrounding tissues. The maximum SNR of pyruvate and lactate were 173:1 and 28:1, respectively. The pyruvate signal in the brain reached its maximum at 9s from the end of injection (Fig 2a), while the maximum lactate signal—corrected for the variable flip angle—appeared at 18s (Fig 3b,c). Figure 3 shows the overlay image of K_{PL} (Fig 3a) and the examples of time courses of pyruvate and lactate with the corresponding curve fits that were corrected for the variable flip angles. K_{PL} was 0.003 ± 0.0005 s^{-1} (mean ± standard deviation, n = 22) for the voxels in the brain and 0.005 ± 0.001 s^{-1} (mean ± standard deviation, n = 9) for the voxels outside the brain, which included vasculature and muscle.

Conclusions: We have established a hyperpolarized ^{13}C metabolic imaging experimental design appropriate for studying patients with brain tumors. This has been used to demonstrate the feasibility of using hyperpolarized [1-^{13}C]-pyruvate for assessing *in vivo* metabolism in a healthy non-human primate brain. Signals from pyruvate and lactate were observed in both the brain and the surrounding tissues. The excellent SNR of pyruvate and lactate within normal brain indicates that pyruvate is able to cross the blood brain barrier and provide signals that can be measured using the pulse sequences and coils that we have developed. The kinetics of the metabolite conversion showed that this approach may be useful in characterizing brain and its surrounding tissues.

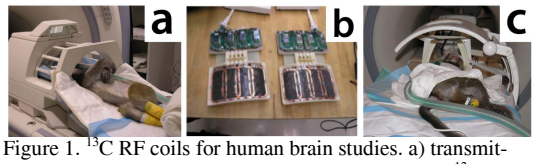

Figure 1. ^{13}C RF coils for human brain studies. a) transmit-receive birdcage volume coil, b) bi-lateral 8 channel ^{13}C receive coils, c) the set up showing the clamshell volumetric ^{13}C transmit coil and bi-lateral 8-channel phased array receive coils.

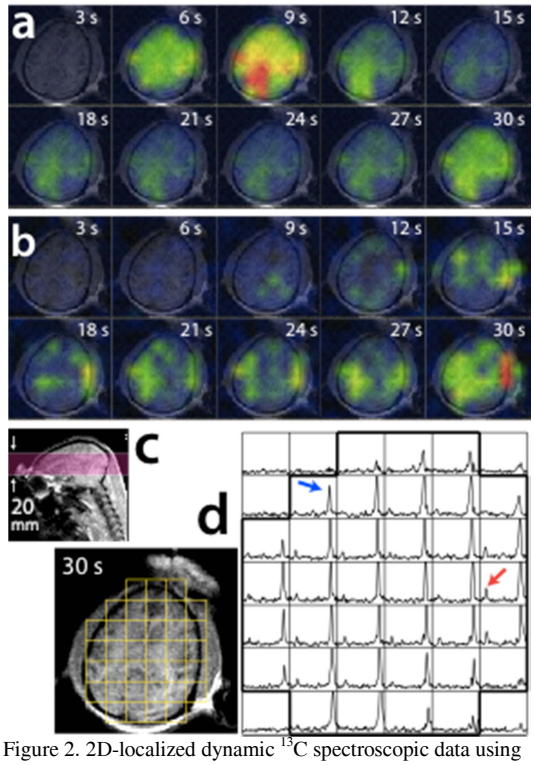

Figure 2. 2D-localized dynamic ^{13}C spectroscopic data using a variable flip angle scheme: a) pyruvate map, b) lactate map, c) T1 sagittal image of the primate brain showing the 20 mm slice where the data was acquired, d) T1 axial image of a non-human primate brain and the corresponding ^{13}C spectra at 30s. The red arrow in d) represents the lactate peak and the blue arrow the pyruvate peak.

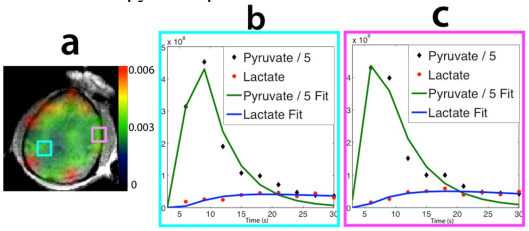

Figure 3. a) The map of apparent rate constants for the conversion of pyruvate to lactate from a non-human primate brain. b) Time courses of pyruvate and lactate, which were corrected for the variable flip angle scheme, and the corresponding curve fits within (b) and outside (c) brain.

References: [1]Nelson et al., *Proc. ISMRM, 17th Annual Meeting.* 2012. p274. [2]Park et al., *J Magn Reson Imaging*. 2011. [3]Park et al., *Magn Reson Med*. 2012. [4]Hu et al., *Magn Reson Imaging*. 2012. [5]Larson et al., *Magn Reson Med*. 2010. [6]Xing, Larson, et al., *Proc ISMRM, 18th Annual Meeting*. 2013, submitted. [7]Zierhut et al., *J Magn Reson*. 2010. **Acknowledgements**: Research support: NIH grants R01EB007588, P41EB13598, an academic-industry partnership grant ITL-BIO04-10148 and a basic research fellowship from the American Brain Tumor Association (Park).