Gadoxetate-Attenuated Hyperpolarized ^{13}C MRI for Selective Assessment of Liver Metabolism

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Introduction Magnetic resonance imaging and spectroscopy using hyperpolarized ^{13}C-labeled compounds enables imaging of metabolism *in vivo* with high sensitivity[1,2]. Because of the macroscopic spatial resolution of current hyperpolarized ^{13}C imaging, it can be challenging to precisely compartmentalize the hyperpolarized MR signal. For example, the hyperpolarized MR signal in the liver is the superposition of metabolism contained in the intravascular, intracellular, and interstitial spaces. In addition, the size of liver tumors can often be smaller than the voxel used for imaging, causing contamination from the signal arising in adjacent normal liver. Previously, gadolinium-based contrast agents have been used to selectively suppress intravascular hyperpolarized signal and help differentiate intravascular vs extravascular metabolism[3]. Gadoxetate disodium (Eovist, Primovist, Bayer Pharmaceuticals) is a clinically used gadolinium-based MRI contrast agent that is actively transported into hepatocytes and then actively excreted into the biliary system. We propose to combine the anatomic specificity of gadoxetate with the metabolic information provided by hyperpolarized ^{13}C imaging to better isolate signal arising from hepatocytes.

Methods 3 healthy Sprague-Dawley rats were imaged using a 3T MRI scanner (MR750, GE Healthcare) and a custom-built dual-tuned transmit-receive coil. 32 mg of [1-^{13}C]pyruvic acid with 15 mM OX63 trityl radical and 1.5 mM Dotarem (Guerbet) were polarized using a Hypersense DNP polarizer (Oxford Instruments) for approximately 1 hour. The solution was dissolved and neutralized to a final pyruvate concentration of approximately 80 mM. Dynamic ^{13}C spectra (flip angle 20^{o}) were obtained from two different 2.0 cm slabs: one placed entirely over the liver (avoiding the heart) and one placed over the kidneys (avoiding the liver) (**Fig. 1**). Data acquisition began 20 s after injection of approximately 2.7 mL of the pyruvate solution. After injection, 10 spectra were acquired every 3 s (total 30 s).

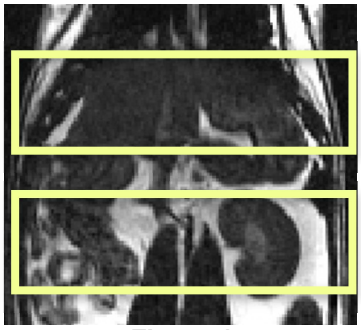

Figure 1

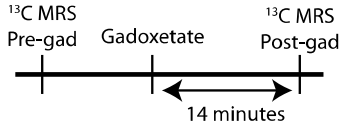

Figure 2

Hyperpolarized ^{13}C experiments were performed prior to and 14 minutes following injection of gadoxetate (0.1 mmol/kg) (**Fig. 2**). A 14 minute time interval was chosen based on preliminary dynamic contrast enhancement experiments (not shown) and to match the timing of the hepatobiliary phase of human imaging with gadoxetate (15-20 minutes). Metabolite signals were quantified by measuring the area under each peak of the magnitude spectra, summed over all time points. Gadolinium arrival within the liver was assessed by 3D T_1-weighted spoiled gradient echo images obtained immediately after the hyperpolarized experiment.

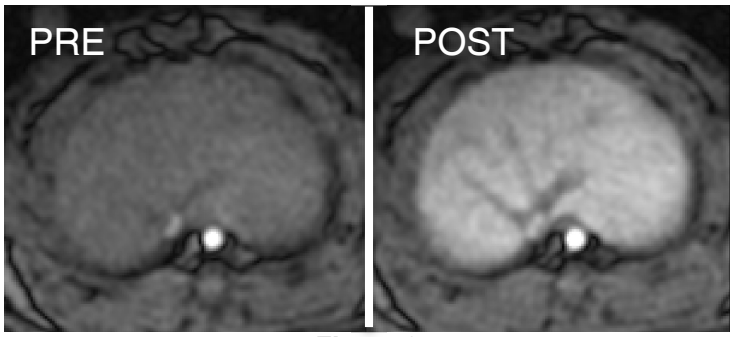

Figure 3

Results T_1-weighted images (**Fig. 3**) confirmed arrival of contrast with enhancement of the liver and hypointense vessels consistent with the hepatobiliary phase of contrast. 1/3 animals showed filling of the gallbladder with contrast (not shown).

Following contrast administration, there was a global decrease in hyperpolarized ^{13}C signal reflected by a decrease in the absolute [1-^{13}C]pyruvate signal (**Fig. 4a**). This global change was not significantly different between the kidney (36%) and the liver (38%). Lactate production was evaluated by measuring the ratio of [1-^{13}C]lactate to [1-^{13}C]pyruvate (**Fig. 4b**). The change in this ratio was variable between animals and, on average, was not significantly different between liver and kidney.

However, the ratio between [1-^{13}C]alanine and [1-^{13}C]pyruvate in the liver consistently decreased in all 3 animals after gadoxetate administration (**Fig. 4c**, average decrease 26%, 95% CI 12-36%). The behavior in the liver clearly differed from that seen in the kidney, where the [1-^{13}C]alanine/[1-^{13}C]pyruvate ratio increased slightly (average increase 17%, 95% CI 7-28%).

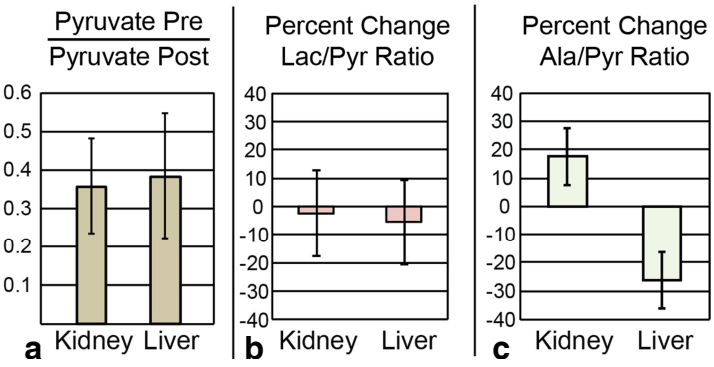

Figure 4

Discussion Gadoxetate injection caused a significant decrease in hyperpolarized [1-^{13}C]alanine observed in the liver as compared to the kidney. Because alanine is chiefly produced inside cells, this indicates that intracellular gadoxetate is causing a hepatocyte-specific reduction in the hyperpolarized MR signal. Future studies with better in-plane spatial localization will be necessary to confirm this effect. Furthermore, titration of the gadoxetate dose and timing will be necessary to optimize the observed intrahepatic signal changes compared to the global blood pool effects. Combined imaging with gadoxetate and hyperpolarized ^{13}C compounds may permit better understanding of intracellular and extracellular hepatocyte metabolism. Furthermore, by suppressing signal from normal hepatocytes, it may permit better selectivity of hyperpolarized signal coming from tumors that do not accumulate gadoxetate.

References: 1. JH Ardenkjaer-Larsen et al *PNAS* 100(18):10158-10163 (2003). **2.** J Kurhanewicz *et al. Neoplasia* 13 (2):pg 81-97 (2011). **3.** MR Smith *et al IEEE Trans Biomedical Imaging* 59 (1):45-49 (2012). **Acknowledgements/Grant Funding**: NIH P41EB013598, RSNA R+E Foundation