Hepatic Hyperpolarized 13C Pyruvate Studies: Origin of Additional in vivo Pyruvate Resonances

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Introduction: Following intra-venous administration of a bolus of hyperpolarized 1-^{13}C-labeled pyruvate, additional high field resonances attributable to pyruvate and pyruvate hydrate are occasionally observed when studying liver metabolism (**Figure 1a,b**) [1]. This study aims to identify the origin of the additional signals via frequency sensitive MRI to probe their location and administration of extracellular contrast agent to investigate their compartmentation. Extracellular gadolinium (Gd) contrast agents such as MultiHance do not ordinarily enter the intracellular space. Since metabolites, unlike water, do not undergo fast trans-membrane exchange, only whilst the contrast agent and metabolite are within the same compartment can the metabolite experience paramagnetic induced relaxation. Consequently, changes in the pyruvate signal following intravenous administration of Gd-chelate would suggest that the metabolite is in an intravascular or extracellular compartment.

Frequency sensitive MRI is used extensively with hyperpolarized ^{13}C in order to monitor metabolites and several resonance frequencies simultaneously. There are different sources of frequency change in MRI, some of which are unrelated to molecule or shim values, and can arise from local field inhomogeneities. Resonance frequency shifts may be caused by regions of differing susceptibility. Examples of structures which exhibit magnetic susceptibility shifts are blood vessels [2] and muscle associated lipid [3]. The shift for a blood vessel is given by $\Delta B_{\parallel}=(X_b-X_t)/3$ and $\Delta B_{\perp}=-(X_b-X_t)/6$ for vessels parallel and perpendicular to the main magnetic field respectively when X_b and X_t are the volumetric susceptibility of blood and tissue respectively[3]. Frequency shifts may be enhanced in the presence of paramagnetic materials such as contrast agents and deoxy-hemoglobin, which can cause a 0.27 ppm shift compared to surrounding tissue [4].

Methods: ^{13}C Polarization was performed using a DNP polarizer (HyperSense®, Oxford Instruments, Tubney Woods, Abingdon, Oxfordshire, UK). A 4.7T Varian (Varian, Palo Alto, CA, USA) horizontal bore small animal scanner together with a surface coil which has both ^{1}H (5 cm diameter) and ^{13}C (3.8 cm diameter) sensitive channels was used to acquire ^{13}C MR images and spectra. In vivo simultaneous ^{1}H and ^{13}C projection multi-echo spoiled gradient echo imaging [5] was also performed on a mouse to determine the spatial locations of the peaks. Scan parameters for the sequence were: TR of 40 ms, ΔTE of 1.2 ms, 32 full echoes, 64 projection angles, 128 readout points, and FOV of 80×80 mm.The acquisition was tuned to allow for sufficiently high spectral resolution to resolve the frequency differences seen in the spectroscopy studies. Mice and rats (n=37) were also scanned using a pulse and acquire spectroscopy sequence localized with the surface coil and MultiHance (0.5 mmol/kg) was injected 10 s after pyruvate administration.

Results: Figure 1a,b shows two different spectra from a normal mouse. Similar twin peaks were seen in 12 out of 37 spectroscopy experiments performed, with an average shift of 1.3±0.4 ppm. Note that in **figure 1a** the pyruvate and pyruvate hydrate are distinctly separated into 2 peaks, both of which are 0.4 ppm apart before intravenous Gd injection and 1.2 ppm apart after Gd injection. The two pyruvate peaks decay at different rates following gadolinium injection, with the high field resonance preferentially undergoing enhanced reduction. These results are corroborated in **figure 1c-f** where the inferior vena cava and the heart are seen at different pyruvate frequencies. In this example, these show an approximate 0.6 ppm difference between the pyruvate in the heart and the pyruvate in the large vein in the abdomen.

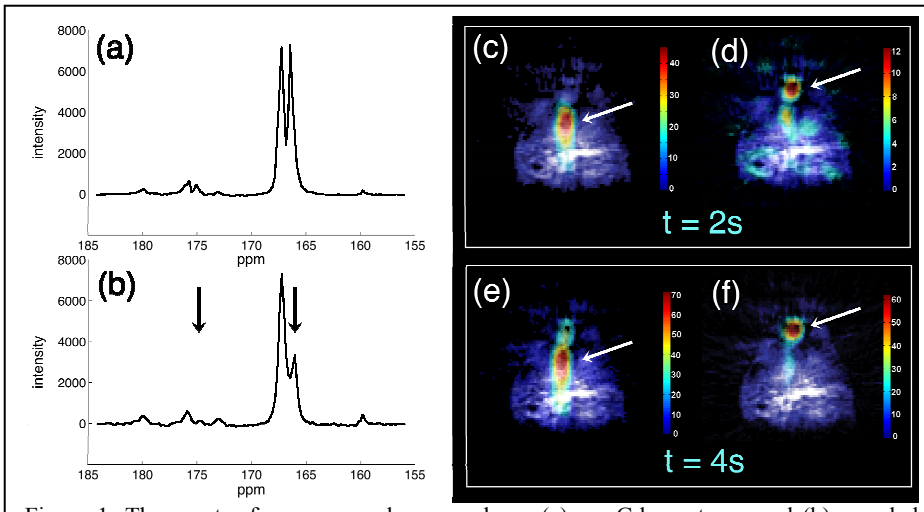

Figure 1: The spectra from a normal mouse show: (a) pre-Gd spectrum, and (b) rescaled post-Gd spectrum separated by 20 s. The peaks are (l-r) lactate, downfield pyruvate hydrate, upfield pyruvate hydrate, alanine, downfield pyruvate, upfield pyruvate, external urea standard. Proton images from a different mouse at t=2s (c,d) and t=4s (e,f) post pyruvate injection with the pyruvate images overlaid. The pyruvate signal in frames (c,d) is 22.9 Hz from the pyruvate signal in frames (e,f). The arrows indicate the different spectral compartments: inferior vena cava(c,e-arrow),and heart (d,f-arrow).

Discussion and Conclusion: The images in **figure 1c-f** demonstrate the difference in frequencies between the pyruvate in the inferior vena cava to the pyruvate in the heart. It is important to note that in **figure 1a,b** the pyruvate and pyruvate hydrate provide additional resonances, whereas their product metabolites do not. This indicates that the pyruvate and pyruvate hydrate primarily remains circulating in major vessels, whereas the metabolites, which are formed intracellularly, are not located in the same compartment. The images in **figure 1c-f** corroborate the previous findings of specific orientation-related peaks as seen in **figure 1a,b**. The variability is the average shift is likely due to different orientations and local susceptibility differences. Due to the recurrence of this phenomenon, both with and without Gd-chelate, this illustrates the potential for resolving spectra associated with macro-structures in the body.

References: [1] Peterson, E.T., et al., *Abstract # 2417*.ISMRM, 2009. [2] Edelman, R.R., et al., MRM, 2007. [3] Szczepaniak, L.S., et al.,MRM, 2002. [4] Spees, W.M., et al., MRM, 2001.[5] Peterson, E.T., et al., *Abstract #449*.ISMRM, 2010.