Suppression of unwanted resonances in hyperpolarized MR studies with neat [1-^{13}C]lactic acid

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Target Audience: MR scientists interested in pulse sequence design for MRSI of hyperpolarized ^{13}C compounds.

Purpose: In addition to being an end product of glycolysis, lactate is a key intermediary in numerous metabolic processes (1), and exists at normally high physiologic concentrations. These factors suggest that hyperpolarized (HP) [^{13}C]lactate is a potentially interesting, safe metabolic imaging probe. Use of neat [1-^{13}C]lactic acid has been found to result in significantly improved polarization over the sodium salt (2). However, concentrated lactic acid is prone to dimerization, leading to spectral contamination with NMR signals from lactides, especially overlapping alanine. **In this work we describe a pulse sequence approach for spectrally-selective, early time-point suppression of undesired resonances in HP spectra derived from dissolution DNP of neat [1-^{13}C]lactic acid.**

Methods: *DNP*- Neat [1-^{13}C]lactic acid (solid at room temperature) was prepared by adding a small amount of water (8% wt/wt) and 15mM OX063, as well as 1mM Dotarem. 64mg of this prep was polarized for 1.25hr and subsequently dissolved in 4.5mL 160mM NaOH/Tris buffer, yielding a 160mM lactate solution with pH~7.0. *MR Experiments*- Experiments were conducted in a clinical GE 3T scanner using a dual-tuned ^{13}C/^{1}H quad volume mouse coil (l=8cm,d=5cm). An initial non-localized HP phantom experiment was conducted to estimate the polarization and T_1, and measure the additional contaminant resonance. The HP lactate solution was repeatedly pulsed by 5° excitation with adiabatic double spin echo refocusing, every 3s over 189s. *In vivo*, the upfield of two additional resonances showed overlap spectrally with HP alanine, hindering accurate measurements of metabolic flux through the ALT pathway. Though uncertain, we believe these resonances arise from lactides. A minimally localized *in vivo* experiment was first conducted to test the efficacy of suppression of the alanine-overlapping dimer using a new pulse sequence, and measure the bulk metabolic dynamics. A rat was infused with 2.5mL 160mM HP lactate over 15s, followed by a short saline flush. Halfway through the infusion, a baseline 5° spectrum was acquired to confirm the level of the dimer *in vivo*, and assess the effectiveness of the suppression pulses to follow. Immediately after the end of injection and a short saline flush, a dimer suppression pulse sequence was executed, consisting of a train of three consecutive spectrally selective, maximum phase 90° RF pulses with center frequency on the dimer, each followed by a crusher gradient. The RF suppression pulse was designed to eliminate the contaminant dimer signal without disturbing nearby lactate or pyruvate resonances (pulse width= 20ms, BW_{FWHM}= 150Hz). The dimer suppression train was followed by dynamic spectroscopy with repeated 5° excitation of an axial slab covering the liver and kidneys, every 3s over 90s. A 3D localized whole rat MRSI experiment was also performed. The suppression train was similarly executed immediately after the end of the infusion, before significant metabolism occurs, followed by a test 5° acquisition to confirm elimination of dimer signal. The 3D EPSI MRSI acquisition started 35s after the start of infusion (1x1x1cm^3, FOV=8x8x18cm^3, TE/TR=140ms/ 215ms, scan duration= 14s).

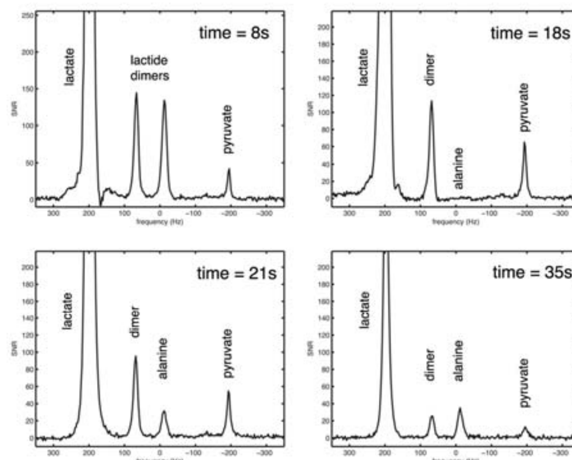

Fig. 1. Dynamic ^{13}C spectra acquired during (8s) and after HP lactate infusion (18-35s), with suppression of lactide dimer at end of infusion (18s).

Results: We measured aqueous lactate T_1= 45s, and polarization of 26% (back-calculated to the time of dissolution). The dimers each had signals of ~3% of the lactate signal at the first time point, with similar T_1's. Spectroscopic results from the minimally localized *in vivo* experiment confirm suppression of the dimer and illustrate the bulk metabolic dynamics (Fig. 1) of HP lactate through pyruvate and alanine *in vivo*. 3D images through the liver and kidneys demonstrate metabolic flux to pyruvate and alanine in these organs (Fig. 2).

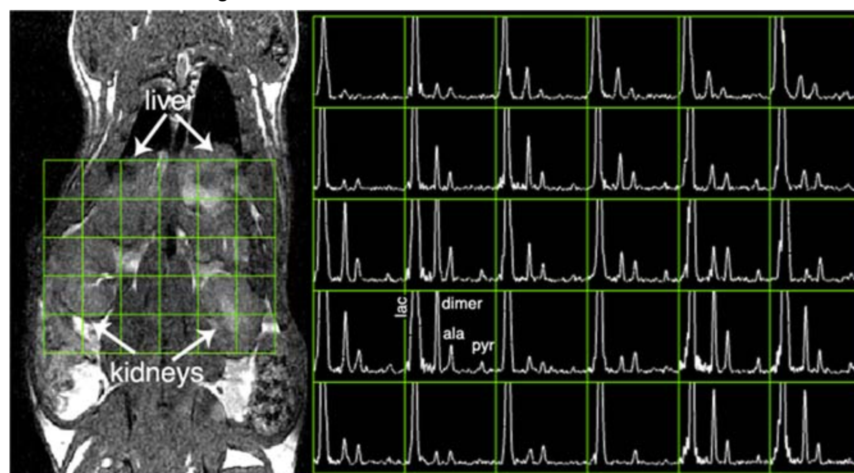

Fig. 2. 3D MRSI data for HP [1-^{13}C]lactate acquired at 35s after start of infusion, with spectrally selective suppression of the lactide dimer overlapping alanine immediately after end of injection, prior to *in vivo* metabolism.

Discussion: This study showed the feasibility of pre-suppressing lactide spectral contaminants in neat [1-^{13}C]lactic acid enabling high SNR HP MR investigations of lactate metabolism *in vivo*. Significant lactate to pyruvate conversion was observed in the kidneys, and alanine signal (i.e. through pyruvate) was observed in kidneys and liver. The high alanine to pyruvate ratio observed may reflect their relative pool sizes, in contrast to results of pyruvate studies.

Conclusion: We have demonstrated feasibility of using spectrally selective suppression pulses for eliminating unwanted resonances in HP MR studies such as with neat [1-^{13}C]lactic acid.

References- 1. Gladden LB. J Physiol. 2004. 2. Chen AP et al. Proc 21st ISMRM. #3928. 2013.