Potential for polarization measurement of pre-polarized [1-^{13}C] pyruvate *in vivo* using Jcc spectral pattern

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Introduction: The ability to accurately measure or predict the polarization of hyperpolarized ^{13}C metabolic imaging substrates at the time of the MR experiment is necessary for quantitative kinetics data or metabolite concentrations. Measuring the asymmetry of one of the nuclei in a coupled spin system may allow the estimation of the polarization while preserving the magnetization of the other nucleus needed for a subsequent imaging or spectroscopy experiment (1-2). Hyperpolarized [1-^{13}C] pyruvate in solution has been utilized to demonstrate non-invasively assess real time metabolism in animal models (3-4). In this study, we demonstrate the potential of using asymmetry of the pyruvate C2 resonance (from 1% natural abundance of [1,2-$^{13}C_2$] pyruvate) to estimate the polarization of the [1-^{13}C] pyruvate *in vivo*.

Methods: Hyperpolarized substrate and hardware: ~30 mg of [1-^{13}C] pyruvic acid (99%, Isotec, Miamisburg, OH) with 15 mM OX63 trityl radical (Oxford Instruments, Abingdon, UK) and 1mM of Gd-DOTA was polarized for each experiment using a Hypersense DNP polarizer (Oxford Instruments). NaOH/Tris/EDTA solution was used to dissolve the sample for a nominal pyruvate concentration of 80 mM with a pH of 7.4. All experiments were performed using a GE MR750 3T Scanner (GE Healthcare, Waukesha WI) equipped with the multinuclear spectroscopy package. A custom-built dual-tuned ^{13}C/^{1}H volume coil was used in all experiments. All data were processed using SAGE software (GE Healthcare). In vitro experiments: A double spin-echo pulse sequence was used in all experiments (n=6) with a 100ms readout window centered on the second spin-echo (TE/TR=140ms/3s, 64 transients) (5). A spectrally selective excitation pulse applied on the C2 pyruvate resonance (90° nominal flip angle, 200 Hz bandwidth, 10^{-4} stopband) was used for the first transient and a conventional non-selective small tip excitation pulse (5° flip angle, ~2 kHz bandwidth) was used in the remainder of the scan. Data acquisition started immediately after ~2ml of the pre-polarized pyruvate solution was placed in the RF coil. The low field transfer from the polarizer to the 3T took either 15s (n=4), or 65s (n=2). Thermal equilibrium signal of each sample was also measured using the same pulse sequence (TE/TR=140ms/300s, 8 transients). Polarization of each sample was estimated by the asymmetry of the C2 pyruvate doublet (corrected for the AB asymmetry) as well as by comparing the polarized and thermal equilibrium signals of the enriched C1 pyruvate resonance. Peak integrals from magnitude mode spectra (pure absorption line shape retained since echoes were acquired symmetrically) were used in all measurements. *In vivo* experiment: 8s after the start of a 2.5ml/12s bolus of pre-polarized 80mM [1-^{13}C] pyruvate solution into the tail vein of a normal Sprague-Dawley rat, selective C2 data acquisition was performed for a single transient as in the in vitro experiments. 15s after the C2 selective spectrum was acquired, 3D CSI data was acquired with the same pulse sequence but using flyback echo-planar readout (non-selective excitation, 10° flip angle, 8x8x16 matrix, 0.5cc spatial resolution) over a 14s period.

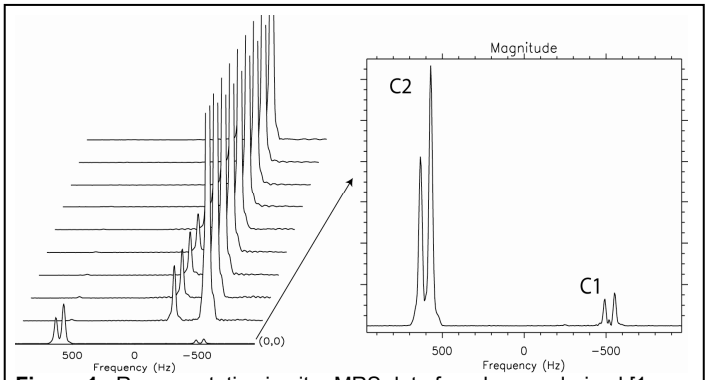

Figure 1. Representative in vitro MRS data from hyperpolarized [1-13C] pyruvate. Asymmetry of the C2 doublet was clearly depicted in the spectrum (1st in the stack) acquired with spectrally selective excitation. The C1 doublet observed in this spectrum (right) is likely the result of 2-spin order coherence transfer.

Results and Discussion: Representative in vitro MRS data of [1-^{13}C] pyruvate with spectrally selective excitation of the C2 pyruvate resonance followed by non-selective excitation are shown in Fig. 1. Asymmetry (due to polarization and AB character) of the C2 doublet from the 1% natural abundance [1,2-$^{13}C_2$] pyruvate is clearly observed in the large tip angle - selective excitation spectrum. Very little of the [1-^{13}C] pyruvate magnetization appeared to have been consumed by the selective excitation. The small C1 doublet observed in the first spectrum (anti-phase in real mode) is likely the result of coherence transfer from the selectively excited C2 resonance. The disagreement between the two methods of polarization measurement was 22% and 20% (of the polarization measured by using C1 pyruvate signal) for the 15s and 65s low field transfer times, respectively. Although different decay constants for the C2 peaks were observed at 3T and 14.1T previously (6), long transfer time at low field didn't seem to contribute additional errors for predicting polarization using C2 asymmetry. Further more, the T1s of the C1 carbon in [1-^{13}C] pyruvate and [1,2-$^{13}C_2$] pyruvate are similar (60s and 56s respectively, at 3T (6)), thus the error contributed by the T1 difference during low field transfer is likely to be insignificant. The errors observed in these experiments may be due to the limited spectral resolution used, thus decreasing the accuracy of the C2 asymmetry estimates. Figure 2 shows an *in vivo* spectrum from C2 selective excitation and CSI data from the same bolus of [1-^{13}C] pyruvate injected into a normal rat. The C2 asymmetry in this spectrum yielded a polarization of 5.1%. In this study, the feasibility of measuring polarization of [1-^{13}C] pyruvate *in vivo* using Jcc spectral pattern is demonstrated. More accurate measurement of the C2 asymmetry and correction for the differential decays of the C2 peaks at the imaging field may be necessary in future studies.

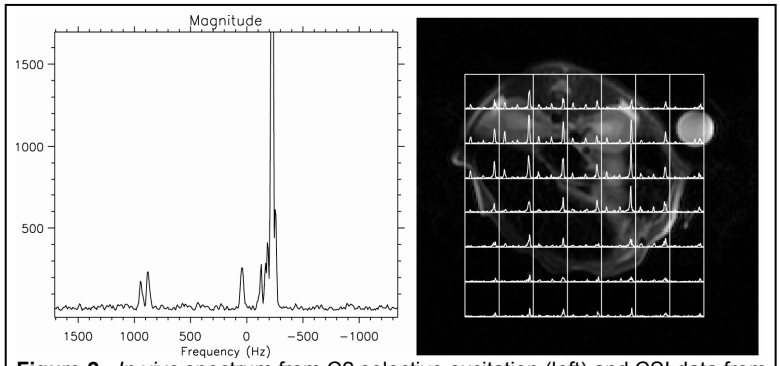

Figure 2. *In vivo* spectrum from C2 selective excitation (left) and CSI data from a slice through the rat kidneys from the same bolus of pre-polarized [1-^{13}C] pyruvate (right).

References: 1. Ardenkjaer-Larsen PNAS 2008;100:10158 2. Merritt JMR (2007), 189:280 3. J Chem Phys 1987;86:3816. 3. Day SE. et al. Nat Med 2007; 13(11):1382-1387. 4. Schroeder M. et al. Proc Nat AcadSci 2008;105:12051–12056. 5. Cunningham CH. et al. JMR 2007;287:357-62. 6. Hurd RE. et al. 50th ENC, p438.