Optimized Sampling of Metabolically Labeled [2-13C]Lactate Following Injection of Hyperpolarized [2-13C]Pyruvate

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Introduction: Time-resolved metabolic imaging following injection of a bolus of hyperpolarized [1-^{13}C]pyruvate has been a very successful method for measuring the rate of C1 isotope labeling of lactate, alanine and bicarbonate. More recently, several groups have also examined time-resolved metabolic spectra following injection of a bolus of hyperpolarized [2-^{13}C]pyruvate, looking at the incorporation of the hyperpolarized carbon-13 label in glutamate, citrate, ketone bodies and acetyl-carnitine (1-6). [2-^{13}C]lactate and [2-^{13}C]alanine are also produced in these studies, but present sampling challenges relative to their C1-labeled counterparts. For example, the spectral separation of C2lac - C2pyr is nearly 10 times as large as that of C1lac - C1pyr. This can be remedied by spectrally selective excitation methods. However, in addition to the spectral bandwidth challenge, the C2 carbon in lactate has a directly bonded proton, which not only splits the signal into a doublet (root 2 loss in SNR in coupled spectra), but also reduces its T_1 lifetime. The purpose of this study is to measure the apparent T_1 of [2-^{13}C]lactate in vivo, in comparison to [1-^{13}C]lactate, and to determine the effective flip-angle vs SNR for both metabolically produced [1-^{13}C]lactate and [2-^{13}C]lactate in time-resolved spectral acquisitions with TR's of 1.5 and 3 seconds.

Method: All measurements were performed on a clinical 3 T GE MR scanner, using a custom-built ^{1}H/^{13}C birdcage coil (Ø = 78mm). Adult male Wistar rats were anesthetized with 1-3 % isoflurane in oxygen (~1.5L/min), then injected with an 80 mM solution of hyperpolarized pyruvate (40 mM [1-^{13}C]pyruvate and 40 mM [2-^{13}C]pyruvate). Spectra were acquired following the injection of the hyperpolarized solution using a time-resolved FID sequence with a 10-degree hard pulse (pulse width = 40 μs). The transmitter frequency was centered between the resonant frequencies of C1 and C2 lactate (117 ppm). Non-localized spectra were sampled over 1 K points at a bandwidth of 10 KHz, Temporal resolution (TR) was set to 3 seconds following a first injection and 1.5 s following a second injection. Each time-resolved scan was sampled for 2 minutes total. The time-resolved data were apodized in the spectral domain with a 10 Hz exponential line broadening. Following FFT, phase and baseline correction, the peak heights of the lactate and pyruvate peaks were measured. The resulting time-courses were fit using a two-site exchange model to estimate apparent conversion rate constants (K*pl's*) and apparent T_1's for lactate. SNR of the time-resolved lactate responses were measured for the 10-deg excitation condition and subsequently used in the calculation of the SNR expected for alternate flip-angles.

Result: As expected the K*pl's* obtained from the fits gave the same result independent of label position or TR (0.010+/-.002). Figure 1 illustrates the fits of C1 pyr-to-lac labeling with a TR = 3 s and Figure 2 illustrates the fit for C2 pyr-to-lac label exchange in the same experiment. The C2pyr response was lower than the C1pyr response, likely due to a combination of lower polarization (14% vs 16%), shorter in vitro liquid state T_1 (48 s vs 60 s), and an increase in the J_{CH} coupling (broader line). The apparent T_1 decay for C2lac under these in vivo conditions was 6 s. This compares with a C1lac apparent T_1 decay of 19 s used as an internal control. SNR vs tip-angle plots are shown for a TR of 3 s in Figure 3 and a TR of 1.5 s in Figure 4.

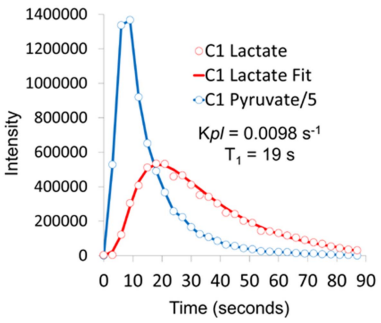

Figure 1. C1 pyr-lac fit (TR 3 s)

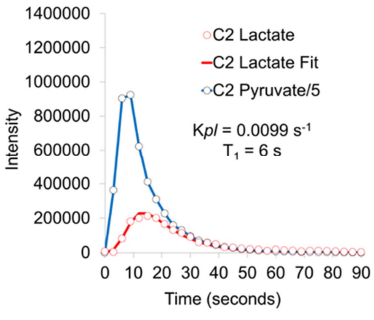

Figure 2. C2 pyr-lac fit (TR 3 s)

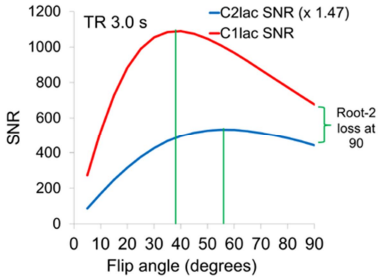

Figure 3. SNR vs flip angle TR 3

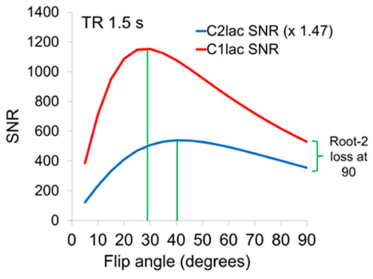

Figure 4. SNR vs flip angle TR 1.5

Discussion & Conclusion: The expectation was that the C2lac T_1 would be on the order of our typical TR times, and that maximum SNR therefore would be a full 90-deg excitation every TR. However, the apparent T_1 of C2lac, at 6 s, was longer than expected and maximum SNR is predicted at around 57-deg every 3 s or 40-deg every 1.5 s. Adjusting for the observed difference in C1 and C2 pyr (1.47), the 90-deg excitation (appropriate for saturation recovery methods), yielded a SNR loss of just root-2, consistent with doubling the noise band for the C2-doublet.

References: [1] Atherton et al, *Circulation.* 2011;123:2552, [2] Schroeder, et al, *Circulation.* 2011;124:1580, [3] Dodd et al., *Cardiovascular Res.* 2012;95:69, [4] Hu, et al, *ISMRM.* 2012;4331, [5] Josan S, et al, *ISMRM.* 2012;4322, [6]Park et al. ISMRM. 2012; 4323.

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