Simultaneous Measurement Carbon-13 MR Spin-Relaxation, Diffusion, and Kinetic Parameters

Christine Leon[1], Cornelius Von Morze[1], Bertram Koelsch[1], Adam B. Kerr[2], Robert A. Bok[1], John M. Pauly[2], John Kurhanewicz[1], Daniel B. Vigneron[1], and Peder E.Z. Larson[1]
[1]*Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, United States,* [2]*Magnetic Resonance Systems Research Laboratory, Department of Electrical Engineering, Stanford University, Stanford, CA, United States*

Introduction: Magnetic resonance spectroscopy (MRS) of hyperpolarized substrates is a powerful tool for investigating tissue metabolism and kinetics *in vivo*[1]. In addition to detecting increased $K_{Pyr\rightarrow Lac}$ in tumors using MAD-STEAM, we recently showed that the $T_{1,Eff}$ of lactate observed after infusion of hyperpolarized pyruvate was significantly shorter in tumors, suggesting a different cellular environment of lactate, in addition to increased $K_{Pyr\rightarrow Lac}$[2]. However, the $T_{1,Eff}$ of lactate as measured using the existing method is subject to both spin-relaxation and diffusion effects. We modified the MAD-STEAM pulse sequence to include varying gradients to separate diffusion from T_1 relaxation effects. This new method allows simultaneous measurement of apparent diffusion coefficients (ADC) and T_1 in addition to multiple rates of conversion, providing further biological information about the cellular environment of the metabolites.

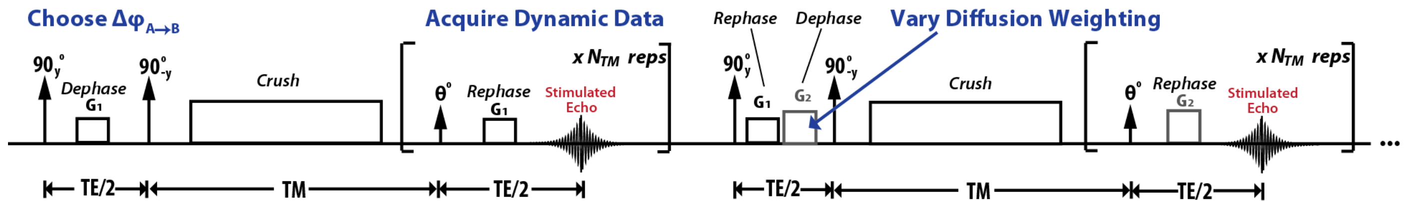

Figure 1. Dynamic diffusion sensitive MAD-STEAM sequence. All data was acquired with slab selection in z, 20x, 1sec temporal resolution, 256 spectral points, 2.5 kHz spectral bandwidth, and adiabatic double spin echo.[5]

Methods: STEAM in the presence of metabolic conversion creates a phase shift dependent on the resonance frequency and echo time (TE), $\Delta\varphi = 2\pi f TE/2$ which can be used to "phase tag" metabolites and directly observe real-time metabolism[2,3]. STEAM can concurrently remove signals from bulk flowing spins, providing improve contrast to cellular metabolism[4]. For validation experiments, TE=13ms was chosen such that $\Delta\varphi_{Pyr\rightarrow Hyd} = \pi/2$, shown in Figure 2. *In vivo* data was acquired with TE=14ms such that $\Delta\varphi_{Pyr\rightarrow Lac} = \pi/2$. With this information the $T_{1,Eff}$ and $K_{Pyr\rightarrow x}$ were calculated using MAD[2]. Since $S(t) \propto e^{-t/T_1} e^{-b(t)D}$, the $1/T_{1,eff,x} = 1/T_{1,x} + (\gamma G_i \delta)^2 ADC_x$, such that the ADCs and T_1s can be estimated by varying the diffusion gradient strength.

Results & Discussion: The measurement of $T_{1,Eff}$ is a combination of both relaxation and diffusion effects, which can be separated using the pulse sequence shown in Figure 1. In Table 1, we observed a decrease in the T_1 relaxation measurements with the addition of GAD and decreases in the ADCs values at cooler temperatures. Hyperpolarized carbon-13 diffusion coefficients, T_1 relaxation, and rates of conversion and exchange were measured simultaneously for the first time *in vivo*, shown in Figure 3. Furthermore, the ADC of lactate that was converted from pyruvate via the intracellular LDH enzyme during the experiment was separated from the ADC of other lactate molecules.

	$K_{Pyr\rightarrow Hyd}$	ADC_{Pyr}	$T_{1,Pyr}$	ADC_{Hyd}	$T_{1,Hyd}$
Room Temperature (~ 24 °C)	0.047 s^{-1}*	24.5x$10^{-4}$$mm^2s^{-1}$	59.0 s	25.0x10^{-4} mm^2s^{-1}	50.0 s
Cooled (~ 5 °C)	0.016 s^{-1}	8.07x$10^{-4}$$mm^2s^{-1}$	52.4 s	10.0x10^{-4} mm^2s^{-1}	45.0 s
With Gadolinium (5% vol)	0.014 s^{-1}	24.0$10^{-4}$$mm^2s^{-1}$	15.0 s	17.1 x$10^{-4}$$mm^2s^{-1}$	13.0 s

Table 1. Diffusion, relaxation, and conversion parameters from a diffusion sensitive MAD-STEAM in a syringe (TE=13ms, b-values: 65-1734s/mm^2).
*This experiment was performed first. Pyruvate and pyruvate hydrate may not have reached equilibrium causing increased exchange.

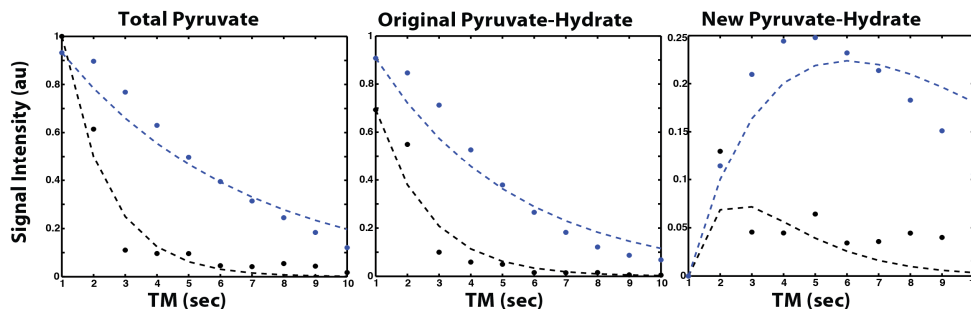

Figure 2. Total Pyruvate, Orginal Pyruvate-Hydrate and New Pyruvate-Hydrate dynamic curves from a diffusion sensitive MAD-STEAM sequence (G1 = 3.04s/mm^2 and G2=1.14s/mm^2, TE=13ms, $\Delta\varphi_{Pyr\rightarrow Lac}=\pi/2$, TR=1s, TE=13ms). Signal was normalized to pyruvate at 1s.

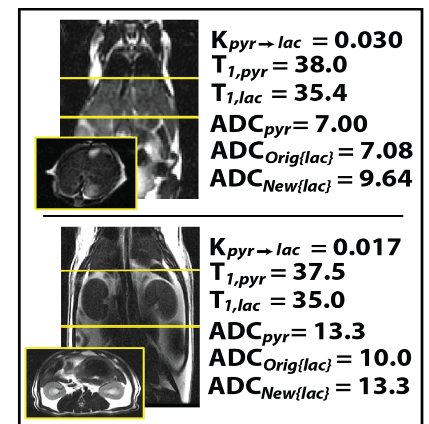

Figure 3. Diffusion, relaxation, and conversion parameters in vivo (TE=14ms, b-values: 65-1734s/mm^2). $ACD_{Orig\{Lac\}}$ and denotes the ADC of lactate that has gone through conversion via the LDH enzyme. $ACD_{New\{Lac\}}$ denotes the ADC of lactate that has not gone through conversion. ADCs, rates, and T1s are reported as x$10^{-4}$$mm^2s^{-1}$, s^{-1}, and

Conclusion: With the removal of confounding vascular signals, improved accuracy of estimation of real-time conversion rates, and simultaneous measurements of ADCs and T_1s, the developed approach provides new quantitative measures of relaxation, diffusion, and conversion rates. The results of this study demonstrate the potential value of this technique to better measure and understand tumor metabolic changes and the cellular environment with carcinogenesis, progression and response to therapy.

References: [1] Kurhanewicz, et al. Neoplasia. 2011; 13(2): 81-97. [2] Leon, et al. Proc Intl Soc Mag Reson Med 20, #180 (2012). [3] Larson, et al. JMR (2012). [4] Larson, et al. IEEE (2012). [5] Cunningham, et al. J Magn Reson 2007; 187:357-362. **Acknowledgements:** The authors acknowledge: Galen Reed, Lucas Carvajal, Peter Shin, Dr. Illwoo Park, and Mark Van Criekinge for assistance performing experiments, as well as Dr. James Tropp for the $^1H/^{13}C$ mouse coil, as well as, funding from NIBIB center grant P41EB01598, NIH P41-EB01359, National Science Foundation Graduate Research Fellowship, and NIH K99 EB012064.