Exchange-linked dissolution agents in 13C metabolic imaging

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Introduction: The conversion of [1-^{13}C]pyruvate to [1-^{13}C]lactate, as observed in hyperpolarized metabolic imaging, is a combination of flux and exchange. Under tracer conditions in whole blood, pyruvate-lactate exchange occurs at a rate 3-5 times the rate of flux (Romijn, Chinkes et al. 1994). High concentrations of exogenous [1-^{13}C]pyruvate, added to cells preconditioned with an increased steady-state level of unlabeled lactate, also yield a concomitant increase in isotope exchange (Day, Kettunen et al. 2007). Recently, the importance of exchange in vivo, under the high bolus concentration and timing of hyperpolarized metabolic imaging, has been demonstrated (Kettunen, Hu et al. 2010). The authors further conclude that steady-state lactate pool size is the likely limit of detection for [1-^{13}C]lactate in regions-of-interest such as blood and muscle. The goal of this study is to use unlabeled lactate in the bolus, to test for pool-size limits, without changing the steady-state condition, prior to the arrival of the bolus. Injection of 40 mM hyperpolarized [1-^{13}C]lactate in a control experiment was designed to provide a measure of the transient increase in lactate pool size for each voxel, and the injection of hyperpolarized [1-^{13}C]lactate in combination with unlabeled 80 mM pyruvate, was used to probe exchange in the reverse direction.

Material and Methods: The experiments were performed on 5 healthy male Wistar rats (200-330g), anesthetized with 1-3% isoflurane in oxygen (~1.5 L/min) Preparation and physiological monitoring of the animals followed the protocol approved by the local Institutional Animal Care and Use Committees. Hyperpolarized 80 mM [1-^{13}C]-pyruvate was prepared using a HyperSense™ polarizer (Oxford Instruments Molecular Biotools, Abington, UK). The dissolution solvent was 40 mM TRIS-80 mM NaOH-2.7 mM EDTA with 40 mM NaCl (control) or with 40 mM sodium lactate. Hyperpolarized solutions of 40 mM [1-^{13}C]lactate were prepared using a dissolution solvent of 40 mM TRIS-2.7 mM EDTA, with 80 mM NaCl (control), or with 80 mM pyruvate. The total dose ranged from 2–3 mL agent, injected over 12 s. All experiments were performed on a 3T Signa™ (GE Healthcare, Waukesha, WI), using a dual-tuned (^{1}H/^{13}C) quadrature rodent coil. Dynamic imaging was performed every 5 s starting at 5 s from start of tail vein injection using 3D-spCSI with a nominal isotropic resolution of 5 mm. Each imaging volume was sampled with 36 5.6-deg excitations. (T_{acq}=4.5s).

Results: The inclusion of unlabeled lactate in the dissolution buffer resulted in increased [1-^{13}C]lactate signal following [1-^{13}C]pyruvate injection in all examined tissue ROIs, thus demonstrating the importance of isotopic exchange and lactate pool size limits in vivo. Figure 1 compares the time-averaged [1-^{13}C]lactate response in a 3DspCSI set of lactate overlay images (left) along with the dynamic response from kidney, from liver, and from a vascular rich ROI (right). Over the four studies, SNR varied by ~20% run-to-run, both with, and without ^{12}C lactate. The average SNR increases were 98% for kidney, 62% for vascular and 50% for liver. Under these conditions contrast-to-noise ratio was also elevated. Pyruvate, and alanine signals were not appreciably changed. In a control experiment, the injection of hyperpolarized [1-^{13}C]lactate showed good distribution to the organs of interest, but significant [1-^{13}C]pyruvate production was only seen when unlabeled pyruvate was added to the buffer

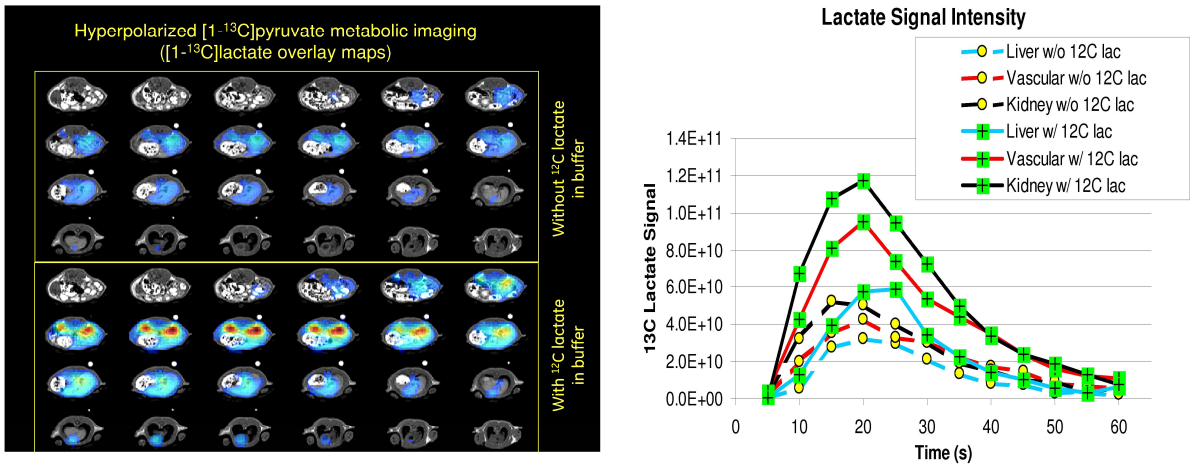

Figure 1. Scaled comparison of lactate from dynamic 3DspCSI images of normal rat with and without 40mM unlabeled sodium lactate in the dissolution buffer. The dynamic time points have been averaged using kidney signal as a weighting factor (left). The time response for kidney, liver and vascular regions of interest are shown on the right.

Discussion: This study introduces and demonstrates the value of exchange-linked dissolution agents in hyperpolarized ^{13}C metabolic imaging experiments. Extension of this strategy to brain, and to a glioma model, also resulted in increased signal. Thus it appears that gains in signal, contrast, and potentially a quantitative measure of exchange vs flux may be possible under a variety of conditions.

Day, S. E., M. I. Kettunen, et al. (2007). Nat Med **13**(11): 1382-1387; Kettunen, M. I., D. E. Hu, et al. (2010). Magn Reson Med **63**(4): 872-880.
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