Investigating Enzyme Activity with Hyperpolarized C-13 Metabolic Activity Decomposition MRI

Leon, C*1, Larson, P*, Kerr, A1, Vigneron, D*

* Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, 94158
† UC Berkeley | UCSF Graduate Group in Bioengineering, University of California, San Francisco & Berkeley, CA
1 Department of Electrical Engineering, Stanford University, Stanford, CA 94035

Tel: 415-476-3343 E-mail: Dan.Vigneron@radiology.ucsf.edu

Summary: Validation of Metabolic Activity Decomposition Stimulated-Echo Acquisition Mode(MAD-STEAM), the first acquisition and reconstruction method for directly observing localized metabolic conversion in vivo.

Biochemical processes observed in cancerous tissues are markedly different than those in similar normal tissues. Hyperpolarized 13C-labelled molecules allow for rapid metabolic MR imaging in vivo, providing new information about these metabolic pathways. Currently, the metabolic profile has been obtained from indirect observations of metabolic flux. The goal of this project was to validate the ability of MAD-STEAM to directly observe localized metabolic conversion in vivo.

Metabolite spins were put in quadrature to differentiate between metabolites previously present in tissue and those generated during a mixing interval. This was accomplished using stimulated-echo acquisition mode (STEAM) encoding which creates sinusoidal modulation in space, cos(x-φ), along the longitudinal axis. This modulation includes a phase shift that depends on the resonance frequency and echo time (TE), φ=2πΔfTE/2. Choosing Δ=π/2 causes the spins generated during the mixing time to be in quadrature. They can be separated during reconstruction enabling direct observation of the label exchange between metabolites.

Fig. 1. Investigation of LDH activity from spectra obtained with MAD-STEAM (TM=0,1,2,…,9 sec) and generation of 13C-labeled lactate with lactate dehydrogenase, nicotinamide adenine dinucleotide (reduced) and hyperpolarized 13C-pyruvate in phosphate buffer solution (right). Imaginary and real dynamic spectra (left) First and last spectra.

Fig. 2. (a) Time series of peak areas of each metabolite from experiment shown in Figure 1 and (b) Time series of peak areas of each metabolite in a normal mouse with MADSTEAM (progressive flip angle, TE =14ms, bandwidth=2500 Hz, spectral points=256).

To validate the technique, dynamic spectra were obtained from solutions containing lactate dehydrogenase (LDH, 2x excess), nicotinamide adenine dinucleotide, reduced (NADH, 4x excess) and 6uL of hyperpolarized [1,13C]-pyruvate in phosphate buffered solution (3mL, pH=7.0) with co-polarization of 15uL of 13C-urea for phase reference.

Pyruvate is of interest because tumors preferentially undergo conversion of pyruvate to lactic acid due to the Warburg effect. Accumulation of the imaginary lactate signal demonstrates real-time conversion of pyruvate to lactate from activity of the LDH enzyme (as shown in Figure 1). Using the same pulse sequence on normal mice (n=5), equivalent results were observed (as shown in Figure 2). This demonstrates the validity of this new method for direct observation of localized metabolic conversion in vivo.


Acknowledgments: Funding from NIH K09 EB012064, RO1 EB007588, American Cancer Society PF-09-036-01-CCE, and NIGMS-IMSD R25-GM56847.