Imaging Real-Time Cancer Metabolism with MAD-STEAM HP ^{13}C MRSI

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Introduction: Recently, it has been shown that with the removal of confounding signals from the vasculature, improved accuracy of estimation of real-time conversion rates, and simultaneous measurement of T1 relaxation times, the Metabolic Activity Decomposition technique [1-3] provided more accurate quantitative measures of relaxation and conversion rates for hyperpolarized (HP) ^{13}C MR. Using MAD-STEAM single-voxel acquisition and reconstruction, real-time conversion and exchange can be directly observed [1]. These quantitative measurements improved the ability to calculate kinetic parameters, which may provide increased specificity for monitoring intracellular enzyme activity [3]. The goal of this project was to develop novel MAD-STEAM spectroscopic imaging methods to investigate real-time metabolism and generate parametric maps of exchange kinetics throughout the tumor and adjacent tissues. This new imaging approach could provide improved specificity to cancer metabolism and localization of those changes

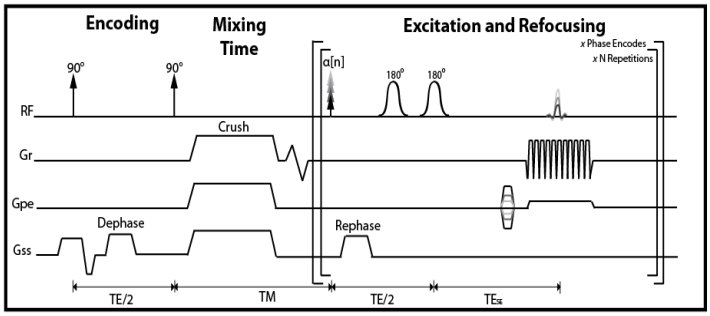

Figure 1. Dynamic Metabolic Activity Decomposition with Stimulated Echo Acquisition Mode (MAD-STEAM) pulse sequence with flyback echo planar spectroscopic imaging (EPSI). All data was acquired with 20mm slab selection in z, 59 spectral points, a progressive flip angle scheme, and adiabatic double spin echo [4]. A symmetrically sampled full echo was acquired to preserve phase

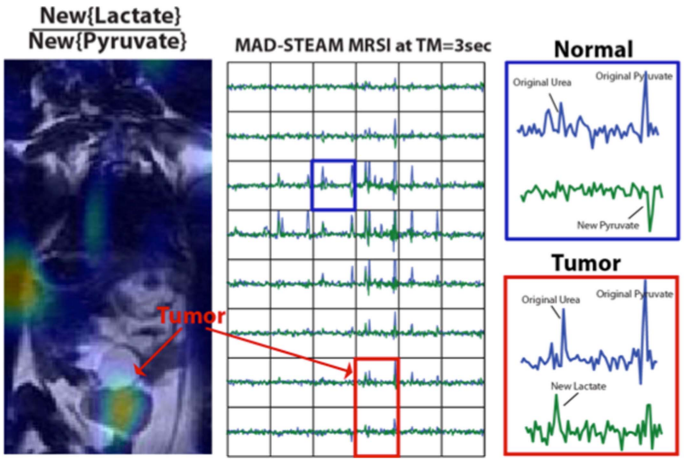

Figure 2. Coronal image from MAD-STEAM MRSI in a transgenic model of prostate cancer (TM = 3 sec, TR = 210msec, xres = 5mm, yres = 10mm, FOV=80mm, reps=4). Sample tumor and normal voxels are shown on the right. Overlay shows New{Lactate}-to-New{Pyruvate}ratio. Window level is 0-10.

Methods: For animal experiments, a 3T clinical MRI system (GE, Waukesha,WI, USA) was used with a dual-tuned mouse birdcage coil based on a design used previously [1, 2]. Using MAD-STEAM, exchanging versus non-exchanging spins were separated based on their phase $\Delta\varphi = 2\pi\Delta f\, TE/2$ [1]. For a main field of 3T, the echo time TE=14ms was chosen. With TE=14ms, the phase of pyruvate to lactate conversion will be $\Delta\varphi_{Pyr\rightarrow Lac} = +\pi/2$ such that the generated and original lactate are in quadrature. Meanwhile, the phase of pyruvate to alanine conversion is $\Delta\varphi_{Pyr\rightarrow Ala} \approx -\pi/2$ at TE=14ms. Since generated and original alanine are not exactly in quadrature, the magnitude was broken into its components based on $\Delta\varphi_{Pyr\rightarrow Ala} = -\pi/2.21$ to separate original and generated alanine [3]. Co-polarization with ^{13}C-urea provided a phase reference to correct for phase shifts caused by homogeneous, bulk motion such as respiration, which would affect all metabolites [1]. Flyback Echo Planar Spectroscopic Imaging was added to the MAD-STEAM sequence pulse sequence, shown in Figure 1, to localize and image enzymatic conversions of hyperpolarized pyruvate throughout the tumor and normal tissues.

Results and Discussion: Real-time generation of lactate was observed in a TRAMP tumor using the MAD-STEAM MRSI sequence as shown in Figure 2. In normal and transgenic mice, dynamic images were obtained to generate parametric maps of $K_{Pyr\rightarrow Lac}$ and $K_{Pyr\rightarrow Ala}$ using three-site exchange and MAD [3]. MAD-STEAM images showed improved contrast to metabolism by suppressing signal from flowing spins. This was demonstrated by a lack of signal in the kidneys and heart. In switchable oncogene-driven model of liver cancer, increased conversion to alanine, $K_{Pyr\rightarrow Ala}$, was observed at during the pre-tumor state (2 weeks after removal of doxycycline). Recently, it has been shown that increased alanine may be a marker of tumor formation [5].

Conclusion: The advantage of the dynamic MAD-STEAM MRSI approach is twofold. First, it improves sensitivity to metabolism by removal of signals within the vasculature. Secondly, it provides robust kinetic modeling with increased specificity to cellular exchange, which can better differentiate tumor versus normal. In the field of oncology in particular, this new technique has great biomedical potential as it could be used to better measure and understand tumor metabolic changes with cancer progression and response to therapy.

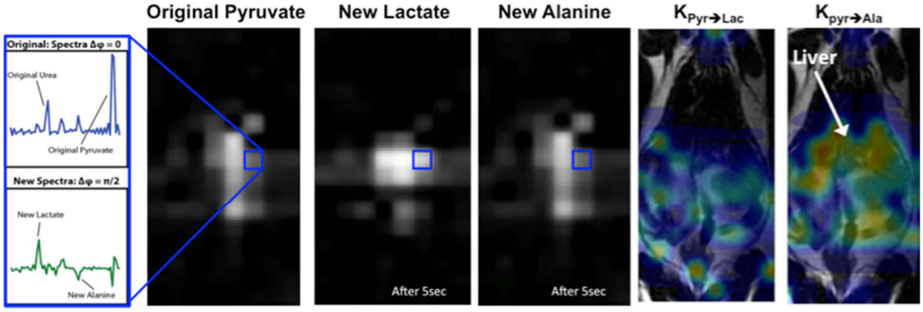

Figure 3. Metabolite maps and paramteric maps from dynamic coronal image of MAD-STEAM (TM = 5 sec, reps = 2, TR = 210msec, xres = 10mm, xres = 7.5mm, TE=14ms, flyback epsi, progressive flip angle). Window level is from 0 to 0.3 s^{-1} for $K_{Pyr\rightarrow Lac}$ and 0 to 0.2 s^{-1} $K_{Pyr\rightarrow Ala}$.

References: [1] Larson, et al. J Magn Reson, 225:71-80 (2012). [2] Larson et al. IEE Trans Med Imaging, 31:265-275 (2011). [3] Leon, et al.; Proc Intl Soc Mag Reson Med 20, #180, (2012). [4] Cunningham, et al. J Magn Reson; 187:357-362, (2007). [5] Hu et al Cell Metab. 14(1):131-142 (2011)

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