

Application of Slice-Localized ^{13}C Dynamic MR Spectroscopy and 2D ^{13}C Dynamic MR Spectroscopic Imaging with Hyperpolarized $[1-^{13}\text{C}]$ -Pyruvate in a Human Glioblastoma Xenograft

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Purpose: The development of dynamic nuclear polarization (DNP) technique and a rapid dissolution process have enabled the real time investigation of in vivo metabolism with more than 10,000-fold signal increase [1]. Time-resolved MR Spectroscopy (MRS) may provide a tool to monitor real time changes in tissue parameters by tracking the dynamic uptake of hyperpolarized $[1-^{13}\text{C}]$ -pyruvate and its conversion to other metabolites. We have applied slice-localized ^{13}C dynamic MRS and multiband RF 2D ^{13}C dynamic MR spectroscopic imaging (MRSI) with hyperpolarized $[1-^{13}\text{C}]$ -pyruvate as a substrate for analysis of a human glioblastoma xenograft.

Methods: Tumors were induced by intracranial implantation of human glioblastoma cells (U-251 MG or U-87 MG) into the brain of athymic rats. Slice-localized ^{13}C dynamic MRS data were acquired from a 15 mm slice through the brain of 6 rats with tumor and 4 rats without tumor using a double spin-echo pulse sequence [2] consisting of a 5-degree flip angle RF excitation and a pair of non-localized 180 degree hyperbolic secant refocusing pulses (TE/TR=35/3000 ms, 5 kHz BW, 2048 spectral points, 3s temporal resolution with a total of 64 time points). 2D ^{13}C dynamic MRSI data were acquired from a 10 mm coronal slice centered at the brain of 3 rats with tumor and 3 rats without tumor using newly designed multiband, variable flip angle, spectral-spatial RF pulses [3] incorporated with a double spin-echo and an echo-planar readout gradient (TE/TR=160/250 ms, 30° flip for lactate, 5° flip for pyruvate, 5x5mm in-plane-resolution, 5s temporal resolution with a total of 20 time points). All data were acquired after the injection of 2.3 ml (100mM) hyperpolarized $[1-^{13}\text{C}]$ -pyruvate (Isotec USA) polarized using a HyperSense® DNP polarizer (Oxford Instruments, UK) and imaged with a GE 3T scanner and a custom-designed $^1\text{H}/^{13}\text{C}$ rat coil. The SNR of lactate and pyruvate were calculated using the peak metabolite heights from the magnitude spectra and normalized by polarization and injection volume. The area under the curve (AUC), maximum peak height, full width half maximum (FWHM), and time to the maximum peak were calculated from the time course plot for lactate and pyruvate.

Results: Figure 1 shows an example of slice-localized hyperpolarized ^{13}C dynamic MRS data from a rat with and without tumor. The FWHM of the lactate curve from the rats with tumor was significantly larger than that from the control rats ($p=0.006$) (Figure 1). A mixture of tissues consisting of brain, muscle, and vasculature from a 15 mm-thick slice contributed to the overall signal and prevented other parameters to show distinction between the two groups. Figure 2 shows an anatomical image and the corresponding lactate and pyruvate dynamic curves from a hyperpolarized 2D ^{13}C dynamic CSI data from a rat with tumor. The lactate curve exhibited a distinctive pattern between the voxel at the tumor (red voxel) and the contra-lateral hemisphere (green voxel). The AUC, maximum peak height, FWHM, and time to the maximum peak from the lactate curve showed a strong trend toward differences between the voxels at tumor and contra-lateral hemisphere or normal brain tissue from the control rats (Figure 3); however, the statistical significance of this relationship was limited by the small sample size ($p=0.1$ for AUC and maximum peak height). Figure 4 shows an example of a metabolic map of lactate and pyruvate over time acquired from a rat with tumor following injection of hyperpolarized $[1-^{13}\text{C}]$ -pyruvate. The maximum pyruvate peak typically preceded the maximum lactate peak and the lactate signal lasted longer than the pyruvate signal.

Conclusions: The results of this study showed potential for applying time-resolved MR spectroscopic imaging to characterize brain tumor. The 2D dynamic CSI provided spatially resolved MRS that allowed for the differentiation of tumor from normal tissue based on the conversion of pyruvate to lactate. The use of a 2D dynamic CSI technique that has a higher time resolution may also provide an improved statistical result between the different tissue types.

References: [1] Golman et al. PNAS, 2006. [2] Cunningham et al. J Magn Reson, 2007. [3] Larson et al. J Magn Reson, 2008.

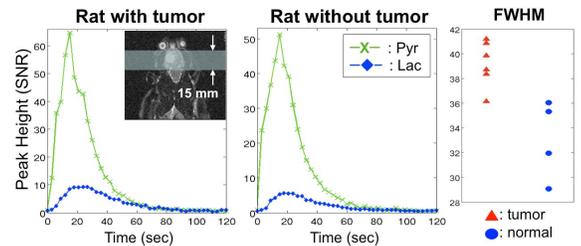


Figure 1: Representative slice-localized ^{13}C dynamic MRS data from a rat with and without tumor. The peak height plots show the time course of hyperpolarized $[1-^{13}\text{C}]$ -pyruvate and its conversion to lactate. A T2 FSE image in coronal plane shows the extent of 15 mm-thick slice used for data acquisition.

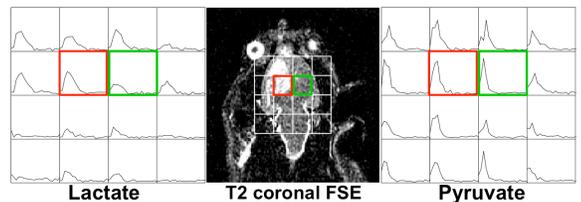


Figure 2: Dynamic metabolic curves of lactate and pyruvate from 2D ^{13}C dynamic CSI from a rat with tumor. The kinetics of lactate at tumor (read voxel) appeared to be different from the one at the contra-lateral hemisphere (green voxel).

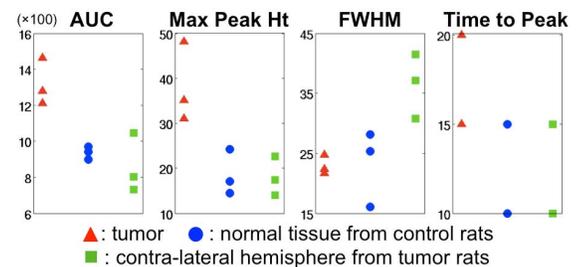


Figure 3: Analysis of the area under the curve (AUC), maximum peak height, full width half maximum (FWHM), and time to the maximum peak from the lactate curve between the voxels at different tissue types.

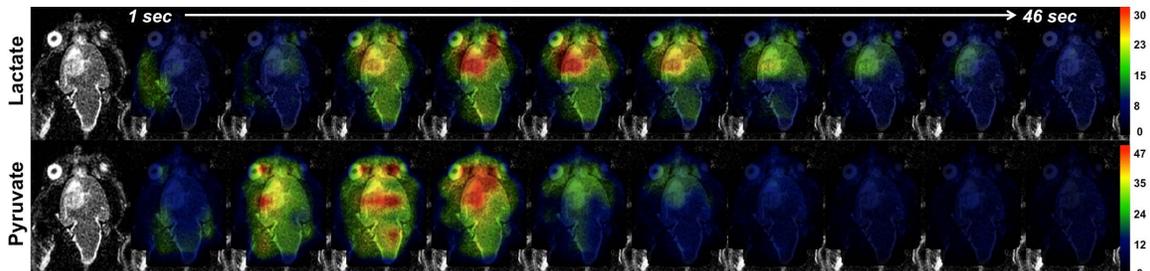


Figure 4: Metabolic map of lactate and pyruvate over time following injection of hyperpolarized $^{13}\text{C}_1$ -pyruvate. Each metabolic map was overlaid over T2 coronal FSE image with 5-second temporal resolution. The maximum pyruvate peak appeared at approximately 15 seconds while the lactate signal was maximum at approximately 20 seconds in the region of tumor and lasted longer than the pyruvate signal.