Assessing tumor microenvironment in rat glioma model using hyperpolarized 13C MRSI with a sliding window

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Target Audience Researchers who are interested in characteristics of hyperpolarized ^{13}C-substrates in cancer.

Purpose *In vivo* characteristics of hyperpolarized ^{13}C-substrates are often critical in the design of optimized pulse sequence as well as in the proper data analysis. By far, T_1 has received most attention since the observation window of hyperpolarized ^{13}C MR signals are T_1-limited. However, T_2 and T_2* also provide useful to understand tissue characteristics and create unique image contrasts[1-4], providing information for alternative MR acquisition strategies[2,3,5]. In this study, we propose a method that measures *in vivo* T_2* using a **sliding window spiral chemical shift imaging** and calculate (1) ***in vivo* T_2* maps** of hyperpolarized ^{13}C-substrates and (2) **B_0 maps** from glioma-implanted rat.

Methods Approximately 10^6 glioma cells are implanted into the right striatum of male Wistar rats ~10 days prior to the ^{13}C imaging (N=5). A spiral chemical shift imaging (spCSI) pulse sequence[6] is used to acquire single time-point metabolite maps of rat brain (four spatial interleaves, spectral width = 932.8 Hz, #echoes = 96, field of view = 43.5×43.5 mm^2, nominal spatial resolution = 2.7×2.7 mm^2, slice thickness = 6-8 mm, acquisition time = 0.5 s) following an *i.v.* injection of 125-mM hyperpolarized [1-^{13}C]pyruvate (injection-to-scan = 25 s, polarized using HyperSense DNP). B_0 field inhomogeneity over the brain is minimized adjusting linear shim currents with ^{1}H PRESS sequence. Custom-made birdcage RF coil (^{1}H-^{13}C dual-tuned) and high-performance insert gradient coil (G_{max} = 500 mT/m, Slew rate$_{max}$ = 1,865 mT/m/ms) are used in a 3T GE Signa clinical MR scanner. To assess T_2* of individual ^{13}C-labeled metabolite, a sliding spectral window (window size = 24 echoes) with varying echo times (ΔTE = 1.07 ms) is applied to the acquired CSI data (**Fig.1**). T_2* maps of [1-^{13}C]pyruvate and [1-^{13}C]lactate are calculated by fitting the temporal decay of each metabolite to an exponential function voxel-wise. For fitting, metabolite maps up to ~35 ms are used to maintain sufficient SNR.

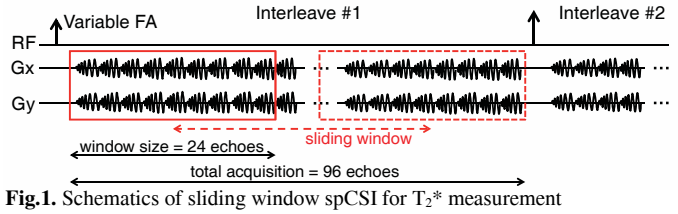

Fig.1. Schematics of sliding window spCSI for T_2* measurement

Results and Discussion Longer [1-^{13}C]lactate T_2*'s (41.0 ± 3.85 ms) were measured from glioma as compared to normal-appearing brain in the contra-lateral side (31.6 ± 5.3 ms, P = 0.08, **Figs.2-3**). T_2* of [1-^{13}C]pyruvate was also longer in glioma (58.9 ± 12.9 ms) than in normal-appearing brain (37.2 ± 6.8 ms, P = 0.01). The T_2* map of ^{13}C-bicarbonate was not reliably measured due to the low SNR. Although T_2* can be affected by other factors such as field inhomogeneity and flow, the longer lactate T_2* in tumor than in normal brain is consistent with longer lactate T_2[1,2] in tumor. Off-resonance effects were detected in the tumor regions despite shimming over the entire brain ($|B_{0,Tumor} - B_{0,NormalBrain}|$ = 0.255 ± 0.034 ppm, P < 0.005, **Fig.3D**). This observation is consistent with the magnetic susceptibility changes in tumor due to paramagnetic blood deposition and diamagnetic calcification around the tumor[7-9]. Considering that the off-resonance effect shortens T_2*, the contrasts between glioma and normal-appearing brain in T_2* maps imply the significant contribution of T_2 differences. A non-exponential attenuation factor detected in lactate is probably due to the strong ^{13}C-^{1}H spin-spin coupling ($J_{CH} \approx 25$ ms)[1,4] (**Fig.2C,D**).

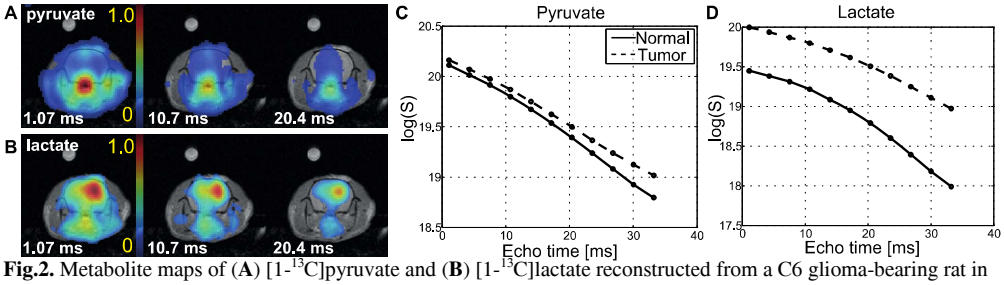

Fig.2. Metabolite maps of (**A**) [1-^{13}C]pyruvate and (**B**) [1-^{13}C]lactate reconstructed from a C6 glioma-bearing rat in right striatum using a sliding spectral window (24 echoes) at 1.07, 10.7, and 20.4 ms of echo times (TEs). Averaged signal decay of (**C**) pyruvate and (**D**) lactate in tumor (dashed line) and normal-appearing brain (solid line) ROIs.

Conclusion The proposed method provides the opportunity to assess complex transverse relaxation mechanism of hyperpolarized ^{13}C-substrates by observing multi-exponential decay patterns of the signal (as compared to the conventional spectral line-width measurement) as well as B_0 off-resonance. The study detected longer T_2* in brain tumor than in normal appearing brain, reflecting T_2 rather than field inhomogeneity. Therefore, the measured T_2* might serve as an indirect measure of relative T_2 of tumor and normal tissue.

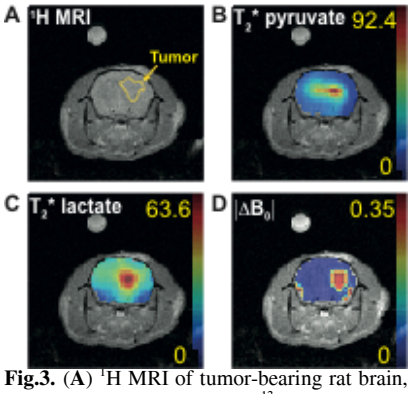

Fig.3. (**A**) ^{1}H MRI of tumor-bearing rat brain, Cerebral T_2* maps of (**B**) [1-^{13}C]pyruvate and (**C**) [1-^{13}C]lactate. Numbers are in [ms]. (**D**) Field map indicates that B_0 field is ~11 Hz (0.3 ppm) shifted in the tumor ROI.

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Acknowledgements NIH: EB009070, AA005965, AA0018681, AA13521-INIA, P41 EB015891, DOD: PC100427, Lucas Foundation, Nadia's gift, and GE Healthcare