Serial characterization of HP [1-13C]pyruvate metabolism in the brains of patients with glioma and healthy controls

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Highlights: Serial hyperpolarized 13C (HP-13C) echo-planar imaging demonstrated aberrant [1-13C]pyruvate metabolism in patients with glioma whose disease has progressed relative to normal-appearing white matter and metabolic changes corresponding to anti-angiogenic agent bevacizumab. Healthy volunteer data showed both consistent and reproducible kinetic profiles in white matter.

INTRODUCTION
Gliomas comprise a heterogeneous class of brain tumors, whose clinical management is complicated by treatment-related changes on standard anatomic imaging. Dynamic hyperpolarized 13C (HP-13C) imaging allows for real-time measurement of metabolism, which may improve glioma surveillance. Here, we focus on characterizing brain metabolism in healthy controls and patients undergoing treatment for recurrent glioma using serial HP-13C metabolic imaging.

METHODS
Serial HP 13C Imaging. A total of 33 serial dynamic HP 13C imaging scans were acquired from 8 patients (4 females, 4 males) with recurrent glioma; 7 scans were also acquired from 3 healthy volunteers (1 female, 2 males), which included test re-test validation. A frequency-specific 2-D multislice EPI sequence (TR/TE=62.5ms/21.7ms, 8 slices, 1.5cm isotropic resolution, 20 timepoints, 3s temporal resolution, $\alpha_{\text{pyruvate}}/\alpha_{\text{lactate}}/\alpha_{\text{bicarbonate}} = 20^\circ/30^\circ/30^\circ$) with spectro-spatial (SPSP) excitation was used to acquire data at 3T.

Polarization and Injection. Dynamic nuclear polarization of [1-13C]pyruvate was performed on a SPINlab system, according to previously described methods2. Upon pharmacist release, a 0.43mL/kg dose of HP [1-13C]pyruvate was injected intravenously at 5mL/s, followed by a 20mL saline flush. The 13C data were obtained after a 5s delay.

Segmentation. Standard proton imaging acquired in a subsequent exam was segmented and aligned to the carbon exam. The regions of interest included: 1) normal-appearing white matter (NAWM) segmented via FSL FAST, the 2) manually-defined FLAIR T2 lesion (T2L), and 3) manually-defined T1-enhancing lesion (T1L). In patients, NAWM was obtained by subtracting the T2L. Voxels containing>30% ROIs were considered in the subsequent analysis.

Kinetic Modeling. EPI data were prewhitened and channel-combined according to a weighted-sum based on the total pyruvate signal. After phasing the complex data and
summing signal within ROIs, the apparent rate constants for pyruvate-to-lactate ($k_{PL}$) and pyruvate-to-bicarbonate ($k_{PB}$) conversion were simultaneously estimated using a two-site exchange model.

RESULTS
Volunteer EPI data demonstrated consistent values of apparent rate constants across subjects in NAWM: $k_{PL,NAWM}=0.017\pm7.9\%$ s$^{-1}$ and $k_{PB,NAWM}=0.0046\pm14\%$ s$^{-1}$ (mean ±mean/SD). Reproducibility was also observed in the test / 30-min re-test volunteer scans: $k_{PL,NAWM}=0.017\pm0.001 / 0.017\pm0.002$s$^{-1}$. Patients collectively demonstrated $k_{PL,NAWM}=0.018\pm16\%$ s$^{-1}$ and $k_{PB,NAWM}=0.058\pm28\%$ s$^{-1}$ (mean±mean/SD; 19 scans) when excluding adjuvant treatment timepoints, which closely matched volunteer kinetic profiles for $k_{PL}$. In 2 patients with progressive disease, the enhancing lesion showed elevated $k_{PL,T1L}=0.041\pm10\%$ s$^{-1}$ (mean/SD; 4 scans) relative to their $k_{PL,NAWM}$ ($p=0.03$, Wilcoxon) and that of other patients ($p=0.002$). Progressive disease also manifested higher T2 lesion $k_{PL,T2L}=0.028$ s$^{-1}$ compared to NAWM ($p=0.04$). Much of the variation in $k_{PL}$ within NAWM, could be accounted for through adjuvant therapy. During administration of anti-angiogenic agent bevacizumab, 2 patients expressed an apparent global increase in $k_{PL,NAWM}$ ($p=0.004$), which was likely owing to decreased extravasation of [1-$^{13}$C]pyruvate from the vasculature. Figure 1 shows serial kpl maps for a patient treated with bevacizmab and the corresponding elevation of $k_{PL}$, along with increased $k_{PL}$ within the Gd-enhancing lesion prior to therapy.

CONCLUSION
Kinetic profiles derived from HP-$^{13}$C metabolic imaging of patients with glioma demonstrated abnormal $k_{PL}$ in cases of progressive disease and $k_{PL,NAWM}$ changes with bevacizumab relative to healthy controls.

![Figure 1. Serial kPL maps derived from HP-$^{13}$C EPI of a patient with glioma. Timepoints (TP) 5 and 6 demonstrate consistent kPL within NAWM and elevated kPL in the Gd-enhancing lesion, indicated by the red arrows. Following the administration of bevacizumab at TP7 and TP8, the Gd-enhancing lesion disappears and kPL becomes globally elevated.](image-url)