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

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***Highlights**: Serial hyperpolarized ^{13}C (HP-^{13}C) echo-planar imaging demonstrated aberrant [1-^{13}C]pyruvate metabolism in patients with glioma whose diease 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 ^{13}C (HP-^{13}C) 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-^{13}C metabolic imaging.

METHODS

Serial HP ^{13}C Imaging. A total of 33 serial dynamic HP ^{13}C 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, $\alpha_{pyruvate}/\alpha_{lactate}/\alpha_{bicarbonate}$ = 20º/30º/30º) with spectro-spatial (SPSP) excitation was used to acquire data at 3T.

Polarization and Injection. Dynamic nuclear polarization of [1-^{13}C]pyruvate was performed on a SPINlab system, according to previously described methods[2]. Upon pharmacist release, a 0.43mL/kg dose of HP [1-^{13}C]pyruvate was injected intravenously at 5mL/s, followed by a 20mL saline flush. The ^{13}C 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±7.9% s^{-1} and $k_{PB,NAWM}$=0.0046±14% s^{-1} (mean ±mean/SD). Reproducibility was also observed in the test / 30-min re-test volunteer scans: $k_{PL,NAWM}$=0.017±0.001 / 0.017±20.002s^{-1}. Patients collectively demonstrated $k_{PL,NAWM}$=0.018±16% s^{-1} and $k_{PB,NAWM}$=0.058±28% 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±10% 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.

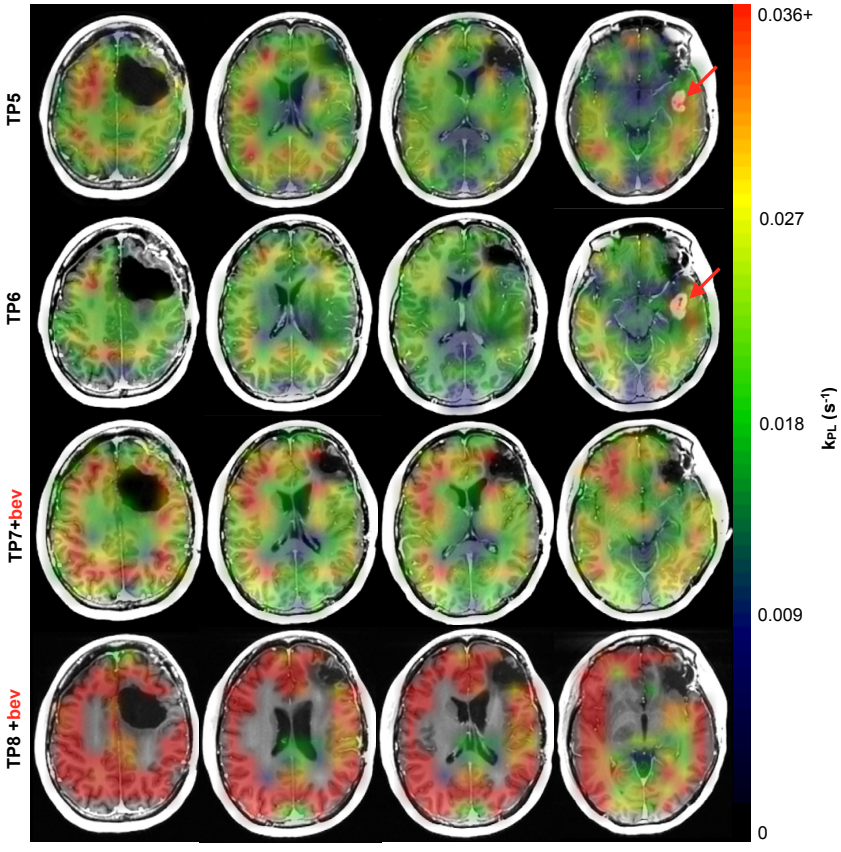

Figure 1. Serial k_{PL} maps derived from HP-^{13}C EPI of a patient with glioma. Timepoints (TP) 5 and 6 demonstrate consistent k_{PL} within NAWM and elevated k_{PL} in the Gd-enhancing lesion, indicated by the red arrows. Following the administration of bevacizumab at TP7 and TP8, the Gd-enhancing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