Title: Probing Cerebral Lactate Compartmentalization with Hyperpolarized Diffusion Weighted ^{13}C MRI

Author List: Jeremy W Gordon, Shuyu Tang, Xucheng Zhu, Daniel B Vigneron, Peder EZ Larson

Highlights: This work demonstrates the feasibility of diffusion weighted hyperpolarized ^{13}C in a clinical setting. This approach could potentially provide insight into lactate efflux in a rapid and non-invasive manner, with applications to the study of transporter expression in malignant tumors and axon-glia metabolic coupling in neuronal metabolism.

Introduction

Hyperpolarization of ^{13}C substrates has been used extensively for metabolic imaging in both pre-clinical[1] and proof-of-concept clinical studies[2] to non-invasively assess metabolic conversion. In addition to the Warburg Effect, many malignant cancers overexpress MCT4, the monocarboxylate transporter primarily responsible for lactate efflux[3,4]. Moreover, recent studies have shown that oligodendrocytes support axonal function through MCT1-based transport of lactate, and this metabolic coupling is crucial for maintaining axon function and neuron survival[5].

Because of structural differences in the intra- and extra-cellular microenvironments, diffusion weighted imaging (DWI) of hyperpolarized lactate (generated intracellularly from hyperpolarized pyruvate via lactate dehydrogenase) could provide unique information on lactate efflux and transporter expression in a rapid, non-invasive manner. In this work, we investigated the feasibility of DWI of lactate generated from hyperpolarized [1-^{13}C]pyruvate in the human brain to assess lactate efflux and compartmentalization in a healthy volunteer.

Methods

Hyperpolarized [1-^{13}C]pyruvate was generated in a SPINlab polarizer operating at 5T and 0.8K. Following dissolution, the sample was injected at a dose of 0.43mL/kg in a healthy volunteer. The acquisition was triggered at bolus arrival within the brain using an integrated RT-Hawk platform for real-time frequency and B1 calibration[6].

Hyperpolarized data were acquired using a double spin-echo EPI sequence. A gradient-echo EPI module was inserted before the first refocusing pulse to provide an internal reference for signal normalization to account for T1 and RF utilization. Scan parameters were 250ms TR, 10ms (GRE) and 142ms (SE) TE, 1.5 x 1.5cm^2 in-plane resolution, one 40mm thick slice, a low b-value of 51 s/mm^2 applied in the Z direction and a high b-value of 319 s/mm^2 applied in either the X, Y, or Z direction. Each timepoint (3.5s temporal resolution) had one gradient-echo pyruvate image and four spin-echo lactate diffusion-weighted images. To isolate the effects of diffusion weighting, spin-echo signal was normalized to the gradient-echo readout for each b-value, with the ADC then calculated over the whole brain as a two-point fit.

Results & Discussion

Figure 1 shows the dynamic hyperpolarized ^{13}C pyruvate and lactate images. Whole brain lactate ADC values were 0.37, 0.29, and 0.41 x 10^{-3} mm^2/s when diffusion gradients were applied in the X, Y, and Z direction, respectively, reasonable values given previously reported

pre-clinical ADC values of lactate[7,8]. The shape and location of the brain is consistent among all lactate images, regardless of b-value or direction, indicating no apparent eddy-current or EPI artifacts. Qualitatively, the signal for both pyruvate and lactate decayed faster compared to a conventional gradient-echo acquisition, where no refocusing was applied. This could be a result of imperfect inversion of the adiabatic RF pulse, as well as saturation of inflowing pyruvate and lactate at the coil boundary since the refocusing pulse was not slice selective[9].

Conclusion: This research demonstrated the feasibility of diffusion weighted hyperpolarized ^{13}C MRI in a clinical setting. Future developments will work on improved RF pulse design and flip angle schemes to increase SNR, enabling more b-values and improved volumetric coverage.

Acknowledgements: P41EB013598**,** R01EB016741, P41EB013598, and American Cancer Society Research Scholar Grant 131715-RSG-18-005-01-CCE.

References:

1.) Albers, M.J., et al., *Hyperpolarized 13C Lactate, Pyruvate, and Alanine: Noninvasive Biomarkers for Prostate Cancer Detection and Grading.* Cancer Res., 2008. **68**(20): p. 8607-8615.
2.) Nelson, S.J., et al., *Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-13C]Pyruvate.* Science Translational Medicine, 2013. **5**(198): p. 198ra108.
3.) Keshari, K.R., et al., *Hyperpolarized 13C-Pyruvate Magnetic Resonance Reveals Rapid Lactate Export in Metastatic Renal Cell Carcinomas.* Cancer Research, 2013. **73**(2): p. 529-538.
4.) Pertega-Gomes, N., et al., *Monocarboxylate transporter 4 (MCT4) and CD147 overexpression is associated with poor prognosis in prostate cancer.* BMC Cancer, 2011. 11(1): p. 312.
5.) Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang P-W, Pellerin L, Magistretti PJ, Rothstein JD. *Oligodendroglia metabolically support axons and contribute to neurodegeneration*. Nature 2012;487:443.
6.) Tang S, Milshteyn E, Reed G, Gordon J, Bok R, Zhu X, Zhu Z, Vigneron DB, Larson PEZ. *A regional bolus tracking and real-time B1 calibration method for hyperpolarized 13C MRI*. Magnetic Resonance in Medicine 2018. https://doi.org/10.1002/mrm.27391.
7.) Pfeuffer J, Lin JC, DelaBarre L, Ugurbil K, Garwood M. *Detection of intracellular lactate with localized diffusion {1H–13C}-spectroscopy in rat glioma in vivo*. Journal of Magnetic Resonance 2005;177(1):129-138.
8.) Koelsch BL, Reed GD, Keshari KR, Chaumeil MM, Bok R, Ronen SM, Vigneron DB, Kurhanewicz J, Larson PEZ. *Rapid in vivo apparent diffusion coefficient mapping of hyperpolarized 13C metabolites*. Magnetic Resonance in Medicine 2015;74(3):622-633.
9.) Zhu X, Gordon JW, Bok RA, Kurhanewicz J, Larson PEZ. *Dynamic diffusion-weighted hyperpolarized ^{13}C imaging based on a slice-selective double spin echo sequence for measurements of cellular transport*. Magnetic Resonance in Medicine 2018. https://doi.org/10.1002/mrm.27501.

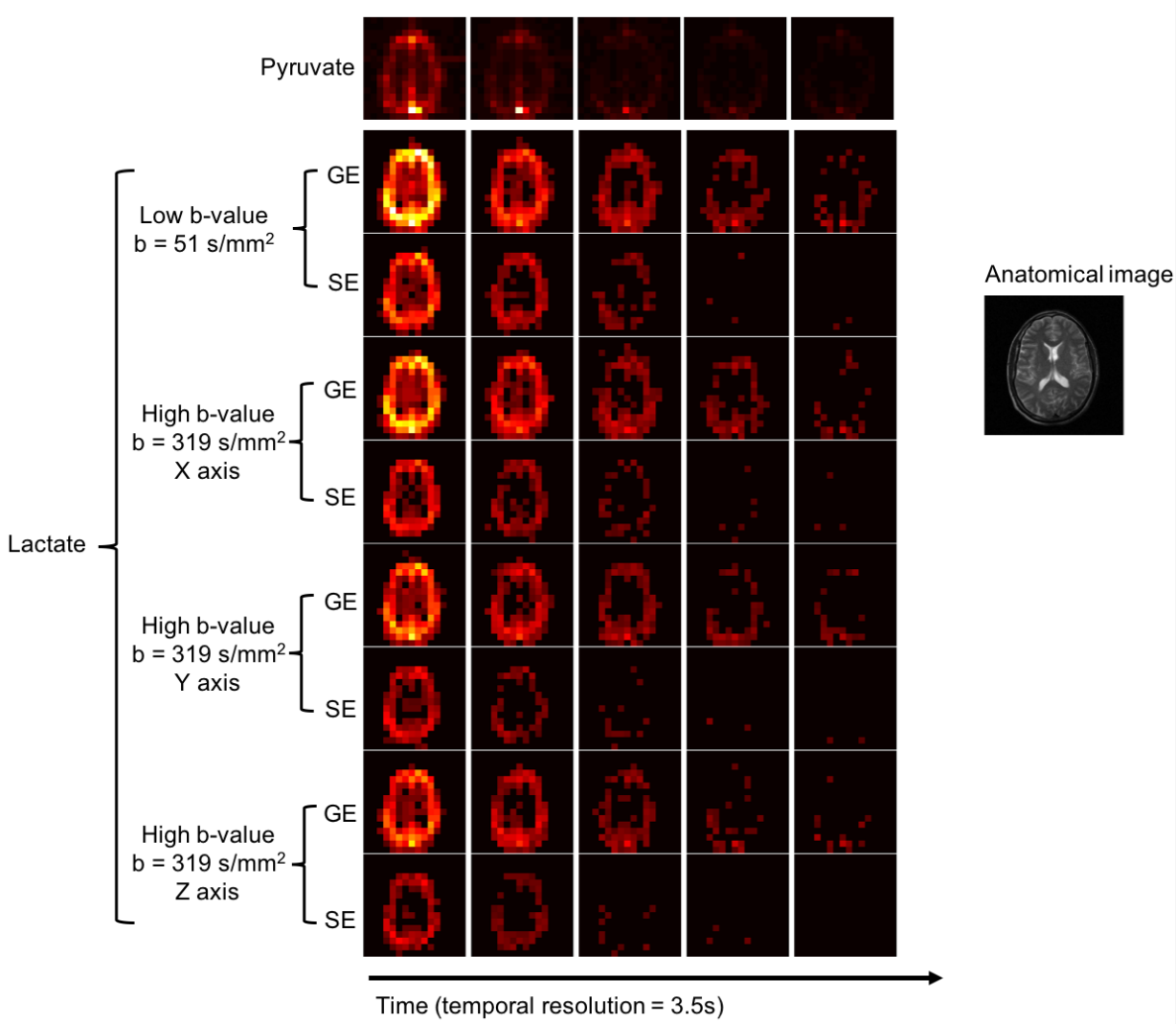

Figure 1. Hyperpolarized ^{13}C pyruvate and lactate images acquired using the diffusion weighted spin-echo sequence described above. All lactate images are displayed at the same scale, but different from the scale used in pyruvate images. Voxels with SNR > 5 are displayed.