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

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Highlights: This work demonstrates the feasibility of diffusion weighted hyperpolarized 13C 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 13C substrates has been used extensively for metabolic imaging in both pre-clinical1 and proof-of-concept clinical studies2 to non-invasively assess metabolic conversion. In addition to the Warburg Effect, many malignant cancers overexpress MCT4, the monocarboxylate transporter primarily responsible for lactate efflux3,4. 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 survival5. 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 [1-13C]pyruvate in the human brain to assess lactate efflux and compartmentalization in a healthy volunteer.

Methods
Hyperpolarized [1-13C]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 calibration6. 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 1.5cm² in-plane resolution, one 40mm thick slice, a low b-value of 51 s/mm² applied in the Z direction and a high b-value of 319 s/mm² 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 13C pyruvate and lactate images. Whole brain lactate ADC values were 0.37, 0.29, and 0.41 x 10⁻³ mm²/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. 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.

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:
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.