

Spin tagging in hyperpolarized carbon-13 metabolic studies

C. H. Cunningham^{1,2}, A. P. Chen³, and R. E. Hurd⁴

¹Dept. of Medical Biophysics, University of Toronto, Toronto, ON, Canada, ²Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, ³GE Healthcare, Toronto, ON, Canada, ⁴GE Healthcare, Menlo Park, CA, United States

INTRODUCTION Numerous studies have demonstrated the feasibility of measuring metabolic products in tissues after the injection of a hyperpolarized carbon-13 labeled substrate such as [1-¹³C] pyruvate (1-2). The observed biochemical reactions are presumed to occur within the cellular cytosol and organelles, so it is therefore reasonable to assume that the measured carbon-13 signals contain a large intracellular component. The hypothesis of this study was that sinusoidal tagging of the longitudinal magnetization could be used to differentiate metabolic products in the intracellular space from those flowing in the blood pool.

METHODS A spectroscopic pulse sequence consisting of a tagging preparation followed by a series of small-tip readouts (Fig. 1) was implemented on a long-bore GE EXCITE 3 T scanner. The first RF pulse (RF1 in Fig. 1) could be toggled between a spectral-spatial pulse that only excites [1-¹³C] pyruvate and a conventional slice selective pulse that excites the spectrum from [1-¹³C] lactate to ¹³C bicarbonate.

Samples of [1-¹³C] pyruvic acid, were polarized using a DNP polarizer (Oxford Instruments, Abingdon, UK). The samples were dissolved to 80 mM concentration and pH ~ 7.4 using a Tris/NaOH/EDTA solvent (2).

Phantom studies were performed to test the pulse sequence and to verify that the spatial tags persisted over a sufficient duration to observe metabolic conversion *in vivo*. One mL of hyperpolarized solution was drawn into a 1 mL syringe and placed within a custom-built transmit/receive dual-tuned volume coil with 10 cm diameter. A 2 ms, 0.5 G/cm encoding gradient was applied along the axis of the syringe, creating tags with a 1 cm period. A 10-degree RF3 pulse (Fig. 1) was used in the phantom studies with an interval of 3 s between each RF3. In one of the experiments, the pulse sequence was run with a spatial encoding gradient during the data readout after each 10-degree RF pulse so that the tags could be visualized.

In vivo data were acquired from the body of normal Sprague-Dawley rats. For each study, 3 mL of hyperpolarized solution was injected through a tail-vein catheter over a period of 8 s, with the data acquisition started 15 s after the beginning of the injection. The encoding gradient was 0.5 G/cm with 2 ms duration applied along the z-axis. A TE of 140 ms was used to ensure that untagged magnetization had decayed prior to data acquisition. Two studies were performed, the first with a conventional pulse for RF1 and the second with a spectral-spatial pulse, spectrally selective on the [1-¹³C] pyruvate resonance, for RF1.

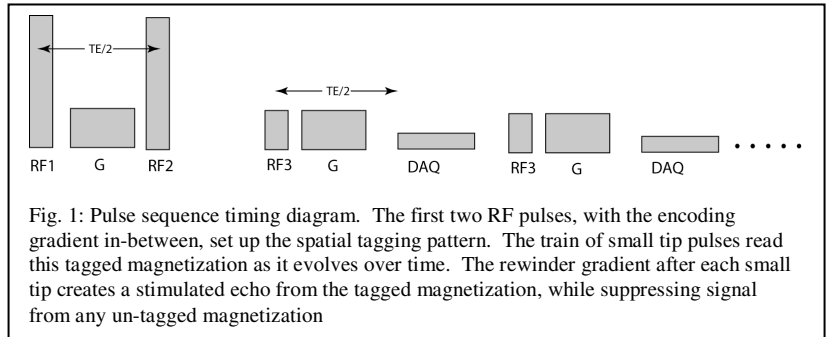


Fig. 1: Pulse sequence timing diagram. The first two RF pulses, with the encoding gradient in-between, set up the spatial tagging pattern. The train of small tip pulses read this tagged magnetization as it evolves over time. The rewriter gradient after each small tip creates a stimulated echo from the tagged magnetization, while suppressing signal from any un-tagged magnetization

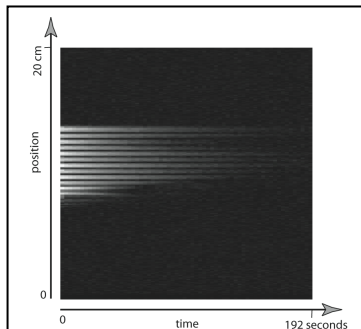


Fig. 2: Data from the phantom study showing the persistence of the spatial tags over time. Fitting of the global decay curve (all tags summed) yielded an apparent T1 of 45 seconds. Note that some regions appear to decay faster than others, which is presumably due to mixing of +z and -z magnetization due to small convection currents within the solution.

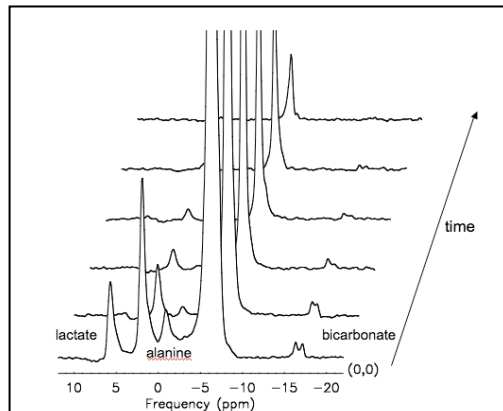


Fig. 3: Data from the rat study using the conventional pulse for RF1. Acquisition parameters were: TE = 140 ms, TR = 2.0 s, RF3 tip angle = 30 degrees. The spectra shown were acquired each TR, 2 s apart. Rapid decay was observed for all spectral lines, except for bicarbonate, which decayed considerably slower.

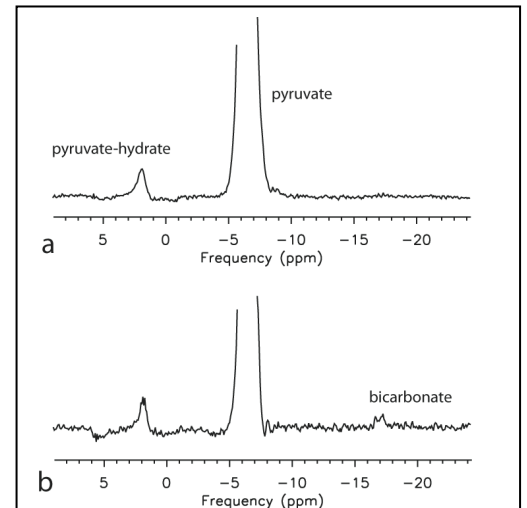


Fig. 4: Data from the rat study using the spectral-spatial pulse for RF1, same parameters as in Fig. 3. (a) The first frame shows that only pyruvate was excited and tagged. (b) The sum of the following 5 frames (10 s of data) shows that bicarbonate was created from this spatially-tagged pyruvate.

DISCUSSION AND CONCLUSIONS A pulse sequence for acquiring spectroscopic data from spatially tagged longitudinal magnetization in hyperpolarized carbon-13 metabolic studies was presented. The hypothesis was that intracellular metabolites would not move over time, so that the tagging pattern would be preserved for these spins and would quickly decay for magnetization in the blood pool. As an added benefit, the tagging could make modeling of the biochemical reactions much more simple than with conventional pulse-acquire acquisitions, since the input function would be a delta function in time (at the instant the tags are created).

All metabolites were observed to decay rapidly following the application of the spatial tags, suggesting that although the biochemical reactions occur within the cytosol, the resulting metabolic products are quickly transported out of cells. The exception was bicarbonate, which decayed much more slowly in Fig.3 and could be seen in Fig. 4, created from spatially-tagged pyruvate. This observation suggests that bicarbonate is much less mobile than the other metabolites, which is consistent with the localization of the corresponding enzymes within the mitochondria.

REFERENCES 1. Golman K et al., Cancer Res 2006;66:10855. 2. Kohler SJ et al., MRM 2007;58:65.