How Does Dose of Hyperpolarized $^{13}C_1$-Pyruvate Affect Metabolic Results in Dog Prostate?

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INTRODUCTION:

Methods to retain dynamic nuclear polarization (DNP) in solution have demonstrated ^{13}C signal signal-enhancements of greater than 10,000-fold as compared to thermal equilibrium [1]. Hyperpolarized $^{13}C_1$-pyruvate has been used to demonstrate metabolic activity in various animals. Canine prostates have been studied to determine the feasibility of translating hyperpolarized $^{13}C_1$-pyruvate research to human prostate cancer patients. A prior study has shown that the level of $^{13}C_1$-pyruvate dose (in ml/kg) can directly affect the metabolic results from dynamic spectroscopic data in rat kidneys and in a transgenic adenocarcinoma of the mouse prostate (TRAMP) model [2]. This current study aims to investigate how $^{13}C_1$-pyruvate dose can affect metabolic results of both spectroscopic imaging and dynamic spectroscopy in the dog prostate.

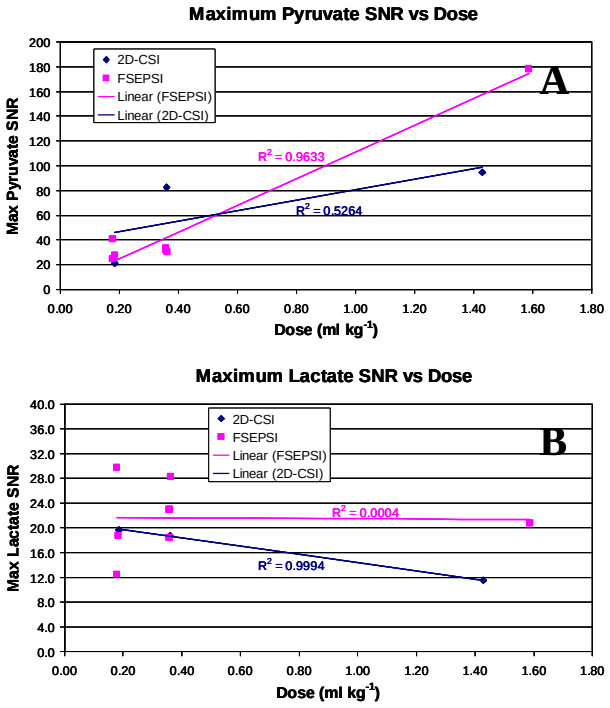
METHODS:

Animal Preparation: Spectroscopic imaging and dynamic spectroscopy were performed on six healthy adult male beagles after receiving varying doses of hyperpolarized $^{13}C_1$-pyruvate. Animal preparation followed an institutionally approved protocol. All experiments were performed on a 3T GE MR system. The coil setup was similar to a previously reported dog study [3]. $^{13}C_1$-pyruvate was polarized using DNP [1] and dissolved in TRIS/EDTA NaOH solution, yielding a 250mM concentration. Typical polarization was 18%. Each MR scan was preceded by an injection of hyperpolarized pyruvate with a volume ranging from 2 to 18mL. Three dose levels were used: 0.18mL/kg, 0.36mL/kg, and 1.43-1.59mL/kg. Each dog was injected and scanned three times at 2-hour intervals.

Data Acquisition: Spectroscopic imaging was acquired 30 seconds after hyperpolarized $^{13}C_1$-pyruvate injection using either a two-dimensional conventional phase-encoding technique (2D-CSI) with a double spin echo acquisition or a three-dimensional echo-planar technique (FSEPSI) incorporating a fast spin echo strategy (multiple slices were imaged sequentially for a three-dimensional result) [4]. Two-dimensional data were acquired with an 8cmx8cm FOV and 5mmx5mm resolution (10cm slice thickness) and spectral bandwidth of 5000Hz. Three-dimensional data were acquired with a 5mm^3 isotropic resolution, FOV of 9cmx8cmx6cm, and 493Hz spectral bandwidth. Dynamic spectroscopic data were acquired within a 6cm slice containing the prostate with a 5000Hz spectral bandwidth and 3 second temporal resolution.

Data Analysis: SNR was calculated on all spectroscopic images as maximum pyruvate and lactate peak height for the three dose levels. SNR values were normalized to 20% polarization and a 5mm slice thickness. Dynamic spectroscopic data were processed and modeled as previously reported [2] and metabolic rate constants were compared across dose levels for pyruvate to lactate conversion and pyruvate to bicarbonate conversion. Peak SNR values (normalized to 20% polarization) for pyruvate, lactate, and bicarbonate, as well as their ratios, were also calculated.

Figure 1. Maximum peak height SNR vs Dose for pyruvate (**A**) and lactate (**B**). Dark blue data are from two-dimensional chemical shift imaging. Pink data are from three-dimensional echo-planar spectroscopic imaging.



RESULTS:

For spectroscopic imaging data, Figure 1 shows maximum SNR values for each dose level for both pyruvate and lactate with the linear best-fit line and R^2 value, separated by imaging technique. SNR values for pyruvate show a strong positive linear correlation with dose; however, there is no positive correlation for lactate SNR (and for 2D-CSI there is a negative SNR correlation with dose). Dynamic spectroscopy shows similar results to the imaging in that the pyruvate to lactate conversion is higher at lower doses (see Table 1). This is also consistent with previously reported data in rat kidneys and TRAMP mice [2]. The peak SNR's and SNR ratios are also consistent with these results: the lactate peak SNR's do not significantly change with dose, and the SNR ratios show an increasing pyruvate to lactate conversion at lower doses. There does not appear to be any significant relationship between dose and bicarbonate SNR or rate of pyruvate to bicarbonate conversion.

CONCLUSION:

This study has demonstrated that although pyruvate SNR increases as the dose of hyperpolarized $^{13}C_1$-pyruvate increases, lactate SNR does not significantly increase with dose in a healthy dog. The injected pyruvate appears to be forming $^{13}C_1$-lactate at a higher rate as the dose of pyruvate decreases, which is consistent with previous studies. Therefore, the real-time detection of newly formed $^{13}C_1$-lactate, a metabolic marker of hypoxia and cancer, does not appear to improve at higher doses of $^{13}C_1$-pyruvate.

Table 1. Dynamic Spectroscopy Results (* = Normalized to 20% polarization)

Dose (ml/kg)	Lactate Peak SNR*	Pyruvate Peak SNR*	Bicarbonate Peak SNR*	Lac:Pyr Peak SNR Ratio	Bic:Pyr Peak SNR Ratio	Bic:Lac Peak SNR Ratio	$k_{pyr\text{-}lac}$ (s^{-1})	kpl_{err}	$k_{pyr\text{-}bic}$ (s^{-1})	kpb_{err}
0.18	249.8	337.5	10.1	0.740	0.030	0.041	0.1078	1.25E-03	0.0059	1.49E-03
0.18	231.0	609.1	29.1	0.379	0.048	0.126	0.0594	1.15E-03	0.0070	1.36E-03
0.18	118.5	584.3	35.7	0.203	0.061	0.301	0.0299	1.06E-03	0.0118	1.45E-03
0.36	241.0	1212.7	49.5	0.199	0.041	0.206	0.0291	2.54E-07	0.0051	9.94E-04
0.36	215.0	753.0	20.6	0.286	0.027	0.096	0.0378	6.94E-07	0.0033	8.92E-05
0.36	340.1	924.2	44.3	0.368	0.048	0.130	0.0545	4.97E-04	0.0067	3.65E-11
1.43	113.3	649.0	32.5	0.175	0.050	0.287	0.0179	2.03E-07	0.0034	5.79E-04

REFERENCES AND ACKNOWLEDGEMENTS: This study was supported by UC Discovery grants LSIT01-10107 and ITL-BIO04-10148, and GE Healthcare.

[1] Golman K, et al. PNAS. Jul 103(30), 11270-11275. [2] Zierhut ML, et al. ISMRM 2007 (#366). [3] Nelson SJ, et al. ISMRM 2007 (#536). [4] Yen YF, et al. ISMRM 2007 (#2928).