

Kinetic modeling of Hyperpolarized ¹³C-Pyruvate with Arbitrary RF flip angles in cancer

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Introduction- The accurate detection and characterization of cancer is still a major problem for the clinical management of individual cancer patients and for monitoring their response to therapy(1). The primary purpose of this research was to model the kinetics of hyperpolarized (HP) pyruvate and urea to provide improved characterization of cancerous tissues when using arbitrary RF flip angles in dynamic MRSI. This modeling has the ability to detect metabolic conversion and perfusion.

Methods- The kinetics of the HP pyruvate magnetization can be modeled as $\frac{d}{dt} \begin{bmatrix} Mp(t) \\ Ml(t) \\ Ma(t) \end{bmatrix} = \begin{bmatrix} -\rho_p - K_{pl} - K_{pa} & 0 & 0 \\ K_{pl} & \rho_l & 0 \\ K_{pa} & 0 & \rho_a \end{bmatrix} \begin{bmatrix} Mp(t) \\ Ml(t) \\ Ma(t) \end{bmatrix}$

where ρ_p , ρ_l , and ρ_a , are the longitudinal magnetization relaxation rates for pyruvate, lactate and alanine, respectively, K_{pl} is the conversion rate from pyruvate to lactate, and K_{pa} is the conversion rate from pyruvate to alanine. The reverse conversion rates were assumed to be negligible. The data was modeled as discrete intervals of relaxation and conversion, followed by RF excitation, and the methods can apply for arbitrary flip angles. The 3D dynamic MRSI used multiband excitation with small flip angles of 6 degrees for pyruvate and urea to minimally perturb their magnetization and larger flip angles of 12 degrees for lactate and alanine to improve SNR (2). Non-linear least squares (NLLS) with Levenberg–Marquardt's (LM) approach was used fit the signal (3). We also found that obtaining a good fit with our SNR required assuming that the relaxation rates, ρ_1 , of pyruvate, lactate, and alanine were identical. We also speculated that the ratio of total lactate signal to total pyruvate signal would be commensurate with K_{pl} . In other words, summing all time points and assuming a constant ratio, we speculate: $\frac{\sum_{i=1}^{Nt} Li}{\sum_{i=1}^{Nt} Pi} = C * K_{pl}$.

Results- Fig. 1 & 2 show elevated K_{pl} values in primary tumors and a metastasis. Spatial heterogeneity in the tumor can be observed. Fig. 3 shows the correlation between K_{pl} and this signal ratio is approximately linear, suggesting either could be used to measure metabolism.

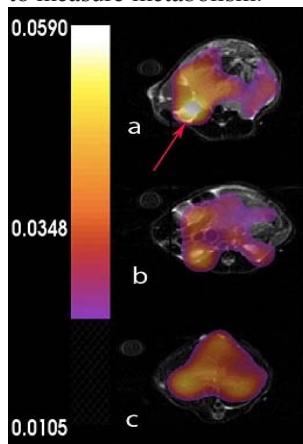


Fig 1. Mapping of K_{pl} in different axial slices: a) prostate cancer (arrow-metastases), b) kidneys, c) liver.

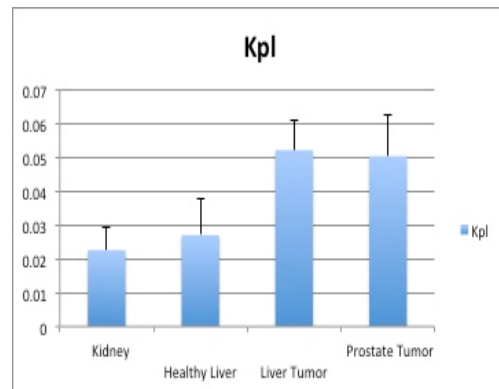


Fig 2. K_{pl} values in four different tissues among seven transgenic mice with prostate (n=4) or liver (n=3) cancer.

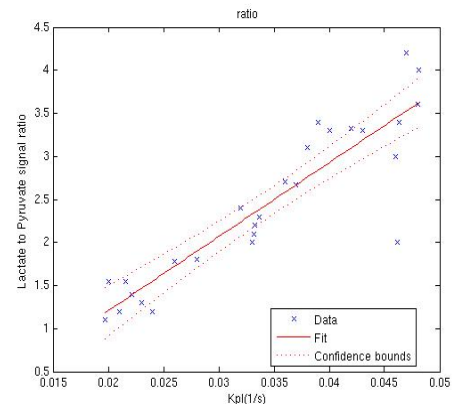


Fig 3. Correlation between K_{pl} and total lactate to total pyruvate signal across all tissues (correlation coefficient of 0.95).

Discussion- The measurement of ρ_1 and metabolic conversion ratio are of practical importance in choosing optimal pulse parameters. In this study, we also measured the ρ_1 of tumor hyperpolarized ¹³C pyruvate and urea. In tumor, the tissue request for blood is high but in a more uncontrolled way because of the abnormality of blood vasculature and circulation inside the tumor. The conversion constant from pyruvate to lactate is high in cancerous tissue with respect to the healthy tissues and the proportional variation of K_{pl} with lactate signal to pyruvate signal ratio is significant. In the area that is suspected to be a necrotic tissue, the vasculature network has very low concentration and therefore the amount of urea perfusion is low. The ratio of pyruvate and its products, including lactate and alanine, to urea is higher in cancerous tissues in comparison to healthy tissues which can a marker for cancerous tissue detection with dynamic MRSI and multiband excitation.

Table1. Average ρ_1 values.

	ρ_1 of Urea (1/s)	ρ_1 of Pyruvate and its products(1/s)
Kidney	0.13	0.09
Healthy Liver	0.075	0.061
Cancerous Liver	0.13	0.077
Prostate Tumor	0.15	0.083

References. 1. Kurhanewicz et al. Neoplasia, 13:. 81-97, 2011. 2. Larson et al. MRM 65:610-9, 2011. 3. Anderson, MRM, 46:1174-88, 2001.