Metabolic rate constant mapping of hyperpolarized 13C pyruvate

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INTRODUCTION: Hyperpolarized [1-^{13}C]pyruvate MR is capable of depicting substrate uptake and conversion towards downstream metabolites such as lactate, alanine, and bi-carbonate. The obtained information displays metabolic conversion impaired by T_1 relaxation and signal depletion due to repetitive excitation. Ideally, it is desired to extract kinetic rate constants for characterizing tissue metabolism, as recently has been demonstrated for slice-selective FID acquisitions [1, 2]. In this work, the two-side, kinetic exchange model is applied for hyperpolarized ^{13}C pyruvate in a way such that it does not involve the time course of pyruvate administration (i.e. the input function), which is generally difficult to obtain. In combination with time-resolved IDEAL spiral CSI [3], the method is demonstrated to generate spatially-resolved rate constant maps.

THEORY and METHDODS: Hyperpolarized pyruvate conversion/exchange is described based on a first order, two-side exchange model between pyruvate (P) and one of its downstream metabolites X (with X = lactate, alanine, or bi-carbonate) (cf. Fig. 1). The dynamic evolution of the longitudinal magnetization of X (M_X) is determined by T_1-relaxation, flip angle (FA) excitation, and metabolic conversion to and from pyruvate (M_P) according to:

$$dM_X/dt = -1/T_{1X}\,M_X - f(FA)M_X - k_{X\to P}M_X + k_{P\to X}M_P = -1/T_{1X,eff}\,M_X + k_{P\to X}M_P\,, \qquad [1]$$

with k denoting the rate constant. For an acquisition requiring N excitations over a time-period T_R the flip angle factor is given by $f(FA)=(1-\cos(FA))^N/T_R$. All the magnetization depletion effects are proportional to M_X and hence can be described by an effective T_1 relaxation time ($T_{1X,eff}$). Above equation neglects in- and outflow effects for the metabolite X (but not for pyruvate), respectively assumes that they are the same. If the time courses for pyruvate (M_P) and X (M_X) are known from measurements, above differential equation can be approximated by difference equations. The relevant parameters $1/T_{1X,eff}$ and $k_{P\to X}$ are then obtained from solving the corresponding system of linear equations in a weighted linear least-square sense:

$$\Delta M_{X,n}/\Delta t_n = -1/T_{1X,eff}\,M_{X,n} + k_{P\to X}M_{P,n}\,, \qquad [2]$$

with n denoting the measurement index and Δt_n the time resolution of the measurement. If a spectral-spatial encoding scheme is used to provide temporally-resolved metabolite maps, Eq. [2] can also be applied on a pixel-by-pixel basis to generate spatially-resolved $T_{1X,eff}$ and $k_{P\to X}$ maps.
Experiments were performed on a 3T GE HDx scanner (GE Healthcare, Milwaukee, WI). [1-^{13}C]pyruvate was hyperpolarized using a HyperSense DNP polarizer (Oxford Instruments, UK). Anesthetized in-vivo rat experiments were performed using 2% isoflurane in oxygen at a rate of ~1.5 l/min. 5ml per kg rat mass of 80mM hyperpolarized ^{13}C pyruvate was injected into the animal's tail vein at an average injection rate of 0.17ml/s. During the experiment the animal's temperature, heart rate and breathing was monitored (SA Instruments, USA). Ethics approval was obtained from the regional governmental commission for animal protection.

RESULTS: Figure 1 shows metabolite time courses obtained from a slice-selective FID measurement (FA=5°, T_R= 1s, 10mm axial slice) and post-processed using a time-domain, amplitude fitting algorithm. The data was acquired using a local, surface transmit-receive ^{13}C coil (diameter=20mm) located around a subcutaneous HCC (hepatocelluar) carcinoma. The red, dashed lines indicate kinetic fitting results for the time window of 10s-60s according to Eq. [2]. The obtained rate constants $k_{P\to X}$ were found to be 0.027s^{-1} and 0.014 s^{-1} for lactate and alanine, respectively.
In addition, spatially-resolved kinetic rate constant mapping was applied using time-resolved, IDEAL spiral CSI [3] (FOV=80mm, 32 time points). Figure 2 shows axial data of a healthy rat [top row: two slice acquisition (liver and kidney (shown)), 2.16s time res] and a rat with a subcutaneous HCC carcinoma (bottom row: single slice acquisition, 2s time res). For visualization purposes spatial thresholding was applied based on pyruvate and lactate/alanine signal levels. In comparison, to the individual metabolite images the rate constant maps suppress regions of high perfusion (e.g. kidney, blood vessel, etc.) in favor of tissue with high metabolic activity (i.e. tumor). In particular, the tumor location can be clearly identified with rate constants as high as 0.020s^{-1} and 0.033s^{-1} for alanine and lactate respectively, which is also consistent with the values of Fig. 1.

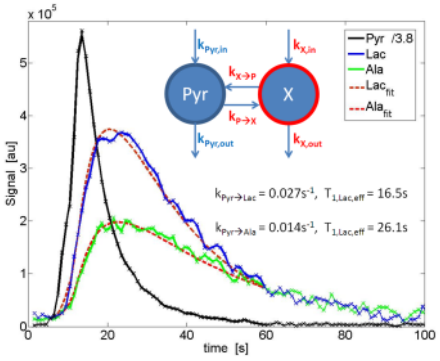

Fig. 1: Schematic of two-side exchange model and kinetic rate constants for subcutaneous HCC carcinoma localized by slice-selective FID and 20mm transmit/receive ^{13}C surface coil.

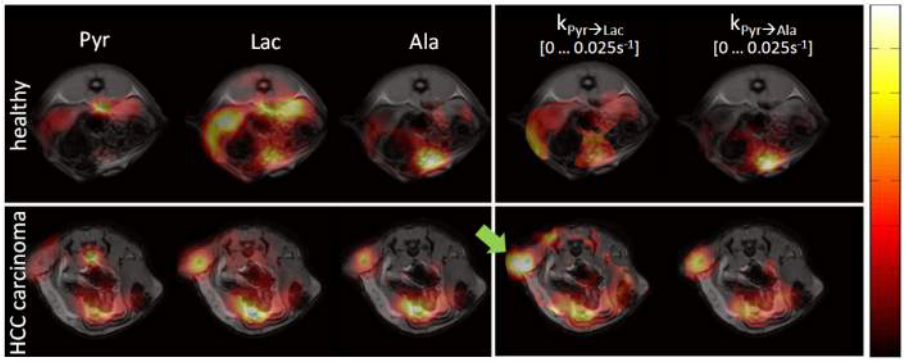

Fig.2: Quantitative lactate and alanine rate constant mapping for healthy (top) and tumor (bottom) rat. $k_{Pyr\to Lac}$ and $k_{Pyr\to Ala}$ clearly light up at HCC carcinoma indicating increased tumor metabolism (green arrow). The metabolite maps are scaled to their individual maxima, whereas rate constant maps are equally scaled to 0…0.025s^{-1}.

DISCUSSION and SUMMARY: A kinetic modeling method has been developed for the extraction of quantitative pyruvate rate constants. The method takes advantage of the fact that metabolic conversion only occurs between pyruvate and the downstream metabolites but not among the conversion products themselves. This allows analyzing the kinetics for each metabolite only in dependence of M_X and M_P. Importantly, the method does not rely on knowledge of the pyruvate input function, which is generally difficult to obtain. In combination with time-resolved, spectral-spatial encoding schemes, the fitting can also be applied on a pixel-by-pixel basis. This results in a new type of quantitative contrast displaying metabolic activity in form of the kinetic rate constants. Concentration dependent saturation effects as well as the quantitative accuracy of the method needs to be investigated in future studies. Ultimately, the method might be particularly useful for the non-invasive localization and characterization of tumors and their response to therapy.

REFERENCES: [1] ML Zierhut et al, ISMRM 2007: p.366. [2] SE Day et al, NatMed 13: 1382-7 (2007). [3] F Wiesinger et al, ESMRMB 2009: p94.
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