In vivo Hyperpolarized ^{13}C Chemical Shift Imaging using Variable Flip Angle and Centric Phase Encoding of Stimulated Mouse Muscle

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Introduction

MR Spectroscopic Imaging (MRSI) of hyperpolarized $^{13}C_1$-pyruvate is a promising technique for *in vivo* mapping of metabolic information [1]. This method is based on **Dynamic Nuclear Polarization (DNP)** followed by a rapid dissolution process to produce a highly polarized metabolic contrast agent. After injection, **$^{13}C_1$-pyruvate and its metabolic products $^{13}C_1$-lactate, $^{13}C_1$-alanine and $^{13}C_1$-bicarbonate can be mapped using a Chemical Shift Imaging (CSI)** sequence. However, given the short life time of hyperpolarized signals, one of the main challenges of ^{13}C hyperpolarized metabolic imaging remains the optimization of Signal-to-Noise Ratio (SNR) and of image quality [2]. In this study, a **Variable Flip Angle (VFA) Centric Phase Encoding (CPE) CSI sequence** was implemented and synchronized with a **multiple bolus** hyperpolarized $^{13}C_1$-pyruvate delivery strategy (Fig. 2) [3] to perform **real-time functional MRSI of skeletal muscle metabolism** during an exercise-mimicking nerve stimulation [4].

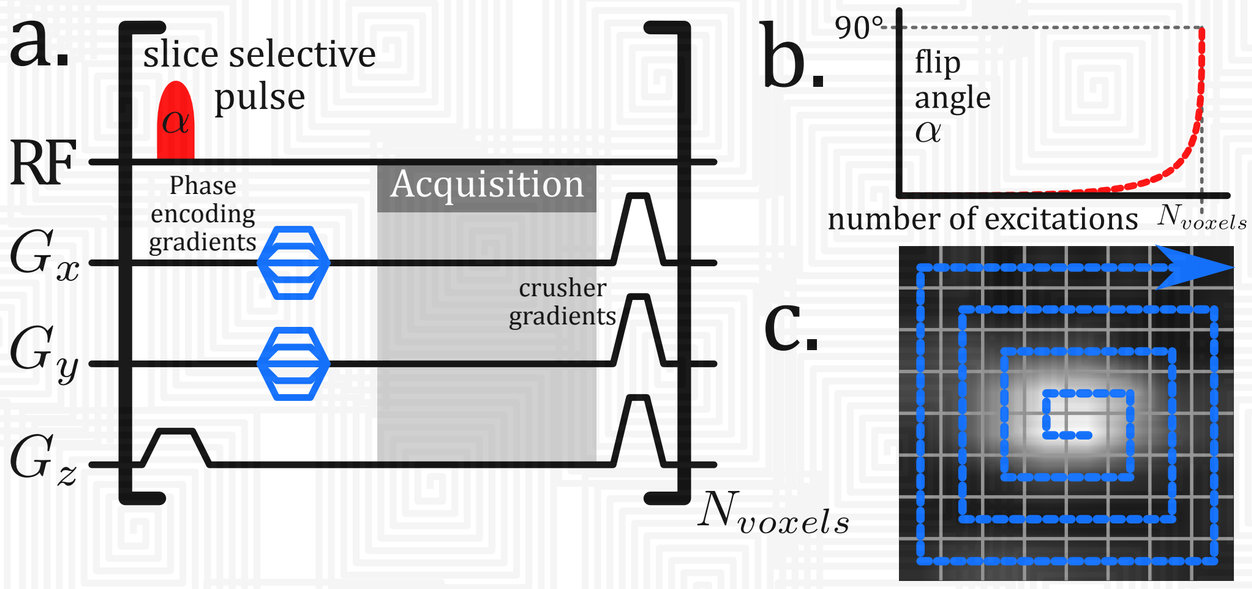

Fig. 1: Variable Flip Angle (VFA) - Centric Phase Encoding (CPE) - Chemical Shift Imaging (CSI) sequence (a), flip angle variation according the number of excitations (b) and CSI k-space filling (c).

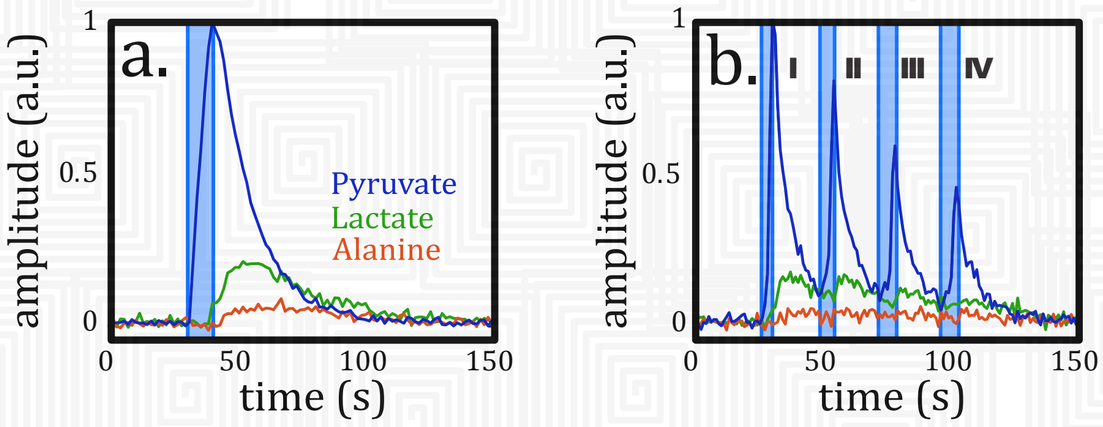

Fig. 2: In vivo (a) conventional and (b) multi-bolus tracer administration of $^{13}C_1$-pyruvate in mouse skeletal muscle.

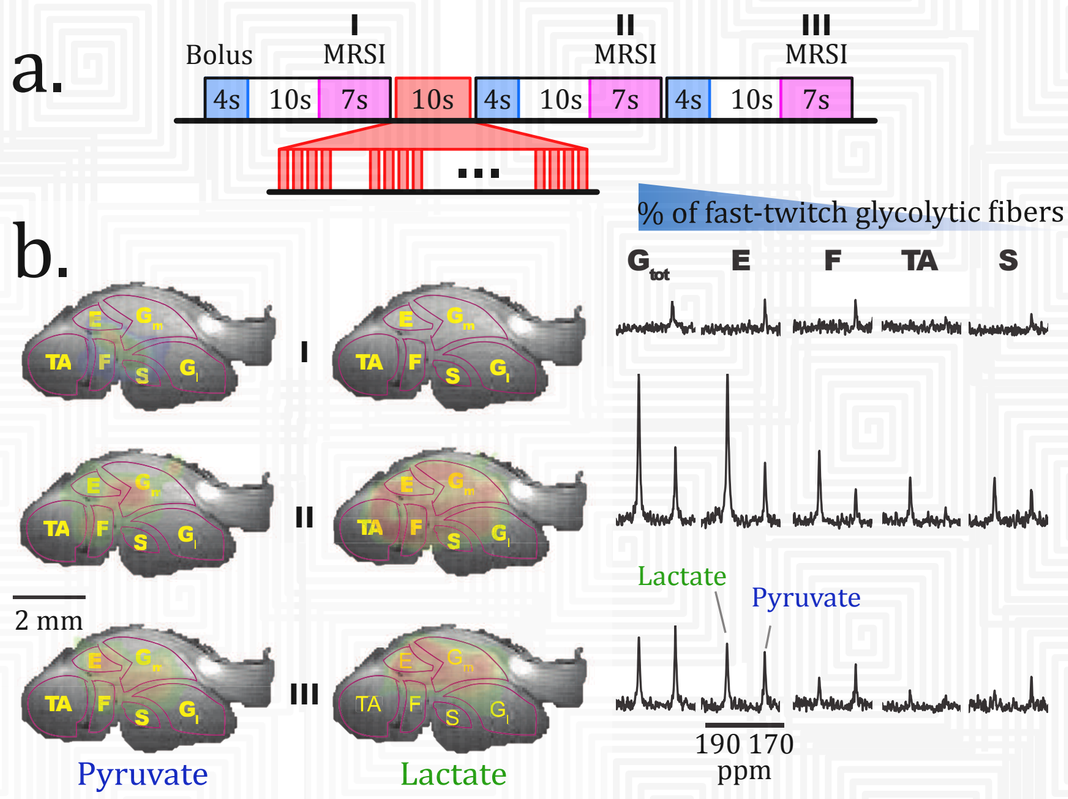

Fig. 3: Functional paradigm for hyperpolarized $^{13}C_1$ magnetic resonance (a) and metabolite maps and spectra for $^{13}C_1$ pyruvate and lactate (b).

Method

Pulse sequence. The VFA-CPE-CSI sequence (Fig. 1a) was fully implemented on a Bruker Biospec 4.7T small animal imaging system equipped with a Doty Scientific 8mm transmit/receiver $^{1}H/^{13}C$ surface coil. ^{1}H MGE anatomic images were acquired using TE/TR=5.38ms/1s. The functional VFA-CPE-CSI acquisitions consisted of 64 phase encoding steps for an 8x8 in plane matrix (Fig. 1c) and a TR of 104ms, resulting in a total **scan time of 6.7s**. The CSI image FOV was 12.5mm x 12.5mm with a 2mm slice selection using a VFA Gaussian pulse (Fig. 1b). The CPE CSI data reconstruction was performed using a Matlab home-made procedure. The JRMUI software was used for data quantification with AMARES.

Hyperpolarization. A sample mixture of neat $^{13}C_1$ pyruvic acid (Sigma) and OX-63 trityl radical (Oxford Instruments) was polarized on an Hypersense operating at 1.4K using microwave irradiation of 95GHz resulting in a 60mM hyperpolarized pyruvate sample was dissolved in pH 7.6 buffer and stored at 1T fringe field during the **injection of three boluses (133µL each)**, timed in synchrony with the external stimulus being imaged.

Muscle Stimulation. Female ICR mice (20 weeks old, 25g body weight) were anaesthetized by I.P. injection of sodium pentobarbital (70mg/kg). The sciatic nerve of the hind limb was surgically exposed, electrode leads fastened to the nerve and inserted in a foot pad, and sutured. The tail vein was catheterized for the hyperpolarized solutions injections. The animals were maintained anesthetized using isoflurane. **Electrical stimulation was performed using 10ms trains of positive 10V/200µs pulses repeated at 10Hz** (Fig. 3a). Data from each animal was collected using 4 experiments repeated under non-stimulated and stimulated conditions.

Results & Discussion

Metabolic functional MRS images were obtained from multiple bolus experiments using VA-CPE-CSI acquisitions are shown in Fig 3b. Pre-stimulation maps show only small amounts of $^{13}C_1$ pyruvate, while **muscle stimulation causes rapid increases in SNR of the pyruvate tracer and increases it's metabolism to $^{13}C_1$-lactate**, particularly in the fast-twitch glycolitic-rich gastrocnemius (G) muscle group.

Conclusion

VFA and CPE strategies implemented within the Bruker Paravision CSI method enabled the **acquisition of metabolic maps with high in-plane resolution for functional imaging of muscle metabolism using multiple boluses of hyperpolarized $^{13}C_1$-pyruvate**.

References

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