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

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Target audience: MRI sequence, hyperpolarized ^{13}C, and muscle metabolism researchers.

Purpose: To develop an optimized and integrated variable flip angle chemical shift imaging sequence using centric phase encoding on the Bruker platform, and utilize it to investigate hyperpolarized $^{13}C_1$-pyruvate metabolism in stimulated mouse skeletal muscle.

Introduction

MR spectroscopic imaging 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), and on 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 time available to utilize the 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 applied for imaging the metabolism of hyperpolarized $^{13}C_1$-pyruvate in mouse skeletal muscle following functional stimulation mimicking exercise [3].

Method

Pulse sequence. The VFA-CPE-CSI sequence was fully implemented in Bruker Paravision. The experiments were performed on a Bruker Biospec 4.7T small animal imaging system equipped with a Doty Scientific 8 mm transmit/receiver $^{1}H/^{13}C$ surface coil. ^{1}H MGE anatomic images were acquired using TE/TR=5.38ms/1s. VFA-CPE-CSI acquisitions generally consisted of 64 phase encoding steps for an 8x8 in plane matrix and a TR of 104ms, resulting in a total scan time of 6.7s. The FID signals were acquired using a non-slice selective VFA Gaussian pulse (from 8 to 90°). By using the surface coil active volume as slice selection, the CSI image FOV was 12.5mm x 12.5mm x approximately 5mm, resulting in a 1.5mm in-plane resolution. The CPE CSI data reconstruction was performed using a Matlab home-made procedure. The JRMUI software was then used for data quantification with AMARES.

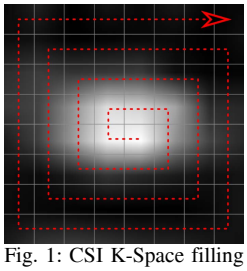

Fig. 1: CSI K-Space filling using CPE.

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. The hyperpolarized sample was dissolved in pH 7.6 buffer before injection of 400µL, 60mM pyruvate.

Muscle Stimulation. Female ICR mice of 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 and a 100 µL transfer line was attached for injecting the hyperpolarized solutions. The animals were maintained anesthetized in the magnet using 1-3% isoflurane in O_2 gas (1L/min). Electrical stimulation was performed using a paradigm of 10ms trains of positive 10V/200µs pulses repeated at 10Hz for 30s. Injection of the hyperpolarized solution began within 5s of the end of the stimulation, and the CSI acquisition was performed 8 s after ending the injection in order to coincide the imaging window with the lactate signal maximum. Data from each animal was collected using 4 experiments repeated under non-stimulated and stimulated conditions; animals were euthanized using an overdose of sodium pentobarbital.

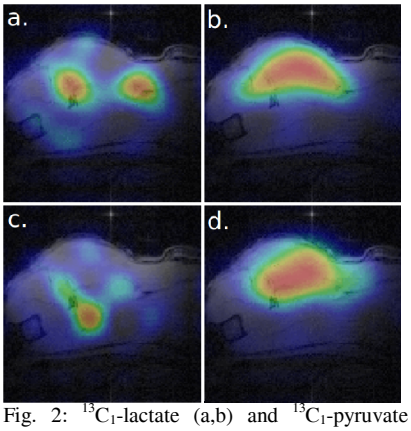

Fig. 2: $^{13}C_1$-lactate (a,b) and $^{13}C_1$-pyruvate (c,d) maps obtained before (left) and after stimulation (right).

Results & Discussion

Fig. 1 shows the k-space filling scheme employed using centric phase encoding. Metabolic maps obtained from VFA-CPE-CSI acquisitions performed on non stimulated and stimulated muscle are shown in Fig. 2. Muscle stimulation causes an increase S/N of the injected hyperpolarized $^{13}C_1$-pyruvate tracer and of its primary metabolite $^{13}C_1$-lactate, allowing us to obtain quality metabolic maps.

Conclusion

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

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