Frequency band-selective spiral CSI: application to imaging cardiac metabolism with hyperpolarized [2-^{13}C]pyruvate

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Introduction

Spectroscopic imaging with hyperpolarized ^{13}C substrates has been widely used to measure metabolic processes in real time in vivo. The most widely used substrate, [1-^{13}C]pyruvate (Pyr), allows the assessment of pyruvate dehydrogenase (PDH) flux, which converts pyruvate to acetyl-CoA releasing the ^{13}C label as $^{13}CO_2$/^{13}C-bicarbonate. There has also been growing interest in using hyperpolarized [2-^{13}C]Pyr, to follow the ^{13}C label into downstream metabolic products including [5-^{13}C]glutamate (Glu), which is in fast exchange with α-ketoglutarate in the tricarboxylic acid (TCA) cycle, [1-^{13}C]citrate (Cit), [1-^{13}C]acetylcarnitine (ALCAR) and [1,3-^{13}C]acetoacetate (Aca) [1-5], indicating incorporation of acetyl-CoA into different metabolic pathways. Previous studies with hyperpolarized [2-^{13}C]Pyr and [1,2-^{13}C]Pyr [1-3] used a surface coil for localization, obtaining spectra from the entire sensitive volume. Chemical shift imaging (CSI) with [2-^{13}C]Pyr is challenging given the wide spectral dispersion of the resonances, e.g. ~150 ppm from [2-^{13}C]alanine (Ala) to [2-^{13}C]Pyr, i.e. ~ 4800 Hz at 3T. Hence, a slice-selective acquisition[4] suffers from severe chemical shift displacement artifact. This work uses a spectrally selective excitation to perform 3D CSI of frequency sub-bands containing metabolites of interest. The frequency sub-band from 170-185 ppm containing Glu, Cit, ALCAR, Aca along with [1-^{13}C]Pyr is of particular interest. Dynamic data were acquired alternately from multiple sub-bands in vivo in rat heart.

Methods

All measurements were performed on a GE 3T MR scanner with a high-performance insert gradient coil (500 mT/m, 1865 mT/m/ms) using a custom-built ^{13}C transmit/receive surface coil (dia=28 mm) placed over the heart. Three rats were injected i.v. with approximately 3 ml of 80-mM solution of [2-^{13}C]Pyr, which was hyperpolarized using HyperSense (Oxford Instruments, UK). Dichloroacetate (DCA) infusion (150 mg/kg) was administered i.v. prior to Pyr injection to stimulate PDH activity and allow Aca detection[3,5].

A spatially non-selective RF pulse was used (4-ms long, 10º flip angle, passband=190 Hz with 1% ripple). The spectral profile is shown in Fig. 1. With the passband centered approximately midway between Glu and [1-^{13}C]Pyr, passband (referred to as Glu band hereon) magnitude at Glu and $^{13}C_1$-Pyr resonances was 90% and [2-^{13}C]Pyr signal was suppressed (ripple ~10^{-5} at 968 Hz from passband center).

Dynamic 3D ^{13}C data were acquired with FOV=80×80×60 mm^3, 5×5×5 mm^3 nominal resolution, 12 z-phase-encoding steps, 2 x-y spiral interleaves, spectral width=607 Hz, 64 spectral points, T_{acq}=2.8s. Imaging started at the same time as Pyr injection. 24 time-points were acquired every 2.8s with the RF passband alternately placed at Glu and [2-^{13}C]Pyr bands (or Glu and [2-^{13}C]lactate (Lac) bands) for successive acquisitions. For the Lac band, the transmit frequency was centered on the down-field peak of the doublet which led to <1% ripple at the Ala doublet to avoid signal contamination from Ala into Lac given the 607 Hz spectral width.

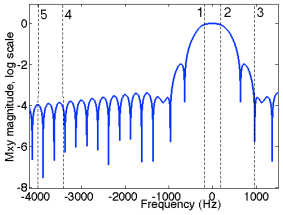

Figure1: Spectral profile of the RF pulse. Lines 1 and 2 indicate chemical shifts of $^{13}C_1$-Pyr and Glu in the passband with ALCAR, Aca and Cit located between them. Signal from $^{13}C_2$-Pyr (line 3) is suppressed. Lines 4 and 5 mark $^{13}C_2$-Lac and $^{13}C_2$-Ala respectively.

Results and Discussion

Figure 2 shows representative time-averaged ^{13}C metabolic maps of [2-^{13}C]Pyr, Glu, ALCAR, Aca and Lac from a slice through the heart and superimposed onto ^{1}H SPGR images. The Lac image is from a separate injection. The spectrum for the Glu band is shown in Fig. 3 along with metabolite time-courses, both from an ROI in the heart. All results were acquired 15 min post-DCA except Lac, which was 2 h post-DCA.

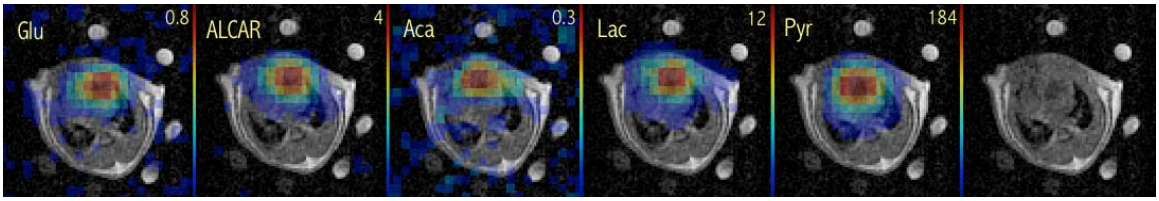

Figure2: Time-averaged ^{13}C metabolic maps of a slice through the heart from a 3D dataset.

Signal from $^{13}C_1$-Pyr (at 1% natural abundance) in the Glu band may be sufficient to provide an estimate of the substrate signal. All 3 sub-bands were not acquired in one dataset as interleaving multiple sub-band acquisitions would lower temporal resolution. While the current implementation performs CSI on all spectral sub-bands, Pyr and Lac can be acquired using imaging rather than a spectroscopic readout to reduce scan time. Given high inflow in heart and limited excitation profile of the surface coil, a 10° flip angle with 24 excitations/volume was used, though a smaller flip angle may be more SNR optimal for other organs. The sequence also allows using different flip angles for Pyr and the metabolic products. As a non-selective RF excitation was employed to avoid chemical shift displacement artifact, the sensitivity profile of the receive coil determines the FOV, in particular the number of slice-encoding steps.

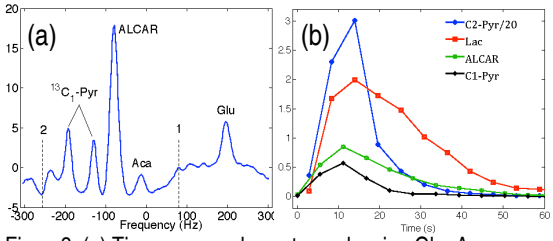

Figure3: (a) Time-averaged spectrum showing Glu, Aca, ALCAR and natural abundance $^{13}C_1$-Pyr doublet. Line 1 shows chemical shift of Cit, though it did not have sufficient SNR here. Line 2 indicates $^{13}C_2$-Pyr signal excited by RF stopband ripples aliased into Glu band. Baseline roll in spectrum is from linear phase correction. (b) Metabolite signal time-courses from heart ROI. Lac was acquired in a separate injection. SNR of Glu and Aca were insufficient to plot time-courses.

Conclusion

This work presents a sequence for 3D CSI of hyperpolarized [2-^{13}C]Pyr using frequency sub-band selective excitation and demonstrates results from an in vivo application to rat heart. It provides a method for dynamic volumetric measurement of metabolism and allows imaging of the downstream metabolic products of acetyl-CoA following a single [2-^{13}C]Pyr injection.

References: [1] Schroeder et al, Circ Cardiovasc Imaging 2012, p201 [2] Chen at al, NMR Biomed 2011, p305 [3] Josan et al, ISMRM 2012, p4322 [4] Park et al, ISMRM 2012, p4323 [5] Hu et al, ISMRM 2012, p4331

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