Simultaneous assessment of cardiac metabolism and perfusion using co-polarized [1-13C]pyruvate and 13C-urea

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Synopsis

Assessment of cardiac metabolism and perfusion using hyperpolarized ^{13}C substrates enables discrimination between viable, hibernating, and non-viable tissue, but current methods require two separate injections of pre-polarized [1-^{13}C]pyruvate and ^{13}C-urea, respectively. We propose to use an infusion of co-polarized [1-^{13}C]pyruvate/^{13}C-urea combined with a flow-sensitized pulse sequence to simultaneously assess both of these parameters in a single injection. Perfusion and metabolic state are modulated using specific interventions, and subsequently detected using the new scan. This probe of both myocardial perfusion and metabolism is anticipated to enable metabolic study of the heart in acute scenarios.

Introduction

The combined assessment of metabolism and perfusion following acute MI would be useful to distinguish between viable, hibernating, and non-viable tissue. Current hyperpolarized ^{13}C MRI-based [1] measurements of these parameters require two separate injections of pre-polarized [1-^{13}C]pyruvate and ^{13}C-urea, respectively. This lengthens scan time and is infeasible in an acute setting. In this abstract, we propose to use an infusion of co-polarized [1-^{13}C]pyruvate and ^{13}C-urea combined with a flow-sensitized spiral-IDEAL pulse sequence to simultaneously assess both myocardial metabolism and perfusion in a single injection.

Methods

Pulse sequence. Fig. 1 shows the multi-echo ECG-gated spiral pulse sequence used to obtain axial dynamic images in the heart. Flow contrast [2,3] was incorporated in alternate frames by inserting a bipolar gradient (m_1 = 332 mT·ms^2/m, orientation in slice direction) between the end of the excitation and the start of the readout. The sequence parameters were: Agilent 7T, 8 echoes + 1 FID, TE_0 = 0.8/4.5 ms without/with flow suppression, ΔTE = 0.5 ms, TR 1 RR, FOV 70x70 mm^2, acquired in-plane res. 1.75x1.75 mm^2, thk 5 mm, readout 10 ms, FA 10°. The time for each set of echoes was 9xRR ≈ 1.5 s.

Co-polarization. [1-^{13}C]pyruvate (14 M) and ^{13}C-urea (6.4 M) were simultaneously polarized with trityl radial (OX63, 15 mM) for 2 hours in a prototype DNP hyperpolarizer[1]. Individual layers were frozen in liquid nitrogen. Dissolution with 5 mL NaOH/EDTA solution resulted in 2 mL of pre-polarized 80 mM [1-^{13}C]pyruvate/64 mM urea, transferred to a magnetic holder (2-10 mT) prior to injection, and injected over 20 seconds via tail vein. The scan was started prior to injection.

In vivo study. Male Wistar rats (2x2 groups of fed vs. fasted and rest vs. stress, n=3 each, weight 447±27 g, HR 370±33 bpm) were scanned supine using a volume Tx birdcage and 2-channel Rx surface array (Rapid

Figures

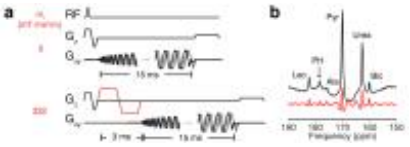

Fig. 1. (a) Pulse sequence for combined perfusion and metabolic imaging. The flow sensitizing gradient is toggled to suppress signal from the cardiac chambers. (b) Sample spectrum obtained without (black) and with (red) flow encoding. Flow encoding reduces the intravascular signal while preserving intracellular (bicarbonate) signal.

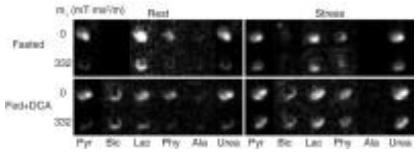

Fig. 2. *In vivo* cardiac 13C images of co-polarized pyruvate and urea and downstream metabolites. Each set of images corresponds to one combination of perfusion and metabolic state.

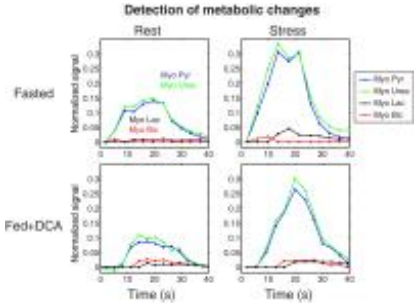

Fig. 3. Time courses showing conversion of hyperpolarized myocardial pyruvate into bicarbonate and lactate, in each combination of perfusion and metabolic state. Adenosine stress increases myocardial blood flow relative to rest. Feeding and DCA injection increases myocardial bicarbonate signal relative to fasting.

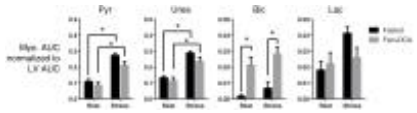

Fig. 4. Measures of perfusion and metabolism using ^{13}C pyruvate/urea co-polarization. The AUC ratio between myocardium and LV is shown for each metabolite. Pyruvate and urea ratios reflect perfusion differences following adenosine stress; bicarbonate ratios reflect PDH flux differences between fasted and fed states.

Biomedical). In fed animals, a bolus of the PDK inhibitor dichloroacetate (DCA, 30 mg/kg, pH 7) was injected 10 minutes prior to the ^{13}C infusion. Stress metabolic and perfusion measurements (n=3) were made under adenosine, a coronary vasodilator (280 μg/kg/min for 10 min).

Image reconstruction. Spiral IDEAL reconstruction was used to transform the multiple echoes to spatial k-space data corresponding to [1-^{13}C]pyruvate, lactate, alanine, pyruvate hydrate, ^{13}C bicarbonate, and ^{13}C urea. The non-Cartesian k-space samples were then converted to an image by NUFFT; images were Hamming filtered to an in-plane resolution of 2.3x2.3 mm^2.

Data analysis. The heart was manually segmented using ^{1}H images into right ventricle (RV), left ventricle (LV), and myocardium. Pyruvate and its downstream metabolic signals were normalized to the maximum (in time) LV pyruvate signal, and urea was similarly normalized to maximum LV signal. The AUC for each metabolite was compared between each condition using two-way ANOVA.

Results and Discussion

Fig. 2 shows images of [1-^{13}C]pyruvate, lactate, bicarbonate, and urea in the heart in the four combinations of metabolic and perfusion states. In the frames where the flow-sensitizing bipolar gradient has been turned on, the bright luminal signal is suppressed, highlighting the metabolic activity within the myocardium. Modulation of perfusion by adenosine stress results in increased myocardial pyruvate and urea signal, consistent with vasodilation. Modulation of metabolic state by feeding and DCA infusion results in increased myocardial bicarbonate signal relative to fasted tissue. The pyruvate and urea time courses (Fig. 3) appear very similar, presumably due to the dose of pyruvate being in excess of PDH/LDH activity in the heart. This supports the use of hyperpolarized ^{13}C-urea as a perfusion agent, as optimized acquisitions which avoid disturbing the pyruvate signal reservoir may improve imaging of bicarbonate/lactate under in states with low PDH/LDH activity. Fig. 4 shows two-way ANOVA results between each condition, showing that perfusion and metabolic state can be independently modulated, and subsequently detected using co-polarized ^{13}C-pyruvate/urea.

Future studies will focus on improving image quality and applications to probe regional changes in metabolism and perfusion. A proton B_0 map [4] could be incorporated into the reconstruction to correct more severe off-resonance artifacts such as those in the posterior aspect of the heart. Alternative excitation schemes [5,6] can be used to take advantage of the additional urea resonance without disturbing the pyruvate magnetization.

Conclusions

A flow-sensitized imaging sequence is used to image a co-polarized preparation of [1-^{13}C]pyruvate and ^{13}C-urea in the rodent heart, enabling simultaneous assessment of both metabolism and perfusion. We anticipate that this strategy will be useful in acute monitoring of metabolic/perfusion changes during ischemia/reperfusion.

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