In vivo Dynamic Cardiac Magnetic Resonance Spectroscopy with hyperpolarized [2-^{13}C] pyruvate in pigs

A. P. Chen[1], A. Z. Lau[2], W. L. Lam[2], N. R. Ghugre[2], G. A. Wright[2], and C. H. Cunningham[2]
[1]GE Healthcare, Toronto, ON, Canada, [2]Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Introduction: Hyperpolarized [1-^{13}C] pyruvate in solution has been utilized to demonstrate non-invasive, real time, metabolic assessment in various tissues *in vivo* (1-2). However, pyruvate labeled at the C1 position does not allow investigation of TCA cycle reactions since the ^{13}C nucleus is carried by CO_2 after the PDH mediated oxidation of the pyruvate molecule. It has recently been shown that pre-polarized [2-^{13}C] pyruvate can be used to monitor TCA cycle metabolism *in vitro* and *in vivo* in rat hearts (3-4). In this study, the feasibility of obtaining dynamic cardiac MR spectroscopic data *in vivo* using hyperpolarized [2-^{13}C] pyruvate on a clinical 3T MR system in pigs is demonstrated.

Methods: Substrate preparation and hardware: ~130 mg of [2-^{13}C] pyruvic acid (99%, Isotec, Miamisburg, OH) with 15 mM OX63 trityl radical (Oxford Instruments, Abingdon, UK) was polarized for each experiment using a Hypersense DNP polarizer (Oxford Instruments). ~6 mL of NaOH/Tris/EDTA solution was used to dissolve the sample for a nominal concentration of 250 mM pyruvate in solution with a pH of 7.4. The solution was diluted by normal saline to the final concentration of 83 mM. All experiments were performed using a GE MR750 3T Scanner (GE Healthcare, Waukesha WI) equipped with the multinuclear spectroscopy package. A custom-built transmit/receive ^{13}C surface coil with ^{1}H blocking was used. Animal preparation: All animal experiments were carried out under a protocol approved by the institutional animal care and use committee. Normal pigs (n=3, body weight ~25 kg) were fasted for one day prior to scanning due to concerns over asphyxiation while under anesthetic in the scanner. In order to raise blood glucose levels, 1 L electrolyte solution (Life Brand, Toronto) containing 25 g glucose was given orally ~1 hour prior to anesthesia. Blood oxygen saturation and heart rate was monitored using a peripheral pulse oximeter placed on the tail. The pigs were placed on a ventilator to maintain respiration at a constant rate of 24 breaths per minute. In vivo MRS experiment: A pulse-and-acquire pulse sequence (hard pulse, pw=192μs, nominal flip angle=10°) was used. ~15 mL (83 mM) hyperpolarized [2-^{13}C] pyruvate solution was injected over 15 s into the right ear vein (~0.05 mmole/kg dose). Data acquisition started at the start of the injection. One spectrum (4096 spectral points, 10 kHz bandwidth) was acquired with cardiac gating every 3 R-R intervals resulting in a temporal resolution of ~2 s.

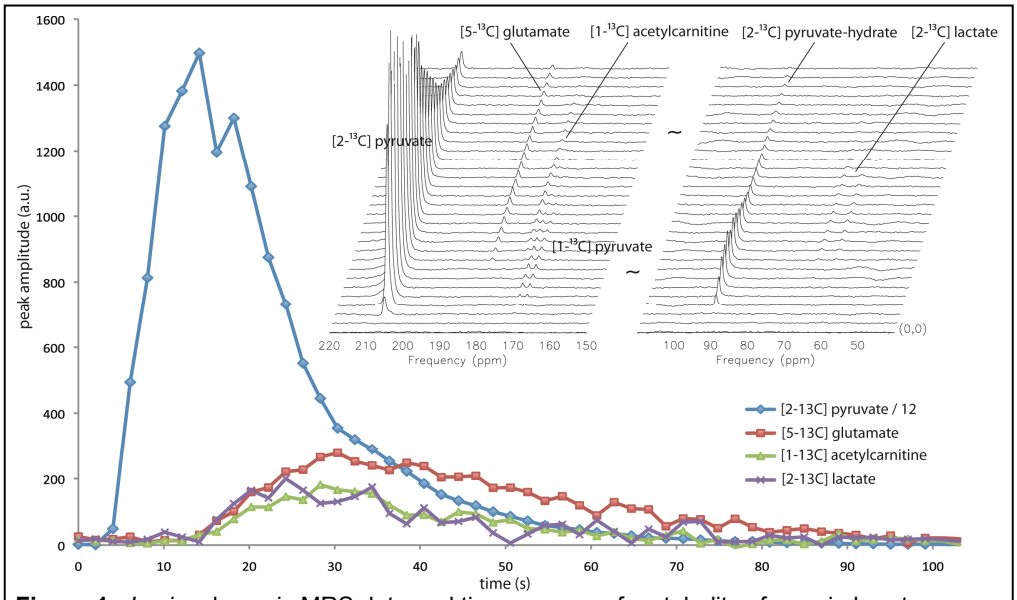

Figure 1. *In vivo* dynamic MRS data and time courses of metabolites from pig heart following injection of hyperpolarized [2-13C] pyruvate.

Results and discussion: Representative *in vivo* dynamic cardiac ^{13}C spectra from pig heart and time courses of the metabolites following injection of pre-polarized [2-^{13}C] pyruvate are shown in Figure 1. Assignments of the resonances were done based on published data (3). Similar to prior reports, [5-^{13}C] glutamate was observed as a result of TCA cycle metabolism; [1-^{13}C] acetylcarnitine and [2-^{13}C] lactate were also observed as a result of the carnitine acetyl transferase (CAT) system and LDH mediated lactate-pyruvate exchange, respectively. However, no detectable citrate or alanine resonances were evident in these studies. This study demonstrated that TCA cycle metabolism could be probed in real time *in vivo* in a large animal model using pre-polarized [2-^{13}C] pyruvate on a clinical MR system. Monitoring TCA cycle metabolism could play an important role in assessing different disease states such as myocardial infarction where identifying the amount of salvageable myocardium is clinically valuable; the technique may also potentially help probe the efficacy of different therapeutic interventions

References: 1. Day SE. et al. Nat Med 2007;13(11):1382-1387. 2. Schroeder M. et al. Proc Nat Acad Sci 2008;105:12051–12056. 3. Schroeder M. et al. FASEB 2009;23(8):2529-38. 4. Tyler DJ. Proceedings, 17th ISMRM annual meeting, Honolulu, 2009. #532.