A feasibility study in mini-pig for heart metabolism with hyperpolarized [1-13C]pyruvate: MRS cardiac modelling and kinetic considerations

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Introduction: Changes in metabolic products of pyruvate can be correlated to the patho-physiological condition of the myocardium.The cardiac oxidation of pyruvate depends on oxygen delivery to myocardium and on the activation state of pyruvate dehydrogenase (PDH), which is located in the mitochondrial matrix [1]. The real time tracking of the metabolic fate of pyruvate in the intact heart with MRS would provide a key information on the state of myocardium in response to a variety of stimuli. This study deal with the real time in vivo cardiac metabolism after intravenous (i.v.) injection of hyperpolarized [1-^{13}C]-pyruvate in the animal of mid size with a clinical 3T scanner with regards to the typical kinetic profile of accumulation of each metabolite and if the typical pattern could be modelled with simple equations [2-3].

Methods

Animal model: Six normal male mini-pigs (35 ±2 kg) were maintained in deep sedation with infusion of midazolam (0.1 mg/kg/h i.v.). A dose of 20 mL was administered over 10 s by manual injection. ^{13}C-1-pyruvate Hyperpolarization has been performed using Dynamic Nuclear Polarization (*Hypersense*). The final injection solution contained 230 mM sodium [1-^{13}C]pyruvate, 100 mM TRIS buffer, 0.27 mM Na_2EDTA and 20 microM Dotarem (Guerbet). Temperature of solution about 37ºC and pH = 7.6. The mini-pigs were examined by ^{1}H MR imaging and hyperpolarized ^{13}C MRS. The experiments were performed on a 3 T GE Signa HDx (GE Healthcare) scanner with a 13C quadrature birdcage coil (Rapid Biomedical). Anatomical imaging was acquired with the body coil and FIESTA sequence (FOV=35, FA=45, TE/TR=1.71ms/3.849ms). ^{13}C dynamic spectra were acquired using elliptic-FIDCSI pulse sequence (bandwidth 5000Hz, 2048 pts). Different normal flip angles were applied to sungroups of two pigs: 10°, 20°, 90°. A long-axis slice of 20 mm was selected during excitation. Spectra covering the heart were acquired from the beginning of the injection of the hyperpolarized [1-^{13}C]pyruvate, every 2 s, for 120 s.

Data processing was performed by using MATLAB and jMRUI 4.0 software tools [4]. The dynamic spectra were phase corrected by adjusting both zero-and first-order frequency-dependent phase components. Pyruvate, pyruvate hydrate, alanine, lactate, and bicarbonate were estimated by using AMARES algorithm included into jMRUI tools. Time courses of metabolites were fitted with FORTRAN code developed in house. The generated pyruvate time courses were also fitted to the gamma variate curve: y=k(t-t0)a exp((t-t0)/b). The gamma curve indices (Mean Transit Time, MTT; Peak Height, PH; Rise Time, RT; Curve area, AUC) were also evaluated [5].

Figure 1

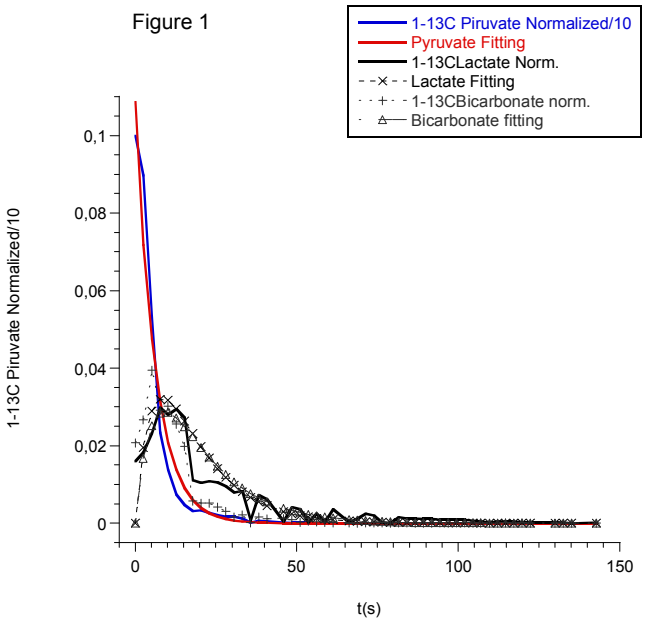

Table 1

Metabolites	MTT (sec)	PH	RT	AUC	Flip angle
PIG 1	15.18	1.25E+11	6.74	1.50E+12	90°
PIG 2	14.00	2.57E+10	5.66	3.57E+11	90°
PIG 3	14.34	1.44E+09	6.49	1.49E+10	10°
PIG 4	13.05	3.44E+09	5.11	4.66E+10	10°
PIG 5	13.92	6.10+E+09	6.44	5.36E+10	20°
PIG 6	9.50	2.71E+10	4.30	1.85E+11	20°
mean	13.3±2.0		5.79±0.95		

Results and discussion

Simple exponential equations [2,3] were used to model the dynamic changes in 1-^{13}C-pyruvate, 1-^{13}C -lactate, 1-^{13}C-alanine and 1-^{13}C-bicarbonate levels after a bolus of the hyperpolarized agent. Spectra obtained with the dynamic acquisition are shown in Figure 1.

The [1-^{13}C]pyruvate, [1-^{13}C]pyruvate hydrate and metabolites peaks ([1-^{13}C]lactate, [1-^{13}C]alanine, and ^{13}C-bicarbonate) have been detected (Figure 1).

Conclusions

A simple kinetic model was based on multicompartmental [2,3] analysis was tested to estimate MRS in healthy pig heart. Relaxation rates ($1/T_1^*$) such as k_{0PYR} (0.1 s^{-1}), and k_{0LAC} (0.07 s^{-1}) k_{0ALA} (0.065 s^{-1}), and k_{0BIC} (0.065 s^{-1}) and k_{LP} (0.0096 s^{-1}), $k_{ALA\text{-}P}$ (0.00005 s^{-1}), $k_{ALA\text{-}P}$ (0.008 $s^{-}1$) have been assessed. The parameters estimate using this approach could be useful for tracking typical kinetic profiles associated to physiological condition as well as for assessing efficacy kinetic constant in vivo. The Authors would like to emphasize that the biochemical significance of these efficacy constant obtained following this kind of approach has still to be clarified and if necessary corrected by physical (like diffusion) and biochemical processes underlying the MRS dynamic data.

In the other hands pyruvate dynamic is well described by gamma variate curve (curve fitting was reliable in all cases with R=0.97±0.013). As expected, the MTT and RT values are strongly reproducible among the experimental model population (Table 1). The mean pyruvate MTT (about 13 sec) is within the decay time (T1) of the hyperpolarized pyruvate injected. PH indices showed a significant variability. AUC index variability is due to high PH value variability (AUC~MTT*PH, MTT variability is low). PH is explained by the different flip angles used in the acquisition. In conclusion gamma variate curve allow a good characterization of pyruvate dynamic as expected.

References

[1] Stanley WC et al. Physiol Rev. 2005 Jul;85(3):1093-129
[2] Mice Matthew L. Zierhut et al. Journal of Magnetic Resonance (2009), doi: 10.1016/j.jmr.2009.10.003
[3] Talia Harris et al www.pnas.org_cgi_doi_10.1073_pnas.0909049106
[4] Naressi A, et al.. MAGMA 12: 141.152 (2001).
[5] Blomley MJK, et al. The British Institute of Radiology 70:351-359 (1997)