Hyperpolarized [1-13C]acetate kinetics and metabolism in translational animal model: cardiac real-time detection of metabolic flux of [13C]acetyl-carnitine in pigs

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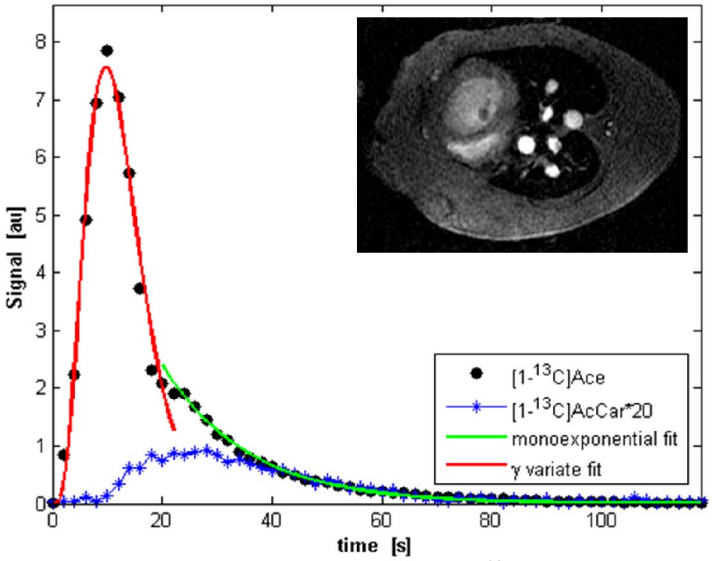
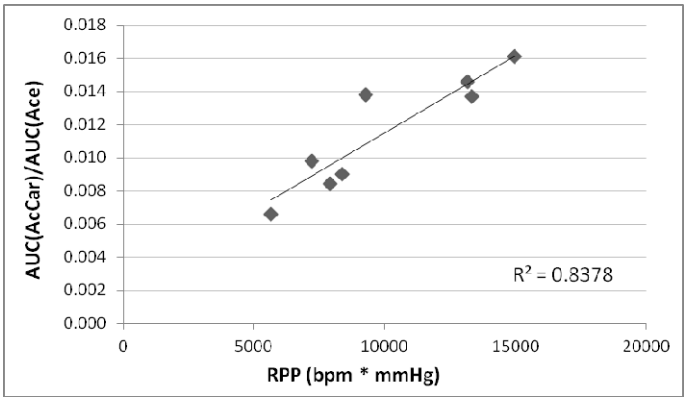
Purpose: Dissolution-DNP together with Magnetic Resonance Spectroscopy (MRS), provides a unique tool for metabolic studies in translational animal model and in real time. We selected [1-^{13}C]acetate[1] (Ace), the most abundant extra- and intra-cellular short-chain fatty acid (SCFA), to clarify a fundamental pathway of the cardiac metabolism. We propose an analysis of total Areas Under the Curve (AUC) of the detected metabolites[2], for real-time assessment of the cardiac metabolic flux and enzymatic reactions of hyperpolarized [1-^{13}C]Ace at 3T, in a large animal model.

Methods: 4 pigs (30±2 Kg) underwent to bolus injection of hyperpolarized Na [1-^{13}C]acetate (3 mmol, 150 mM), at rest and after administration of dobutamine (20γ for 5 min), to increase cardiac workload. Dissolution-DNP of Na [1-^{13}C]Ace large volumes[3] (600 µL, [^{13}C]=7.3 M) was set up. ^{13}C-spectroscopic signal was acquired every 2 s for 120 s, from an axial slice selected through the heart of the pig (slice thickness = 40 mm), using a (slice-selective) pulse-and-acquire sequence (soft pulse excitation, bandwidth 2200Hz, 2048 pts, 10° flip angle). A 3T GE Excite HDXt clinical scanner (GE Healthcare, USA) and a ^{13}C quadrature birdcage coil (Rapid Biomedical, Germany) were used for the experiments. Dynamic metabolic curves were extracted using AMARES implemented in jMRUI 3.0; fitting and AUC estimation of the metabolic curves were performed in Matlab.



(left) Fig. 1: Typical profile and fitting of the [1-13C]Ace and [1-13C]AcCar metabolic curves obtained in the pig heart at 3 T; a reference anatomical 1H image of the pig myocardium is displayed in the inset. *(down)* Fig. 2: The correlation of the AUC ratio AcCar/Ace is reported(n=4,R2=0.84)



Results: The spectroscopic signals of [1-^{13}C]Ace and of its by-product [1-^{13}C]acetyl-carnitine (AcCar) were detected in a selected slice covering the heart of the pig. We found a bimodal shape for the kinetics of [1-^{13}C]Ace in vivo, which could be modeled using a γ-variate and a mono-exponential function (Fig.1). We recorded a significant correlation (R^2=0.84, Fig.2) between the ratio of [1-^{13}C]AcCar to [1-^{13}C]Ace AUC and the measured Rate Pressure Product (RPP = heart rate (bpm) * systolic pressure (mmHg)).

Discussion & Conclusion: The rapid uptake and compartmentalization of [1-^{13}C]Ace by myocardial cells was suggested by the biphasic shape of its metabolic curve; moreover the amount of produced [1-^{13}C]AcCar quantitatively correlated with the inotropic workload of the heart. Our findings demonstrate the sensitivity of this approach in a translational large animal model, thus proving the feasibility of cardiac metabolism assessment in vivo with MRS of hyperpolarized [1-^{13}C]Ace, with future relevance for pre-clinical and clinical studies.

References: 1. Bastiaansen JAM et al. BBA 1830 (2013); 4171–4178; 2. Hill DK et al. PLOS ONE 2013; 8(9): e71996; 3. Flori A et al. Appl. Magn. Reson. 2012; 43: 299-310.