Hyperpolarized Metabolic MR Imaging of Acute Myocardial Changes and Recovery Upon Ischemia-Reperfusion

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Introduction: Dissolution Dynamic Nuclear Polarization (DNP) allows for real-time in-vivo MR imaging of metabolic processes in the heart[1]. The aims of the present study were to establish a rat model of myocardial ischemia-reperfusion and to study the acute metabolic changes and recovery of the myocardium following short periods of left coronary artery occlusion using intravenous injection of hyperpolarized pyruvate.

Methods: A closed-chest rat model was established using an inflatable balloon occluder secured around the left coronary artery[2]. Female Sprague Dawley rats (250-300g) were anaesthetized using 1-2% isoflurane in an air/oxygen (4:1) mixture and then placed in a Bruker Biospec 9.4T small animal MR system 5-7 days after surgery. To enhance bicarbonate signal, animals received an iv glucose/potassium infusion. The tubing of the occluder was connected to extension tubing to allow occlusion while the animal remained in the bore of the MR system. A birdcage dual 1H/13C coil (Rapid Biomedical, Wurzburg, Germany) was used for transmission, and a 13C surface coil from the same vendor was used for signal reception. A custom-built multi-sample DNP polarizer[3] was employed to polarize samples containing 25.4 µL [1-13C]-pyruvic acid and 13.5 mM trityl radical doped with 1.5 mM Dotarem. The rats were injected with 1.4 ml of the DNP solution at 5 stages: baseline, on reperfusion after 15 minutes of coronary occlusion, after 30 and 60 minutes and 1 week after ischemia/reperfusion. Only a subgroup of 5 animals was kept alive for the 1 week measurement. The study has been conducted in adherence with the Swiss Law for Animal Protection. Metabolic data were acquired with a multiband pulse in combination with a multi-echo single-shot EPI readout[4] with the following parameters: initial echo time 5.31 ms, echo time increment 383 us, number of echoes 7, field of view 60x40mm^2, 69% partial Fourier acquisition in phase-encode direction, in-plane resolution 1.25x1.25 mm^2, slice thickness 5 mm. Each readout was triggered to end-systole and the seven readouts were repeated every 1.5 s during a total scan duration of 5 min. Images were reconstructed using the IDEAL approach[5]. The conversion of pyruvate into lactate and bicarbonate was imaged alongside with cine wall motion and late gadolinium enhancement (LGE) imaging (Figure 1). Following imaging, the heart was removed and stained to delineate the area-at-risk (AAR). Signal intensity-time curves of pyruvate, lactate and bicarbonate were integrated to obtain the area-under-the curve[6] (AUC, Figure 2). Four myocardial segments were analyzed and classified as AAR or remote myocardium according to staining results. Regional wall motion and systolic wall thickening were scored in the same four segments using a five point grading scale: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; and 5, dyskinetic. LGE was quantified on the basis of the amount of hyperenhancement in the midventricular slice of each region using the following scale: no hyperenhancement, 1, 0-33% scar; 2, 34-66% scar; 3 67-100% scar. Student's t-test was used to assess statistical significance.

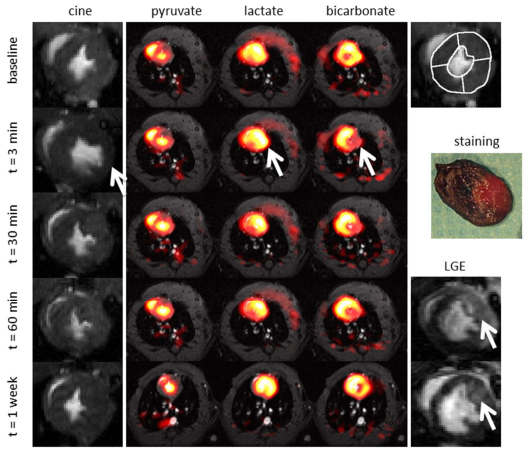

Figure 1: *Example images at the 5 time points in one animal. Left: Cine images show reduced systolic wall thickening in the AAR (arrow) on reperfusion after coronary occlusion. Middle: Metabolic maps of pyruvate, lactate and bicarbonate. Lactate is increased and bicarbonate decreased in the AAR. Right: LGE showing myocardial enhancement in the AAR. The myocardial AAR was determined by Evans blue staining.*

Results: Data were successfully collected in 10 animals (Figure 3). By inflating and deflating the balloon, the coronary artery could reversibly be occluded/reopened. Occlusion led to hypokinesia and acute injury in the AAR. At 3, 30 and 60 minutes after ischemia/reperfusion the ratio of lactate to bicarbonate was significantly different in the AAR from the remote area ($p<0.001$). At 1 week after ischemia/reperfusion the lactate/bicarbonate ratio was lower compared to the 60-minute scan, and not significantly different from the remote area anymore.

Discussion: Hyperpolarized metabolic MR imaging allows the study of transient changes in cardiac metabolism following ischemia/reperfusion. Myocardial metabolism was abnormal in the area-at-risk during the first 60 minutes following ischemia, but returned to normal one week later.

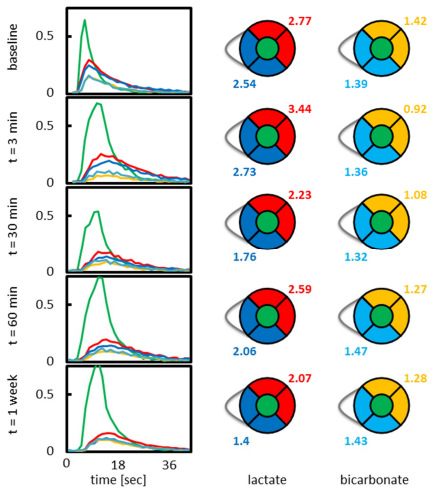

Figure 2: *Left: Example time-resolved signals of pyruvate in the blood pool (green), lactate and bicarbonate in the AAR (red, orange) and remote myocardium (blue, cyan). Right: AUC values for lactate and bicarbonate in the AAR (red, orange) and remote myocardium (blue, cyan). Immediately after reperfusion, the ratio of lactate to bicarbonate is increased in the AAR (red/orange) vs. remote myocardium (blue/cyan) but reduces at 30 and 60 min after reperfusion indicating normalization of metabolism after the transient ischemic event.*

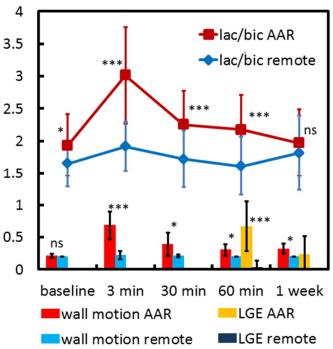

Figure 3: *The AUC lactate/bicarbonate ratio in the AAR increased following 15 min of myocardial ischemia, remained abnormal during the first 60 min following ischemia and returned to base level at one week. The lower half of the figure shows that the AAR developed a localized hypokinesia following ischemia which recovered over time. The AAR showed late gadolinium enhancement at 60 min which reduced 1 week later. Wall motion and LGE scores are normalized to one. Mean values (±std) over all subjects are displayed.*

References: 1. Schroeder, M.A. et al. *Circulation* (2011) **2.** O h-Ici, D. et al. *Int. J. Cardiovasc. Imaging* (2014) **3.** Krajewski, M. et al. *ISMRM* (2013) **4.** Sigfridsson, A. et al. *Magn. Reson. Med.* (2014) **5.** Reeder, S.B. et al. *Magn. Reson. Med.* (2004) **6.** Hill, D.K. et al. *PLoS ONE* (2013)