Hyperpolarized ^{13}C imaging of metabolic remodeling in a porcine cardiac ischemia-reperfusion model

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Introduction: Non-localized 13C MR spectroscopy studies on ex vivo and in vivo hearts following perfusion of pre-polarized [1-13C] pyruvate have shown that metabolic changes in substrate usage occur following induction of ischemia [1-3]. Previously we reported a dual-gated (respiratory and cardiac) imaging pulse sequence for time-resolved imaging of [1-13C] pyruvate, [1-13C] lactate, and 13C bicarbonate in vivo [4,5]. In this study, hyperpolarized (HP) 13C imaging was investigated as a tool to characterize cardiac metabolic remodeling following acute myocardial infarction (AMI) in vivo in a porcine ischemia-reperfusion model.

Methods: Animals: All animal experiments were approved by the local animal care committee. Female Yorkshire pigs (n=6, wt = 25kg) were prepared as previously described [4] and subjected to 60 min balloon LAD occlusion, followed by reperfusion.
Imaging: The animals were scanned using a 3T GE MRI (MR 750, GE Healthcare) with a 13C transmit volume coil and a dual-tuned 1H/13C receive-only surface coil (Rapid Biomedical). Three time points were investigated: pre-occlusion (ctrl), ~45 min post-reperfusion (post), and one week post-occlusion (1 wk). Pyruvate, bicarbonate, and lactate (pyr, bic, lac) were imaged using a time-resolved dual-gated 13C spiral imaging pulse sequence enabling whole-heart coverage [4,5]. Short axis images were acquired at end-expiration in diastole (6 slices, 24 breaths/min, Tread = 32 ms (single-shot), Thk/Spc = 10/1 mm, FOV 48cm, in-plane res. 10x10 mm^2). 15 mL of 83 mM HP [1-13C] pyruvate was injected i.v. over 15 s. The sequence was started with a 10 s delay after the start of the injection. A SSFP sequence in cine mode was used for functional assessment. A contrast-enhanced IR-GRE sequence was used for infarct assessment.
Analysis: ROIs were contoured in the anterior myocardium ("AM") and in the left ventricle ("LV"). Metabolic ratios were computed by dividing max mean AM bic and lac by max mean LV pyr for each animal.

Results and Discussion: We observed two distinct phenotypes, corresponding to stunning and infarction, following 60 min LAD occlusion. Fig. 1(left) shows short axis images in stunned myocardium. Bicarbonate recovery at 1 week indicated the reversible nature of the injury. Cine MR revealed akinesis in the antero-septal wall. Fig. 1(right) shows short axis images in infarcted myocardium. DE revealed an antero-septal infarct near the apex, consistent with LAD occlusion. The observed global changes in apparent PDH flux (bicarbonate production) following ischemia are consistent with previous cardiac HP MRS studies in ex vivo and in vivo hearts [2,3]. The appearance of elevated myocardial lactate in the peri-infarct region is presumably an indication of the area-at-risk, reflecting the potentially viable state of the myocardium in that region. Furthermore, the defect in the lactate image in Fig. 1(right) is presumably due to a combination of reduced perfusion and non-viable myocardium. Fig. 2 quantifies the changes in bic and lac production, and ejection fraction at each time point.

Conclusion: A dual-gated rapid 13C imaging sequence was used to observe in vivo conversion of HP pyruvate into bicarbonate and lactate in real-time, in an ischemia-reperfusion model. Distinct metabolic remodeling patterns in stunned and infarcted myocardium were observed, potentially enabling a clinically feasible assessment of salvageable myocardium (the area-at-risk) in myocardial infarction.

References: [1]Ardenkjaer-Larsen et al. PNAS USA 2003;100(18):10158–10163. [2]Merritt et al. MRM 2008;60(5):1029-36. [3]Golman et al. MRM 2008;59(5):1005-1013. [4] Lau et al. MRM 2010;64(5):1323-31. [5] Lau et al. ISMRM 2011 (#3532)
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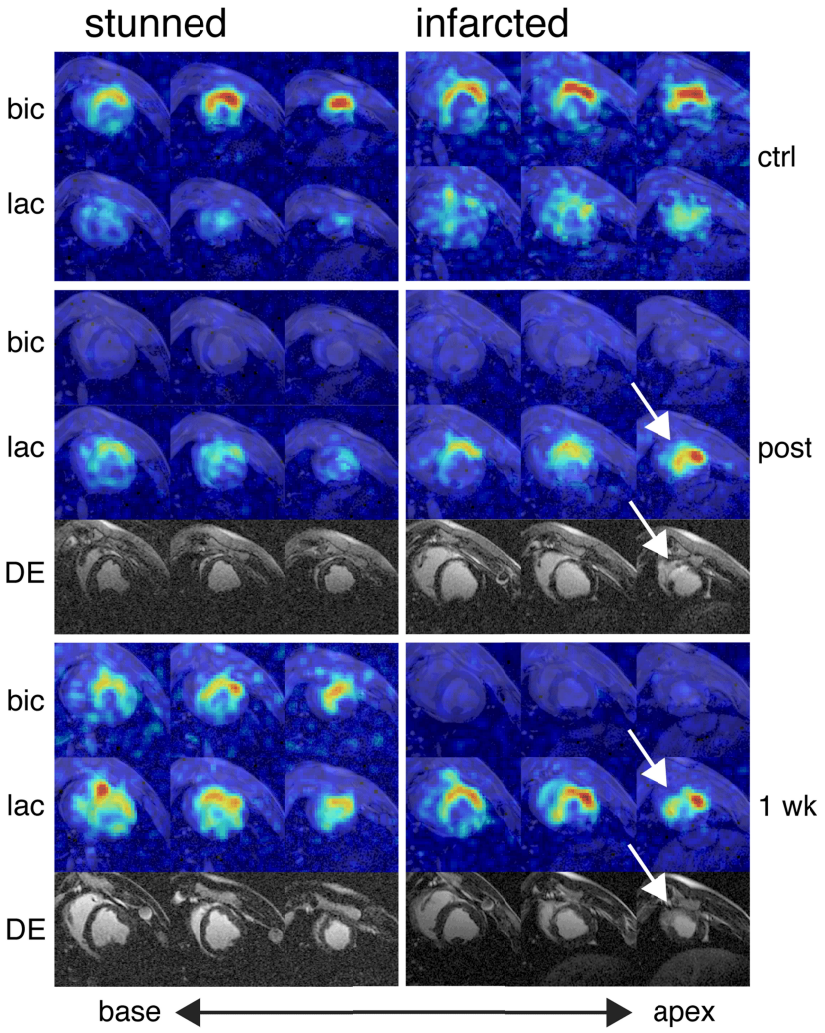

Fig. 1. Short axis images following 60 min LAD occlusion. The colour scale runs from blue (0%) to red (100%), and is scaled to the max baseline value (bic) and 1 wk value (lac). **(left)** Consistent with myocardial stunning, DE revealed no infarct post-reperfusion. Cine MR revealed antero-septal akinesis. Apparent PDH flux was reduced at 45 min with recovery at 1 wk. **(right)** Consistent with AMI, DE revealed an enhancing antero-septal infarct near the apex (arrow) at both 45 min and 1 wk. Apparent PDH flux did not recover at 1 wk. Interestingly, a defect in myocardial lactate (arrows) was observed in the infarct region, with elevated lactate in the peri-infarct region.

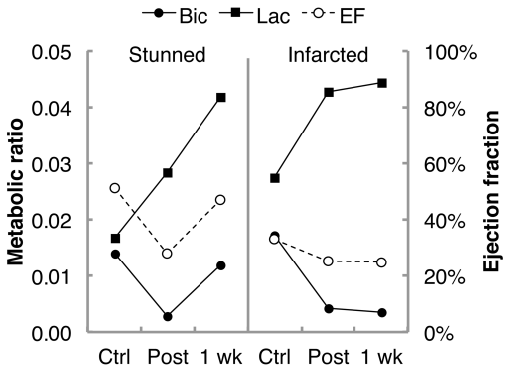

Fig. 2. Changes in bicarbonate (closed circles) and lactate (closed squares) ratios, and ejection fraction (open circles) following 60 min LAD occlusion in stunned (left) and infarcted (right) myocardium.