Reproducibility of free-breathing dual-gated hyperpolarized 13C imaging measurements of cardiac metabolism

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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]. The development of rapid pulse sequences for hyperpolarized 13C imaging allows investigation of spatially varying metabolic changes occurring in vivo [4]. Previously we reported a dual-gated (respiratory and cardiac) multi-slice imaging pulse sequence for time-resolved imaging of [1-13C] pyruvate, [1-13C] lactate, and 13C bicarbonate in vivo [4,5]. In this study, we investigated the reproducibility of these free-breathing measurements in a cohort of normal pigs.

Methods: Animals: All animal experiments were approved by the local animal care committee. Female Yorkshire pigs (n=12, 20 scans, wt=25kg) were prepared as previously described [4]. The pigs were fasted the night prior to the scan and were given 1L electrolyte-sugar solution containing 25g glucose (Life Brand) to drink 2 hours prior to the scan to raise plasma glucose.

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). Pyruvate, bicarbonate, and lactate (pyr, bic, lac) were imaged using a time-resolved dual-gated spiral 13C imaging pulse sequence enabling whole-heart coverage [4,5]. Short axis images were acquired at end-expiration in diastole (2 or 6 slices, 24 breaths/min, Tread = 64 or 32 ms (single-shot), Thk/Spc = 10/1 mm, FOV 48cm, in-plane res. 10.7x10.7 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.

Analysis: ROIs were contoured in the anterior myocardium ("AM") and in the left and right ventricles ("LV", "RV"). In each ROI, the mean signal was calculated (signal / volume). Metabolic ratios were computed by dividing bic and lac signals by pyr signals. The following pyr normalization factors were used: 1. Maximum total (LV+RV) pyr ("total"), 2. Pyr signal during the 11th frame ("late"), 3. Maximum LV pyr signal ("max LV"). The coefficient of variation (%CV = SD / Mean) was used as a measure of variability.

Results and Discussion: In vivo short axis 13C images are shown in Fig. 1. The dynamic time course of HP pyruvate, bicarbonate, and lactate in their respective compartments is shown in Fig. 2. In Fig. 3, the variability for each normalization method is compared to no normalization. For both bicarbonate and lactate, normalization reduced the variability in the metabolic ratio. The intention was to remove inter-scan differences in polarization, cardiac output, injection timing, and coil positioning as contributing factors to measured metabolic signals. The residual %CV value presumably represents the inherent metabolic variability in this cohort of normal pigs. In this cohort, "max LV" normalization minimized %CV for bicarbonate (56%), while "total" normalization minimized %CV for lactate (28%). While using the max LV segmented pyruvate signal as normalization leads to a higher %CV for lactate, this imaging-based measurement may be useful in diseased states in which cardiac function is impaired, leading to altered cardiac hemodynamics. The lower lactate variability relative to bicarbonate is presumably due to lower baseline variability in lactate dehydrogenase (LDH) activity compared to pyruvate dehydrogenase (PDH) activity. Along with increases in LDH activity in ischemia (as opposed to a decrease in PDH activity) [2], this finding suggests lactate imaging may be a sensitive imaging target for myocardial ischemia in vivo.

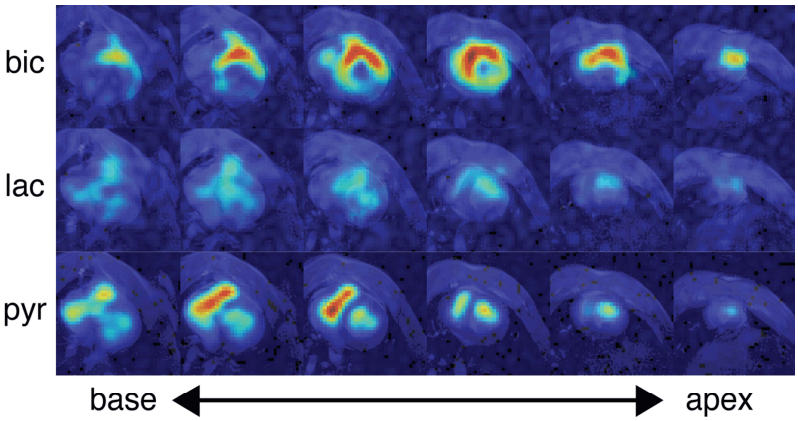

Fig. 1. Short axis images of bic, lac, pyr acquired using the time-resolved dual-gated 13C imaging sequence. The colour scale runs from blue (0%) to red (100%), and is scaled to the max bic intensity (bic, lac) and max pyr intensity (pyr). The bic and lac images are taken from the time point with maximum signal, and the pyr images are taken from the time point with maximum LV signal.

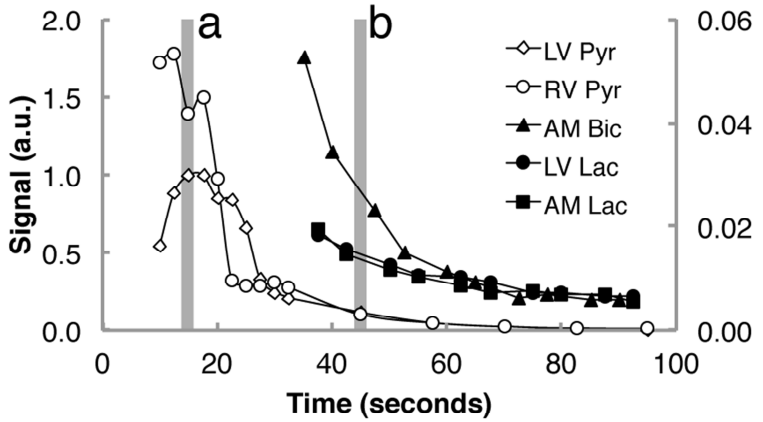

Fig. 2. Representative HP 13C time course of pyr (left axis), bic, and lac (right axis) obtained using the time-resolved dual-gated 13C imaging sequence. The time points for (a) "total", "max LV" and (b) "late" pyruvate signal are indicated with gray vertical bars.

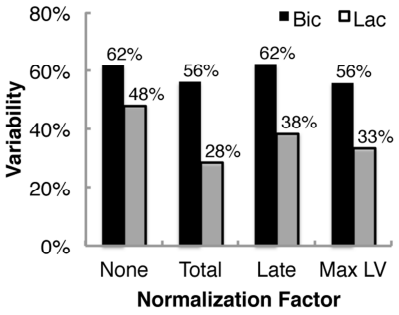

Fig. 3. Variability in bic and lac ratios measured across a cohort of normal pigs, using 3 different normalization factors. The %CV was found to be systematically lower when the pyruvate-based normalization factor was applied.

Conclusion: The reproducibility of real-time metabolic measurements made using a time-resolved, dual-gated 13C imaging sequence was investigated in a cohort of normal pigs. First-pass images of HP pyruvate in the cardiac chambers were used to normalize imaging measurements, with potential application towards clinically relevant quantitative measurements of metabolism in a heterogeneous population. Our results suggest that lactate imaging may be a sensitive marker of metabolic remodeling in ischemic heart disease.

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). **Acknowledgements:** NSERC, CIHR, MCMM, GE Healthcare, HSF NA7074.