# Hyperpolarized [1-$^{13}$C]-Lactate as a Tool for the In Vivo Investigation of Cardiac Metabolism

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## Introduction

Among its many applications, hyperpolarized [1-$^{13}$C]-pyruvate is used to study cardiac metabolism in healthy and diseased states [1,2]. The fact that lactate has low toxicity and serves as an important energy source for the heart [3] suggests that hyperpolarized lactate might be an alternative substrate for probing heart metabolism. Chen et al. [4] demonstrated the feasibility of both polarizing [1-$^{13}$C]-lactate and detecting its metabolic conversion in vivo. The aim of this work was to apply hyperpolarized [1-$^{13}$C]-lactate to the measurement of cardiac metabolism and compare it to [1-$^{13}$C]-pyruvate as a substrate.

## Materials and Methods

All measurements were performed on a clinical 3T MR scanner (GE Healthcare, Waukesha, WI) equipped with self-shielded gradients (40 mT/m, 150 mT/m/ms). A custom-built dual-tuned ($^1$H/$^{13}$C) quadrature coil ($\varnothing$ =80 mm, length=90 mm) was used for both RF excitation and signal reception. Healthy male Wistar rats (215-368 g) were anesthetized with 1-3% isoflurane in oxygen (~1.5 L/min). The animals were injected in a tail vein with 2.4-3 mL of either a 40-mM [1-$^{13}$C]-lactate or 80-mM [1-$^{13}$C]-pyruvate solution. Hyperpolarization via DNP was achieved using HyperSense (Oxford Instruments Molecular Biotools, Oxford, UK). Blood glucose levels (BGLs) were measured multiple times throughout each experimental session.

A slice-selective pulse-and-acquire free induction decay (FID) sequence with an excitation flip angle of 5.625º was used to acquire $^{13}$C-spectra every 3 s over a 3-min period from a single 15-mm axial slice through the heart. Dynamic metabolic imaging was performed using spiral chemical shift imaging (spCSI) with a nominal isotropic resolution of 5 mm (FOV = 80×80×60 mm$^3$, 16×16×12 matrix, $T_{acq}$ = 4.5 s). A 42-mm axial slab was excited, which comprised the heart and parts of the liver. Twelve data sets were acquired every 5 s starting 5 s after begin of injection.

The undersampled spCSI data were reconstructed as described in [5] with an extra step of apodization and FFT along the slice direction. Time courses and metabolic images of pyruvate (Pyr), lactate (Lac), and bicarbonate (Bic) were calculated by integrating the signal around each peak in absorption mode.

## Results and Discussion

Figure 1 compares the time courses of Pyr, Lac, and Bic acquired with FID after injections of hyperpolarized [1-$^{13}$C]-pyruvate and [1-$^{13}$C]-lactate. Both isotopic exchange and metabolic flux contribute to the conversion between Pyr and Lac as the lactate dehydrogenase (LDH) catalyzed reaction is readily reversible. By contrast, the appearance of Bic reflects flux through pyruvate dehydrogenase (PDH) when Pyr is converted to acetyl coenzyme A via decarboxylation [1]. When lactate was injected, Bic was detected at similar levels as Pyr. With both substrates, the time course of Bic reaches a maximum at around 20 s. However, its subsequent decay appears to be faster with lactate as the substrate. With half of the substrate concentration, the maximum Bic signal after lactate injection was approximately 40-45% of the Bic level after pyruvate injection despite the fact that Lac had to be converted first to Pyr. Note that the signal levels reflect not only the concentration, but also polarization. In phantom experiments the $T_1$ of Lac was measured to be ~40 s compared to ~60 s for Pyr. As the FID data was not localized within the slice, spCSI was performed to better characterize the spatial origin of the hyperpolarized signals. Although the spatial resolution was not sufficient to differentiate between myocardium and blood, the metabolic images of Lac and Bic shown in Fig. 2 demonstrate that the signals from substrate and product were predominantly from the heart.

The [1-$^{13}$C]-lactate sample was prepared using the sodium salt of lactate, which limited the maximum concentration to approximately 40 mM in the final solution. Higher concentrations are possible by preparing the sample using lactic acid. Given the low toxicity of lactate, higher doses than used with pyruvate could be potentially administered in vivo. This could increase the signal level of the products if the reactions are not saturated.

## Conclusion

The presented data demonstrate that bicarbonate as a secondary product of hyperpolarized [1-$^{13}$C]-lactate can be detected in the heart. Therefore, hyperpolarized lactate can be used as an alternative substrate to probe cardiac metabolism.

## References

[1] Merritt ME et al. PNAS USA 2007;104:19773. [2] Schroeder MA et al. PNAS USA 2008;105: 12051. [3] Taegtmeyer H Curr Probl Cardiol 1994; 19:59. [4] Chen AP et al. MRI 2008; 26:721. [5] Mayer D et al. MRM 2009; 62:557.
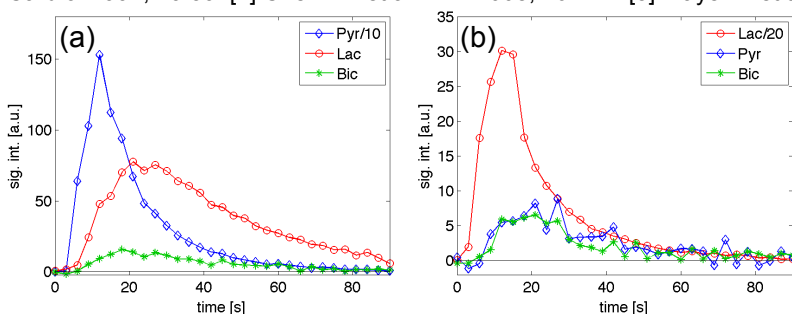
Fig. 1: (a) Time courses of Lac, Pyr, and Bic from a 15-mm slice through a rat heart in vivo after injection of 2.8 mL hyperpolarized [1-$^{13}$C]-pyruvate (BGL = 137mg/dL). (b) Same as (a), but after injection of 2.8 mL hyperpolarized [1-$^{13}$C]-lactate (BGL = 146 mg/dL).
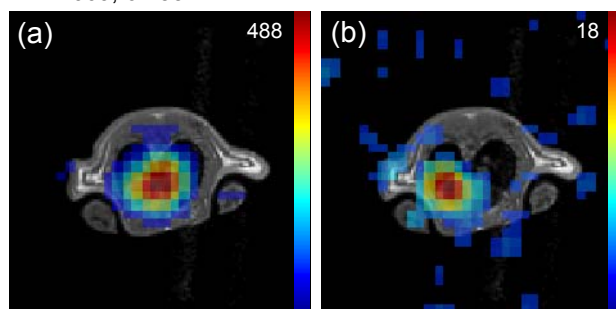


Fig. 2: Metabolic images of (a) Lac and (b) Bic from a slice through the heart acquired with dynamic spCSI after injection of hyperpolarized [1-$^{13}$C]-lactate. The images were averaged over 4 time points (10 to 25 s).