

Compartmentation in the Myocardium: On the Fate of Exogenous Versus Glycolytically Derived Pyruvate

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Target Audience

Researchers studying substrate competition and energy metabolism in the heart as well as users of hyperpolarization technology.

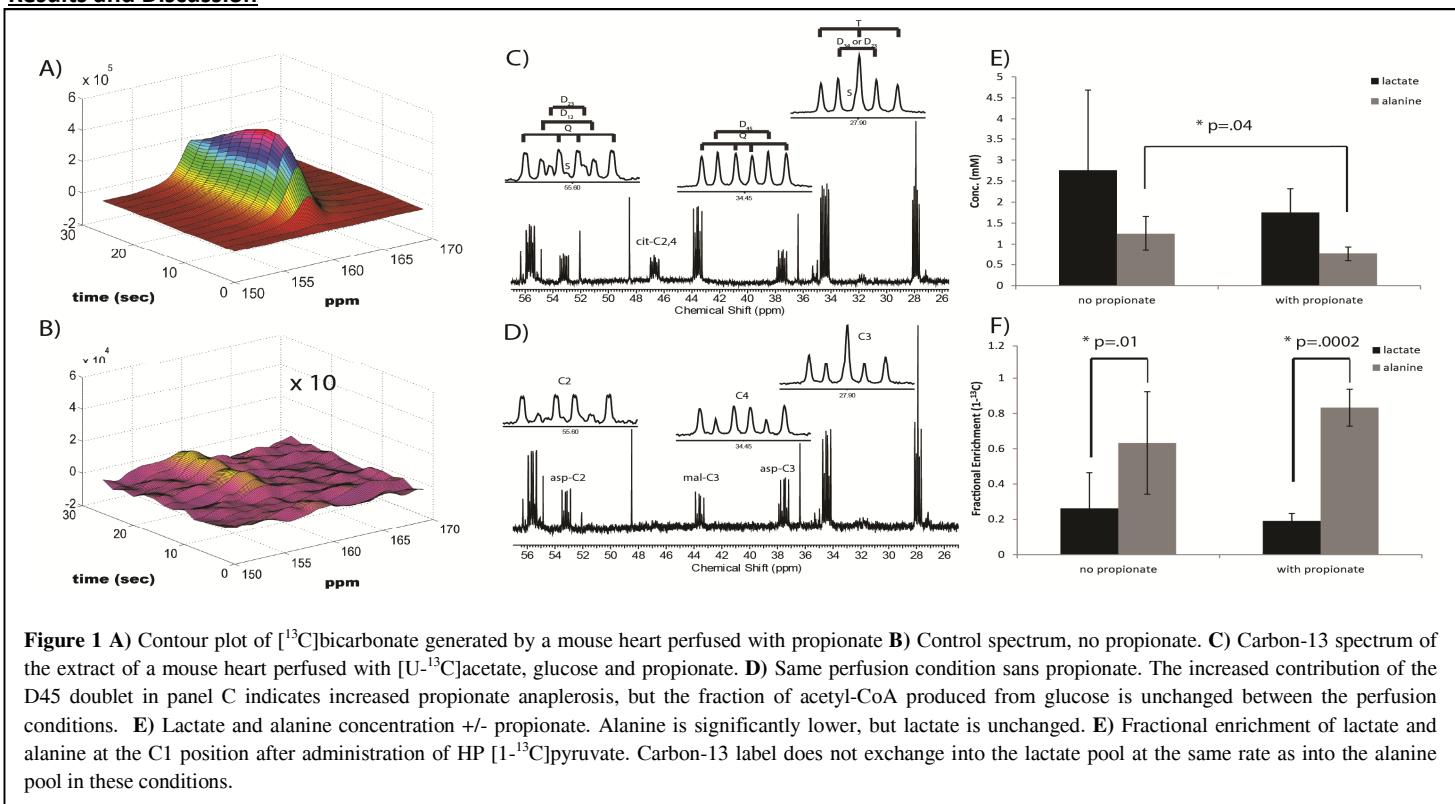
Purpose

The development of hyperpolarized (HP) imaging with ¹³C has largely been driven by a logical connection between the Warburg effect and the appearance of lactate following the injection of HP pyruvate (1). The rationale for imaging the heart is not as clear, as substrate competition between fatty acids, carbohydrates, and ketones will have a large effect on the observed results. A ubiquitous model used for metabolic studies is the glucose perfused heart. Here, the perfused mouse heart is studied in a condition where glucose oxidation is inhibited; nonetheless, pyruvate is avidly oxidized as evidenced by the appearance of [¹³C]bicarbonate when HP [1-¹³C]pyruvate is administered (Figure 1A). This study aims to produce a comprehensive picture of energy metabolism in the mouse heart in the context of substrate competition.

Experimental Methods

[1-¹³C]pyruvic acid was polarized in a HyperSense polarizer. Hearts were excised from fed C57BL/6 mice under general anesthesia and perfused using standard Langendorff methods at 100 cm H₂O and 37°C. A perfusate with 2 mM sodium acetate and 8.25 mM unlabeled glucose was used as a control; the test case included 2 mM propionate as well. Various isotopic labeling schemes were used. HP [1-¹³C]pyruvate was injected and spectra acquired every 2 seconds. Hearts were freeze clamped within 4 minutes of the HP pyruvate injection to minimize changes in the steady-state isotopic labeling patterns. The extracts of the frozen hearts were used for ¹³C NMR isotopomer analysis.

Results and Discussion



After injection of HP [1-¹³C]pyruvate, [¹³C]bicarbonate production was lower in the control condition (Figure 1, A,B), indicating increased PDC flux when propionate is present. Isotopomer analysis indicated that under *both* conditions glucose had a maximal contribution to acetyl-CoA production of 3 % (Panel C,D). Furthermore, propionate lowers the abundance of alanine in the freeze clamped heart while not changing the lactate concentration significantly (Panel E). Finally, the presence of propionate increases the fractional enrichment of alanine derived from the injection of [1-¹³C]pyruvate, but lactate is again unchanged (Panel F). Other experiments show that lactate is preferentially derived from glucose in the perfusate, not from the injected HP pyruvate. A two compartment model of the heart is necessary to explain the observed data.

Conclusions

[¹³C]bicarbonate appearance after injection of HP [1-¹³C]pyruvate is not a proxy of glucose oxidation in the heart. The appearance of HP lactate may underestimate the actual change in [lactate] under certain nutritional conditions.

References

1. Nelson SJ, Kurhanewicz J, Vigneron DB, Larson PE, Harzstark AL, Ferrone M, et al. Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-¹³C]Pyruvate. *Science translational medicine*. 2013;5(198):198ra08. doi: 10.1126/scitranslmed.3006070. PubMed PMID: 23946197.