

ORAL PRESENTATION

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# Real time measurement of myocardial substrate selection *in vivo* using hyperpolarized $^{13}\text{C}$ magnetic resonance

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## Background

Cardiac dysfunction is often associated with a shift in substrate preference and metabolism, but current *in vivo* techniques only provide information on substrate uptake. Hyperpolarized (HP) MR has the unique ability to detect metabolism *in vivo* and is highly specific. To evaluate the prospects for measuring myocardial substrate selection *in vivo*, HP [1- $^{13}\text{C}$ ]pyruvate and [1- $^{13}\text{C}$ ]butyrate were co-infused into rats.

## Methods

Pyruvate and butyrate were hyperpolarized by DNP. After dissolution the samples were automatically infused into fed or fasted animals. Myocardial metabolism was detected using a train of cardiac triggered 30° adiabatic inspection pulses applied every 3 s at 9.4T with  $^1\text{H}$  decoupling. Metabolite ratios were calculated to assess overall consumption of the imaging agents.

## Results

Downstream metabolites of butyrate including ketone bodies  $\beta$ -hydroxybutyrate (BHB) and acetoacetate, acetylcarnitine, butyrylcarnitine, citrate, and glutamate, were observed *in vivo* and affected by fasting (1A) and co-infusion of pyruvate (1B). Pyruvate competed with butyrate for the production of acetyl-CoA as evidenced by changes in the production of bicarbonate (2C), acetylcarnitine (1D,2E), glutamate (1E,1G) and acetoacetate (1C,1F).

## Fed state

Mitochondrial pseudoketogenesis facilitated the labeling of the ketone bodies, and no evidence of true ketogenesis

was observed. The competition presented by butyrate results in a decrease in the bicarbonate signal (2C, 2G). From the perspective of butyrate metabolism, the glutamate (1E, 1G) decreased and the appearance of acetoacetate (1C, 1F) was nearly quenched. The acetylcarnitine increase (1D) and decrease in glutamate and acetoacetate signals were modulations due to competition from pyruvate for the limited number of free CoA units in the mitochondria, and the antiporting of acetoacetate when pyruvate enters the mitochondria.

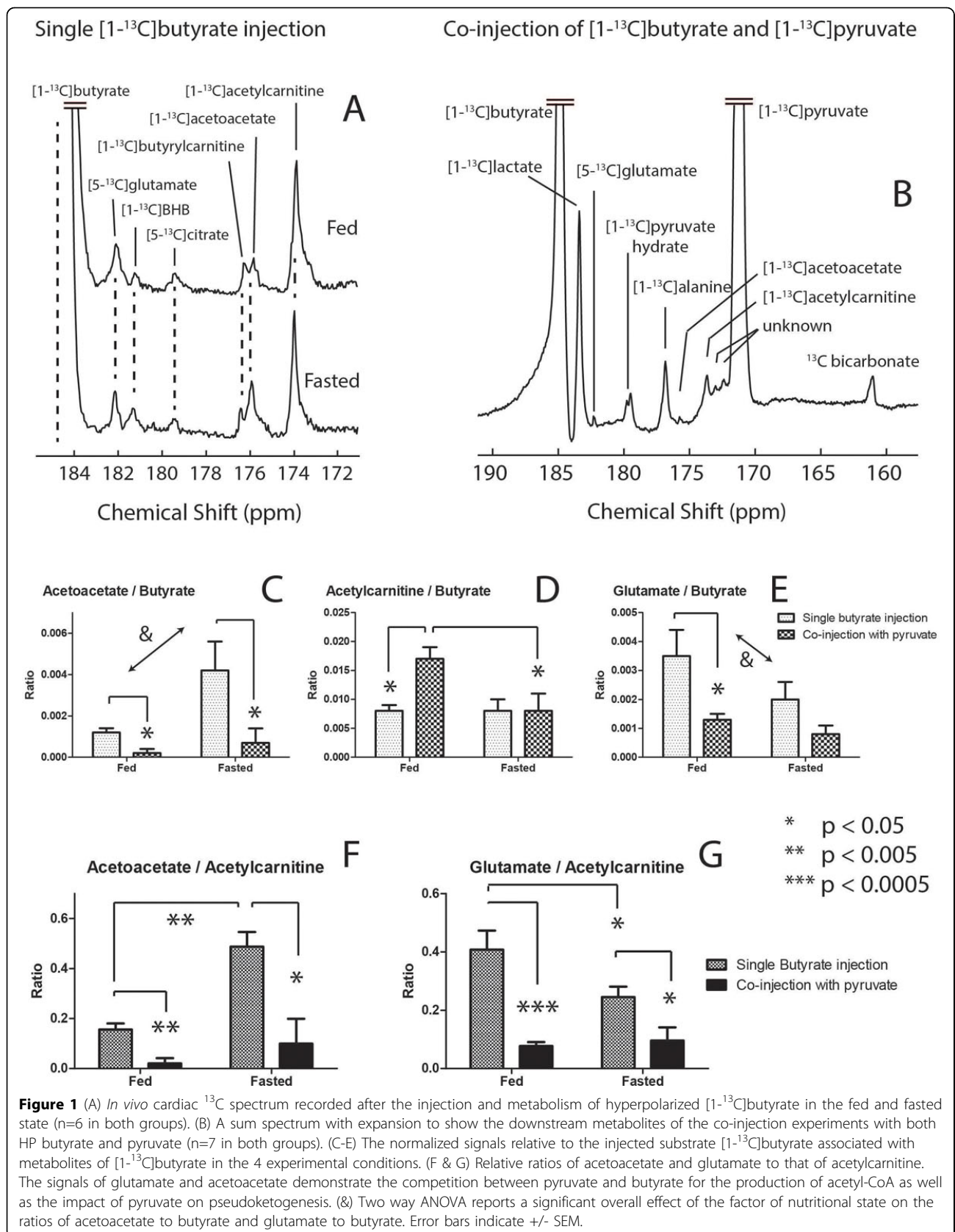
## Fasted state

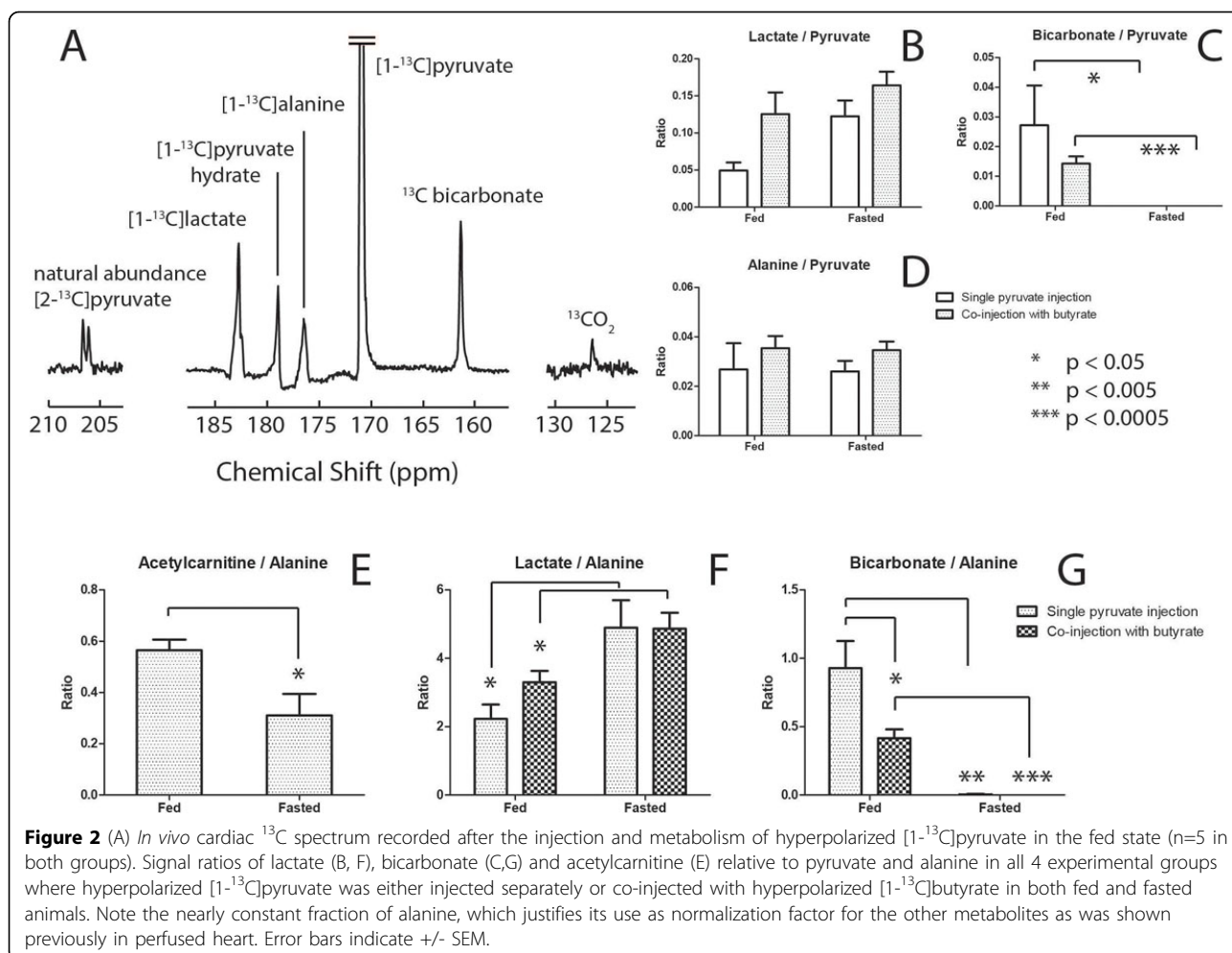
Different enzyme expressions and circulating substrates in the fasted myocardium reduced PDH flux (2C) and increased lactate, interpreted as a redox state increase. Glutamate was lower (1E, 1G) while pool sizes remain unchanged, indicating decreased  $^{13}\text{C}$  labeling. An increase in acetoacetate was observed (1C, 1F). With increased circulating ketones, label exchange into acetoacetate is facilitated, decreasing the fraction of label available for production of acetylCoA and glutamate. Acetylcarnitine (2E) rose and a drop in bicarbonate (2C, 2G) was observed. The change in glutamate to acetylcarnitine ratio decreased significantly upon introduction of pyruvate (1G).

## Conclusions

Pyruvate and butyrate competed for the production of acetyl-CoA and fasting produced logical changes in the observed spectra. Co-infusion of HP metabolic fuels is a one of a kind method for assessing myocardial substrate preference *in vivo*. The combination of HP  $^{13}\text{C}$  technology and co-administration of two separate imaging agents enables noninvasive and simultaneous monitoring of both fatty acid and carbohydrate oxidation in the heart.

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