

Estimates of the Appropriate Pyruvate Dose for Hyperpolarized ^{13}C Cardiac Imaging

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Introduction

Detection of hyperpolarized [$1\text{-}^{13}\text{C}_1$]-pyruvate and metabolic products such as [$1\text{-}^{13}\text{C}_1$]-lactate and $^{13}\text{CO}_2$ in ischemic and reperfused myocardium may provide a fundamentally new diagnostic method in clinical cardiology (1,2). Since blood contains other substrates, the concentration of hyperpolarized (HP) [$1\text{-}^{13}\text{C}_1$]-pyruvate must compete against normally-available substrates for metabolism by the heart (3). Common illnesses and brief fasting cause elevations of plasma ketones and fatty acids (3) and for this reason the effective concentration of pyruvate for ^{13}C cardiac imaging will be sensitive to the condition of the patient. Further, pyruvate at high concentrations may reduce blood pressure (4). The purpose of this study was to determine 1) the threshold concentration of pyruvate needed to compete effectively with other molecules for metabolism in the heart, and 2) the threshold concentration of pyruvate for reduced cardiac function in a standard model for pharmacological studies.

Methods

Hearts were excised from anesthetized Sprague-Dawley rats (300-350 g) and perfused with Krebs-Henseleit medium in a standard working mode (ref. 5, perfusate supplied through the left atrium). Cardiac output, developed pressure, coronary flow and oxygen consumption were measured. The perfusion medium contained substrates mimicking either a "fed" or "fasted" condition. The "fed" mixture contained glucose (10 mM), lactate (1.2 mM), pyruvate (0.12 mM), [$1,3\text{-}^{13}\text{C}_2$]-acetoacetate (0.17 mM), and physiological long chain fatty acids (0.4 mM, all [^{13}C], bound to 3% BSA). The "fasted" mixture contained glucose (4.9 mM), lactate (0.89 mM), pyruvate (0.08 mM), [$1,3\text{-}^{13}\text{C}_2$]-acetoacetate (1.2 mM), long chain fatty acids (total 0.85 mM, all [^{13}C]). Six groups of hearts ($n=3\text{-}5$ in each group) each received a different concentration of [$3\text{-}^{13}\text{C}_1$]-pyruvate to test the effect of varying [pyruvate] on metabolism of fatty acids and ketones. Three additional groups of hearts were exposed to high concentrations of pyruvate (10, 15 or 25 mM) plus "fed" substrates to assess cardiac toxicity. Fatty acid, ketone and pyruvate oxidation was measured by ^{13}C NMR isotopomer analysis of tissue extracts (4).

Results

Under "fed" conditions, fatty acids are the dominant energy source for the heart. As the [pyruvate] increases, its contribution to acetyl-CoA and $^{13}\text{CO}_2$ production increases and oxidation of fatty acids and ketones are both suppressed. At a threshold [pyruvate] of 3 mM, pyruvate effectively suppressed oxidation of both fatty acids and ketones; the contribution of pyruvate to CO_2 production was ~80% (Figure 1). Under "fasted" conditions, ketones are the dominant substrate for metabolism. At 6 mM [pyruvate], the contribution of pyruvate to CO_2 production was about 33% (Figure 2) with persistent oxidation of both fatty acid and ketones. Under steady-state conditions, oxygen consumption, developed pressure and cardiac output were maintained at all [pyruvate] up to 25 mM. However, during the switch to 10, 15 or 25 mM pyruvate there was a transient (~ 1 min) decrease in cardiac output and a smaller decrease in developed pressure.

Conclusions

Pyruvate at 3 mM or higher suppresses oxidation of fatty acids and ketones at physiological concentrations. Under conditions consistent with fasting, diabetes or other states, pyruvate at 6 mM was oxidized at a significantly higher rate but it did not completely suppress oxidation of fats or ketones. Based on these studies, a minimum target [pyruvate] for cardiac exams is about 3 - 6 mM in the coronary arteries. Although transient hemodynamic effects were observed at [pyruvate] > 10 mM, hearts quickly recovered normal oxygen consumption and function even at 25 mM pyruvate.

References

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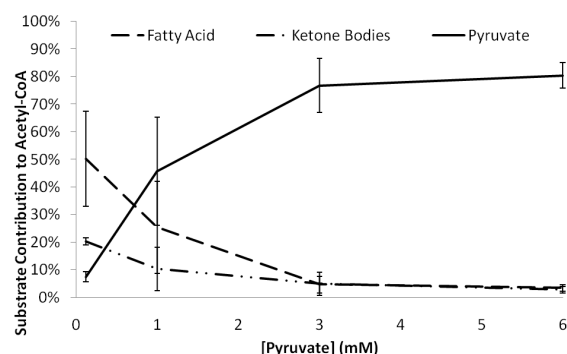


Figure 1. Effect of graded [pyruvate] on oxidation of ketones and long chain fatty acids in the "fed" condition. Results are mean \pm s.d.

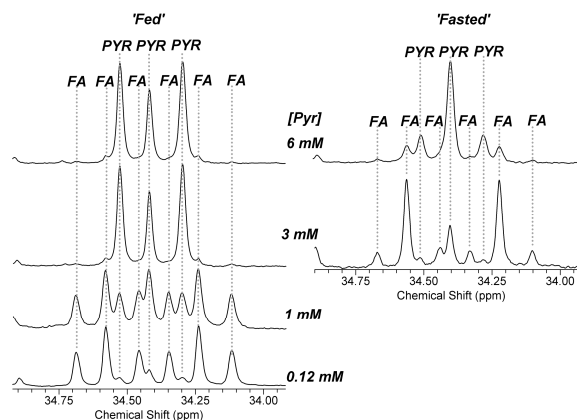


Figure 2. Glutamate ^{13}C isotopomer analysis. Left: ^{13}C spectra of glutamate C4 resonance under "fed" perfusion conditions. Right: "fasted" conditions. As [pyruvate] is increased, its contribution to acetyl-CoA increases and completely suppresses fatty acid oxidation in the "fed" but not "fasted" condition.