

The acute effects of metformin on cardiac and hepatic metabolism: a hyperpolarized [1-13C]pyruvate magnetic resonance spectroscopy study

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Target: Researchers interested in metabolism, hyperpolarized MR and heart disease.

Introduction: Metformin is the most commonly prescribed drug for type II diabetes and reduces the risk of cardiovascular complications from this disease¹. Metformin's mechanism of action is uncertain and contentious, though recent evidence suggests that it alters the cellular redox state, improving glycaemic control by inhibiting the conversion of hepatic gluconeogenic precursors to glucose². Whether metformin also alters cardiac metabolism is unknown, in part because of the difficulty in measuring cardiac metabolism *in vivo*. Hyperpolarized [1-¹³C]pyruvate magnetic resonance spectroscopy can measure flux between pyruvate and lactate with spatial localization to an organ of interest³ and is thus an ideal tool to address this problem. We therefore used hyperpolarized [1-¹³C]pyruvate magnetic resonance spectroscopy to investigate the acute effects of metformin infusion upon cardiac and hepatic metabolism.

Methods: Study design: Wistar rats (n=6-7 per group) were anaesthetised and given an intravenous infusion of either saline (control) or metformin at one of two doses designed to provide pharmacoequivalence with plasma levels typically seen in diabetic patients (10 mg or 50 mg) via a tail vein catheter. Hyperpolarized MR protocol: [1-¹³C]pyruvate acid was hyperpolarized in a prototype hyperpolarizer as described previously³. Pre-polarised pyruvate was administered as a bolus (1 ml of 80 mM solution over 10 s) 45 minutes following the control or metformin infusion. Slice selective spectra were acquired interleaved over the following two minutes from two axial slabs covering the heart and liver (350 μ s sinc pulse, 1 cm thick excitation, 8 kHz bandwidth, 15° FA, TR 1s, both slices ECG gated). Experiments were performed on an Agilent 7 T preclinical scanner with a volume transmit/two channel surface receive array (Rapid Biomedical GMBH). Reconstruction &

Analysis: Multicoil spectra were pre-whitened and added in phase. Spectra from the heart and liver were then temporally summed and quantified in jMRUI using the AMARES algorithm⁴. One way ANOVA with Bonferroni correction for multiple comparisons was used to examine differences between the treatment groups.

Results: As shown in Figure 1, a 50 mg infusion of metformin significantly increased the cardiac [1-¹³C]lactate to [1-¹³C]pyruvate ratio compared to the control infusion (0.13 \pm 0.01 versus 0.09 \pm 0.01, P<0.05) with no change in the cardiac pyruvate dehydrogenase (PDH) flux ([1-¹³C]bicarbonate to [1-¹³C]pyruvate ratio 0.082 \pm 0.008 versus 0.081 \pm 0.007, P=ns). Metformin had no effect upon hepatic [1-¹³C]lactate to [1-¹³C]pyruvate ratio or PDH flux.

Discussion and Conclusions: An acute infusion of 50 mg metformin significantly increased the cardiac [1-¹³C]lactate:[1-¹³C]pyruvate ratio, suggesting an increase in the size of the cardiac lactate pool and/or increased lactate dehydrogenase activity. These findings demonstrate that metformin has a previously unknown effect upon cardiac metabolism, and may reflect the inhibition of cardiac mitochondrial glycerophosphate dehydrogenase. On-going studies will explore the chronic effects of metformin in both control and diabetic animals.

References:

1. UK PDS Group *Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS-34)*. The Lancet. 1998;352:854-865.
2. Madiraju A K, Erion D M, et al., *Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase*. Nature. 2014.
3. Schroeder M A, Cochlin L E, et al., *In vivo assessment of pyruvate dehydrogenase flux in the heart using hyperpolarized carbon-13 magnetic resonance*. Proceedings of the National Academy of Sciences. 2008;105(33):12051-12056.
4. Stefan D, Di Cesare F, et al., *Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package*. Measurement Science and Technology. 2009;20(10):104035.

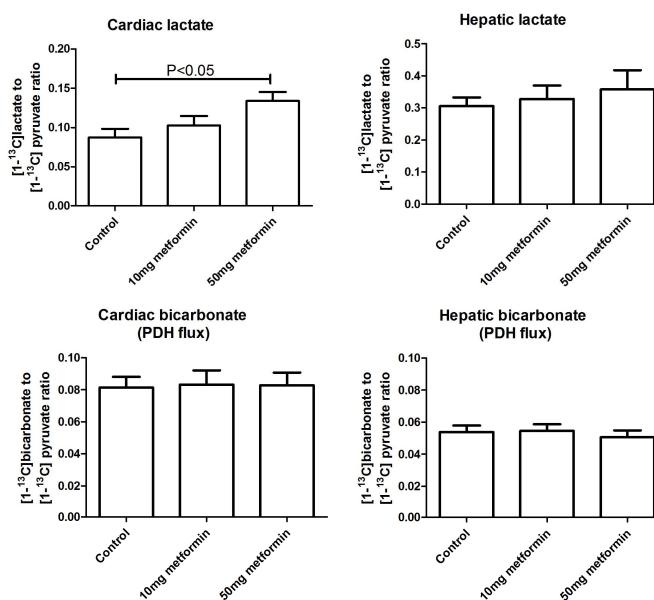


Figure 1: An infusion of 50mg metformin significantly increased cardiac [1-¹³C]lactate to [1-¹³C]pyruvate ratio, without affecting cardiac PDH flux. There was no change in hepatic [1-¹³C]lactate to [1-¹³C]pyruvate ratio or PDH flux.