Regulating Myocardial Metabolism by Infusion of Glucose, Insulin and Potassium in Hyperpolarized [1-^{13}C]Pyruvate MRS Studies

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Introduction: Changes in myocardial metabolism play an important role in the etiology of different cardiac diseases, such as myocardial ischemia and heart failure (1, 2). Under normal conditions the heart utilizes mainly free fatty acids (FFA) for energy production, with little contribution from glucose, especially during fasting when the blood glucose level is low (3). MR Spectroscopy (MRS) with hyperpolarized ^{13}C labelled pyruvate is a sensitive, non invasive method for assessing regional changes in myocardial glucose metabolism (4). The technique can visualize the conversion of [1-^{13}C]pyruvate into [1-^{13}C]lactate, [1-^{13}C]alanine and [^{13}C]bicarbonate through specific enzymes in real time. [^{13}C]bicarbonate is especially interesting because it gives information about the pyruvate dehydrogenase (PDH) enzyme that regulates the conversion of [1-^{13}C]pyruvate to acetyl-CoA, which enters the Krebs cycle for energy production. However, measuring [^{13}C]bicarbonate can be complicated because the PDH activity depends on a constant high glucose availability, which can be difficult to control during in vivo MR-experiments.

The aim of this study was to examine if infusion of a mixture of glucose, insulin and potassium (GIK) after fasting could increase myocardial PDH activity in rats, seen as an increase in [^{13}C]bicarbonate signal after iv injection of hyperpolarized [1-^{13}C]pyruvate. This would optimize the technique, making it more sensitive for assessing changes in myocardial metabolism caused by disease. A similar procedure called the insulin clamp model is used in clinical 18F-FDG PET imaging, for assessing myocardial viability in patients with ischemic heart disease (5).

Methods: Two groups of Sprague Dawley rats were examined. The first group received a high dose of GIK (25mg/kg/min glucose, 5mU/kg/min insulin and 20 mmol/kg/min potassium). The second group received a lower dose (15 mg/kg/min glucose, 3 mU/kg/min insulin and 20 mmol/kg/min potassium). Both groups of rats were scanned three times with hyperpolarized [1-^{13}C]pyruvate: 1) In a fasted state (over night), 2) After one hour of GIK infusion and 3) One hour after end of GIK infusion. Blood glucose and plasma FFA were measured prior to each scan. The MR-experiments were performed on a 4.7T preclinical MR-system (Varian Inc. USA). [1-^{13}C]pyruvate was hyperpolarized using a HyperSense (Oxford Instruments, UK). One mL of 80 mmol/L hyperpolarized [1-^{13}C]pyruvate was injected as a bolus and dynamic ^{13}C-MRS spectra were acquired for 3 minutes with 1 s temporal resolution from a 5 mm long-axis slice using a ^{13}C four channel array coil placed over the heart. Cardiac ^{13}C-MRS spectra were analysed using the AMARES algorithm in jMRUI.

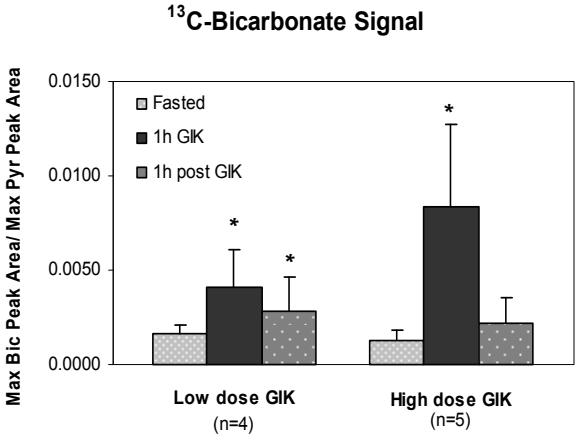

Figure 1: Effect of glucose, insulin and potassium (GIK) infusion on cardiac ^{13}C-bicarbonate MRS-signal in rats. * P<0.05 vs fasted.

Results: The effect of GIK infusion on the [^{13}C]bicarbonate signal is shown in figure 1. In both groups the signal from [^{13}C]bicarbonate is very low after fasting. After one hour of GIK-infusion the [^{13}C]bicarbonate signal increase by 145% in the low dose group and by 558% in the high dose group compared to fasted (a factor 3.85 more in the high dose group compared to the low dose group). One hour post infusion of GIK, the [^{13}C]bicarbonate signal decreased by 32% in the low dose group and by 74% in the high dose group, almost back to baseline level. The increase in [^{13}C]bicarbonate signal were correlated to the blood glucose and FFA levels. No significant change in plasma FFA was observed (Table 1).

Table 1: Blood glucose and plasma FFA levels

	Low dose			High dose		
Parameters mmol/L	**Fasted**	**1h GIK**	**1h post GIK**	**Fasted**	**1h GIK**	**1h post GIK**
Glucose	6.14 ± 1.9	14.98±2.4	7.42 ± 1.5	5.50±0.9	16.97±5.6	8.47±3.8
FFA	1.73±0.66	1.40±0.41	2.33±0.56	1.45±0.70	1.56±0.71	2.05±0.27

Conclusion: This study demonstrate that infusion of GIK can increase the signal from [^{13}C]bicarbonate significantly in cardiac hyperpolarized [1-^{13}C]pyruvate studies. The elevated [^{13}C]bicarbonate signal indicates an increased flux of [1-^{13}C]pyruvate through PDH and a shift of the myocardial substrate preference towards glucose.

In conclusion, regulation of myocardial metabolism by GIK optimizes the hyperpolarized ^{13}C-MRS technique by increasing its sensitivity to assess changes in myocardial metabolism.

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