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CHRONIC HYPOXIA CAUSES NO CHANGE IN CARDIAC PYRUVATE DEHYDROGENASE FLUX IN THE CONTROL OR DIABETIC RAT: AN IN VIVO STUDY

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Introduction In the healthy heart, approximately 30% of the cells' energy comes from glucose oxidation and the remaining 70% from fatty acids. On exposure to hypoxia, the balance is altered, with increased reliance on glycolysis due to reduced oxygen availability.

Pyruvate dehydrogenase (PDH) is the enzyme that stands as the gatekeeper between glycolysis and the Krebs' cycle. It has previously been demonstrated that hypoxia causes increased expression of pyruvate dehydrogenase kinase (PDK) 1, an enzyme that inhibits PDH. Upregulation of PDK1 enhances inhibition, and it can therefore be hypothesised that PDH flux will be decreased.

In the diabetic heart there is a preference for fatty acid use even in the presence of elevated circulating glucose. Exposure to hypoxia and the associated upregulation of glycolysis, may to some extent rebalance fuel selection. However, it is not known if this would be the case as it has also been suggested that the diabetic heart is compromised in terms of its ability to respond to hypoxia.

The advent of hyperpolarized carbon-13 (^{13}C) magnetic resonance spectroscopy (MRS) has enabled the visualisation of metabolism in real-time and *in vivo*. ^{13}C-labelled pyruvate can be injected into an anaesthetised animal in an MRS system, and spectra

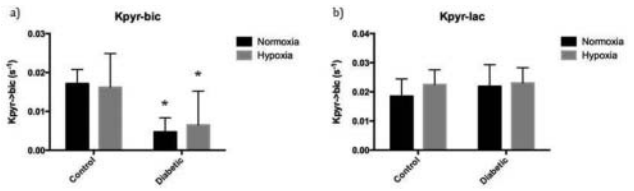

Figure 1 a) Cardiac PDH flux and b) ^{13}C lable transfer to lactate, *P<0.05 compared to controls.

acquired (one per second over one minute) to show the metabolism of pyruvate and therefore the flux through PDH.

Using hyperpolarized ^{13}C MRS, this study has investigated *in vivo* alterations in glucose metabolism in hypoxia in comparison with normoxia, and how these alterations are affected by diabetes.

Methods A rat model of late-stage type 2 diabetes was induced by high fat feeding and injection of streptozotocin (25mg/kg). Diabetic and control (chow-fed) animals (n=8) were housed for 3 weeks either in hypoxia (one week gradual acclimatisation and two further weeks at 11% oxygen) or normoxia. Animals were then anaesthetised and scanned in a 7T MRS system, with an injection of hyperpolarized [1-^{13}C]-labelled pyruvate and cardiac spectra acquired over ~1 min. Animals were terminated after scanning, blood samples taken and tissue samples freeze-clamped for later analysis. Data were analysed using jMRUI and the AMARES package, and the conversion of pyruvate into bicarbonate taken as a measure of PDH flux.

Results There were no alterations in cardiac PDH flux (Kpyr-bic) observed in hypoxic control animals when compared to normoxic controls. There were also no changes in ^{13}C label transfer to lactate (Kpyr-lac). Diabetic animals in both normoxia and hypoxia demonstrated decreased PDH flux when compared to controls, however there was no interaction in terms of PDH flux between the hypoxic and diabetic conditions (Figure 1).

Conclusions We have observed no alteration in cardiac PDH flux caused by three weeks of chronic hypoxia. In addition, whilst there was a significant reduction in PDH flux in diabetes, exposure to chronic hypoxia had no further metabolic effect on PDH flux.