Pyruvate dehydrogenase activation normalises carbohydrate metabolism and diastolic function in the diabetic heart

Lydia Le Page[1], Oliver Rider[2], Andrew Lewis[2], Lucia Giles[1], Vicky Ball[1], Latt Mansor[1], Lisa Heather[1], and Damian Tyler[1]

[1]Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom, [2]Oxford Centre for Clinical Magnetic Resonance Research, Oxford, United Kingdom

Background: The diabetic heart has an increased susceptibility to cardiovascular disease[1] with alterations in cardiac metabolism considered an important contributor. Pyruvate dehydrogenase (PDH) is a key regulatory enzyme in the metabolism of glucose and its activity is reduced in diabetes[2]. Dichloroacetate (DCA) is a potent activator of PDH and it has previously been shown to normalise blood glucose levels in diabetes. However, its effects on *in vivo* PDH flux and the relationship with cardiac function have not been explored.

Aim: To assess cardiac and hepatic PDH flux and cardiac function *in vivo* in a diabetic rodent model following treatment with dichloroacetate.

Methods: Diabetes was induced in male Wistar rats with three weeks feeding of a high-fat diet and an injection of 25 mg/kg streptozotocin. DCA was administered for one month (1mM in drinking water, neutralised to pH 7.2). Subsequently, animals were anaesthetised and placed in a 7 T MRI system. Approximately 30 mg of [1-^{13}C]pyruvic acid doped with 15 mM trityl radical (OX063, GE Healthcare) and a trace amount of Dotarem (Guerbet, France) was hyperpolarized with 30 min of microwave irradiation. The sample was subsequently dissolved in a pressurised and heated alkaline solution, containing 100 mg/L EDTA. This mixture yielded a solution of 80 mM hyperpolarized sodium [1-^{13}C]pyruvate with a polarization of ~30% at physiological temperature and pH, of which 1 ml was administered to the animal over 10 seconds via a tail vein catheter. Hepatic and cardiac spectra were acquired over 1 minute. ^{13}C spectra were referenced to the [1-^{13}C]pyruvate resonance and fitted using the AMARES algorithm in the jMRUI software package. Spectra were corrected for DC offset using the last half of acquired points. ^{13}C-label transfer from pyruvate to bicarbonate was used as a measure of PDH flux. Echocardiography was used to assess cardiac function, with E/E' ratios used as a measure of diastolic function.

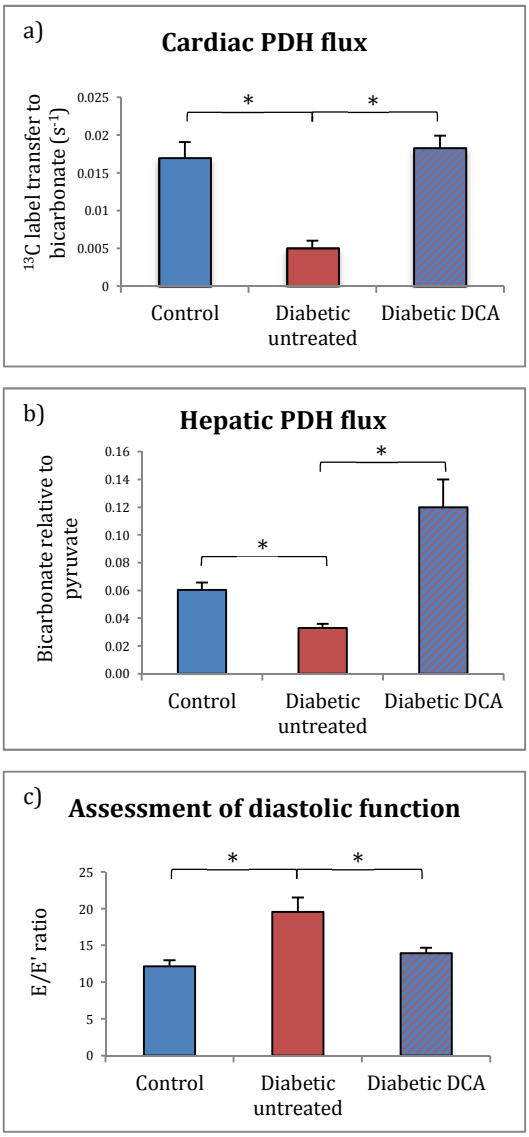

Figure: ^{13}C label transfer from pyruvate to bicarbonate in the a) heart and b) liver. c) Assessment of diastolic function by echocardiography using the E/E' ratio

Results: Treatment with DCA reduced blood glucose and insulin levels, as shown in previous studies. Metabolism of hyperpolarized pyruvate showed a significant reduction in cardiac and hepatic PDH flux in diabetic animals. However, in the diabetic group, DCA restored cardiac PDH flux to control levels and elevated hepatic PDH flux beyond control levels (Figs. a & b). It also reduced epididymal fat pad weight, indicative of whole body fat reduction. Diastolic dysfunction was observed in the diabetic heart; however, it was not seen in diabetics treated with DCA (Fig. c). Increasing E/E' (i.e. worse diastolic function) correlated with decreasing PDH flux ($p=0.003$).

Conclusion: We have shown that treatment with dichloroacetate results in normalisation of both cardiac function and PDH flux in the diabetic heart. This would suggest that activation of PDH is a promising target for the treatment of diabetic cardiomyopathy.

References: [1]WHO, 2013. [2]Seymour and Chatham, J. Mol. Cell. Cardiol. 1997. [3]Stacpoole *et al.*, NEJM, 1992. [4]Mansor *et al.*, Cardiov. Diabetology, 2013. [5]Schroeder *et al.*, PNAS, 2008.