Investigation of *In Vivo* Pyruvate Dehydrogenase Flux in Hypertension Induced Cardiac Hypertrophy

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Introduction: Cardiac hypertrophy is an independent risk factor associated with heart failure and is characterised by significant metabolic adaptation which may underpin functional deterioration [1]. Hypertrophy often occurs secondarily to hypertension, which is exacerbated by dietary excess and obesity. Using the novel technique of dynamic nuclear polarisation, we have investigated the relationship between cardiac structure/function and *in vivo* flux through the pyruvate dehydrogenase (PDH) complex in an experimental model of cardiac hypertrophy exposed to a "western style diet" (with high fat and high sucrose content).

Method: Aortic constriction (AC) was induced surgically in male Sprague Dawley rats (n = 12, ~250 g) under aseptic conditions as described previously [1]. Control animals (CON, n = 12) underwent a sham procedure. The animals' diet was either switched 24 hr post-surgery to a western style diet (45% saturated fat, 16% sucrose) or maintained on standard laboratory chow. Cardiac structure/function and metabolism were then assessed, as described below, on two separate days, 4 weeks post-surgery.

MRS/MRI Protocol: [1-^{13}C]pyruvate was hyperpolarised and dissolved as previously described [2]. Approximately 1 ml of 80 mM hyperpolarised [1-^{13}C]pyruvate was injected into the tail vein of an animal placed in a 7 T Varian MRI scanner. Cardiac localised ^{13}C spectra were collected every second over one minute. Animals were anaesthetised again 48 hr later and cardiac function assessed *in vivo* using cine MRI. Subsequently, animals received a [2-^{13}C]pyruvate scan in the same way as previously described [3]. Data were analysed using jMRUI and fitted to a kinetic model, allowing determination of the rate of DNP labelled [1-^{13}C]pyruvate incorporation into bicarbonate for assessment of PDH flux and [2-^{13}C]pyruvate incorporation into TCA cycle intermediates as a measure of oxidative flux.

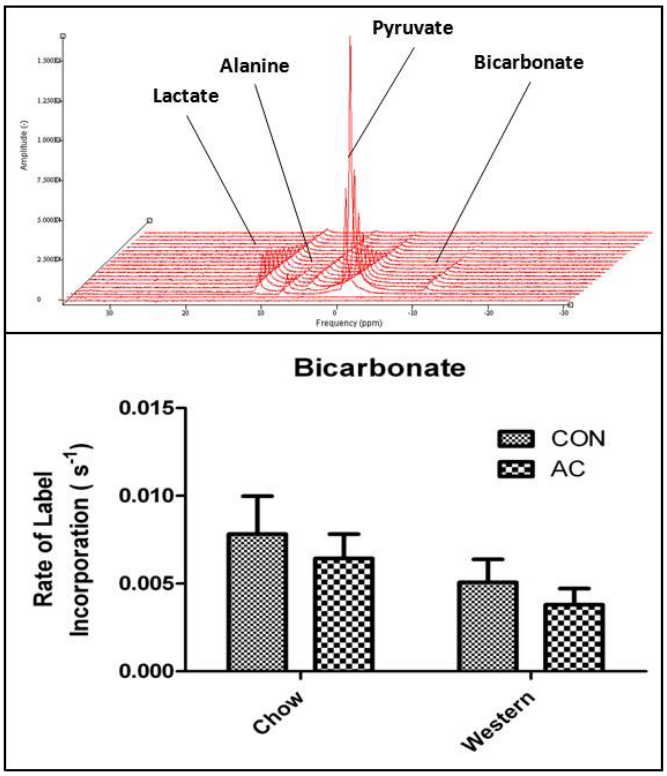

Figure 1: Top – Example time-course of spectra obtained from the *in vivo* rat heart. Bottom – Rate of incorporation of ^{13}C label into bicarbonate as a marker of PDH flux.

Results: 4 weeks post induction of AC, animals demonstrated significantly increased left ventricular mass but showed no alteration in stroke volume, cardiac output or ejection fraction. The increase in cardiac mass was unaffected by dietary intake. There was no apparent alteration in either PDH flux (Figure 1) or the rate of ^{13}C label incorporation into any TCA cycle intermediate at this early time point.

Discussion: Although there was evidence of morphological hypertrophic adaptation at this early 4 week time point, there was no evidence of any metabolic changes. Maintenance of cardiac function in both AC and CON groups are suggestive of a compensated phase of hypertrophy. With an extended duration of hypertrophy, metabolic alterations may become more apparent and could act as prognostic indicators of the severity of cardiac dysfunction. This cohort of animals will be further studied at 9 & 14 weeks post-surgery to examine the development of metabolic alterations in the setting of cardiac hypertrophy.

References: [1] Akki A & Seymour A-ML (2009) Cardiovas Res 81:61-7 [2] Schroeder MA et al (2008) Proc Natl Acad Sci 105: 12501-6, [3] Schroeder MA et al (2009) FASEB J 23: 2529-38

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