ENHANCED GLUCOSE OXIDATION HAS NO EFFECT ON HYPERTROPHIC PROGRESSION IN THE ABDOMINAL AORTIC BANDING MODEL OF LEFT VENTRICULAR HYPERTROPHY

Lucia F Giles[1], Vicky Ball[1], Carolyn A Carr[1], Anne-Marie L Seymour[2], Lydia Le Page[1], Lucy Ambrose[1], and Damian J Tyler[1]

[1]*Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, Oxfordshire, United Kingdom,* [2]*Department of Biological Sciences, University of Hull, Hull, United Kingdom*

Introduction: Left ventricular hypertrophy (LVH) is an independent risk factor in the development of heart failure [1]. LVH initially acts as a compensatory mechanism, but eventually becomes detrimental with the subsequent decline into heart failure characterised by a shift from predominantly fatty acid oxidation towards enhanced glucose utilisation [2]. Despite an increased dependence on glucose utilisation, reduced coupling between glycolysis and glucose oxidation has been observed in the hypertrophied heart which may account for the energy depletion associated with the development of heart failure [3]. Dichloroacetate (DCA) is a potent activator of pyruvate dehydrogenase (PDH) promoting coupling between glycolysis and glucose oxidation. This work aimed to explore whether the treatment of rats with DCA following the establishment of LVH post-abdominal aortic constriction (AC), would restore the coupling between glycolysis and glucose oxidation and attenuate the negative effects of hypertrophy.

Methods: LVH was surgically induced in male Sprague-Dawley rats (AC; n = 22; 200-250 g) following constriction of the abdominal aorta as previously described [1]. Control rats (Sham; n = 18; 200-250 g) underwent the same procedure but without constriction of the aorta. Metabolic, structural and functional parameters were assessed in the heart *in vivo* at 4, 9 and 14 weeks post-surgery using hyperpolarized [1-^{13}C]pyruvate and cine MRI. Approximately 1 ml of 80 mM [1-^{13}C]-labelled sodium pyruvate was injected into an anaesthetised rat via a tail vein cannula. Individual cardiac-localised ^{13}C spectra were acquired every second over a period of 60s and incorporation of the [^{13}C]label into bicarbonate was used as an *in vivo* measure of PDH flux. Cardiac structure and function were subsequently assessed using cine MRI. DCA treatment (0.75 g L^{-1}) was administered in drinking water to a subset of Sham (DCA Sham; n = 7) and AC (DCA AC; n = 11) rats from 5 weeks post-surgery for 13 weeks following the establishment of hypertrophy. Control treated Sham (Control Sham; n = 11) and AC (Control AC; n = 11) rats were maintained on standard laboratory water. Glycolytic flux was also assessed at 18 weeks post-surgery in hearts perfused with [^{3}H]glucose via the Langendorff method.

Results: The development of left ventricular hypertrophy was established in AC rats vs. Sham rats (817±10 mg vs 943±30 mg; $p < 0.0005$) at 4 weeks post-surgery accompanied by no change in PDH flux or label incorporation into lactate. DCA treatment was shown to significantly increase PDH flux in DCA-treated rats compared with Control-treated rats at 9 and 14 weeks (Fig 1; $p < 0.01$) post-surgery irrespective of hypertrophy. However, hypertrophic development was sustained at both 9 and 14 weeks (Fig 1; $p < 0.005$) post-surgery in AC rats irrespective of DCA treatment. Glycolytic flux was significantly enhanced in the AC group relative to the Sham group (Fig 1; $p < 0.05$) irrespective of treatment at 18 weeks post-surgery.

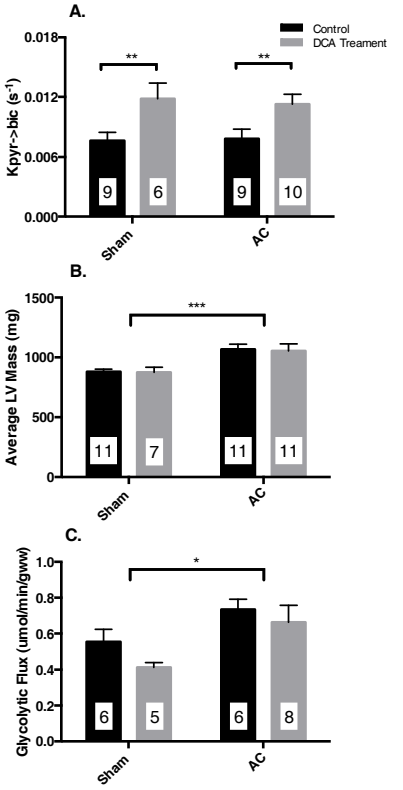

Figure 1 The Effects of DCA Treatment on LVH. A. PDH flux at 14 Weeks Post-Surgery. B. Average LV Mass at 14 Weeks Post-Surgery. C. Glycolytic Flux at 18 Weeks Post-Surgery

Discussion & Conclusions: Consistent with reduced coupling between glycolysis and glucose oxidation, glycolytic flux was increased in the presence of hypertrophy with no associated change in PDH flux. DCA treatment was shown to up-regulate PDH flux *in vivo* promoting coupling between glycolysis and glucose oxidation however, this had no effect on hypertrophic development. This suggests that uncoupling between glycolysis and glucose oxidation may not play a role in hypertrophic progression but further work is required to investigate whether increased coupling between glycolysis and glucose oxidation may prevent the subsequent decline into heart failure. Additionally, immediate treatment with DCA post-surgery may prevent the development of hypertrophy and provides an additional avenue for investigation.

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