

passaging, these results provide useful insights into changes that might happen with age in children resulting from mitochondrial replacement therapy.

P20 **STUDY OF INSULIN CARDIOVASCULAR RESISTANCE IN AN ANIMAL MODEL OF CHILDHOOD OBESITY BY OVER-FEEDING DURING LACTATION**

¹L Guerra- Menéndez, ²S Amor, ²B Martín-Carro, ²D González Hedström, ²A Tejera, ¹B Oltra, ¹R Arriazu, ¹G Diéguez, ²AL García-Villalón, ²M Granado. ¹Departamento de Fisiología, Facultad de Medicina, Universidad San Pablo CEU; ²Departamento de Fisiología, Facultad de Medicina, Universidad Autónoma de Madrid

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Childhood obesity is a pandemic that has become one of the major public health problems of the 21st century. The aim of this work was to analyse cardiovascular insulin sensitivity in an experimental model of early overnutrition.

Male 21-day-old Sprague-Dawley rats were used. On the day of weaning offspring were weighed and sacrificed by decapitation. Hearts were mounted in a Langendorff system whereby increasing doses of insulin were administered (10–10–10–7M). In addition, 2mm rings of aorta were mounted in an organ bath and precontracted with phenylephrine (10–7.5 M). Changes in isometric tension were recorded after addition of cumulative insulin doses (10–8–10–5.5 M) in the presence or absence of L-NAME (10–4M).

On the day of weaning, the body weight of offspring raised in reduced litters was significantly higher than that of control pups. Hearts from overfed offspring showed lower contractility (dp/dt) both at baseline and in response to increasing doses of insulin than controls. Insulin induced greater vasodilation of the coronary arteries in the hearts of offspring from C12 than in offspring from C3. Similarly, the aortic rings from overfed offspring showed decreased insulin relaxation in the aortic rings compared to controls, an effect that was blocked by the preincubation of the arterial rings with the N-oxide synthase inhibitor L-NAME.

Overfeeding during lactation in rats is associated with cardiovascular insulin resistance both in the heart and in the aorta. This fact could be associated, at least in part, with the higher incidence of cardiovascular diseases in individuals with long-standing obesity.

P21 **CARDIAC METABOLISM IN PATIENTS WITH HEART FAILURE WITH MID-RANGE EJECTION FRACTION**

MJ Hundertmark, CT Rodgers, O Rider, S Neubauer, M Mahmood. Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, UK

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Rationale Disturbance in cardiac energy metabolism is a key feature of heart failure (HF). It is unknown whether HF with mid-range left ventricular (LV) ejection fraction (HFmrEF), defined by LVEF 40%–49%, represents a separate clinical entity and whether there are distinct cardio-metabolic changes compared with HF patients with more severely reduced EF (HFrEF – LVEF <40%). We sought to investigate this by assessing myocardial energetics (phosphocreatine-to-adenosine

triphosphate – PCr/ATP) and myocardial triglyceride (MTG) content in both HFmrEF and HFrEF.

Methods 53 subjects (13 HFmrEF, 13 HFrEF and 25 age, sex and BMI-matched controls) underwent cardiovascular magnetic (MR) resonance at 3 Tesla (3T) to assess left ventricular (LV) volumes and function, 31P-MR spectroscopy (MRS) to measure myocardial PCr/ATP, and 1H-MRS to measure MTG content.

Results There were no significant differences in PCr/ATP ratios between the two HF groups (HFmrEF 1.69±0.39 vs HFrEF 1.64±0.41 HFrEF, p<0.05), and both were significantly lower than controls (1.96±0.27, p<0.05). Similarly, MTG was not significantly different between HFmrEF (0.61%±0.39%) and HFrEF (0.71%±0.49%), both significantly higher than in controls (0.42%±0.16%, p<0.05). Interestingly, similar levels of PCr/ATP and MTG changes were observed in both HF groups despite significant differences in LV volumes (HFmrEF 192±45 vs HFrEF 270±92, p<0.001) and EF (HFmrEF 46±3 vs HFrEF 31±6, p<0.001).

Conclusion Our results indicate no differences in energetic and lipid derangement between HFmrEF and HFrEF. This emphasises the need for a new phenotyping model for HF patients based on factors other than LVEF.

P22 **CARDIAC ENERGY METABOLISM INCREASES WITH KETONE OXIDATION**

¹Cher-Rin Chong, ²Mark Cole, ¹Carolyn Carr, ¹Henry Lee, ¹Brianna Stubbs, ¹Azrul bin Abdul Kadir, ¹Rhys Evans, ¹Pete Cox, ¹Kieran Clarke. ¹Department of Physiology, Anatomy and Genetics, University of Oxford, UK; ²School of Life Sciences, University of Nottingham, UK

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Rationale The oxidation of ketone bodies plus glucose improves the efficiency of the working rat heart by ~30% compared to glucose alone.¹ However, perfusions of hearts with ketones alone led to gradual functional decline with reduced flux through α -ketoglutarate dehydrogenase.² We have shown that the rate of d- β -hydroxybutyrate (β HB) oxidation in isolated perfused rat heart increases with the glycogen content via replenishing anaplerotic substrates. Therefore, we aimed to determine whether the availability of glycogen increases the oxidation of ketones and improves myocardial energetics.

Methods Hearts from male Wistar rats (320–360 g) were isolated and perfused with buffer to alter the glycogen content, before perfusion with either 11 mM glucose or 11 mM glucose plus 4 mM β HB. Fully relaxed 31P-MR spectra were acquired at each stage of the protocol to measure pH, PCr, Pi and ATP concentrations ([PCr], [Pi], [ATP]). Results were analysed using 2-way ANOVA with Bonferroni's correction.

Results [ATP] remained constant under all perfusion conditions, irrespective of the cardiac glycogen content. In hearts with high glycogen, addition of β HB increased [PCr] by 41%, from 15.4±0.5 to 21.7±0.5 mM, and Δ GATP by –6.3 kJ/mol (both p<0.001). In low glycogen hearts, addition of β HB did not alter [PCr] or Δ GATP.

Conclusion High glycogen concentrations increased the oxidation of β HB, thereby improving cardiac energetics.

REFERENCES

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