P23 ESSENTIAL BUT PARTIALLY REDUNDANT ROLES FOR POU4F1/BRN-3A AND POU4F2/BRN-3B TRANSCRIPTION FACTORS IN THE DEVELOPING HEART

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Rationale Transcription factors (TFs), which control cardiac gene expression, are important regulators of normal heart development and aberrant expression can contribute to congenital heart defects (CHD), associated with embryonic or neonatal lethality. Brn-3a/POU4F1 and Brn-3b/POU4F2 TFs are expressed in hearts and isolated cardiomyocyte cultures. Studies in injured mouse heart showed that Brn-3b promoted apoptosis if coexpressed with p53 whereas Brn-3a protected against p53 mediated death. Their roles in the developing heart are not known so formed the basis for these studies.
Results Brn-3a and Brn-3b displayed partial compensatory effects in developing mouse hearts because increased Brn-3b in Brn-3a knock-out (KO) hearts supported survival during gestation, whereas double KO mutants (Brn-3a-/-:Brn-3b-/-) showed early embryonic lethality (e9.5). Brn-3a and Brn-3b are highly conserved (>80%) between mouse and zebrafish (ZF) so studies with morpholino oligonucleotides (MO) were used to show that reducing both Brn-3a and Brn-3b caused significant cardiac defects (abnormal looping and valve formation) in double morphants, not seen in single or control morphants. However, increased Brn-3b and its target genes e.g. cyclin D1 in Brn-3a KO mutant hearts during mid-gestation correlated with hyperplastic growth in valve/septum. At later stages, loss of Brn-3a and increased Brn-3b resulted in cardiomyocyte apoptosis, ventricular wall/septal thinning/non-compaction that may contribute to death of Brn-3a KO mutants soon after birth.
Conclusion Our results suggest essential but partially redundant roles for Brn-3a/POU4F1 and Brn-3b/POU4F2 transcription factors (TFs) in the developing heart.

P24 THE FORWARD MYOCARDIAL CREATINE KINASE REACTION IS INCREASED IN OBESITY

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Background Obesity is associated with impaired myocardial energetics (reduced phosphocreatine to adenosine triphosphate ratio (PCr/ATP)). However, LV systolic function is usually preserved, suggesting that the rate of ATP delivery to the contractile apparatus may be maintained. We hypothesised that the forward rate constant of the creatine kinase (CK) reaction would increase to compensate for the reduced substrate pool.
Methods 145 participants across a range of BMIs were recruited. All underwent CMR at 3T to determine LV geometry and function. Group A (75 individuals) underwent 31 P-MRS to assess PCr/ATP. The remaining 70 (group B) – 51 obese (BMI 36.1±5.3), and 19 normal weight (BMI 23.9 ±3.9) – underwent Triple Repetition time Saturation Transfer 31P-MRS to determine CK kf.
Results Body fat mass and PCr/ATP were negatively correlated in group A ($r=-0.457$, $p<0.001$). In group B, there were no differences between LV EDV, mass or LVEF between the groups (all $p<0.05$). CK forward rate constant (kf) was higher in obese participants than normal weight (CK Kf 0.20±0.12 s-1 vs 0.09±0.07 s-1; $p=0.001$). Myocardial CK kf increased in proportion to body fat ($r=0.283$, $p=0.026$).
Conclusions We studied the effect of obesity on CK kinetics in the human heart, and have demonstrated that, despite a fall in PCr/ATP with increasing body fat, the CK reaction rate is higher in obesity than in normal weight. This may reflect a compensatory increase in CK activity to maintain ATP delivery rates and attempt to preserve cardiac function despite a diminished substrate pool.

P25 HEART FAILURE INCREASES MYOCARDIAL S-NITROSYLATION

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The availability of ATP is a limiting factor to cardiac contraction. ATP is predominantly produced by mitochondria via oxidative phosphorylation. Nitric oxide acts as a competitive inhibitor of complex IV and following ischemia, S-nitrosylation has been shown to inhibit complex I activity. Given the established role for nitric oxide in the regulation of oxidative phosphorylation, it is the aim of this study to determine if nitric oxide signalling plays a regulatory role in ATP production in the failing heart.

An ovine tachypaced model of heart failure has been used. 4–6 weeks tachypacing resulted in an increase in left ventricular diameter (3.10±0.06 cm to 4.04±0.13 cm, $p<0.01$, $n=5$) and a reduction in left ventricular contractility (0.47±0.01 to 0.20±0.03, $p<0.01$, $n=5$). Following sacrifice, left ventricular, posterior free wall samples were snap frozen and enriched for S-nitrosylation using resin assisted capture. Samples were quantified using mass spectrometry. 232±18 discrete proteins were identified as nitrosylated in the control myocardium. This increased to 314±28.3 in the heart failure ($p=0.02$, $n=6$). Additionally, 79% of nitrosylated proteins also showed an increase in S-nitrosylation abundance. Several specific sites of S-nitrosylation in heart failure were identified within the electron transport chain; the subunits NDUFS1, SDHA and UQCRH all had a greater than 1 fold increase in nitrosylation in the disease state.

This study is the first to demonstrate a gross increase in the level of myocardial S-NO, and several specific mitochondrial sites of nitrosylation in heart failure. Future work will investigate the functional consequence of nitrosylation at these sites.

P26 INHIBITION OF MITOCHONDRIAL FISSION DECREASED ENDOTHELIAL CELL VON WILLEBRAND FACTOR CONTENT AND GAP JUNCTION COMMUNICATION

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The endothelium is the innermost layer of vascular cells, with a central role in maintaining vascular health. Within endothelial cells, mitochondria play important roles in calcium