(ROS) are known to play a central role in the tissue damage caused by ischaemia-reperfusion injury (IRI), yet the use of antioxidant supplements in large scale clinical trials has been shown to have no beneficial effect and indeed some studies have suggested that the addition of exogenous ROS may decrease infarct size. This suggests that mitochondria may exhibit a biphasic response to ROS, termed mitohormesis, characterised by beneficial effects at low doses and detrimental effects at high doses. To investigate this phenomenon, a tool is required to precisely titrate mitochondrial ROS. MitoParaquat is a novel mitochondria-targeted molecule that redox cycles at complex I to produce superoxide, closely mimicking the production of superoxide as the proximal ROS species *in vivo*. Here it is used to investigate the role of ROS in protection against acute myocardial IRI.

Methods Male C57BL6/J mice aged 8–10 weeks were administered MitoParaquat or vehicle only control by intravenous injection 15 min before the induction of 30 min myocardial ischaemia by ligation of the left anterior descending coronary artery. After 2 hours of reperfusion, infarct size was determined by tripheyltetrazolium chloride staining.

Results MitoParaquat decreased infarct size relative to vehicle only control (42.3±4.3%) at doses of 1 nmol (30.0±4.0%), 100 pmol (22.7±2.3%), and 10 pmol (24.2±2.0%). At 1 pmol, no significant difference from vehicle only control was observed (41.5±8.6%), and at 5 nmol it was found to be lethal. There was no significant difference in the area at risk between any groups.

Conclusions First and foremost, the generation of low doses of exogenous ROS by MitoParaquat is shown to be protective against acute myocardial IRI *in vivo*. MitoParaquat is shown to exhibit a hormetic dose response curve, with protection conferred only in an intermediate dose range with high doses found to be lethal and infarcts from low dose not significantly different from control. Further work is required to determine the mechanism by which this cardioprotection occurs.

209 EVALUATION OF ACUTE CARDIAC DAMAGE IN A PORCINE MODEL OF DEFIBRILLATION

[1]Fiona Rogan*, [2]Rebecca Funston, [1]Brian Meenan, [1]George Burke. [1]*Ulster University*; [2]*HeartSine Technologies*

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Introduction Transthoracic defibrillation is performed to correct life threatening cardiac arrhythmias of the heart, i.e. ventricular fibrillation (VF) and ventricular tachycardia (VT). These are due to chaotic electrical excitation of the heart chambers and loss of coordinated contraction of myocytes that could induce cardiac arrest. Resuscitation guidelines recommend defined defibrillation energies for patient recovery, research indicates that these techniques may cause myocardial damage. However, there is limited information regarding the defibrillation potentially damaging effects on the tissues of the heart at structural and genomic levels. This study investigates the extent of myocardial injury associated with the use of increasing energies (75J, 150J, 200J and 360J) of defibrillation in a porcine model of cardiac arrest using genomic, histological and ultrastructural analysis techniques.

Methodology General anaesthesia was induced in swine models (Ã¢â€ °Ë†10–40 kg) in accordance with The Home Office guidelines. VF was induced and defibrillation administered, each animal receiving 20 shocks at the defibrillation energy protocol at 3 min intervals followed by 6 hour recovery period. Upon completion, animals were humanely euthanised. Cardiac tissues were excised and processed for genomic, histological and ultrastructural analyses and examination.Results: Haemodynamic results demonstrated ROSC occurred in all pigs. Troponin I levels were elevated 3–4 hours after the completion of defibrillation protocol. Gross pathological examination demonstrated no unusual changes. Histological and SEM analysis indicate defibrillation causes changes to the porcine cardiac tissue as evidenced by instances of hypereosinophilia, increased collagen-I deposition and areas of multifocal acute subendocardial, epicardial and myocardial necrosis. qPCR analysis indicates defibrillation induces genomic changes, there was an upregulation in the mRNA expression of structural and inflammation related genes such as Collagen-I, IL-6/18 and MCP1. Hydroxyproline analysis and SEM imaging also illustrated minor changes in collagen content and structural appearance of the tissue, further supported with Image J colour hue analysis.

Discussion The current paradox is cardiac defibrillation depends on the successful selection of energy to generate sufficient current flow through the heart to achieve defibrillation, whilst causing minimal injury to the heart. At this acute timeframe (post protocol), the animal models illustrated biological effects from repeated defibrillation upon cardiac tissues at a structural and genomic level and suggests there is a cardioprotective measure taken by the cardiomyocytes due to electrical overstimulation. In conclusion, these results show repeated defibrillation at increasing energies produces immediate changes to the functional myocardium at a genomic, microscopic and ultrastructural level.

210 SYNDECAN-4/FGF-2/PKCA SIGNALLING REGULATES VASCULAR SMOOTH MUSCLE CELL CALCIFICATION VIA CROSS-TALK WITH TGFB

[1]Samantha Borland*, [1]Shona Borland, [2]Mark Morgan, [3]Sheila Francis, [4]Catherine Merry, [1]Ann Canfield. [1]*University of Manchester*; [2]*University of Liverpool*; [3]*University of Sheffield*; [4]*University of Nottingham*

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Vascular smooth muscle cells (VSMCs) were induced to mineralise with β-glycerophosphate (β-GP). Controls were cultured without β-GP. FGF-2 mRNA (~40-fold increase, P<0.001) and protein (~2-fold increase, P<0.05) expression are significantly increased in mineralising VSMCs. FGF-2 also localises to sites of calcification within human atherosclerotic plaques. The expression of syndecan-4, a heparan sulphate proteoglycan which acts as a co-receptor for FGF-2 signalling, is also increased in mineralising VSMCs (~5-fold, P<0.001) and co-localizes with FGF-2 in human calcified atherosclerotic plaques. Exogenous FGF-2 inhibits VSMC mineralisation (P<0.001) and this inhibition is reduced when syndecan-4 expression is knocked-down using siRNA.

Biochemical inhibition of FGFR signalling using a pan FGFR inhibitor (BGJ398) increases transforming growth factor-β1 (TGFβ1)-induced Smad2 phosphorylation in VSMCs. As TGF β1 increases mineral deposition by VSMCs (~2-fold, P<0.01), the relationship between FGF and TGFβ signalling in VSMC mineralisation was investigated. Inhibiting FGFR signalling using BGJ398 or knocking-down syndecan-4 expression in VSMCs