attached to limbs and using power lab charts ECG monitored and analysed. Following monitoring of rhythm for 24 hours, all animals were sacrificed and myocardial tissue was collected to analyse Pak1 protein.

Results The administration of fingolimod led to significantly better and fast recovery as compared to the control group. The episodes of AF recorded during 24 hours in the treated group was low versus the control group (p0.001). We also investigated Pak1 protein by western blot and immunohistochemistry. Expression of Pak1 observed higher in the fingolimod-treated group(p0.05).

Conclusion Sphingosine 1-phosphate receptor agonist fingolimod plays important role in prevention of AF-related to cardiac surgery by activating the Pak1 pathway.Fingolimod is FDA-approved sphingolipid that can be the potential therapeutic drug for post-operative AF prophylaxis.

Young Investigator Prize

A ENDOTHELIUM-DERIVED EXTRACELLULAR VESICLES PROMOTE SPLENIC MONOCYTE MOBILISATION IN MYOCARDIAL INFARCTION

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Background Following acute myocardial infarction (AMI), monocytes are rapidly mobilised from the spleen to peripheral blood, from where they undergo transcriptional activation and infiltrate injured tissue, with potential to contribute to both injury and repair. The mechanism by which the injured myocardium signals splenic-monocyte mobilisation remains poorly understood. Recent work shows extracellular vesicles (EV, which carry proteins, microRNA/mRNA) are a means of rapid cell-to-cell communication, which, combined with knowledge of their composition and propensity to be taken up by other cells, suggests a possible role in signalling. Here we show that AMI results in a net increase in circulating endothelial cell (EC)-EV that induce splenic monocyte motility *in vivo* and cellular transcription.

Methods Platelet-poor plasma was collected from patients with ST-segment elevation-AMI (STEMI) and mice subjected to AMI. EV were isolated by ultra-centrifugation and analysed for size/number by Nanoparticle Tracking Analysis, western blot (EV-markers: ALIX, TSG101, CD69, CD9 and Hsp70), ELISA for EC markers (CD31, ICAM-1, P-selectin, E-selectin and VCAM-1), electron microscopy and for EV-miRNAs. Human and mouse EC were used *in vitro* to evaluate EV release, injected into wild-type or $CD68^{GFP+}$ naïve mice to assess bio-distribution, splenic-monocyte mobilisation, uptake by monocytes, cellular mRNA transcription and cell motility.

Results Acutely (24 hours) after AMI there is a significant increase in circulating EV in humans ($p<0.01$) and mice ($p<0.001$) that later subsides. Plasma EV number correlates with myocardial injury in humans ($R2=0.52$, $p<0.01$). Plasma EV display EC-surface markers and show enrichment for vascular cell adhesion moleculae-1 (VCAM-1) in AMI ($p<0.05$). *In vitro* pro-inflammatory cytokines significantly increase EV production by EC, whereas 'anti-inflammatory' IL-4 and IL-6 had no effect. Inflammatory-EC-EV displayed significant enrichment of VCAM-1 ($p<0.05$). *In-vitro* labelled EC-EV accumulate in monocytes. Inflammatory-EC-EV significantly enhanced macrophage chemokineses ($p<0.05$) and chemotaxis to MCP-1 ($p<0.05$), a response that was abolished by pre-incubating EC-EV with an anti-VCAM-1 antibody ($p<0.05$). Injected labelled EC-EV accumulate in the spleen, interact with splenic monocytes and induce splenic-monocyte mobilisation and peripheral monocytosis *in-vivo* ($p<0.01$). Human plasma-EV show enrichment for 12 miRNAs in AMI, including EC-associated miR-126–3p/5p. miRNA-mRNA target gene prediction and functional enrichment analysis show roles for these miRNAs in the positive regulation of chemotaxis, cellular growth and proliferation. EC-EV significantly induced alterations in mRNA of motility genes by reducing PLEXIN-B2 ($p<0.001$), a negative regulator of motility and increasing ITGB2 ($p<0.001$) expression in monocytes.

In conclusion (1) AMI surges plasma EV; (2) Plasma-EV protein composition is consistent with EC origin. (3) Injected EV localise to the spleen and (4) mobilise splenic monocytes. (5) In culture, EC increase EV release, enhance monocyte motility and (6) regulate genes that are important in cellular movement. These demonstrate a novel role for EC-derived EV in monocyte activation after AMI.

B MITOCHONDRIAL FUNCTION REGULATES ARTERIAL AGEING IN MICE

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Background Mitochondrial DNA (mtDNA) damage is present in ageing tissues, and may promote loss of tissue function. However whether mtDNA damage or mitochondrial dysfunction is either present in the ageing vasculature or contributes to vascular ageing is unknown.

Objective To determine the time course of functional and structural changes in normal arterial ageing in mice, the effect of vessel ageing on mitochondrial function, and whether decreased or increased mtDNA damage delays or promotes vascular ageing respectively.

Methods and Results Wild-type (WT) C57Bl/6 mice were studied at 8, 22, 44 and 72 wk of age by ultrasound imaging and intra-arterial blood pressure measurements using single and dual pressure catheters to provide a range of functional parameters of arterial ageing. Vascular ageing was detected in WT mice between 22-44wk of age, with reduced carotid arterial compliance and distensibility and increased □ stiffness index (□SI), and increased aortic pulse wave velocity (PWV) (all $p<0.05$). No additional changes were noted between 44-72wk. Aortic collagen content and elastin breaks also increased by 57% and 4-fold respectively (both $p<0.05$) between 22-44wk. Similarly, mtDNA copy number assessed by quantitative PCR decreased significantly between 22-44wk

($p<0.05$) and mitochondrial respiration assessed by a Seahorse flux analyser decreased by 25% ($p<0.05$).

To determine the effects of mtDNA damage, we studied arterial ageing in mice that overexpressed the mitochondrial helicase Twinkle (Tw^+), or with a mutation in the proof-reading ability of the mitochondrial polymerase gamma (PolG). Twinkle expression restored mtDNA copy number with concurrent improvement in mitochondrial respiration. Twinkle expression delayed all physiological parameters of vascular ageing, associated with decreased collagen and elastin breaks ($p<0.05$). In contrast, PolG mice with increased mtDNA damage showed accelerated vascular ageing compared to controls ($p<0.05$).

Conclusions We have identified multiple, reproducible parameters of arterial ageing in mice that are detected at far earlier time points than previously described; in particular, compliance, distensibility and □SI at 44wk provide the earliest discrimination. Arterial mitochondrial function reduces markedly with age, and accelerates vascular ageing, whereas augmenting mitochondrial function delays ageing, identifying prevention of mtDNA damage and dysfunction as a therapeutic target in ageing.

C HYPERPOLARIZED MAGNETIC RESONANCE IMAGING OF CARDIAC INFLAMMATION AND REPAIR

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Myocardial infarction (MI) remains a major killer despite highly optimised systems for the delivery of primary percutaneous coronary intervention (PPCI), highlighting a need for novel therapeutics that could be administered in the days following the event. The healing myocardium undergoes a macrophage driven inflammatory response which is a compelling therapeutic target, though clinical exploration of this process has been limited because conventional imaging techniques cannot assess cellular inflammation in the heart.

We hypothesised that the huge increases in signal-to-noise ratio provided by hyperpolarized MRI could provide a solution to this problem. In rodent models, hyperpolarized [1–13C]pyruvate MRI using a custom designed metabolite mapping sequence *in vivo* demonstrated that experimental MI caused intense [1–13C]lactate signal in healing myocardial segments at both day 3 (paralleling the maximal 'inflammatory' phase of the macrophage response) and also at day 7 ('reparative' phase), compared to sham operated controls. Monocyte/macrophage depletion using clodronate liposomes normalised the [1–13C]lactate signal at both timepoints.

Gene expression analysis of monocytes/macrophages sorted from infarct tissue demonstrated regulation of key enzymes of glycolysis, suggesting that monocyte/macrophage recruitment and metabolic reprogramming of those cells underlies the high lactate signal detected. Hyperpolarized [1–13C]pyruvate MR spectroscopy in macrophage-like cell suspensions confirmed that cellular activation and polarisation almost doubles hyperpolarized lactate label flux rates *in vitro*; blockade of glycolysis with 2-deoxyglucose (2-DG) in activated macrophage-like cells normalised lactate label flux rates and also markedly inhibited production of key pro-inflammatory cytokines at both mRNA and protein level, without major cytotoxicity.

Systemic administration of 2-deoxyglucose following rodent MI normalised hyperpolarized [1–13C]lactate signal in healing myocardial segments and also caused dose dependent improvement in IL-1β expression in infarct tissue, providing proof-of-concept of 'MR visible' immunomodulation. Furthermore, cine MRI demonstrated improvements in myocardial remodelling and systolic function in 2-DG treated rats at 3 months. Finally, we present initial human experience of cardiac hyperpolarized [1–13C]pyruvate MR, demonstrating unprecedented improvements in signal-to-noise ratio and highlighting the potential for rapid clinical translation of these findings.

We conclude that hyperpolarized MRI provides a novel biomarker of cardiac inflammation and repair post-MI by detecting the induction of an immuno-metabolic pathway in cardiac macrophages which controls key inflammatory cytokine production and influences myocardial remodelling. In addition to a role in the development of novel therapeutics to improve remodelling post MI, hyperpolarized MRI may have broad applications in other inflammatory cardiovascular diseases.

D ATHEROSCLEROTIC INFLAMMATION IMAGING USING ^{68}GA-DOTATATE PET VS. ^{18}F-FDG PET: A PROSPECTIVE CLINICAL SUDY WITH MOLECULAR AND HISTOLOGICAL VALIDATION

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Background Inflammation drives atherosclerotic plaque rupture underlying most clinical events. While inflammation can be measured using 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET), 18F-FDG lacks cell-specificity and is unreliable for coronary imaging owing to myocardial signal spillover. Up-regulation of somatostatin receptor-2 (SST2) occurs in activated macrophages offering a novel inflammation imaging target.