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 ($p<0.001$). We also investigated Pak1 protein by western blot and immunohistochemistry. Expression of Pak1 observed higher in the fingolimod-treated group ($p<0.05$).

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 ($R^2=0.52$, $p<0.01$). Plasma EV display EC-surface markers and show enrichment for vascular cell adhesion molecule-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 chemokines ($p<0.05$) 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 $\square$ stiffness index ($\square$ 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