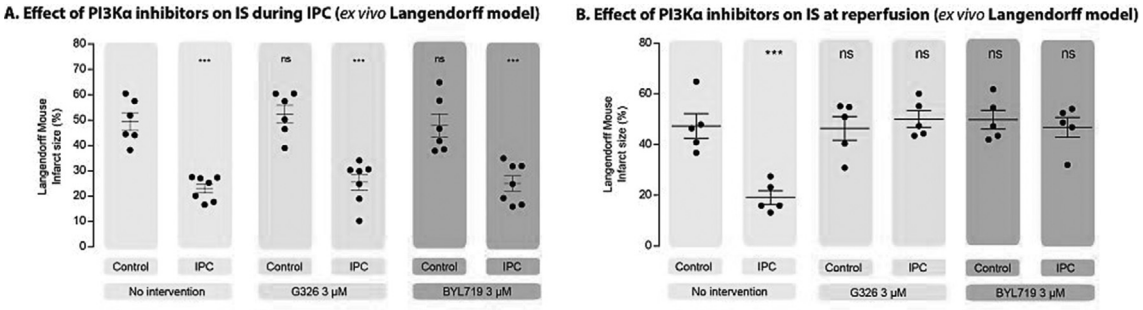
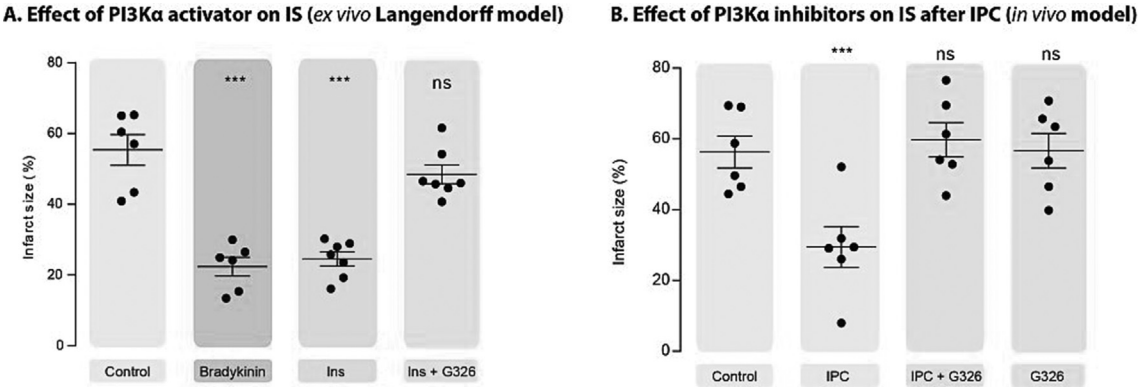


Abstract 193 Figure 1 A. Effect of PI3Ka inhibitors on IS during IPC (*ex vivo* Langendorff model) B. Effect of PI3Ka inhibitors on IS at reperfusion (*ex vivo* Langendorff model)



Abstract 193 Figure 2 A. Effect of PI3Ka activator on IS (*ex vivo* Langendorff model) B. Effect of PI3Ka inhibitors on IS after IPC (*in vivo* model)

194 MITOCHONDRIAL FUNCTION REGULATES ARTERIAL AGEING IN MICE

Kirsty Foote*, Johannes Reinhold, Nichola Figg, Martin Bennett. *University of Cambridge*

10.1136/heartjnl-2017-311726.192

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 ÃƒÅ¸ stiffness index (ÃƒÅ¸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 bSI 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.