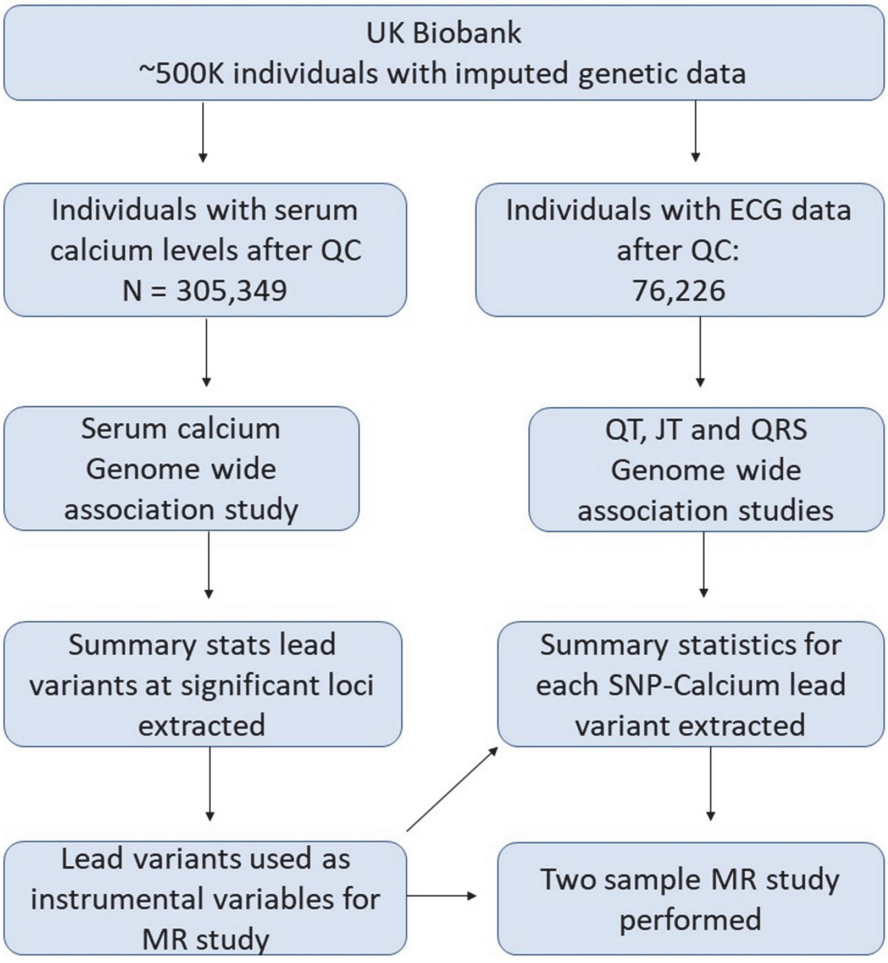

Abstract BS8 Figure 1

Conflict of Interest None

BS9 REGIONAL ALTERATIONS TO THE TRANSVERSE-TUBULE NETWORK IN AN OVINE MODEL OF MYOCARDIAL INFARCTION

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The highly organised transverse tubule (t-tubule) network consisting of invaginations of the cell sarcolemma facilitates synchronous cardiac myocyte contraction. This study aimed to investigate post-myocardial infarction (MI) t-tubule remodelling in infarct border and remote regions in a translationally relevant ischaemia reperfusion injury MI model.

Six adult sheep were used in this study (n=3 MI, n=3 control). Eight weeks after MI, left ventricular tissue was collected from the remote and border MI regions and from control sheep, processed and imaged using 3D scanning electron microscopy. The t-tubule network was manually segmented using 3dmod. One-way ANOVA with Tukey's post-hoc correction, unpaired t-tests or Mann-Whitney U test were used where appropriate.

Marked disorganisation of the t-tubule network was observed in the border region following MI. Quantitative analysis revealed that in comparison to the control sheep myocardium, the MI border zone had a decreased t-tubule count (0.07 ± 0.007 tubules per µm3 in control vs 0.05 ± 0.004 tubules per µm3 in border; p = 0.02) and showed t-tubule dilation (405 ± 22 nm in control vs 533 ± 30 nm in border; p = 0.02). Whilst there was minimal disorganisation and loss of t-tubules in the MI remote region, we observed increased t-tubule length as a fraction of the cell diameter (0.41 ± 0.04 in control vs 0.56 ± 0.04 in remote; p = 0.045). In addition to gross t-tubule remodelling, we also noted post-MI fragmentation of t-tubules, particularly in the border region. In comparison to control, the number of t-tubule fragments per µm3 was increased in the post MI heart (control, 0.17 ± 0.1 fragments per µm3; border, 2.21 ± 0.7 fragments per µm3; remote, 1.20 ± 0.4 fragments per µm3; p = 0.04 border vs control; p = 0.02 remote vs control). The volume occupied by fragments as a percentage of the cell volume was also higher following MI (control, 0.003 ± 0.002 %; border, 0.071 ± 0.023 %; remote 0.014 ± 0.005 %; p = 0.003 border vs control; p = 0.013 border vs remote). Whilst there was no difference in fragments density between the remote and border regions, there was an increase in the volume of cell occupied by fragments in the MI border region compared to remote. This is explained by a larger average fragment

volume in the border region (0.04 ± 0.006 μm3 in border vs 0.01 ± 0.002 μm3 in remote; p < 0.001).

Our research shows remodelling of the t-tubule network in the post-MI sheep myocardium. We noted reduced t-tubule count, t-tubule fragmentation, and dilation of remaining t-tubules. Importantly our work shows that these changes occur in a regional manner, being most pronounced in the border region. These changes may reflect regional wall stresses post-MI, and we speculate that our observations may result in region-specific changes to systolic calcium and contractility post-MI.

Conflict of Interest Authors declare that there is no conflict of interest.

BS10 A CARVEDILOL ANALOGUE, VKII-86, PREVENTS HYPOKALAEMIA-INDUCED VENTRICULAR ARRHYTHMIA THROUGH NOVEL MULTI-CHANNEL EFFECTS

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Background and Purpose Hypokalaemia is the most common electrolyte disturbance with a significant mortality due to the occurrence of ventricular arrhythmia. There is currently no available treatment to prevent ventricular arrhythmia in patients susceptible to hypokalaemia, such as those with heart failure. Potassium supplementation alone is not sufficient to alter mortality. QT prolongation and intracellular Ca2+ loading with subsequent diastolic Ca2+ release via ryanodine receptors (RyR2) are considered the predominant arrhythmogenic mechanisms in hypokalaemia-induced ventricular arrhythmia. We investigated the antiarrhythmic actions of two RyR2 inhibitors: dantrolene and VKII-86, a carvedilol analogue with no β-blocking activity, in hypokalaemia.

Methods Surface ECG and ventricular action potentials (APs) were recorded from whole-heart murine Langendorff preparations. Ventricular arrhythmia incidence was compared in hearts perfused with low [K+], and those pre-treated with dantrolene or VKII-86. Whole-cell patch clamping was used in murine and canine ventricular cardiomyocytes to study the effects of dantrolene and VK-II-86 on AP parameters in normal and low [K+] and the effects of VK-II-86 on the inward rectifier current (IK1), late sodium current (INa_L) and the L-type Ca2+ current (ICa). Effects of VKII-86 on IKr were investigated in HEK-293 cells transfected with KCNH2.

Results Dantrolene significantly reduced the incidence of ventricular arrhythmias induced by low [K+] in explanted murine hearts by 94%, whereas VKII-86 prevented all arrhythmias, p<0.001. VKII-86 prevented hypokalaemia-induced AP prolongation and depolarization of the resting membrane potential (p<0.001) but did not significantly alter AP parameters under normokalaemic conditions. Hypokalaemia was associated with a significant reduction of IK1 and IKr, and a significant increase in INa-L, and ICa. VK-II-86 prevented all hypokalaemia-induced changes in ion-channel activity (p<0.05 in each case).

Conclusions and Implications VKII-86 prevents hypokalaemia-induced arrhythmogenesis by normalising intracellular calcium homeostasis and repolarization reserve. The fact that VKII-86 does not have beta-blocking activity and does not alter AP parameters in normal [K+] is promising for future tolerability and electrophysiological drug safety testing, respectively. This unique pharmacological profile may provide an exciting treatment option in hypokalaemia and other arrhythmias caused by delayed repolarization or Ca2+ overload such as heart failure and the Long QT Syndromes.

Conflict of Interest None

BS11 INHIBITION OF VEGF SIGNALLING MITIGATES THE HEREDITARY HAEMORRHAGIC TELANGIECTASIA-LIKE PHENOTYPE IN ENDOGLIN MUTANT ZEBRAFISH

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Introduction Hereditary haemorrhagic telangiectasia (HHT) is characterised by arteriovenous malformations (AVMs). Large AVMs may affect lungs, liver and brain, whilst telangiectases in mucocutaneous tissues are prone to haemorrhage. HHT type I is caused by loss-of-function ENG mutations. There is growing evidence targeting VEGF signalling is beneficial in HHT. However, VEGF signalling is complex and drives numerous downstream pathways, and it is not clear which are critical to target. We therefore pharmacologically inhibited either global VEGF signalling or components of downstream pathways in zebrafish eng mutants to determine which pathways drive the HHT phenotype.

Methods We studied zebrafish in a Tg(kdrl:Hsa.HRAS-mCherry)s916 background which fluorescently labels endothelial cells. The effect of engmu130 mutation and/or 24hr treatment with VEGF pathway inhibitors on vascular development was quantified by lightsheet fluorescence microscopy in 3d post fertilisation embryos (10-15/group).

Results engmu130 embryos had a significantly enlarged dorsal aorta (DA) diameter (wt 22.3μm ± 0.9μm, mut 26.1μm ± 0.3μm, p<0.01) and posterior cardinal vein (PCV) (wt 25.4μm ± 0.4μm, mut 29.1μm ± 0.4μm, p<0.001). Consequently, blood flow is shunted directly from the DA to the PCV, bypassing intersegmental vessels, recapitulating the AVM phenotype of HHT. Treatment of engmu130 embryos with the VEGF receptor tyrosine kinase inhibitor Tivozanib prevented enlarged major vessels in engmu130 mutants; DA diameter (wt+Tivozanib 21.8μm ± 0.8μm, mut+Tivozanib 23.2μm ± 0.6μm) and PCV (wt+Tivozanib 24.4μm ± 0.4μm, mut+Tivozanib 26.1μm ± 0.6μm). Inhibiting eNOS and p38MAPK had no detectable effect, whilst inhibiting TOR or MEK prevented the enlarged vessel phenotype. Combining subtherapeutic doses of both TOR and MEK inhibitors also prevented vessel enlargement, suggesting synergy between these pathways.

Conclusion The HHT-like phenotype of zebrafish eng mutants can be mitigated by inhibition of the TOR and MEK pathways of VEGF signalling. These represent potential therapeutic targets in HHT.

Conflict of Interest The authors declare that there is no conflict of interest