from explanted aortas ($p<0.05$). Explanted aortas from Nox2-Tg had significantly higher levels of secreted pro-inflammatory cytokine, cyclophilin A (Cypa) at both baseline and after 5 days of in vivo AngII treatment compared to WT littermates. Compared to primary WT EC and VSMC, Nox2-Tg primary EC, but not primary VSMC, had increased ROS production which was accompanied by increased Cypa secretion and ERK1/2 activation. Furthermore, conditioned media from Nox2-Tg EC induced a greater ERK1/2 phosphorylation compared to the media of WT controls. In conclusion, we demonstrate for the first time that a specific increase in endothelial ROS through the over-expression of Nox2 is sufficient to induce aortic dissection in response to AngII stimulation. Endothelial secreted Cypa could be the signalling mechanism by which increased endothelial ROS regulates the inflammatory response and the susceptibility to aortic dissection.

D ENDOTHELIUM SPECIFIC INSULIN RESISTANCE LEADS TO ACCELERATED ATHEROSCLEROSIS: A ROLE FOR REACTIVE OXYGEN SPECIES

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Background Global insulin resistance and endothelial dysfunction have been identified as predisposing factors for atherosclerosis. However, it is unclear whether selective insulin resistance in endothelial cells alone, is sufficient to promote atherosclerosis. We addressed this question by crossing Endothelial Specific Mutant Insulin Receptor Over-expressing (ESMIRO) mice with ApoE$^{-/-}$ mice. ESMIRO mice over-express a human insulin receptor with an Ala-Thr1134 mutation in the tyrosine kinase domain (which disrupts insulin signalling) selectively in endothelial cells under the control of the tie-2 promoter/enhancer.

Methods Male ApoE$^{-/-}$/ESMIRO mice were compared with sex-matched littermate ApoE$^{-/-}$ mice (both on a C57Bl6 background) after feeding a Western-style diet for 12 weeks.

Results ApoE$^{-/-}$/ESMIRO mice were morphologically indistinguishable from ApoE$^{-/-}$ control littermates and showed normal development with no differences between groups in body mass. Heart rate, systolic blood pressure, glucose tolerance, insulin sensitivity and fasting glucose levels were similar in ApoE$^{-/-}$/ESMIRO and ApoE$^{-/-}$ mice. ApoE$^{-/-}$/ESMIRO cultured endothelial cells demonstrated insulin resistance through significantly reduced insulin mediated eNOS activity ($p=0.003$). Aortic lipid deposition along the whole aorta, assessed by en-face oil red O staining, was similar in ApoE$^{-/-}$ESMIRO and ApoE$^{-/-}$ mice (6.4%±0.5% vs 5.8%±0.5%; $p=0.39$). Analysis of lipid deposition along the lesser curvature of the aortic arch revealed a significant increase in ApoE$^{-/-}$ESMIRO when compared to controls (9.4±0.89 vs 12.43±1.19% $p=0.035$). Atherosclerotic lesion area in cross sections of aortic sinus was also significantly increased in ApoE$^{-/-}$/ESMIRO mice compared to ApoE$^{-/-}$ controls (24.8%±2.4% vs 16.6%±2.4%; $p=0.02$). Vascular function assessed through relaxation responses of aortic rings in response to the endothelial specific vasodilator acetylcholine revealed that aortic rings from ApoE$^{-/-}$/ESMIRO mice had blunted relaxation responses to acetylcholine (Emax ApoE$^{-/-}$ 102.88±6, Emax ApoE$^{-/-}$/ESMIRO 65±41%, $p=0.02$), which was restored by the superoxide dismutase mimetic and antioxidant MnTMPyP (Emax ApoE$^{-/-}$/ESMIRO without MnTMPyP 65±41%, with MnTMPyP 112±15% $p=0.048$). Endothelial cells from ApoE$^{-/-}$/ESMIRO mice had significantly increased basal generation of superoxide (1.87-fold increase compared to ApoE$^{-/-}$ $p<0.05$) which was blunted by the selective NADPH oxidase inhibitor gp91ds-tat (11% reduction ±0.02, $p=0.03$) and the non-selective NO synthase inhibitor L-NMMA (6% reduction ±0.01, $p=0.03$).

Conclusions Endothelial specific insulin resistance is sufficient to promote atherosclerosis and increase lesion area in ApoE null mice potentially via the increased ROS displayed in this model. This suggests that enhancing endothelial insulin sensitivity may be an appropriate target to prevent atherosclerosis in insulin-resistant conditions.

E RIGHT VENTRICULAR ORIGIN OF ARRHYTHMIAS IN *SCN5A*+/− MICE IS DUE TO REDUCED NA+ AND HIGHER K+ CHANNEL EXPRESSION AND FUNCTION

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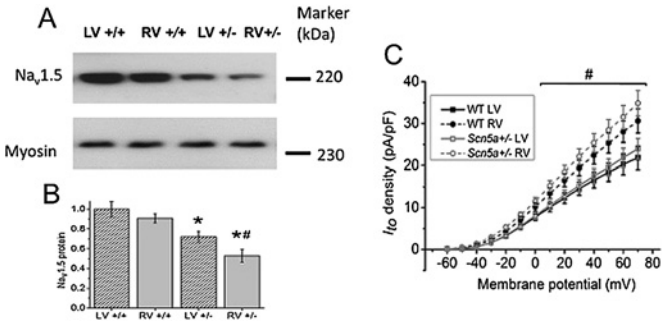
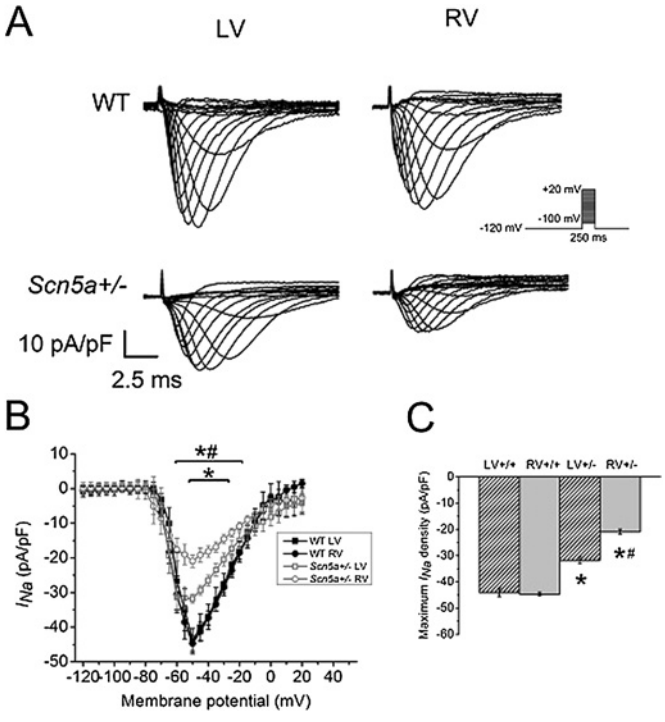
Introduction Brugada syndrome is associated with ventricular tachycardia originating in the right ventricle (RV); this has been



Abstract E Figure 1



Abstract E Figure 2

attributed to either depolarisation abnormalities or increased repolarisation heterogeneities. We have used a heterozygotic *Scn5a*+/− murine model to investigate the underlying mechanisms for the predisposition of the RV to arrhythmias.

Methods and Results $Na_v1.5$ mRNA and protein expression were lower in *Scn5a*+/− than wild-type (WT) hearts, with a further reduction in the RV compared to left ventricle (LV) (Abstract E figure 1A,B, n=4, significant differences: * = WT vs *Scn5a*+/−; # = LV vs RV). There were higher expression levels of $K_v4.2$, $K_v4.3$ and $KChIP_2$ in RV than LV in both groups. Action potential (AP) upstroke velocity was decreased in *Scn5a*+/− (RV: 59.43±2.70 V/s to 30.26±4.03 V/s, p<0.0001, n=20), and furthermore was smaller in RV than LV. AP durations were smallest in the RV of *Scn5a*+/− myocytes. RV transient outward current density (I_{to}) was greater than LV in both WT and *Scn5a*+/− (Abstract E figure 1C, n=17), with similar voltage dependence of activation. Time constants of inactivation were larger in RV than LV, and voltage dependence of inactivation was shifted to more negative values in RV compared to LV, but to more positive values in *Scn5a*+/− compared to WT. Maximum Na^+ current density (I_{Na}) was decreased in *Scn5a*+/−, with a further reduction in the RV (Abstract E figure 2A–C, n=17). Voltage dependence of activation was unchanged, but inactivation was shifted to more negative values in *Scn5a*+/−. Maximum persistent Na^+ current density (I_{pNa}) was decreased in a similar pattern to I_{Na} (RV: −0.30±0.03 pA/pF, n=15 vs −0.17±0.02 pA/pF, n=22, p=0.0009).

Conclusion Our findings show preferential upregulation of the single Scn5a gene in the LV of the *Scn5a*+/− mice compared to RV. The reduced expression of Na^+ channels in RV leads to smaller I_{Na}, resulting in slowed conduction, and smaller I_{pNa}, which in combination with increased I_{to}, results in shorter AP durations and greater heterogeneity of repolarisation, thus suggesting arrhythmogenesis may be initiated by both abnormal depolarisation and repolarisation in the RV of *Scn5a*+/− hearts. Insight into the molecular mechanisms of arrhythmias could prove crucial in planning possible new pharmacological therapies for a disease where the mainstay of treatment is cardioverter-defibrillator implantation.