OVEREXPRESSION OF ENDOTHELIAL INSULIN-LIKE GROWTH FACTOR-1 RECEPTORS (IGF-1R): A NOVEL ROLE FOR IGF-1R IN ENDOTHELIAL FUNCTION AND REPAIR
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Introduction Endothelium-derived nitric oxide (NO) is a critical regulator of vascular homeostasis, repair and regeneration. We recently demonstrated that reducing insulin-like growth factor-1 receptor (IGF-1R) numbers in the endothelium, thereby decreasing the proportion of insulin resistant hybrid receptors, enhances NO bioavailability and increases endothelial cell (EC) insulin sensitivity (Abbas*, Imrie*, Viswambharan* et al. Diabetes 2011;60:2169–76).

Methods To examine the effect of increasing IGF-1R in EC we generated transgenic mice overexpressing the human IGF-1R in EC (human IGF-1R endothelium overexpressing mice (hIGFREO)). Glucose and insulin sensitivity were measured by tolerance testing generated transgenic mice overexpressing the human IGF-1R in EC

Results Increased endothelial IGF-1R numbers had no effect on glucose tolerance or insulin sensitivity in hIGFREO mice compared to wild-type (wt) littermates and fasting plasma glucose, insulin and IGF-1 levels were analysed by ELISA. The response of aortic rings to increasing doses of phenylephrine (PE), generated transgenic mice overexpressing the human IGF-1R in EC (human IGF-1R endothelium overexpressing mice (hIGFREO)). Glucose and insulin sensitivity were measured by tolerance testing and plasma insulin and IGF-1 levels were analysed by ELISA. The response of aortic rings to increasing doses of phenylephrine (PE), with and without L-NNMMA (a NO inhibitor), were measured by DAF fluorescence, the conversion of L-arginine to L-citrulline, and western blotting respectively. Endothelial regeneration was investigated by guide-wire injury of the femoral artery with quantification of Evans-blue dyed denuded area and migration assays were performed in response to VEGF by H&E staining.

Conclusions These data provide the first experimental demonstration that localised β-AR stimulation can produce spatio-temporal synchronisation of SR Ca2+ overload and release in the intact heart and highlight the critical nature of the source-sink balance in the initiation of focal arrhythmias.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY-LIKE PHENOTYPE REVEALED BY ENDURANCE TRAINING IN HETEROZYGEOUS DESMOGLEN2 MUTANTS
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Background Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare cardiomyopathy but significantly contributes to sudden cardiac death in young otherwise healthy patients, especially long durance athletes. 5%–10% of patients with ARVC harbour mutations in the extracellular domains of the desmoglein (Dsg) 2 gene. To assess the role of DSG2 in the ARVC pathomechanism, mice lacking exons 4–6 of the endogenous Dsg2 gene (Dsg2mt) were generated. Homozygous Dsg2mt/mice developed dilatation of ventricles and pronounced fibrosis. Heterozygous Dsg2mt/wt mutants, however, did not show such morphological alterations.

Objective To study whether physical exercise provokes a cardiac phenotype in Dsg2wt/mice they were subjected to endurance training together with wild-type (WT) littermates.

Methods/Results Group swimming training sessions were performed 6 times a week starting with 5 min and gradually incrementing to 90 min/d for 7 weeks. Echocardiography was performed before and after training using a small animal ultrasound unit. Right ventricular (RV) diameters were increased in Dsg2mt/wt mice both compared to pretraining and compared to WT after training. Right ventricular function was also decreased after training compared to pretraining and compared to WT littermates (see Abstract 111 table 1 for values, *p<0.05, d = diastolic, s = systolic, LV = left, RV = right, short axis view, FAC = fractional area shortening, HR = heart rate). Neither left ventricular diameters nor function differed between Dsg2wt/wt and compared to WT after training. Right ventricular (RV) diameters were increased in Dsg2mt/wt mice both compared to pretraining and compared to WT after training. Right ventricular function was also decreased after training compared to pretraining and compared to WT littermates (see Abstract 111 table 1 for values, *p<0.05, d = diastolic, s = systolic, LV = left, RV = right, short axis view, FAC = fractional area shortening, HR = heart rate). Neither left ventricular diameters nor function differed between Dsg2wt/wt