in both groups had medication changed however the ABPM group were significantly more likely to have antihypertensive therapy added at 19.4% vs 1.8% (p=0.0053). Discussion: In a secondary care syncope clinic ABPM is more likely to be performed in patients with a history of hypertension. Despite OH often being due to medication, the need for adequate BP control is important in reducing risk of cardiovascular morbidity. Current ESC guidance targets BP for those aged 65 and over to be under 139/79 if tolerated. In symptomatic OH patients it is crucial to establish accurate blood pressure measurements in order to assess need for additional therapy. This can be provided by a 24 hour ABPM. Management of these patients must balance their symptoms with their comorbidities and target blood pressure control.

Conclusion Using 24 hour ABPM in OH patients can aid clinical decision making in the sub-group with hypertension to guide the need for alteration/ addition of antihypertensive therapy.

Conflict of Interest nil

Young Investigators Award

A THE ENDOTHELUM AS A PARACRINE MODULATOR OF ADIPOSE FUNCTION: A ROLE FOR ENDOTHELIAL IGF-1R IN THE SETTING OF NUTRITIONAL OBESITY

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In obesity the relationship between white adipose tissue expansion and neovascularisation becomes uncoupled leading to inadequate perfusion of adipose tissue. Under these circumstances the secretory profile of adipocytes becomes unfavourable and pro-atherosclerotic.

We hypothesised that reducing endothelial insulin like growth factor 1 receptor (IGF-1R) expression affects adipose tissue remodelling as a result of communication between endothelial cells and adipocytes.

To study the effect of endothelial IGF-1R deficiency, we developed a mouse with inducible endothelial specific IGF-1R deficiency (ECIGF-1RKd). In the context of diet induced obesity, ECIGF-1RKd mice were more insulin sensitive and had increased energy expenditure compared to littermate controls. ECIGF-1RKd mice also had favourable changes specific to the white adipose tissue, including; increased uncoupling protein-1 and vascular endothelial growth factor expression, enhanced endothelial sprouting and greater vascularisation.

The mechanisms underpinning the specific effect of endothelial specific IGF-1R deficiency on white adipose tissue were then explored in more detail. Lineage tracing experiments revealed an altered secretome which caused browning of white adipose tissue, including; increased uncoupling protein-1 and vascular endothelial growth factor expression, enhanced endothelial sprouting and greater vascularisation.

Reperfusion-induced calcium overload profoundly affects the extent of myocardial injury following ischemia, impacting long-term morbidity and mortality. Reactive oxygen species play a crucial role in shaping the amplitude and spatiotemporal patterns of the intracellular calcium signal, but the mechanism governing this interplay remain unclear. Here we show that, in vivo, myocardial ischemia and reperfusion (I/R) potent induce formation of an intermolecular-disulfide within the type I regulatory subunits of protein kinase A (PKARια), both in mice and in humans. This conformation does not increase intrinsic PKA catalytic activity, but rather promotes AKAP-mediated subcellular compartmentalization of PKARια to the lysosome, where it inhibits calcium release from two pore channels and prevents global calcium release from nearby ryanodine receptors. This regulatory mechanism is shown to be crucial for limiting I/R-induced cell death, as ‘redox dead’ Cys17Ser PKARια knock-in mice, which are incapable of undergoing Rια disulfide formation, display substantially larger infarct sizes with concomitant reductions in left ventricular contractile recovery, both of which are prevented by inhibition of lysosomal calcium release at the time of reperfusion. These findings reveal a hitherto unknown role for PKARια, in its disulfide-activated state, to regulate calcium homeostasis and, in this way, potently protect the myocardium from post-ischemic injury.

B OXIDIZED PKARια PROTECTS AGAINST ISCHEMIA-REPERFUSION INJURY BY INHIBITING LYsOSOMAL-TRIGGERED CALCIUM RELEASE

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C IN-VIVO GRAFTING OF LARGE ENGINEERED HEART TISSUE PATCHES FOR CARDIAC REPAIR

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Introduction Engineered heart tissue (EHT) strategies, by combining cells within a hydrogel matrix may overcome the limitations of intracoronary/myocardial cell delivery routes. EHTs regenerate heart muscle in small animal models but data
regarding clinically relevant engineered heart tissue (EHT) patches large enough for first-in-human studies are lacking.

**Methods** An upscaled EHT patch (approx. 3 cm × 2 cm × 1.5 mm) consisting of 15–20 million human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) embedded in a fibrin based hydrogel was developed. A rabbit myocardial infarction model was then developed to test for feasibility and efficacy of EHT grafting.

**Results** The patches began to beat spontaneously within 3 days of fabrication and after 28 days of dynamic culture (late EHTs) contained hiPSC-CMs which were more aligned; showed better contraction kinetics, and faster calcium transients.

We then tested the EHT patch *in-vivo* using a rabbit model. Patches were applied to infarcted hearts (n=14 [n=7 EHT vs n=7 sham]). Sham operations used non-cellular fibrin patches. Blinded echocardiographic analysis revealed a significant improvement in function in infarcted hearts that underwent EHT patch grafting (n=7; absolute difference of 10.04 ± 3.1% over sham group; fractional area change, P<0.001).

In-vivo telemetry recordings (n=5 MI/sham vs n=7 MI/EHT) indicated that no clinically relevant arrhythmia was seen in the MI/EHT group and arrhythmia provocation protocols (ex vivo n=5 MI/sham vs n=6 MI/EHT) confirmed that the patch was not pro-arrhythmic (arrhythmia inducibility score 5.6 ± 1.0 [MI/patch] vs 5.0 ± 0.6 [MI/sham]; p=ns).

**Conclusion** An upscaled clinically relevant EHT patch was developed and improved function in infarcted hearts without causing arrhythmia. Therefore EHT may have specific advantages over the direct intramyocardial injection of cells.

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**Abstracts**

**DIABETES MELLITUS GENERATES THE SUBSTRATE FOR ATRIAL FIBRILLATION BY CAUSING A LOCALISED CONDUCTION BLOCK**

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**Introduction** Diabetes mellitus (DM) is an important risk factor for atrial fibrillation (AF) – the most common heart rhythm disorder. However, the mechanisms underlying this association are poorly understood. In addition, patients with DM often have comorbidities, such as obesity, hypertension, dyslipidaemia, that are also independently associated with increased risk for AF. The aim of this project was to explore whether prolonged hyperglycaemia alone is sufficient to increase the risk of AF.

**Methods** Multiple low-dose (50 mg/kg over 5 days) intraperitoneal injections of streptozotocin were used to induce DM in C57BL/6 mice. After 12 weeks of DM, left ventricular (LV) systolic and diastolic function was characterised using echocardiography. In *vivo* atrial electrophysiological properties and arrhythmia inducibility were assessed using transesophageal atrial pacing. Atrial conduction time and action potential duration (APD) and conduction velocity were measured by optical mapping of isolated atria.

**Results** Diabetic mice had significantly higher probability of *in vivo* AF induction (15±3% vs. 6±1%, in controls, p=0.005, n=24–26/group), atrial ECG conduction abnormalities (longer PQ interval in diabetic mice: 44±1 ms vs. 39±1 ms in controls, p=0.001, n=24–26/group), but without any changes in the P wave duration, RR, QRS or QT intervals. Diabetic mice developed modest LV diastolic dysfunction (tissue Doppler E'/A' 1.02±0.05 vs. 1.20±0.06 in controls, p=0.04, n=11–12/group), but no LV systolic dysfunction. In addition, diabetic mice also had larger relative LA size (LA area/body weight 0.28±0.01 mm²/g vs. 0.23±0.01 mm²/g in controls, p=0.001, n=11–12/group). Optical mapping revealed a two-fold greater conduction time in diabetic left atria (LA) (39±3 ms vs. 22±2 ms in controls, p=0.0006, n=6/group), without differences in the right atrial (RA) conduction time. The APD was not significantly different in RA or LA. The regional analysis of optical mapping recordings demonstrated a significant decrease in the conduction velocity in the medial part of the RA resulting in increased conduction wavefront roughness in the LA. Finally, the medial part of the diabetic RA also had a significantly higher total collagen content (5.5±0.5 μg/mg vs. 9.1±0.6 μg/mg in controls, p=0.0002, n=9–11/group), and a decrease in the connexin 43 levels (0.92±0.05 vs. 0.66±0.04 in controls, p=0.001, n=7–8/group), with no significant changes in other parts of the atria.

**Conclusions** Prolonged hyperglycaemia alone is sufficient to cause pathological remodelling making atria more susceptible for AF. Diabetic hearts also have modest LV diastolic dysfunction, relative LA enlargement, but no LV systolic dysfunction. In this study, we provide evidence of a novel mechanism where localized (rather than global) atrial fibrosis in a critical area causes a focal conduction defect and predisposes diabetic mice to AF.

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**MACHINE LEARNING WALL THICKNESS MEASUREMENT IN HYPERTROPHIC CARDIOMYOPATHY EXCEEDS PERFORMANCE OF WORLD EXPERTS**

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