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) showed the development of several mature characteristics when compared to early patches (<14 days from fabrication). 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<0.01).

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.

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

Klemen Ziberna*, Alexandra S Mighiu, Alice Recalde, Barbara Casadei, Ricardo Carnicer. *Radcliffe Department of Medicine, Division of Cardiovascular Medicine, University of Oxford, Oxford, UK*

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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 transoesophageal 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 mm^2/g vs. 0.23±0.01 mm^2/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±0.4 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.

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

[1,2]João B Augusto*, [1,2]Rhodri Davies, [1,2]Anish Bhuva, [1,2]Kristopher Knott, [1,2]Andreas Seraphim, [1,2]Mashael Al-Farih, [1,3]Clement Lau, [1,2]Rebecca Hughes, [1,2]Luís Lopes, [1]Hunain Shiwani, [4,5]Bernhard Gerber, [6,7]Christian H Craig, [8,9]Ntobeko Ntusi, [10]Gianluca Pontone, [11]Milind Y Desai, [12]John P Greenwood, [12]Peter P Swoboda, [2]Gabriella Captur, [13,14]João Cavalcante, [15]Chiara Bucciarelli-Ducci, [1,3]Steffen E Petersen, [16,17]Erik Schelbert, Charlotte Manisty [1,2], [1,2]James C Moon. *[1]Cardiac Imaging Department, Barts Heart Centre, St Bartholomew's Hospital, London, UK; [2]Institute for Cardiovascular Science, University College of London, London, UK; [3]William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, UK; [4]Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires St. Luc UCL, Woluwe St. Lambert, Belgium; [5]Pôle de Recherche Cardiovasculaire (CARD), Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium; [6]The Prince Charles Hospital, Brisbane, Queensland, Australia; [7]University of Queensland and Griffith University School of Medicine, Queensland, Australia; [8]Division of Cardiology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa; [9]Cardiovascular Magnetic Resonance Congress of South Africa, Cape Town, South Africa; [10]Cardiac Department, Centro Cardiologico Monzino, Milano, Italy; [11]Heart and Vascular Institute Cleveland Clinic Foundation Cleveland OH; [12]Multidisciplinary Cardiovascular Research Centre and Division of Biomedical Imaging, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK; [13]Minneapolis Heart Institute, Department of Cardiology, Abbott Northwestern Hospital, Minneapolis, Minnesota; [14]Valve Science Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; [15]Bristol Heart Institute, Bristol National Institute of Health Research (NIHR) Biomedical Research Centre, University Hospitals Bristol NHS Trust and University of Bristol, Bristol, UK; [16]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [17]Cardiovascular Magnetic Resonance Center, UPMC Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania*

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