Abstract B54 Figure 1

B55 **DIABETIC CARDIOMYOPATHY IS ASSOCIATED WITH LOSS OF ENDOTHELIAL GLYCOCALYX IN CORONARY MICROVESSELS AND ANGIOPOIETIN 1 RESTORES ENDOTHELIAL GLYCOCALYX AND CORRECTS CARDIAC FUNCTION**

¹Yan Qiu*, ¹Raina Ramnath, ¹Sophie Jenner, ¹Sarah Fawaz, ²Kenton Arkill, ¹Chris Neal, ¹Paul Verkade, ³Stephen White, ¹Andrew Salmon, ¹M.-Saadeh Suleiman, ¹Gavin Welsh, ¹Rebecca Foster, ¹Paolo Madeddu, ¹Simon Satchell. ²University of Nottingham; ³Manchester Metropolitan University

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Introduction Endothelial glycocalyx (eGlx) contributes to the microvascular permeability barrier and its dysfunction correlates with albuminuria in diabetic nephropathy. Albuminuria is a potent risk factor for cardiovascular disease. We therefore hypothesised that coronary microvascular eGlx damage also occurs in diabetic cardiomyopathy (DCM).

Methods Diabetes was induced in FVB mice with streptozotocin (STZ). DCM was assessed with echocardiography by E/A ratio. A group of diabetic FVB mice received Angiotensin 1 (Ang1) after DCM development.

Results FVB mice developed DCM at 7 weeks post STZ injection. Labelling with MAL-I, a specific lectin that binds to eGlx, was reduced in diabetic heart capillaries (DCM vs. ctrl: 1.64±0.27 vs. 2.70±0.27). Electron microscopy of diabetic heart capillaries showed decreased eGlx depth (DCM vs. ctrl: 14.54±0.79 vs. 27.88±5.82nm), increased perivascular space (DCM vs. ctrl: 2.08±0.22 vs. 0.54±0.11fold) and thickened endothelial cells (DCM vs. ctrl: 0.30±0.04 vs. 0.22±0.01µm).

Partial depletion of eGlx in rat hearts with the combination of heparanase and chondroitinase led to decreased cardiac output (enzymes vs. ctrl: 63.47±10.14% vs. 91.68±9.82%).

Ang1 improved diastolic function of FVB mice with DCM (DCM vs. DCM+Ang1: 1.05±0.08 vs. 1.35±0.09 fold relative to pre-treatment). In Ang1-treated diabetic mice, eGlx thickness in heart capillaries (DCM vs. DCM+Ang1: 13.87±0.87 vs. 24.55±2.02nm) and eGlx coverage (DCM vs. DCM+Ang1: 48.08±3.07% vs. 82.44±5.43%) were improved, and

the increased perivascular space due to oedema in DCM normalised (DCM vs. DCM+Ang1: 2.08±0.13 vs. 0.23±0.03fold). **Conclusion** We have shown DCM development is associated with eGlx damage and that injury to eGlx impairs cardiac function. Recovered heart function with Ang1 treatment parallels reversal of eGlx loss. As such, correction of eGlx damage may have therapeutic potential for DCM and other diabetic vascular complications.

Conflict of interest None

B56 **ENDOTHELIAL-SPECIFIC ERG DELETION LEADS TO DRAMATIC REDUCTION IN CARDIOPULMONARY FUNCTION**

¹Neil Dufton*, ¹Mohamed Bellahcene, ²Alex Sardini, ¹Graeme Birdsey, ¹Michael Schneider, ¹Anna Randi. ¹Imperial College London; ²MRC

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Heart and lung function work in partnership to maintain cardiovascular and tissue homeostasis. Endothelial (EC)-specific transcription factor ERG is a master regulatory of EC lineage and homeostasis expressed in all vascular beds. We have shown that loss of ERG expression leads to endothelial dysfunction and tissue fibrosis in mouse. Furthermore, we have established ERG loss as a hallmark of patients with chronic disease, such as atherosclerosis and end-stage liver disease. In this study we aimed to determine the functional impact of chronic EC dysfunction on the cardiopulmonary system.

Methods 6-week-old VEC-iCre Erg-fl/fl mice were treated with tamoxifen i.p. to induce EC-specific deletion (ErgiEC-KO); mice were profiled longitudinally for 30 days compared to littermate control mice (Ergfl/fl). We assessed cardiac function by electrocardiography (ECG), recorded in conscious mice twice a week using the ECGenie platform, and echocardiography (Echo) at day 14 and 30. Tissue structure and endothelial profiling was assessed by immunohistochemistry in both heart and lung tissue. In a second set of experiments we treated mice ErgiEC-KO with tamoxifen for 14 days prior to trans-

Abstract BS6 Figure 1

verse aortic constriction (TAC) to induce elevated cardiovascular load.

Results ECG measurements revealed that ErgiEC-KO had significantly reduced heart rate and lengthened cQT interval occurring from one week after ERG-deletion. Echo showed significantly reduced ejection fraction and fractional shortening in ErgiEC-KO. Tissue profiling at day 30 post-tamoxifen found a significant increase in ErgiEC-KO heart/body weight ratio. Immunohistochemistry revealed significant cardiomyocyte hypertrophy together with increased SMA and pSMAD3 in all regions of the heart. We observed significant thickening of the right ventricular wall, in line with signs of inflammation, fibrosis and haemorrhage in lung tissue from ErgiEC-KO. Interestingly, phenotypic changes in pulmonary microvascular EC were homogeneous while cardiac microvascular EC had geographical and subset-specific variations. TAC surgery resulted in all ErgiEC-KO reaching endpoint within 28 days (n=5) with significant heart dilation and reduced cardiac function. Notably all ErgiEC-KO exhibited severe inflammation and loss of lung structure. (Figure 1)

Conclusion Systemic deletion of EC-specific ERG significantly influences the microvascular profile, structural integrity and

function of cardiopulmonary system. This study highlights that impaired EC functional can rapidly influence ventricular repolarisation and cardiac function. Furthermore, we uncover that chronic EC dysfunction in ErgiEC-KO causes systemic mechanisms and organotypic phenotypes affect the heart and lung emphasizing the role of the endothelium in regulating cardiovascular function.

Conflict of interest No

BS7

ANGIOTENSIN-(1-9) INHIBITS NEOINTIMA FORMATION IN A MURINE VEIN GRAFT MODEL AND MODULATES ERK1/2 PHOSPHORYLATION AND MICRORNA-132 PATHWAYS IN HUMAN VASCULAR SMOOTH MUSCLE CELLS

¹Stacy Robertson*, ¹Stuart Nicklin, ¹Clare McKinney, ¹Lisa McArthur, ¹Christian Delles, ¹Graeme Milligan, ¹Simon Kennedy, ²Andrew Baker. ¹University of Glasgow, ²University of Edinburgh

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Introduction Vascular smooth muscle cell (VSMC) migration is integral to vascular remodelling in acute vascular injury.