Results In T2DM but not non-diabetic cells, IL-6 significantly elevated OCR and this was not associated with any significant difference in levels of IL-6-stimulated JAK-mediated STAT3 phosphorylation in cells from T2DM versus non-diabetic patients. However, the JAK1/2 inhibitor, ruxolitinib (0.1 μM) significantly abolished this IL-6-stimulated increase in OCR of T2DM. Also, IL-6 elevated ECAR in both T2DM and non-diabetic cells via a ruxolitinib-dependent mechanism. Same pattern was observed in response to HSV-SMC mitogen PDGF.

Conclusion Data from this study suggest that T2DM alters HSV-SMCs metabolic responses to proinflammatory stimulus IL-6 and mitogen PDGF. This alteration was abolished by ruxolitinib which suggests a JAK-mediated modulation of mitochondrial function of HSV-SMCs, hence a potential therapeutic target in T2DM-induced vein graft failure. Conflicts of interest: None

BS6

DECIPHERING THE LOCAL IMMUNE LANDSCAPE IN ATRIAL FIBRILLATION: THE ROLE OF TISSUE-RESIDENT T CELLS

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Abstract BS6

Introduction Systemic markers of inflammation strongly correlate with an increased risk of atrial fibrillation (AF). However, the local immune drivers of this increased AF risk remain poorly defined. Recently, a wealth of imaging data has established the volume of adipose tissue overlying the heart, epicardial adipose tissue (EAT), as an independent risk factor for all forms of AF. However, the immune profile of EAT driving this increased AF risk again remains undefined. Currently, human tissue studies are sparse with patients typically poorly matched for baseline clinical characteristics. This study sought to systematically define the immunological signature of EAT in a propensity-matched cohort of cardiac surgical patients with a prior history of AF and those in sinus rhythm.

Methods Adult patients with an established history of AF and those with no prior history of AF undergoing cardiac surgery were recruited to undergo EAT, blood and subcutaneous adipose tissue (systemic and adipose tissue controls) sampling. Patients were propensity-matched to ensure baseline clinical variables were similar across the groups. The tissue samples were immediately taken to the laboratory for immune cell isolation, flow cytometry and T lymphocyte cell stimulation assays. Bulk EAT RNA sequencing analysis was performed on a cohort of patients to determine whole tissue RNA expression changes and in 2 patients paired EAT and right atrial appendage (RAA) tissue samples underwent single-cell RNA sequencing with proteomic analysis alongside T-cell receptor sequencing.

Results A cohort of 44 propensity-matched patients was identified (table 1). T lymphocytes were the predominant immune cell type and T cell subset analysis in a sub-cohort of 18 patients revealed a highly significant increase in both EAT-resident CD4+ (p<0.05) and CD8+ (p<0.001) memory T cell populations in AF patients (figure 1). T cell stimulation assays demonstrated a highly significant correlation with the proportion of tissue-resident memory (TRM) CD4+ T cells in EAT and the pro-inflammatory cytokines interferon-γ (p=0.0072) and interleukin-17 (p=0.0042) [figure 2]. In contrast, similar absolute numbers of other immune cell types in the EAT were observed between the two groups while bulk RNA sequencing analysis demonstrated broadly similar immune mediator expression levels between the groups. On a single cell level, similar immune cell clusters were observed between the EAT
and RAA while T cell receptor sequencing confirmed the same T cell clones to be present in the RAA as the EAT.

Conclusions and Implications AF carries a unique EAT-resident T cell signature which correlates with the production of the pro-inflammatory cytokines interferon-γ and interleukin-17. Single-cell RNA-sequencing analysis confirms EAT to be the immune reservoir of the heart and EAT sampling can provide an accurate readout of the immune landscape of the underlying cardiac tissue. Targeting this local resident T cell population may unlock a novel angle in the management of the inflammatory and fibrotic components of AF genesis.

**BS7 NEUROHUMORAL RESPONSES IN TAKOTSUBO SYNDROME**

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Background We investigate if renin-angiotensin and endothelin-1 response pathways follow the same pattern of recovery as left ventricular ejection fraction in patients with takotsubo syndrome.

Methods Ninety takotsubo syndrome patients [n=30 in each of ‘acute’, ‘convalescent’ (3–5 months) and ‘recovered’ (> 1 year) groups] who were on minimal or no medication and were free of any significant cardiac/metabolic co-morbidities, and 30 healthy controls were studied. Serum concentrations of renin, angiotensin converting enzyme, angiotensin II, big endothelin-1, endothelin-1 were measured using commercially available ELISA, and BNP was measured using an immunoassay.

Results Left ventricular ejection fraction was 38 ± 1.6 % in acute, 63 ± 2.0 % in convalescent and 64 ± 2.6 % in recovered takotsubo syndrome patients. As shown in the Figure, serum renin concentrations are persistently elevated after a takotsubo episode (p=0.03 vs controls). Angiotensin converting enzyme levels are significantly depressed during the acute phase compared to convalescent (p=0.004), recovered takotsubo (p=0.02) or controls (p=0.03). Angiotensin II is increased in takotsubo patients (p<0.001 vs controls) remaining persistently elevated long-term in the recovered group (p=0.03 vs controls). B-type natriuretic peptide concentrations remain elevated after a takotsubo episode compared to controls (p=0.003). Big endothelin-1 levels are unchanged, but endothelin-1 is significantly lower after takotsubo syndrome compared to controls (p=0.03).

Conclusions Despite ‘normalisation’ of the left ventricular ejection fraction, there is long-term maladaptive activation of renin-angiotensin system in takotsubo syndrome patients. This suggests therapy aimed at modulating this pathway may be beneficial in the long-term.