This is a peer-reviewed, accepted author manuscript of the following conference paper: Coyle, C, MacLean, M & Tian, L 2024, 'Sex differences in the right ventricle in the Sugen-Hypoxia rat model of pulmonary arterial hypertension', *Circulation*, vol. 150, no. Suppl_1, A4137364. https://doi.org/10.1161/circ.150.suppl_1.4137364

Sex differences in the right ventricle in the Sugen-Hypoxia rat model of pulmonary arterial hypertension

Chelbi Coyle, Margaret R. MacLean, Lian Tian

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

2500 characters (about 360-630 words)

Background: An unexplained estrogen puzzle exists in pulmonary arterial hypertension (PAH): PAH occurs ~4 fold more frequently in women than men; however, women with PAH have better right ventricular (RV) function and survival than the men. Sex differences and the associated mechanism in RV in PAH are not well understood.

Aim: To characterize sex differences in RV function and structure in PAH.

Methods: Sprague-Dawley rats were injected with Sugen (SU5416, 25mg/kg), and subjected to 3 weeks of hypoxia, followed by 5 weeks of normoxia. Control rats received vehicle and stayed in normoxia for up to 8 weeks. RV pressure-volume, mitochondrial properties, weight, myocyte size, cell proliferation, and interstitial and perivascular (right coronary arteries, RCA) fibrosis were obtained.

Results: Sugen-Hypoxia (SuHx) caused significant increases in RV systolic pressure (RVSP) and effective arterial elastance (Ea) in both sexes ($P<0.05$), but caused slightly greater increase in RV end-systolic elastance (Ees) in females vs males, leading to a preserved RV-pulmonary artery coupling (Ees/Ea) in females and a significant decrease in Ees/Ea in males ($P<0.05$). SuHx caused a significant increase in RV diastolic pressure only in males ($P<0.05$), which is associated with significantly higher amount of RV interstitial fibrosis in males vs females. In addition, SuHx caused significant increase in cell proliferation in both sexes ($P<0.05$) though with slightly greater in crease in males, which is well correlated with RV interstitial fibrosis. Whilst there was no sex difference in RV hypertrophy in SuHx rats as indicated by both fulton index and myocyte size, female RV had smaller myocytes than males at baseline,

indicating a greater increase in myocyte size in response to SuHx. Finally, there was a significant increase in RCA fibrosis in male SuHx rats ($P<0.05$) but not in females, potentially leading to a greater degree of ischemia in male SuHx RV, and this is consistent with impaired mitochondrial properties (decreased mitochondrial fusion, membrane potential and superoxide) in male SuHx rat RV ($P<0.05$) but preserved mitochoindrial properties in females.

Conclusions: SuHx resulted in similar level of RV afterload in both sexes, but compared to males, RV in females responded differently in both function (Ees and mitochondrial properties) and structure (myocyte size and fibrosis). Future studies on the associated mechanism are needed to gain therapeutic insight for RV in PAH.