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**Background:** Exercise-induced pulmonary hypertension (EIPH) portends early stage PH. However, there are no rodent models of EIPH, and its pathogenesis remains unclear. We hypothesized that ZSF-1 rats (which have metabolic syndrome and develop heart failure with preserved ejection fraction (HFpEF), treated with and without sugen (SU5416) to induce pulmonary vascular remodeling, would display EIPH with alterations in pulmonary artery vascular smooth muscle cell (PAVSM) soluble guanylate cyclase (sGC)-mediated signaling.

**Methods and Results:** We utilized ZSF-1 lean (Ln), obese (Ob), and obese treated with SU5416 (OS) (N=5-8/group). RV and LV catheters were implanted to evaluate hemodynamics-at rest (R) and during exercise (EX). During exercise, Ob rats showed significantly increased RV systolic pressure (R vs EX, Ln 28.8+/−1.0 vs 39.9+/−1.4; Ob 29.1+/−1.0 vs 53.2+/−2.9#; OS; 38.0+/−1.1 vs 69.2+/−2.4# mmHg; * p<0.05 vs same group at rest, # p<0.05 vs EX Ln), and increased LV end-diastolic pressure. Echocardiography post-exercise showed († p<0.05 vs Ln) increased RV diastolic dimension in Ob (3.3+/−0.1mm†) and OS (4.0+/−0.1mm†) compared to Ln (2.7+/−0.1mm), and increased total pulmonary resistance index (Ob 2.6+/−0.1†; OS 3.9+/−0.3†; Ln 1.5+/−0.05), revealing RV dysfunction and exercise intolerance. Ln and Ob had similar RV function at rest, whereas OS rats showed significantly worse RV dysfunction, suggesting advanced HFpEF/PH. MRI showed no differences at rest between Ln and Ob in the cardiac contraction-dependent change of PA diameter (ΔPAp), whereas post-dobutamine challenge, Ob rats had significantly decreased ΔPAp (Ln 1.0+/−0.08; Ob 0.66+/−0.06mm†). While Ln (R 18+/−2.5; EX 35+/−2.9pM/ml*) increased plasma cGMP levels after exercise, Ob (R 8.6+/−1.7#; EX 6.0+/−1.4# pM/ml) and OS (R 9.3+/−0.9; EX 11+/−2.5# pM/ml) had lower cGMP levels at rest that did not increase after exercise. Compared to cultured Ln PAVSM cells, Ob cells had lower relative sGC protein levels (Ln 1.0+/−0.06; Ob 0.5+/−0.04†) and cGMP production (Ln 2. 1±0.3; Ob, 0.8±0.2 μM/mg protein†).
Conclusions: This novel model shows exercise-induced PH and RV dysfunction, in which a deficit in PAVSM cell sGC activity occurs with lower cGMP levels and vascular responses to exercise.

Keyword: Exercise, pulmonary hypertension