Title: Postnatal Hyperoxia Exposure Durably Impairs Right Ventricular Function and Mitochondrial Biogenesis with Age

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Abstract:

Introduction: Prematurity complicates 12% of births, and young adults with a history of prematurity develop right ventricular hypertrophy (RVH) and impairment. Long term risk and mechanisms of pulmonary vascular (PV) disease and ventricular-vascular uncoupling following prematurity remain poorly defined. Methods: Pups from timed-pregnant Sprague Dawley rats were randomized to normoxia or hyperoxia (FIO2 0.85) exposure for the first 14 days of life, a common model of prematurity related lung disease. After aging to 1 year in standard conditions, rats underwent hemodynamic assessment followed by tissue harvesting for biochemical and histological evaluation. Results: Aged hyperoxia exposed (Hx) rats developed significantly greater RVH ($p<0.001$), associated with a 40% increase in RV systolic pressures ($p<0.001$). Although cardiac index was similar between groups, Hx rats demonstrated a reduced RV ejection fraction ($p=0.01$) and significant RV-PV uncoupling ($p<0.001$). Hx rats demonstrated a significant increase in RV mitochondrial number, yet a marked decrease in genes associated with mitochondrial biogenesis. In addition, there was evidence of mitochondrial DNA damage following Hx, suggesting potential oxidant stress and mitochondrial dysfunction as the cause of long term RV dysfunction. Conclusions: Aged Hx rats recapitulate many features of young adults born premature, including increased RVH and decreased RV ejection fraction. These rats also demonstrate chronic pulmonary hypertension, increased RV mitochondrial number, decreased mitochondrial biogenesis, and mitochondrial DNA damage, suggesting a possible mechanism for RV dysfunction in this population. Further evaluation of long term mitochondrial function is warranted in both animal models of premature lung disease and in adults born preterm.