Environmental hypoxia during perinatal life enhances erythropoiesis and pulmonary vascular dysfunction in response to chronic hypoxia during adulthood

William Mundo, MDc, MPH[1]; Gabriel Wolfson[2]; Do Park[2], Colleen Glyde Julian PhD[2]
[1]University of Colorado School of Medicine, Aurora, CO
Division of Biomedical Informatics and Personalized Medicine, Department of Medicine, University of Colorado, Aurora, CO

School of Medicine
UNIVERSITY OF COLORADO | ANSCHUTZ MEDICAL CAMPUS

BACKGROUND

- Pulmonary hypertension (PH) is a progressive, life-threatening disease that often develops secondary to chronic hypoxia of cardiopulmonary disease or high-altitude (HA) residence (> 2500m), and over 140 million persons live > 2500m globally
- Perinatal exposures affect physiological function and disease susceptibly across the life span
- Impaired fetal growth and insufficient oxygenation in early life impedes pulmonary vascular remodeling and causes structural changes that persist into adulthood.
- Retrospective data indicates that HA Andean residents with early-stage PH are 6 times more likely to have experienced hypoxia during perinatal life.
  - ➢ Limitations: (1) retrospective design = could not fully account for the effect of unknown environmental exposures between gestation and adulthood, and (2) all subjects were HA residents = not possible to determine whether pulmonary vascular outcomes would also be present under normoxic conditions

KEY: Understanding the impact of hypoxia during perinatal life on pulmonary vascular function of affected offspring in later life under normoxic conditions and in response to a secondary hypoxic challenge is crucial to identify risk factors for public health prevention and therapeutic management of pulmonary vascular disease.

AIM & HYPOTHESIS

AIM: Using an animal model, assess the impact of perinatal hypoxia and excessive erythrocytosis (EE) and pulmonary vascular function in hypoxic and normoxic conditions

HYPOTHESIS: Perinatal hypoxia increases the incidence of EE and pulmonary vascular dysfunction in response to a secondary hypoxic exposure and normoxic conditions during early adulthood.

METHODS

Experimental Animals: All procedures were approved by IACUC and compliant with the Guide for the Care of Laboratory Animals, Animal Welfare Act. Female and male mice aged 10-14 weeks were paired under standard conditions and randomly assigned to one of four study groups:

METHODS

1) Normoxic controls (n =15)
2) Perinatal normoxia and early adulthood hypoxia (n =15)
3) Perinatal and early adulthood hypoxia (n = 13)
4) Perinatal hypoxia and early adulthood normoxia (n = 8)

Hemodynamic Analyses: Echocardiograms were performed in male offspring at 8 weeks of age to assess for pulmonary hypertension, pulmonary artery blood flow and right ventricle hypertrophy, right ventricle (RV) anterior wall thickness, and pulmonary artery acceleration time/flow velocity

Direct Measurement of RV Systolic Pressure: RV-septum was visualized, and a catheter was inserted to assess hemodynamics. Mice were euthanized and tissue was harvested

Tissue Sampling: Hematocrit, hemoglobin and RV/LV+S weight were assessed. Lung tissue was analyzed for lung structure.

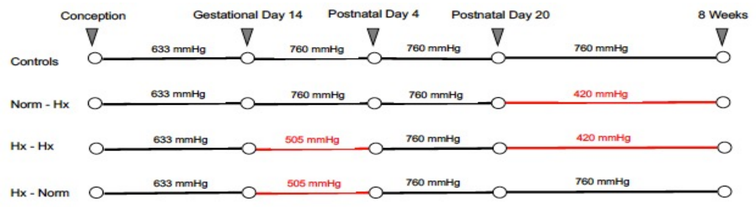

Figure 1. Experimental Protocol

Results

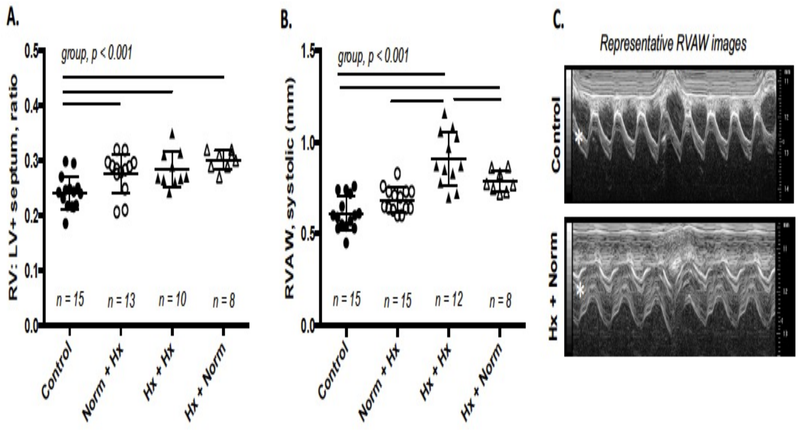

Figure 2. Perinatal hypoxia increases right ventricular anterior wall thickness in later life, even after the absence of secondary hypoxic exposure

- Increased RVSP by 79% (25.2 vs 45.2 mmHg, p<0.0001), raised hematocrit by 34% (40.2% vs 53.8%, p<0.0001), and enhanced RV:LV+septum weight ratio 15% (0.24 vs 0.27, p<0.05)

Results

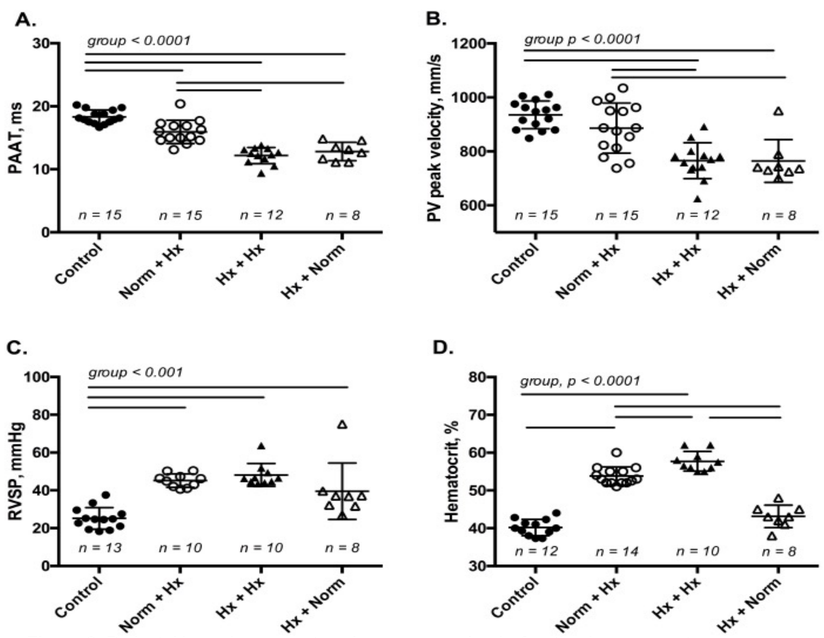

Figure 3. Perinatal hypoxia augments pulmonary vascular dysfunction in response to sustained hypoxia from 3 to 8 weeks of age and impairs pulmonary function in early adulthood under normoxic conditions.

- Reduced PAAT 15% (18.32 vs 15.93, p<0.001), and increased the magnitude of pulmonary vascular dysfunction and polycythemia in response to secondary hypoxic exposure during adulthood in male offspring only
- Perinatal hypoxia exaggerated the associated reduction of PAAT (15.9 vs 12.8, p<0.0001) and PV peak flow velocity (765 vs 886, p<0.001) and hematocrit (57.7% vs 53.8%, p<0.001)

Conclusion and Discussion

- Hypoxic exposure in early life may be a valuable indicator for the risk of developing pulmonary vascular disease in later life in response to a secondary hypoxic "hit" *as well as* under normoxic conditions.
- Consistent with observations that hypoxia in early life influences pulmonary vascular function and cardiopulmonary vascular adaptation
- The molecular and physiological mechanisms underlying the link between perinatal hypoxia and pulmonary vascular health in later life are currently being explored. On-going work focuses on the role epigenetic regulation of hypoxia-sensitive pathways known to influence pulmonary vascular development

ACKNOWLEDGEMENTS: This study was funded and supported by NIH Grant R01 HL138181: Epigenetic and Fetal Origins of Pulmonary Hypertension and the CU School of Medicine Diversity, Research, Equity in Academic Research program.