

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

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BACKGROUND

METHODS

Results

- 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 susceptibility 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

- 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.

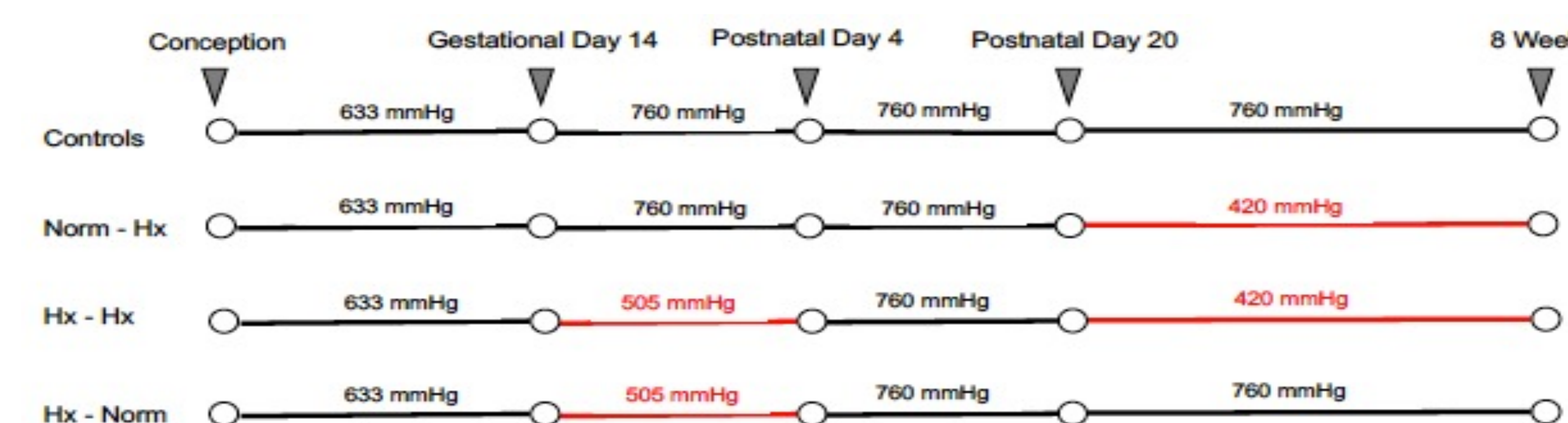


Figure 1. Experimental Protocol

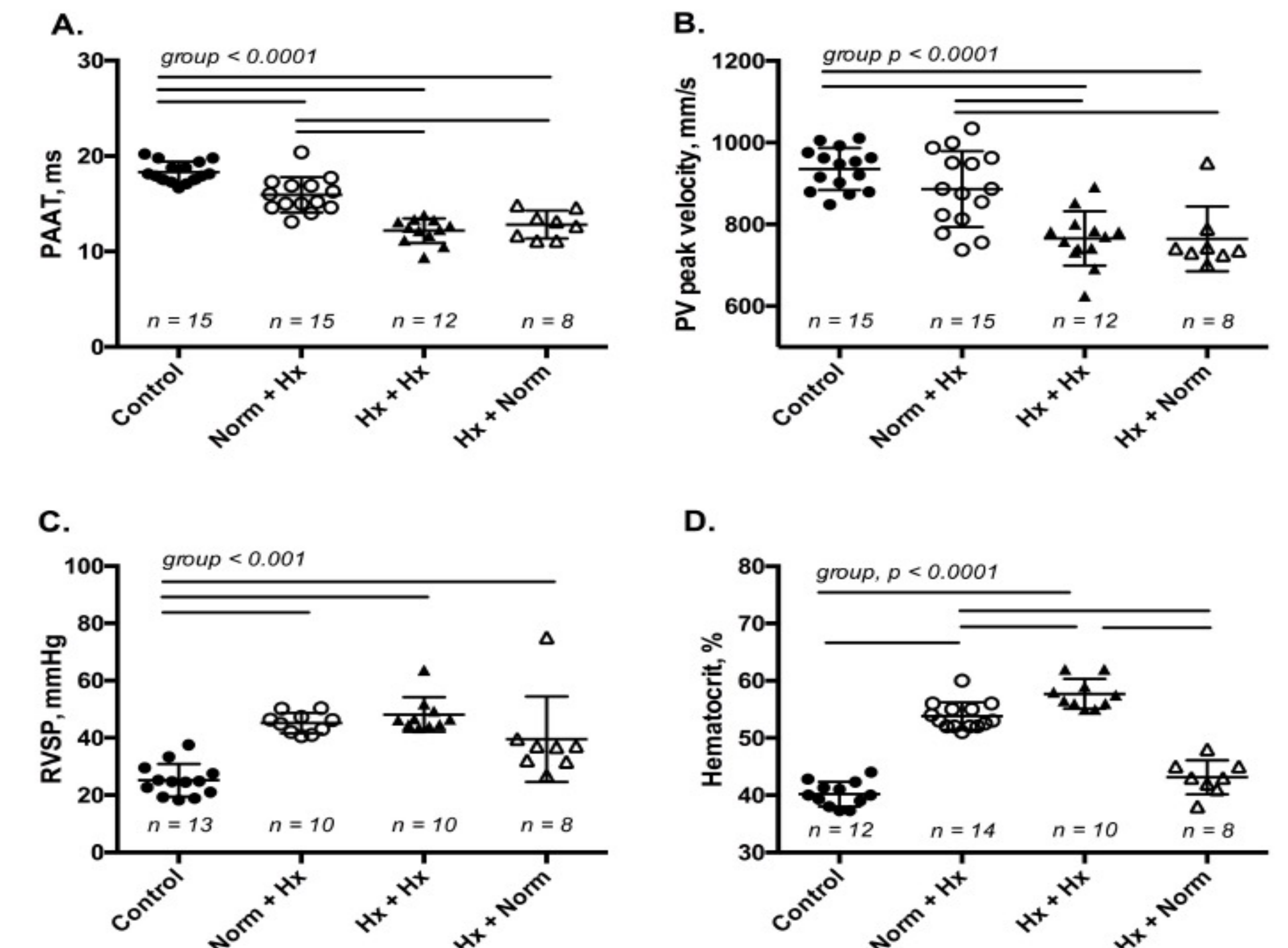


Figure 3. Perinatal hypoxia augments pulmonary vascular dysfunction in response to sustained hypoxia from 3 to 8 weeks of age and impairs pulmonary function in early adulthood under normoxic conditions.

- 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

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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:

Results

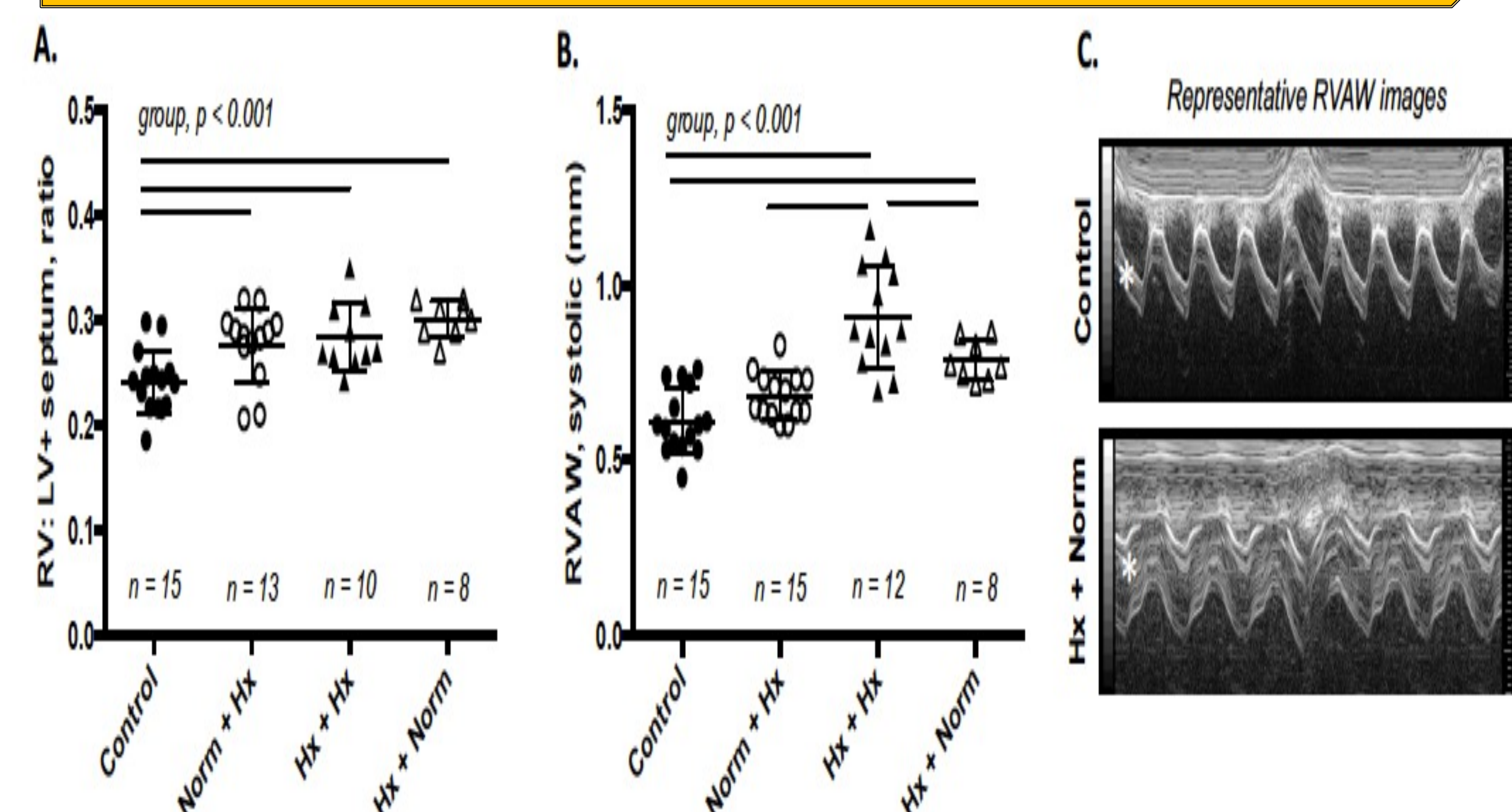


Figure 2. Perinatal hypoxia increases right ventricular anterior wall thickness in later life, even after the absence of secondary hypoxic exposure

- 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, $p < 0.05$)