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Men are from Mars, Women are from Venus. Gender specific changes in pulmonary function in 1 year old rats after neonatal hyperoxia exposure

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Rationale: Preterm birth affects about 11% of pregnancies worldwide. The Institute of Medicine estimated the cost associated with premature birth to be \$36 billion in 2016. Lungs in preterm infants are in the critical saccular stage of lung development and susceptible to the oxygen-induced chronic lung disease known as bronchopulmonary dysplasia (BPD). BPD is characterized by functional abnormalities including decreased saccular/alveolar septation, decreased microvascular cross-sectional area with or without pulmonary hypertension, airway injury with or without increased airway reactivity, and abnormalities of control of breathing in various combinations. While the initial inflammation improves, chronic inflammation ensues for a long time. We tested how neonatal hyperoxia exposure affects lung function one year after birth. We postulated an increase in lung collagen levels reflected by reduced pulmonary function.

Methods: 6 newborn male and female rats in each group were exposed to Hyperoxia (Hx; 85% O₂) or Normoxia (Nx; 21% O₂) for 14 days, then aged to 1 year in Nx. At one year, lung function was measured using a FlexiVent (Scireq, Montreal, Canada). Using a single frequency forced oscillation manoeuvre and a low-frequency forced oscillation technique the lung was tested for compliance and resistance. Total lung collagen was determined by a colorimetric assay using Ehrlich's reagent.

Results: Analysis of one year old rats showed no difference in weight and body length between the Nx and the Hx group within each gender. The inspiratory capacity (IC) was significantly higher in the Hx exposed male rats compared to the Nx exposed male rats (12.6±0.6 ml vs 14.0±0.9 ml; p=0.02). The difference in IC in female rats was significantly lower in the Hx group compared to the Nx group (11.3±0.4 vs 10.1±0.6 ml; p=0.002). Dynamic compliance was significantly increased in the male Hx group compared to the male Nx group (1.43±0.05 vs 1.61±0.11 ml/cm H₂O; p=0.04). In contrast, the female Hx group showed significantly reduced compliance compared to the female Nx group (1.32±0.05 vs 1.15±0.17 ml/cm H₂O). In addition, the PV loop area was higher in the male Hx group compared to the male Nx group and no difference was found between the two female groups. Total collagen in lung tissue was not different between the male Hx and Nx groups but was higher in the female Hx compared to the Nx group.

Conclusion: One year after neonatal Hx exposure, the male lung shows increased compliance and inspiratory capacity compared to the Nx exposed rats suggesting a trend to emphysema. In contrast, female rats show signs of lung fibrosis reflected by reduced compliance and increased total collagen content. This data suggests that neonatal oxygen exposure initiates alterations in inflammatory and repair pathways that are different between male and female rats.

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