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Abnormal Ventilatory Responses in Adults Born Prematurely

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To the Editor

Perinatal hyperoxia in preterm infants is associated with several well-known sequelae, including bronchopulmonary dysplasia and retinopathy of prematurity. Hyperoxia also induces alterations in cardiopulmonary control (e.g., preterm infants treated with hyperoxia lack normal ventilatory responses to hypoxia and hyperoxia).^{1,2} It has not been determined whether these impairments diminish with age. Thus, we sought to determine whether or not ventilatory dysfunction persists in adults who were born prematurely.

We measured the ventilatory responses to 5 minutes of isocapnic, isobaric hypoxia (in which the fraction of inspired oxygen [FIO_2] was 0.12) and hyperoxia (in which the Fio_2 was 1.0) in 13 adults born prematurely who were recruited from the Newborn Lung Project³ (a cohort with a mean [$\pm$ SD] age of 21 ± 1 years, a gestational age of 32 weeks, and a gestational weight of 1500 g) and from age-matched adults born at full term. Preterm adults were clinically indistinguishable from full-term adults, having similar pulmonary function and exercise capacity (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). However, the hypoxic ventilatory response was substantially reduced in preterm adults (0.13 ± 0.25 liters per minute per $-\text{SpO}_2$, where $-\text{SpO}_2$ denotes a negative change in oxygen saturation as measured by pulse oximetry) as compared with full-term adults (0.42 ± 0.30 liters per minute per $-\text{SpO}_2$; $P = 0.008$) (Fig. 1). Moreover, two preterm adults hypoventilated, which resulted in an increase in the partial pressure of end-tidal carbon dioxide (PETCO_2). As expected, 60 seconds of hyperoxia induced respiratory depression from baseline in all full-term adults ($-29.6 \pm 20.1\%$) but in only 8 of 13 preterm adults. The mean response was also reduced in the preterm population ($-3.0 \pm 26.9\%$; $P = 0.01$).

In rodents, perinatal hyperoxia disrupts the development of carotid chemoreceptors.⁴ The strong relationship between the hypoxic and hyperoxic ventilatory dysfunction in the preterm adults (Fig. 1) suggests a common impairment in chemoreceptor function that may be due to carotid chemoreceptor dysfunction. Our most compelling finding is that abnormal ventilatory responses were manifested only when these preterm adults, who appeared to be clinically normal, were stressed by breathing hypoxic and hyperoxic gas. This finding may have important clinical implications.⁵ We found that some preterm adults paradoxically hypoventilate with hypoxia.

In summary, adults with a history of preterm birth have abnormal ventilatory responses to hypoxia and hyperoxia, possibly due to disrupted chemoreceptor development. We speculate that these underappreciated abnormalities in ventilatory control may have important clinical consequences, including an increased risk of disordered breathing during sleep and in response to high altitude and anesthesia. Additional investigations into the mechanisms and long-term disease risks of this population are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Ventilatory Responses to Hypoxia and Hyperoxia in Adults Born Prematurely as Compared with Adults Born at Full Term

All full-term adults (controls) had increased ventilation in response to hypoxia (fraction of inspired oxygen [FIO_2] = 0.10); paradoxically, some preterm adults hypoventilated in response to hypoxia and reported presyncopal symptoms at the end of the trial (Panel A; boxes depict the median and first and third interquartile ranges, with whiskers indicating maximum and minimum responses). After 60 seconds of hyperoxia (FIO_2 = 1.0), ventilation was depressed in all full-term adults, but this response was blunted in preterm adults (Panel B; points represent the mean $\pm$ SD). The blunting of hyperoxic and hypoxic ventilatory responses was correlated in preterm adults, suggesting a common cause of ventilatory dysfunction (Panel C). The Δ symbol denotes change, SpO_2 oxygen saturation as measured by pulse oximetry, and $\dot{V}_E$ volume expired.