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Rodent models of respiratory control and respiratory system development—Clinical significance

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ABSTRACT

The newborn infant's respiratory system must rapidly adapt to extra-uterine life. Neonatal rat and mouse models have been used to investigate early development of respiratory control and reactivity in both health and disease. This review highlights several rodent models of control of breathing and respiratory system development (including pulmonary function), discusses their translational strengths and limitations, and underscores the importance of creating clinically relevant models applicable to the human infant.

1. Background

At parturition, the newborn's respiratory system rapidly adapts from an intra-uterine liquid environment, where gas exchange was reliant upon placental blood flow, to a new extra-uterine air environment. The newborn lung must now exchange gas to achieve adequate oxygenation and ventilation. The neonatal transition starts with peripheral and central respiratory control centers initiating the first breaths of air, expanding the lungs, driving further absorption of fetal lung fluid, and increasing the partial pressures of oxygen in the bloodstream (PaO_2). When the umbilical cord is clamped, systemic vascular resistance rises and pulmonary vascular resistance falls, thereby initiating a functional closure of fetal pulmonary shunts (foramen ovale, ductus arteriosus) and establishing circulation that will persist into adulthood (Goldsmith, 2015). While most infants transition without incident, up to 10% of newborns will need some respiratory assistance following birth (Wyckoff et al., 2015). Sustaining adequate ventilation and oxygenation requires a central respiratory drive, adequate muscle strength and chest wall recoil, clearance and opening of the airways, with functional gas-exchange and blood flow now occurring in the lung (Sinha and Donn, 2006). Disruptions of any aspects of the neonatal respiratory transition can result in insufficiency and needs for interventions such as positive airway pressure, mandatory ventilation, and supplemental oxygen (O_2).

The field of neonatology has benefitted greatly from respiratory system discoveries made utilizing translational newborn animal models. Investigation of premature delivery or perinatal asphyxia in large animals, such as ovine, porcine, and primate models, have shaped neonatal resuscitation and early respiratory practices, as well as, informed upon longer term respiratory and developmental outcomes. These models are highly specialized, labor-intensive, and costly because they often require surgical interventions, mechanical ventilation, sedation, intravenous nutrition, and continuous monitoring in appropriately staffed and equipped animal intensive care units. This review will focus on the more accessible and less costly term rodent models that leverage the order's relatively immature lung and respiratory development at birth, and readily available immunohistochemical and genetic techniques to investigate neonatal respiratory disease.

We will highlight several small animal models of respiratory system development and how perturbations such as premature lung and respiratory development, infection, and early respiratory exposures can result in clinically relevant respiratory disease in human infants.

2. Neonatal breathing

Swallowing of amniotic fluid and diaphragmatic excursion are critical for the fetal development and growth of the lung. Ultrasound detection of human fetal breathing movements is reported as early as 11 weeks of gestation, with more regular detection as the fetus matures and phasic patterns are observed during times of rapid-eye-movement sleep (Jansen and Chernick, 1991). Multiple transmitters have been shown to influence fetal breathing including gamma-aminobutyric acid, corticotrophin-releasing factor, prostaglandins, and serotonin (Abu-Shaweesh, 2004). The human fetus is responsive to hypercapnia showing increased fetal breathing, but a paradoxical initial depression

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of breathing during hypoxia, emphasizing the inhibitory pathways of hypoxia sensitive centers rostral to the medullary system (Jansen and Chernick, 1991).

Breathing maturation is on a continuum from early fetal to late neonatal life. As such, postnatal respiratory activity can also be irregular with periods of eupnea, apnea, periodic breathing, and tachypnea. Respiratory control of the neonate is predominantly inhibitory in nature from peripheral afferents to central respiratory reflex responses - manifesting a decreased response to carbon dioxide, paradoxical responses to hypoxia, exaggerated reflex apnea, and irregularities of sustained breathing patterns including periodic breathing and central apnea (Abu-Shaweesh, 2004). Frank apneas and a distinct amount of tonic diaphragmatic activity are more commonly observed in the premature neonate (Beck et al., 2011) and incidence of apnea does not equal that of a term neonate until around 43–44 weeks corrected gestational age (Ramanathan et al., 2001). Of concern, apneas and subsequent increased intermittent hypoxemia events in premature neonates have been associated with numerous neonatal morbidities and hospital mortality (Poets et al., 2015; Di Fiore et al., 2016; Fairchild et al., 2018).

Much of animal modeling has focused on measurements of the neonatal responses to hypoxemia and/or hypercapnia following an exposure or insult to perturb the normal function of the developing respiratory control centers (Table 1). In control animals, an anticipated increase in measurements of minute ventilation would occur in response to challenges with inhaled hypoxic or hypercarbic gases. The hypoxic ventilatory response (HVR) is bi-phasic in nature, with neonates displaying an initial increase in tidal volume and respiratory rate that lasts 1–2 min, followed by a decline in minute ventilation to below baseline (Abu-Shaweesh, 2004). The initial acute phase of the HVR is due to stimulation of peripheral chemoreceptors primarily in the carotid body, which can be eliminated by carotid body denervation in the neonatal rat, whereas, the late phase hypoxic ventilatory depression is central in origin (Fung et al., 1996). The hypercapnic ventilatory response (HCR) is both peripherally (10–40% of the total HCR) and centrally mediated (Abu-Shaweesh, 2004) and results in increased minute ventilation and prolongation of expiratory duration (Abu-Shaweesh et al., 1999).

2.1. Rodent model - sustained hypoxia

As described above, the fetus leaves a relatively hypoxemic (PaO_2 25–30 mm Hg) intrauterine environment supported by the placenta and transitions to a relatively hyperoxic air environment (Abu-Shaweesh, 2004). Neonatal rat and mouse models have utilized exposures to sustained hypoxia during early development of respiratory control to alter this transition. Rat pups raised in hypoxia have attenuation of the HVR (Eden and Hanson, 1987; Bavis et al., 2004; Reeves and Gozal, 2006b; Stryker et al., 2018), mediated in-part by reduced carotid body potassium-channel current density thereby preventing type 1 cell depolarization in response to acute hypoxia (Wyatt et al., 1995). Sustained hypoxia models vary in the severity, duration, and timing of hypoxia exposures with the magnitude of HVR attenuation dependent upon the duration, intensity, and hypoxia patterns (Prabhakar and Kline, 2002; Reeves and Gozal, 2006a). Additionally, gender and strain of the animals should be taken into account when translating discoveries (Bavis et al., 2004; Subramanian et al., 2007).

Table 1
Rodent Models of Neonatal Breathing.

Perinatal Exposure(s)		Acute Response to Inhaled Gas Challenges
Sustained Hypoxia	(alone)	↓HVR
Sustained Hyperoxia	(alone)	↓HVR, ↓HCR
	WITH Intermittent Hypercapnea/Hypoxia	Ø HVR
Intermittent Hypoxia	Prenatal	↓HVR
	< 10 day duration	↑HVR
	> 30 day duration	↓HVR
Hypercapnea	Intermittent	↑HVR, Ø HCR
	Sustained	↓HCR
Lipopolysaccharide	Prenatal	↑HVR, ↑HCR
	< 2 days of age	↓HVR
	5-8 days of age	Ø HVR
	10 days of age	↓HVR
	20 days of age	Ø HVR

Hypoxic Ventilatory Response (HVR); Hypercapnic Ventilatory Response (HCR).

2.2. Rodent model - sustained hyperoxia

Akin to the relative hyperoxic transition of birth and practice of supplemental O_2 use for neonatal respiratory insufficiency, rodent models have likewise investigated the effects of early exposures to sustained hyperoxia on the developing respiratory control centers. Delivery room resuscitation with 100% O_2 has been shown to depress respiratory drive in the term human neonate (Vento et al., 2001), as well as, the neonatal rat (Bookatz et al., 2007). Premature infants with respiratory insufficiency often require some amount of supplemental O_2 (Welsford et al., 2019) and may require supplemental O_2 for prolonged durations with potentially untoward effects upon respiratory control (Katz-Salamon and Lagercrantz, 1994). In sustained hyperoxia rat models, the carotid body is reduced in size with a decreased number of chemoafferent neurons compared to room air raised pups (Erickson et al., 1998; Bavis et al., 2013). Rats raised in hyperoxic conditions show a marked attenuation of the HVR (Carroll et al., 2009; Bavis et al., 2013; Bierman et al., 2014) and HCR (Bavis et al., 2017) with long-term deficits in the HVR lasting well into adulthood (Ling et al., 1996; Fuller et al., 2002). While the acute HVR is attenuated in rats raised in neonatal hyperoxia, the late phase of the HVR shows sustained increases in ventilation when compared to the classical bi-phasic decline in minute ventilation observed in control animals (Bavis et al., 2010; Hill et al., 2013), indicating impairments in the peripheral chemoreceptors with a compensatory increase in excitatory effects within the central nervous system. Remarkably, intermittent hypercapnia (Bavis et al., 2007) or intermittent hypercapnic hypoxia (Bavis et al., 2019) during sustained hyperoxia background restores the HVR. Additionally, the HVR can be subsequently rescued from the effects of sustained neonatal hyperoxia if pups are later exposed to a course of sustained or intermittent hypoxia (Fuller et al., 2001; Bisgard et al., 2005). While the mechanisms underlying recovery of the HVR are still under investigation, the carotid body size has been shown to increase in volume following the secondary exposure to hypoxia potentially conferring remediation of hypoxia sensing and triggering in the peripheral arterial chemoreceptors (Wenninger et al., 2006).

2.3. Rodent model - intermittent hypoxia

Due to an immature respiratory drive and underlying pulmonary insufficiency, premature infants may have over 100 intermittent hypoxemia events daily (Martin et al., 2011). These O_2 desaturation events are likely an indicator of respiratory and clinical instability and have been associated with adverse neonatal outcomes (Poets et al., 2015; Di Fiore et al., 2016; Fairchild et al., 2018). Rodent models have used both prenatal and postnatal cycles of intermittent hypoxia (IH) exposures to mimic these clinical events on the developing respiratory control system. Pregnant rats exposed to IH during late gestation gave birth to offspring with increased baseline ventilation and an attenuated peak HVR (Gozal et al., 2003). Ventilatory effects of postnatal IH depends greatly on the patterns and timing of exposures - displaying both beneficial and detrimental effects on respiratory control. Short duration exposures of the neonatal rat to IH (< 10 days) resulted in elevated carotid body sensory response to hypoxia (Peng et al., 2004) and an

unchanged or augmented peak HVR (Peng et al., 2004; Julien et al., 2011) with variable effects on the late phase HVR (Gozal and Gozal, 1999; Julien et al., 2011; Mayer et al., 2013). Conversely, longer-term chronic exposure to neonatal IH for 30 days resulted in increased baseline ventilation (Reeves and Gozal, 2006a,b; Reeves et al., 2006) and an attenuated HVR (Reeves and Gozal, 2006b; Reeves et al., 2006).

2.4. Rodent model - hypercapnia

Disordered breathing, hypoventilation, rebreathing, and apneas may also be associated with intermittent hypercapnia in the neonate. There has been a trend in neonatal practice of permissive hypercapnia to alleviate lung trauma from excessive tidal volumes during invasive ventilation and limit the overall duration of mechanical ventilation in the fragile premature newborn. As such, models have also investigated exposures to intermittent and chronic hypercarbic gases in neonatal rat pups. Intermittent hypercapnia alone elicits an enhanced HVR when compared to room air controls, without an observed difference in the HCR (Steggerda et al., 2010). Interestingly, combined intermittent hypercapnic hypoxia caused an increase in carotid body size with a modest decrease in the HVR from baseline while reducing the HCR (Bavis et al., 2019). Chronic hypercapnia in neonatal rats results in transient increases in ventilation with a reduction of the acute HCR immediately following exposure; the elevated baseline ventilation and blunted HCR recovers following return to room air (Rezzonico and Mortola, 1989; Bavis et al., 2006).

2.5. Rodent model - inflammatory and infectious exposures

Premature labor is often triggered by infection. Additional inflammatory exposures, both infectious and noninfectious, coupled with an immature immune system and underdeveloped anti-oxidant and anti-inflammatory defenses often leads to an unbalanced pro-inflammatory state that may contribute further to breathing instability in premature neonates (Di Fiore et al., 2013) and infants at risk for sudden infant death syndrome (SIDS) (Weber et al., 2008). Rodent models have utilized gram-negative endotoxin, lipopolysaccharide (LPS), to produce an inflammatory state and measure respiratory control. LPS administered prenatally to pregnant mice to mimic systemic maternal inflammation and chorioamnionitis resulted in offspring with increased apnea frequency, elevated baseline ventilation, an increased HVR, and an increased HCR compared to aged-matched controls (Samarasinghe et al., 2015). Conversely, postnatal systemic administration of LPS to the newborn rat at 2 days of age resulted in attenuation and delay of the HVR (Master et al., 2015), increased spontaneous intermittent hypoxemia, and attenuated hypoxic chemosensitivity of the carotid nerve sinus with an associated decrease in carotid body volume of type II cells (Master et al., 2016). In a postnatal infection/inflammation model utilizing LPS to create circumstances surrounding a SIDS scenario (Weber et al., 2008), attenuations of the early and late phase of the HVR are observed following systemic LPS administered to rat pups at 10 days of age, with notable increases in same day mortality (Rourke et al., 2016). Interestingly, signifying a critical window of vulnerable postnatal respiratory development in the neonatal rat, systemic LPS at 5–8 days of age (McDonald et al., 2016a,b; Rourke et al., 2016) and 20 days of age (Rourke et al., 2016) did not have an observed effect upon the HVR or mortality compared to saline controls. In a separate model of pneumonia and pulmonary infection, neonatal rat pups that received intratracheal LPS had an attenuated HVR with no observed effect upon the HCR (Balan et al., 2012; Ribeiro et al., 2017).

2.6. Translational aspects of rodent models of neonatal breathing

As one can appreciate, there is a diverse range of neonatal rodent models of breathing, all providing important clues to the peripheral and central chemoreceptors, rhythm generators, and abilities to respond to ventilatory challenges with important translational insights to the bedside clinician. Inherent to most animal models, an insult or experimental intervention must be introduced to perturb a system that otherwise functions and develops normally under typical neonatal conditions. For example, severe sustained exposure to hypoxic gas may be necessary to develop the required disease phenotype, out of proportion to the hypoxemia a newborn human would experience when using continuous pulse oximetry monitoring.

The most premature infants may spend months of their lives on respiratory support, including supplemental O_2. Despite receiving supplemental O_2, due to their underlying respiratory insufficiency, it would be relatively rare that their arterial PaO_2 would be maintained in sustained hyperoxemia ($PaO_2 > 150$) thus affecting the central and peripheral chemoreceptors. Rodent models utilizing extremes of hyperoxic gas exposures and sustained hyperoxemia may be of less clinical relevance in regards to control of breathing (but may still have important implications to the development of the lung itself, see discussion of neonatal lung and airway disease models). Rather the premature neonate is more likely to have episodes of hypoxemia, hypercapnia (both intermittent and sustained), and rebound re-oxygenation and hyperoxemia (Abu-Shaweesh, 2004; Di Fiore et al., 2013, 2016). We speculate that mixed models, including those that induce a pro-inflammatory state, are the most translational to the bedside condition. As such, it can be difficult to ascertain what aspects may be detrimental and protective unless each condition is tested both individually and in combination. Of note, any alteration from the control state, whether it is attenuation or hypersensitive responses to respiratory stimuli likely indicate unstable breathing in the neonate (Table 1).

3. Neonatal lung and airway disease

Premature infants are at risk for long-term pulmonary morbidity from childhood into adulthood, with those born more premature experiencing the highest incidence of respiratory disease (Fawke et al., 2010; Been et al., 2014; Vollsaeter et al., 2015; Priante et al., 2016). Bronchopulmonary Dysplasia (BPD), the most common severe respiratory sequelae of premature birth, is clinically defined for those infants who require respiratory support at 36 weeks corrected gestational age (Walsh et al., 2004). Previously, lung pathology in “Old BPD” as first described by Northway et al. was characterized by alveolar fibrosis, thickened septa, and smooth muscular hyperplasia (Northway et al., 1967). More recently with gentle ventilation strategies, surfactant replacement therapy, and lower use of supplemental O_2, chronic lung disease of prematurity termed “New BPD” demonstrates less fibrotic changes with emphasis upon alveolar simplification and abnormal microvasculature (Jobe, 2011). Functionally, infants with “New BPD” experience early evidence of obstructive lung disease persisting into adolescence, increased airway reactivity and wheezing disorders, and reduced diffusing capacity for carbon monoxide with normal alveolar volume (Baraldi et al., 2009; Balinotti et al., 2010; Brostrom et al., 2010; Ahlfeld and Conway, 2014; Been et al., 2014). Though the greatest morbidity is seen in infants with BPD, non-BPD infants receiving supplemental O_2 also are at high-risk for developing symptomatic airway dysfunction (Stevens et al., 2010; Di Fiore et al., 2019). Numerous risk factors contribute to the pathogenicity of airway reactivity including neonatal O_2 injury, mechanical ventilation, and inflammation (Reyburn et al., 2012). Taken together, premature infants as a group are at heightened risk for developing airway hyperreactivity (Grischkan et al., 2004; Jaakkola et al., 2006; Been et al., 2014) and childhood wheezing (Been et al., 2014; Edwards et al., 2016). Furthermore, longer-term cohorts following premature infants show obstructive lung disease persisting into adolescence and adulthood (Fawke et al., 2010; Doyle et al., 2017).

The development of translational rodent animal models has been critical in understanding normal and abnormal lung development. During early human fetal development, airway smooth muscle

Table 2
Rodent Models of Neonatal Lung and Airway Disease.

Perinatal Exposure(s)	Parenchymal Changes		Baseline Mechanics		Airway Hyperreactivity
	Alveolarization	*Smooth Muscle*	*Resistance*	*Compliance*	*Methacholine Response*
Sustained Hyperoxia					
Mild (< 40% O2)	↓	↑↑	↑ or Ø	↓ or Ø	↑↑
Moderate (50-70% O2) > 4 days	↓	↑ or Ø	↑ or Ø	↓ or Ø	↑
Severe (> 70% O2) < 4 days	↓↓	↑	↓	↑↑	↑ or Ø
Severe (> 70% O2) > 4 days	↓↓	↑	↑	↓	↑ or Ø
WITH Intermittent Hypoxia	↓↓	↑	Ø	Ø	↑
WITH Non-Invasive CPAP	↑	–	↓	↑	–
Intermittent Hypoxia	Ø	Ø	Ø	Ø	Ø
Positive Pressure					
Invasive (Ventilation)	↓	↑ or Ø	Ø	Ø	↑↑
Non-Invasive (CPAP)	↓	↑	Ø	Ø	↑↑
Prenatal Lipopolysaccharide	↓or Ø	↑ or Ø	↑	↓	↑
WITH Hyperoxia	↓	↑	↑	↓	↑ (but not additive)

Continuous Positive Airway Pressure (CPAP).

differentiates from the mesenchyme of the primordial lung and envelops the emerging bronchial tree. Airway smooth muscle layers are present by the end of the human embryonic period that extend from the proximal trachea to the distal terminal lung sacs, and are innervated by an extensive nerve plexus comprised of nerve trunks and ganglia (Schaffer and Marla, 2011). The fetal lung and airways continue to develop through the pseudoglandular and canalicular stages of differentiation. Airway smooth muscle at these early stages provides phasic rhythmic contractility with smooth muscle present in all the conducting airways by 23 weeks gestation (canalicular stage) and autopsy evidence of hypertrophic changes by 10 days of age in infants developing chronic lung disease (early saccular stage) (Sward-Comunelli et al., 1997). Though fully viable at birth, the term rodent is born in the saccular stage of lung development and thus does not yet have differentiated alveoli, allowing for careful modeling of prenatal and environmental exposures (hyperoxia, hypoxia, and infection/inflammation) to determine their pathogenic effects commonly associated with BPD and airway hyperreactivity, as briefly summarized in Table 2 (Amy et al., 1977; Berger and Bhandari, 2014, O'Reilly and Thebaud, 2014).

3.1. Rodent model - sustained hyperoxia

The most commonly used rodent models of neonatal lung disease involves exposure to sustained hyperoxic gas in attempts to recapitulate the pathologic features of BPD in both the airway and emerging alveolus (Berger and Bhandari, 2014; Silva et al., 2015). These models utilize O_2 concentrations ranging from mild (40% O_2) to severe (100% O_2) hyperoxia spanning several developmental lung stages (Berger and Bhandari, 2014, O'Reilly and Thebaud, 2014). Based on each exposure paradigm, different effects can be seen on the developing airway and alveolus depending on the dose and duration of O_2 treatment. The presence of so many exposure protocols in the literature has both positive and negative consequences for investigators studying neonatal O_2 exposures. When aggregated together, the experimental diversity allows investigators to characterize a dose response in each lung compartment (airway and alveolus) across several developmental windows (saccular, primary alveolarization, and bulk alverolarization); perhaps improving translational relevance because premature infants are exposed to a variety of doses and durations of supplemental O_2 with risk for development of BPD correlated with daily O_2 exposures (Wai et al., 2016; Raffay et al., 2019). Conversely, the lack of a "gold standard" decreases reproducibility, requiring investigators to re-characterize their respective paradigm depending on O_2 dose, O_2 duration, rodent species, environmental conditions (e.g. altitude, temperature, humidity), and other factors that may affect the models' performance.

Multiple rodent models of hyperoxia have shown structural (airway smooth muscle proliferation or hypertrophy, diminished airway tethering) and functional (increased baseline resistance or airway contractility) changes under hyperoxic conditions. Baseline lung function assessments (without methacholine or ovalbumin challenge) vary based upon severity and duration of hyperoxia exposure. The alveolar epithelium in term rodents exposed to sustained hyperoxia has altered development with decreased alveolarization and gas exchange, increased fibrosis, and increased inflammation (Vogel et al., 2015). Functionally, hyperoxia-induced changes in alveolar architecture (40% to 100% O_2 for 4 days) have effects on both baseline resistance and compliance with a direct relationship between O_2 dose, degree of alveolar simplification and baseline compliance (Yee et al., 2009). This same paradigm shows changes in cellularity of the alveolar epithelium with expansion followed by reduction in Type II pneumocytes (Yee et al., 2014). Minimally increased baseline airway resistance and decreased compliance was observed in juvenile (3 week old) mice after mild hyperoxia (40% O_2 for 7 days) (Wang et al., 2014). Longer duration severe hyperoxia (> 70% O_2 for > 4 days from birth) impacts multiple stages of rodent lung development and results in much of the previously described "Old BPD" phenotype which includes lung fibrosis, increased baseline resistance and decreased compliance in juvenile rodents (Warner et al., 1998; Auten et al., 2007; Velten et al., 2010; Hansmann et al., 2012; James et al., 2013). Conversely, short duration high doses (100% O_2 for 4 days) show alveolar simplification with decreased baseline resistance and increased compliance in adult mice (Yee et al., 2009; Regal et al., 2014). The variable differences in baseline function, likely correlate with the balance of alveolar simplification and airway tethering, fibrotic lung changes, and resting airway tone. Preclinical therapeutics attempting to reverse alveolar simplification and changes in lung function show promise with concomitant exposures of hyperoxia and various agents, such as, ethyl nitrite during hyperoxia (> 95% O_2 for 8 days) (Auten et al., 2007), interlukin-1 antagonism (65% O_2 for 28 days) (Royce et al., 2016), peroxisome proliferator-activated receptor-γ agonism (70% O_2 for 10 days) (Takeda et al., 2009), vitamin D (85% O_2 up to 21 days) (Yao et al., 2017), as well as, various cell (Augustine et al., 2017) and exosome based therapies (Willis et al., 2018).

The study of airway resistance and hyperreactivity is of particular interest in hyperoxic BPD rodent models because premature human infants with and without BPD have increased wheezing and use of bronchodilator medications associated with the intensities of neonatal supplemental O_2 exposures (Stevens et al., 2010; Di Fiore et al., 2019). Studies describing airway hyperreactivity in rodents generally use methacholine or allergic ovalbumin challenge; administering increasing doses and assessing airway contraction or pulmonary function until maximal effect is reached. Juvenile mice exposed to mild hyperoxia

(40% O_2 for 7 days) have increased smooth muscle proliferation and increased *in vivo* and *in vitro* airway hyperreactivity to methacholine challenge, but the effect was blunted at higher levels of hyperoxia (70% O_2 for 7 days) (Wang et al., 2014; Onugha et al., 2015) – an observation paralleled *in vitro* using human fetal airway smooth muscle cells (Hartman et al., 2012). Various levels and durations of moderate hyperoxia (50–65% O_2 for 7–28 days) in newborn mice display *in vivo* airway hyperreactivity to methacholine at 3 weeks of age (Raffay et al., 2014; Faksh et al., 2016; Raffay et al., 2016) and *in vitro* airway hyperreactivity at 4 weeks of age (Royce et al., 2016). Similarly, rats exposed to moderate hyperoxia (60% O_2 for 14 days) had increased bronchial airway smooth muscle contractility (Belik et al., 2003). One important consideration is that airway hyperreactivity measured by methacholine-induced change in luminal area via a living lung slice requires time after exposure to develop, exhibiting an evolving phenotype as the animals age (Onugha et al., 2015). Indeed, airway smooth muscle proliferation persists when mice are aged (10 months) after neonatal exposure (65% O_2 for 14 days) with adult animals displaying fewer bronchiolar-alveolar attachments (O'Reilly et al., 2014). As such, severe hyperoxia in excess of 70% O_2, results in adult hyperreactivity to methacholine at 6 weeks (Hansmann et al., 2012) and 8 weeks (Kumar et al., 2016) with no observed effect to ovalbumin sensitization in adulthood (Regal et al., 2014). Finally, therapeutic studies in moderate hyperoxia models show pups retain variable capacity for acute reversal of airway contractility with agents such as sodium nitroprusside and adenosine triphosphate (Belik et al., 2003), and β2-adrenergic agonist (Raffay et al., 2014; Royce et al., 2016), as well as, attenuated hyperresponsiveness following inhaled S-nitrosoglutathione treatment in juvenile (3 week) and adult (6 week) animals (Raffay et al., 2016).

The translational relevance of any particular neonatal lung injury model is determined by the timing, dose, and duration of any given hyperoxia exposure. To complicate matters, the phenotype of BPD has changed as neonatal care has evolved over the years, now characterized by airway dysfunction, alveolar simplification, microvascular simplification, and minimal fibrosis. The heterogeneity in term rodent models shows the wide array of phenotypic changes that can be induced by hyperoxic exposure - with high dose and prolonged hyperoxia exposures likely modeling the most severe present-day BPD or the fibrotic and obstructive "Old BPD" while moderate and/or short courses of hyperoxia likely better aligning with airway hyperreactivity and diminished alveolarization of the "New BPD" phenotype. Regardless, modeling in term rodents can be difficult because they are able to achieve normal saturations and oxygenation while breathing room air despite their relatively immature stage of lung development. Therefore, the partial pressure of blood oxygen (PaO_2) in hyperoxic term rodent models is likely supraphysiologic, and exceeds that of O_2-treated premature infants. This has implications for extrapulmonary effects of hyperoxia in the developing heart, brain, and other organs (Yee et al., 2018). However, we speculate that the local and direct effects of hyperoxia on the developing rodent and human lung results in much of the observed pathology. As such, robust rodent models of hyperoxia should be reproducible, use concentrations and durations of supplemental O_2 most consistent with those reported in premature infants, and concentrate on phenotypically recapitulating the relevant changes observed in humans.

3.2. Rodent model - sustained hyperoxia with superimposed intermittent hypoxemia

As discussed earlier, premature infants with immature control of breathing and apnea of prematurity often experience hypoxemic episodes that require supplemental O_2. These swings in O_2 exposures and saturations are unique to premature infants, thus the rodent models created to mimic the clinical observations on lung development are relatively sparse. Intermittent hypoxemia in premature infants occurs infrequently around the time of birth, then increases to > 100 daily episodes during peak incidence at 1 month postnatal age (Di Fiore et al., 2010). Though sustained hyperoxia is most commonly used to perturb lung development, some investigators have superimposed intermittent hypoxia (IH) onto these models.

There is diversity in the exposures utilizing IH, similar to those previously discussed with sustained hyperoxia. IH episodes range from low number/long duration to high number/short duration during the exposure period and most outcomes concentrate on swings in oxygenation exacerbating oxidative stress resulting in abnormal lung development. One mouse model used multiple brief cycles of repeated IH with superimposed hyperoxia (10% O_2 for 1 min followed by transient increase to 50% O_2 with gradual washout to room air repeating every 10 min, 24 h/day) showing altered airway hyperreactivity and increased oxidative stress with hypoxia/hyperoxia exposure (Dylag et al., 2017). Other mouse models have successfully used longer cycles (2 h 12% hypoxia/2 h 50% hyperoxia/20 h room air for 6 days) or (65% O_2 with 8% O_2 for 10 min once daily for 28 days) to show that markers of oxidative stress and arrest of alveolarization may be exacerbated by decreased VEGF and/or anti-oxidant capacity (Ratner et al., 2009; Elberson et al., 2015). Another model exposed rats to sustained hyperoxia (60% O_2 for 14 days) followed by IH (10% O_2 every 10 min 4 times daily during days 15–28) showing persistent alveolar simplification and pulmonary capillary rarefication in the hypoxia/hyperoxia animals compared to those recovered in room air (Mankouski et al., 2017). Finally, investigators looking at reversing the harmful effects of oxidative stress used a rat protocol (50% hyperoxia with 12% O_2 for 2 min, 12 times a day for 14 days) with treatment of a superoxide dismutase mimetic partially restoring alveolarization and the microvasculature (Chang et al., 2013). Taken together, these studies highlight the significant differences in both gender, species (mouse or rat), or strain (primarily mouse) when executing sustained hyperoxia studies, which has implications both for translational relevance and transgenic approaches (Whitehead et al., 2006; Leary et al., 2019; Tiono et al., 2019).

There is translational strength in using hyperoxia with IH because it closely mimics the conditions observed in premature infants. The most translationally relevant protocols approximate the number and duration of intermittent hypoxemic events, which tend to be continuous (24 h/day), high in frequency (> 100 episodes/day), and short (1–20 minutes) in duration. The clinical observations are only scratching the surface on how magnitude, frequency, and severity of these events impact premature infants' pulmonary morbidity (Fairchild et al., 2018; Di Fiore et al., 2019; Raffay et al., 2019). There are current clinical trials capitalizing on more detailed bedside monitoring that can also give translational insight into the animal modeling of BPD (Dennery et al., 2019). Refinement and continued investigation in rodents will be critical to elucidate the mechanisms involved in intermittent hypoxemia, immature control of breathing, and respiratory outcomes.

3.3. Rodent model - positive pressure

Respiratory support of premature infants often involves invasive (mechanical ventilation, high frequency ventilation) or non-invasive (non-invasive positive pressure ventilation, continuous positive airway pressure (CPAP), nasal cannula) interfaces to deliver inspired gas. Many studies of positive pressure ventilation are performed in large animal models, which have limitations of cost, labor, and sample size. Until recently, rodents undergoing positive pressure ventilation required a non-recoverable tracheostomy, making longitudinal studies impossible to perform. However, some investigators have developed devices that utilize oral/nasal interfaces to deliver positive pressure ventilation to neonatal rodents and study their effects on airway physiology and lung development.

Rodent models of positive pressure ventilation employ either invasive (intubation and ventilation) or non-invasive (CPAP) for brief

periods (2–4 h) using normoxic or hyperoxic gases. Ventilation of nursing pups makes continuous ventilation difficult and requires they be returned to their mother for nutritional support or given short term IV and/or gavage feeds. Invasive ventilation of the 5–6 day old mouse in normoxia has been shown to arrest alveolar development (Mokres et al., 2010). In an invasive ventilation rat model, 8 day old rats that were intubated and ventilated for 4 h displayed increased airway hyperreactivity to methacholine at 10 days of age both in the presence and absence of hyperoxia exposure (Iben et al., 2006). Similarly, non-invasive CPAP models (3 h/day for 7 days) in normoxia showed increased airway hyperreactivity to methacholine challenge and mild alveolar simplification, potentially indicating distending trauma to the developing murine small airways and lungs with CPAP of 6 cmH_2O (Mayer et al., 2015). Interestingly, when the same investigative group added hyperoxia (50% O_2) to CPAP, the animals receiving the combined exposures had lower baseline resistance and higher compliance compared to hyperoxia alone with the additional benefit of attenuated alveolar simplification (Reyburn et al., 2016).

Given the relative scarcity of positive pressure rodent ventilation models, the techniques used in the selected studies gives promise for their continued development. Using an occlusive mask, as employed in the CPAP models, minimizes injury and creates a proper seal, ensuring pressure is delivered to the lungs non-invasively. Future protocols can be designed to capitalize and expand on these techniques, concentrating on the combined effects of positive pressure ventilation and changes in O_2 exposure (hyperoxia, hypoxia/hyperoxia) as discussed above.

3.4. Rodent model - inflammatory and infectious exposures

Intrauterine infection and inflammation are triggers for premature birth, setting off an inflammatory cascade in the premature infant that can have wide-ranging effects upon multiple organ systems. There have been many epidemiologic studies showing chorioamnionitis induces premature labor and is associated with worse neonatal lung outcomes (Hartling et al., 2012). Infectious or inflammatory stimuli often put the infant in a compromised physiologic state, acting as a “double hit” and are thus exacerbated by the effects of mechanical ventilation and supplemental O_2 therapy. Inflammation is thought to play a prominent role in the pathogenesis of BPD suggesting anti-inflammatories may reduce its harmful effects and minimize lung damage (Wright and Kirpalani, 2011).

Animal models of inflammation and/or infection leverage these clinical circumstances to create a “double hit”: a perinatal inflammatory response with subsequent O_2 exposure that exacerbates the injurious stimulus. Investigators have induced prenatal inflammation with systemic maternal lipopolysaccharide (LPS) injection during pregnancy and placed offspring in either normoxia or hyperoxia, displaying variable degrees of increased airway resistance and hyperreactivity, decreased lung compliance, increased airway smooth muscle thickness, as well as, alveolar simplification (Velten et al., 2010; Nold et al., 2013; Faksh et al., 2016). Similarly, rats receiving intraamniotic LPS followed by neonatal hyperoxia had airway hyperreactivity, increased airway smooth muscle actin deposition, and alveolar remodeling (Choi et al., 2013). Another study of intraamniotic LPS exposed rats raised in normoxia with caffeine supplementation showed reduced inflammatory cytokines IL-1β and CD68 with partial restoration of lung function measurements (Koroglu et al., 2014). Finally, additional treatment strategies for perinatal inflammation involve either transgenic rodent models, cytokine antagonists, or neutralizing antibodies to block molecules commonly implicated in BPD (Wright and Kirpalani, 2011). These approaches have largely been extrapolated from human data in infants with evolving BPD by placing treated mice in hyperoxia and demonstrating beneficial effects ranging from blocking polymorphonuclear cell infiltration to improving O_2-induced perturbations in lung morphology.

Rodent models of inflammation and infection are translationally relevant because many of them are taken directly from observations during pregnancy and the neonatal period. Though transgenic approaches are unlikely to result in clinical use in the near future, they can still elucidate mechanisms of tissue injury and repair. There is an urgent need for safe, effective, and evidence-based treatments to reduce pulmonary morbidity in premature infants; translational animal models can be a first step in developing such therapies.

3.5. Translational aspects of rodent models of lung and airway development

Rates of BPD over the last decade have not decreased, and alarmingly, may be increasing with improved survival of the most premature infants (Stoll et al., 2015). Furthermore, diagnosis and treatment of obstructive lung disease and airway hyperreactivity is a major challenge in former premature infants with and without underlying BPD. It is vital that underlying biologic mechanisms be addressed, and this is best realized in robust newborn animal models. Rodent data points to multiple anatomic and neural contributors to long-term airway hyperreactivity elicited by neonatal lung injury, particularly exposure to hyperoxia, but emerging clinical and basic science evidence points to an interaction of exposures to supplemental O_2 with antenatal and postnatal inflammation, as well as, positive airway pressure effects elicited by the various ventilatory modes used to support the premature infant. With important clinical implications, neonatal rodent data would suggest that exposure to modest supplemental O_2 and/or the pressure effects of CPAP predispose to later airway reactivity. In contrast, more severe O_2 and inflammatory exposures resulting in BPD parenchymal lung injury in the form of alveolar simplification, a poorly tethered airway, increased baseline resistance, and airway smooth muscle hypertrophy may be implicated in airway collapse resulting in hyperreactivity (Table 2). Identification of high-risk exposures and mechanisms of injury may lead to better targeted therapies that will include longer-term respiratory follow-up and testing beyond just a patient’s initial neonatal intensive care unit hospitalization.

4. Conclusions

While there is still much to be learned about the contributors to the normal and abnormal maturation of the newborn’s respiratory system, neonatal rodent models have been used successfully to investigate the early development of respiratory control, lung development, and airway reactivity in both health and disease. As we refine the measurements and importance of respiratory events, such as intermittent hypoxemia, and our understanding of “old” and “new” BPD grows, the newborn term rodents allow for considerable flexibility to test various models and conditions of the developing respiratory system. Through the use of perinatal and postnatal exposures to inflammation, inhaled gases, and positive pressure; researches have created clinically relevant models of neonatal respiratory disease to uncover mechanisms of injury and test therapies that will lead to improved respiratory health in infancy and beyond.

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References

Abu-Shaweesh, J.M., 2004. Maturation of respiratory reflex responses in the fetus and neonate. Semin. Neonatol. 9 (3), 169–180.
Abu-Shaweesh, J.M., Dreshaj, I.A., Thomas, A.J., Haxhiu, M.A., Strohl, K.P., Martin, R.J., 1999. Changes in respiratory timing induced by hypercapnia in maturing rats. J. Appl. Physiol. 87 (2), 484–490 (1985).
Ahlfeld, S.K., Conway, S.J., 2014. Assessment of inhibited alveolar-capillary membrane

structural development and function in bronchopulmonary dysplasia. Birth Defects Res. A Clin. Mol. Teratol. 100 (3), 168–179.
Amy, R.W., Bowes, D., Burri, P.H., Haines, J., Thurlbeck, W.M., 1977. Postnatal growth of the mouse lung. J. Anat. 124 (Pt 1), 131–151.
Augustine, S., Avey, M.T., Harrison, B., Locke, T., Ghannad, M., Moher, D., Thebaud, B., 2017. Mesenchymal stromal cell therapy in bronchopulmonary dysplasia: systematic review and meta-analysis of preclinical studies. Stem Cells Transl. Med. 6 (12), 2079–2093.
Auten, R.L., Mason, S.N., Whorton, M.H., Lampe, W.R., Foster, W.M., Goldberg, R.N., Li, B., Stamler, J.S., Auten, K.M., 2007. Inhaled ethyl nitrite prevents hyperoxia-impaired postnatal alveolar development in newborn rats. Am. J. Respir. Crit. Care Med. 176 (3), 291–299.
Balan, K.V., Kc, P., Mayer, C.A., Wilson, C.G., Belkadi, A., Martin, R.J., 2012. Intrapulmonary lipopolysaccharide exposure upregulates cytokine expression in the neonatal brainstem. Acta Paediatr. 101 (5), 466–471.
Balinotti, J.E., Chakr, V.C., Tiller, C., Kimmel, R., Coates, C., Kisling, J., Yu, Z., Nguyen, J., Tepper, R.S., 2010. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am. J. Respir. Crit. Care Med. 181 (10), 1093–1097.
Baraldi, E., Carraro, S., Filippone, M., 2009. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. Early Hum. Dev. 85 (10 Suppl), S1–3.
Bavis, R.W., Fallon, S.C., Dmitrieff, E.F., 2013. Chronic hyperoxia and the development of the carotid body. Respir. Physiol. Neurobiol. 185 (1), 94–104.
Bavis, R.W., Johnson, R.A., Ording, K.M., Otis, J.P., Mitchell, G.S., 2006. Respiratory plasticity after perinatal hypercapnia in rats. Respir. Physiol. Neurobiol. 153 (1), 78–91.
Bavis, R.W., Li, K.Y., DeAngelis, K.J., March, R.J., Wallace, J.A., Logan, S., Putnam, R.W., 2017. Ventilatory and chemoreceptor responses to hypercapnia in neonatal rats chronically exposed to moderate hyperoxia. Respir. Physiol. Neurobiol. 237, 22–34.
Bavis, R.W., Millstrom, A.H., Kim, S.M., MacDonald, C.A., O'Toole, C.A., Asklof, K., McDonough, A.B., 2019. Combined effects of intermittent hyperoxia and intermittent hypercapnic hypoxia on respiratory control in neonatal rats. Respir. Physiol. Neurobiol. 260, 70–81.
Bavis, R.W., Olson Jr, E.B., Vidruk, E.H., Fuller, D.D., Mitchell, G.S., 2004. Developmental plasticity of the hypoxic ventilatory response in rats induced by neonatal hypoxia. J. Physiol. 557 (Pt 2), 645–660.
Bavis, R.W., Russell, K.E., Simons, J.C., Otis, J.P., 2007. Hypoxic ventilatory responses in rats after hypercapnic hyperoxia and intermittent hyperoxia. Respir. Physiol. Neurobiol. 155 (3), 193–202.
Bavis, R.W., Young, K.M., Barry, K.J., Boller, M.R., Kim, E., Klein, P.M., Ovrutsky, A.R., Rampersad, D.A., 2010. Chronic hyperoxia alters the early and late phases of the hypoxic ventilatory response in neonatal rats. J. Appl. Physiol. 109 (3), 796–803 (1985).
Beck, J., Reilly, M., Grasselli, G., Qui, H., Slutsky, A.S., Dunn, M.S., Sinderby, C.A., 2011. Characterization of neural breathing pattern in spontaneously breathing preterm infants. Pediatr. Res. 70 (6), 607–613.
Been, J.V., Lugtenberg, M.J., Smets, E., van Schayck, C.P., Kramer, B.W., Mommers, M., Sheikh, A., 2014. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med. 11 (1), e1001596.
Belik, J., Jankov, R.P., Pan, J., Tanswell, A.K., 2003. Chronic O2 exposure enhances vascular and airway smooth muscle contraction in the newborn but not adult rat. J. Appl. Physiol. 94 (6), 2303–2312 (1985).
Berger, J., Bhandari, V., 2014. Animal models of bronchopulmonary dysplasia. The term mouse models. Am. J. Physiol. Lung Cell Mol. Physiol. 307 (12), L936–947.
Bierman, A.M., Tankersley, C.G., Wilson, C.G., Chavez-Valdez, R., Gauda, E.B., 2014. Perinatal hyperoxic exposure reconfigures the central respiratory network contributing to intolerance to anoxia in newborn rat pups. J. Appl. Physiol. 116 (1), 47–53 (1985).
Bisgard, G.E., Olson Jr., E.B., Bavis, R.W., Wenninger, J., Nordheim, E.V., Mitchell, G.S., 2005. Carotid chemoafferent plasticity in adult rats following developmental hyperoxia. Respir. Physiol. Neurobiol. 145 (1), 3–11.
Bookatz, G.B., Mayer, C.A., Wilson, C.G., Vento, M., Gelfand, S.L., Haxhiu, M.A., Martin, R.J., 2007. Effect of supplemental oxygen on reinitiation of breathing after neonatal resuscitation in rat pups. Pediatr. Res. 61 (6), 698–702.
Brostrom, E.B., Thunqvist, P., Adenfelt, G., Borling, E., Katz-Salamon, M., 2010. Obstructive lung disease in children with mild to severe BPD. Respir. Med. 104 (3), 362–370.
Carroll, J.L., Kim, I., Dbouk, H., Yang, D.J., Bavis, R.W., Donnelly, D.F., 2009. Time-dependence of hyperoxia-induced impairment in peripheral chemoreceptor activity and glomus cell calcium response. Adv. Exp. Med. Biol. 648, 299–306.
Chang, M., Bany-Mohammed, F., Kenney, M.C., Beharry, K.D., 2013. Effects of a superoxide dismutase mimetic on biomarkers of lung angiogenesis and alveolarization during hyperoxia with intermittent hypoxia. Am. J. Transl. Res. 5 (6), 594–607.
Choi, C.W., Kim, B.I., Mason, S.N., Potts-Kant, E.N., Brahmajothi, M.V., Auten, R.L., 2013. Intra-amniotic LPS amplifies hyperoxia-induced airway hyperreactivity in neonatal rats. Pediatr. Res. 74 (1), 11–18.
Dennery, P.A., Di Fiore, J.M., Ambalavanan, N., Bancalari, E., Carroll, J.L., Claure, N., Hamvas, A., Hibbs, A.M., Indic, P., Kemp, J., Krahn, K.N., Lake, D., Laposky, A., Martin, R.J., Natarajan, A., Rand, C., Schau, M., Weese-Mayer, D.E., Zimmet, A.M., Moorman, J.R., 2019. Pre-Vent: the prematurity-related ventilatory control study. Pediatr. Res.
Di Fiore, J.M., Bloom, J.N., Orge, F., Schutt, A., Schluchter, M., Cheruvu, V.K., Walsh, M., Finer, N., Martin, R.J., 2010. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. J. Pediatr. 157 (1), 69–73.
Di Fiore, J.M., Dylag, A.M., Honomichl, R.D., Hibbs, A.M., Martin, R.J., Tatsuoka, C., Raffay, T.M., 2019. Early inspired oxygen and intermittent hypoxemic events in extremely premature infants are associated with asthma medication use at 2 years of age. J. Perinatol. 39 (2), 203–211.
Di Fiore, J.M., Martin, R.J., Gauda, E.B., 2013. Apnea of prematurity–perfect storm. Respir. Physiol. Neurobiol. 189 (2), 213–222.
Di Fiore, J.M., Poets, C.F., Gauda, E., Martin, R.J., MacFarlane, P., 2016. Cardiorespiratory events in preterm infants: interventions and consequences. J. Perinatol. 36 (4), 251–258.
Doyle, L.W., Carse, E., Adams, A.M., Ranganathan, S., Opie, G., Cheong, J.L.Y., G. Victorian Infant Collaborative Study, 2017. Ventilation in extremely preterm infants and respiratory function at 8 years. N. Engl. J. Med. 377 (4), 329–337.
Dylag, A.M., Mayer, C.A., Raffay, T.M., Martin, R.J., Jafri, A., MacFarlane, P.M., 2017. Long-term effects of recurrent intermittent hypoxia and hyperoxia on respiratory system mechanics in neonatal mice. Pediatr. Res. 81 (4), 565–571.
Eden, G.J., Hanson, M.A., 1987. Effects of chronic hypoxia from birth on the ventilatory response to acute hypoxia in the newborn rat. J. Physiol. 392, 11–19.
Edwards, M.O., Kotecha, S.J., Lowe, J., Richards, L., Watkins, W.J., Kotecha, S., 2016. Management of prematurity-associated wheeze and its association with atopy. PLoS One 11 (5), e0155695.
Elberson, V.D., Nielsen, L.C., Wang, H., Kumar, H.S., 2015. Effects of intermittent hypoxia and hyperoxia on angiogenesis and lung development in newborn mice. J. Neonatal. Med. 8 (4), 313–322.
Erickson, J.T., Mayer, C., Jawa, A., Ling, L., Olson Jr, E.B., Vidruk, E.H., Mitchell, G.S., Katz, D.M., 1998. Chemoafferent degeneration and carotid body hypoplasia following chronic hyperoxia in newborn rats. J. Physiol. 509 (Pt 2), 519–526.
Fairchild, K.D., Nagraj, V.P., Sullivan, B.A., Moorman, J.R., Lake, D.E., 2018. Oxygen desaturations in the early neonatal period predict development of bronchopulmonary dysplasia. Pediatr. Res.
Faksh, A., Britt Jr., R.D., Vogel, E.R., Kuipers, I., Thompson, M.A., Sieck, G.C., Pabelick, C.M., Martin, R.J., Prakash, Y.S., 2016. Effects of antenatal lipopolysaccharide and postnatal hyperoxia on airway reactivity and remodeling in a neonatal mouse model. Pediatr. Res. 79 (3), 391–400.
Fawke, J., Lum, S., Kirkby, J., Hennessy, E., Marlow, N., Rowell, V., Thomas, S., Stocks, J., 2010. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. Am. J. Respir. Crit. Care Med. 182 (2), 237–245.
Fuller, D.D., Bavis, R.W., Vidruk, E.H., Wang, Z.Y., Olson Jr, E.B., Bisgard, G.E., Mitchell, G.S., 2002. Life-long impairment of hypoxic phrenic responses in rats following 1 month of developmental hyperoxia. J. Physiol. 538 (Pt 3), 947–955.
Fuller, D.D., Wang, Z.Y., Ling, L., Olson, E.B., Bisgard, G.E., Mitchell, G.S., 2001. Induced recovery of hypoxic phrenic responses in adult rats exposed to hyperoxia for the first month of life. J. Physiol. 536 (Pt 3), 917–926.
Fung, M.L., Wang, W., Darnall, R.A., St John, W.M., 1996. Characterization of ventilatory responses to hypoxia in neonatal rats. Respir. Physiol. 103 (1), 57–66.
Goldsmith, J.P., 2015. Overview and initial management of delivery room resuscitation. Fanaroff & Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant 1. Elsevier, pp. 460–470.
Gozal, D., Gozal, E., 1999. Episodic hypoxia enhances late hypoxic ventilation in developing rat: putative role of neuronal NO synthase. Am. J. Physiol. 276 (1 Pt 2), R17–22.
Gozal, D., Reeves, S.R., Row, B.W., Neville, J.J., Guo, S.Z., Lipton, A.J., 2003. Respiratory effects of gestational intermittent hypoxia in the developing rat. Am. J. Respir. Crit. Care Med. 167 (11), 1540–1547.
Grischkan, J., Storfer-Isser, A., Rosen, C.L., Larkin, E.K., Kirchner, H.L., South, A., Wilson-Costello, D.C., Martin, R.J., Redline, S., 2004. Variation in childhood asthma among former preterm infants. J. Pediatr. 144 (3), 321–326.
Hansmann, G., Fernandez-Gonzalez, A., Aslam, M., Vitali, S.H., Martin, T., Mitsialis, S.A., Kourembanas, S., 2012. Mesenchymal stem cell-mediated reversal of bronchopulmonary dysplasia and associated pulmonary hypertension. Pulm. Circ. 2 (2), 170–181.
Hartling, L., Liang, Y., Lacaze-Masmonteil, T., 2012. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch. Dis. Child. Fetal Neonatal Ed. 97 (1), F8–F17.
Hartman, W.R., Smelter, D.F., Sathish, V., Karass, M., Kim, S., Aravamudan, B., Thompson, M.A., Amrani, Y., Pandya, H.C., Martin, R.J., Prakash, Y.S., Pabelick, C.M., 2012. Oxygen dose responsiveness of human fetal airway smooth muscle cells. Am. J. Physiol. Lung Cell Mol. Physiol. 303 (8), L711–719.
Hill, C.B., Grandgeorge, S.H., Bavis, R.W., 2013. Developmental hyperoxia alters CNS mechanisms underlying hypoxic ventilatory depression in neonatal rats. Respir. Physiol. Neurobiol. 189 (3), 498–505.
Iben, S.C., Haxhiu, M.A., Farver, C.F., Miller, M.J., Martin, R.J., 2006. Short-term mechanical ventilation increases airway reactivity in rat pups. Pediatr. Res. 60 (2), 136–140.
Jaakkola, J.J., Ahmed, P., Ieromnimon, A., Goepfert, P., Laiou, E., Quansah, R., Jaakkola, M.S., 2006. Preterm delivery and asthma: a systematic review and meta-analysis. J. Allergy Clin. Immunol. 118 (4), 823–830.
James, M.L., Ross, A.C., Nicola, T., Steele, C., Ambalavanan, N., 2013. VARA attenuates hyperoxia-induced impaired alveolar development and lung function in newborn mice. Am. J. Physiol. Lung Cell Mol. Physiol. 304 (11), L803–812.
Jansen, A.H., Chernick, V., 1991. Fetal breathing and development of control of breathing. J Appl Physiol. Appl. Physiol. 70 (4), 1431–1446.
Jobe, A.H., 2011. The new bronchopulmonary dysplasia. Curr. Opin. Pediatr. 23 (2), 167–172.
Julien, C.A., Joseph, V., Bairam, A., 2011. Alteration of carotid body chemoreflexes after neonatal intermittent hypoxia and caffeine treatment in rat pups. Respir. Physiol. Neurobiol. 177 (3), 301–312.
Katz-Salamon, M., Lagercrantz, H., 1994. Hypoxic ventilatory defence in very preterm infants: attenuation after long term oxygen treatment. Arch. Dis. Child. Fetal Neonatal Ed. 70 (2), F90–95.

Koroglu, O.A., MacFarlane, P.M., Balan, K.V., Zenebe, W.J., Jafri, A., Martin, R.J., Kc, P., 2014. Anti-inflammatory effect of caffeine is associated with improved lung function after lipopolysaccharide-induced amnionitis. Neonatology 106 (3), 235–240.
Kumar, V.H., Lakshminrusimha, S., Kishkurno, S., Paturi, B.S., Gugino, S.F., Nielsen, L., Wang, H., Ryan, R.M., 2016. Neonatal hyperoxia increases airway reactivity and inflammation in adult mice. Pediatr. Pulmonol. 51 (11), 1131–1141.
Leary, S., Das, P., Ponnalagu, D., Singh, H., Bhandari, V., 2019. Genetic strain and sex differences in a hyperoxia-induced mouse model of varying severity of bronchopulmonary dysplasia. Am. J. Pathol. 189 (5), 999–1014.
Ling, L., Olson Jr, E.B., Vidruk, E.H., Mitchell, G.S., 1996. Attenuation of the hypoxic ventilatory response in adult rats following one month of perinatal hyperoxia. J. Physiol. 495 (Pt 2), 561–571.
Mankouski, A., Kantores, C., Wong, M.J., Ivanovska, J., Jain, A., Benner, E.J., Mason, S.N., Tanswell, A.K., Auten, R.L., Jankov, R.P., 2017. Intermittent hypoxia during recovery from neonatal hyperoxic lung injury causes long-term impairment of alveolar development: a new rat model of BPD. Am. J. Physiol. Lung Cell Mol. Physiol. 312 (2), L208–L216.
Martin, R.J., Wang, K., Koroglu, O., Di Fiore, J., Kc, P., 2011. Intermittent hypoxic episodes in preterm infants: do they matter? Neonatology 100 (3), 303–310.
Master, Z.R., Kesavan, K., Mason, A., Shirahata, M., Gauda, E.B., 2015. Effect of lipopolysaccharide exposure on structure and function of the carotid body in newborn rats. Adv. Exp. Med. Biol. 860, 115–121.
Master, Z.R., Porzionato, A., Kesavan, K., Mason, A., Chavez-Valdez, R., Shirahata, M., Gauda, E.B., 2016. Lipopolysaccharide exposure during the early postnatal period adversely affects the structure and function of the developing rat carotid body. J. Appl. Physiol. 121 (3), 816–827 (1985).
Mayer, C.A., Ao, J., Di Fiore, J.M., Martin, R.J., MacFarlane, P.M., 2013. Impaired hypoxic ventilatory response following neonatal sustained and subsequent chronic intermittent hypoxia in rats. Respir. Physiol. Neurobiol. 187 (2), 167–175.
Mayer, C.A., Martin, R.J., MacFarlane, P.M., 2015. Increased airway reactivity in a neonatal mouse model of continuous positive airway pressure. Pediatr. Res. 78 (2), 145–151.
McDonald, F.B., Chandrasekharan, K., Wilson, R.J., Hasan, S.U., 2016a. Cardiorespiratory control and cytokine profile in response to heat stress, hypoxia, and lipopolysaccharide (LPS) exposure during early neonatal period. Physiol. Rep. 4 (2).
McDonald, F.B., Chandrasekharan, K., Wilson, R.J., Hasan, S.U., 2016b. Interactive effects of maternal cigarette smoke, heat stress, hypoxia, and lipopolysaccharide on neonatal cardiorespiratory and cytokine responses. Am. J. Physiol. Regul. Integr. Comp. Physiol. 311 (6), R1113–R1124.
Mokres, L.M., Parai, K., Hilgendorff, A., Ertsey, R., Alvira, C.M., Rabinovitch, M., Bland, R.D., 2010. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice. Am. J. Physiol. Lung Cell Mol. Physiol. 298 (1), L23–35.
Nold, M.F., Mangan, N.E., Rudloff, I., Cho, S.X., Shariatian, N., Samarasinghe, T.D., Skuza, E.M., Pedersen, J., Veldman, A., Berger, P.J., Nold-Petry, C.A., 2013. Interleukin-1 receptor antagonist prevents murine bronchopulmonary dysplasia induced by perinatal inflammation and hyperoxia. Proc. Natl. Acad. Sci. U. S. A. 110 (35), 14384–14389.
Northway Jr, W.H., Rosan, R.C., Porter, D.Y., 1967. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N. Engl. J. Med. 276 (7), 357–368.
O'Reilly, M., Harding, R., Sozo, F., 2014. Altered small airways in aged mice following neonatal exposure to hyperoxic gas. Neonatology 105 (1), 39–45.
O'Reilly, M., Thebaud, B., 2014. Animal models of bronchopulmonary dysplasia. The term rat models. Am. J. Physiol. Lung Cell Mol. Physiol. 307 (12), L948–958.
Onugha, H., MacFarlane, P.M., Mayer, C.A., Abrah, A., Jafri, A., Martin, R.J., 2015. Airway hyperreactivity is delayed after mild neonatal hyperoxic exposure. Neonatology 108 (1), 65–72.
Peng, Y.J., Rennison, J., Prabhakar, N.R., 2004. Intermittent hypoxia augments carotid body and ventilatory response to hypoxia in neonatal rat pups. J. Appl. Physiol. 97 (5), 2020–2025 (1985).
Poets, C.F., Roberts, R.S., Schmidt, B., Whyte, R.K., Asztalos, E.V., Bader, D., Bairam, A., Moddemann, D., Peliowski, A., Rabi, Y., Solimano, A., Nelson, H., I. Canadian Oxygen Trial, 2015. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA 314 (6), 595–603.
Prabhakar, N.R., Kline, D.D., 2002. Ventilatory changes during intermittent hypoxia: importance of pattern and duration. High Alt. Med. Biol. 3 (2), 195–204.
Priante, E., Moschino, L., Mardegan, V., Manzoni, P., Salvadori, S., Baraldi, E., 2016. Respiratory outcome after preterm birth: a long and difficult journey. Am. J. Perinatol. 33 (11), 1040–1042.
Raffay, T., Kc, P., Reynolds, J., Di Fiore, J., MacFarlane, P., Martin, R.J., 2014. Repeated beta-adrenergic receptor agonist therapy attenuates the response to rescue bronchodilation in a hyperoxic newborn mouse model. Neonatology 106 (2), 126–132.
Raffay, T.M., Dylag, A.M., Di Fiore, J.M., Smith, L.A., Einisman, H.J., Li, Y., Lakner, M.M., Khalil, A.M., MacFarlane, P.M., Martin, R.J., Gaston, B., 2016. S-nitrosoglutathione attenuates airway hyperresponsiveness in murine bronchopulmonary dysplasia. Mol. Pharmacol. 90 (4), 418–426.
Raffay, T.M., Dylag, A.M., Sattar, A., Abu Jawdeh, E.G., Cao, S., Pax, B.M., Loparo, K.A., Martin, R.J., Di Fiore, J.M., 2019. Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age. Pediatr. Res. 85 (3), 318–323.
Ramanathan, R., Corwin, M.J., Hunt, C.E., Lister, G., Tinsley, L.R., Baird, T., Silvestri, J.M., Crowell, D.H., Hufford, D., Martin, R.J., Neuman, M.R., Weese-Mayer, D.E., Cupples, L.A., Peucker, M., Willinger, M., Keens, T.G., G. Collaborative Home Infant Monitoring Evaluation Study, 2001. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. JAMA 285 (17), 2199–2207.
Ratner, V., Slinko, S., Utkina-Sosunova, I., Starkov, A., Polin, R.A., Ten, V.S., 2009. Hypoxic stress exacerbates hyperoxia-induced lung injury in a neonatal mouse model of bronchopulmonary dysplasia. Neonatology 95 (4), 299–305.
Reeves, S.R., Gozal, D., 2006a. Changes in ventilatory adaptations associated with long-term intermittent hypoxia across the age spectrum in the rat. Respir. Physiol. Neurobiol. 150 (2-3), 135–143.
Reeves, S.R., Gozal, D., 2006b. Respiratory and metabolic responses to early postnatal chronic intermittent hypoxia and sustained hypoxia in the developing rat. Pediatr. Res. 60 (6), 680–686.
Reeves, S.R., Mitchell, G.S., Gozal, D., 2006. Early postnatal chronic intermittent hypoxia modifies hypoxic respiratory responses and long-term phrenic facilitation in adult rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 290 (6), R1664–1671.
Regal, J.F., Lawrence, B.P., Johnson, A.C., Lojovich, S.J., O'Reilly, M.A., 2014. Neonatal oxygen exposure alters airway hyper-responsiveness but not the response to allergen challenge in adult mice. Pediatr. Allergy Immunol. 25 (2), 180–186.
Reyburn, B., Di Fiore, J.M., Raffay, T., Martin, R.J., Prakash, Y.S., Jafri, A., MacFarlane, P.M., 2016. The effect of continuous positive airway pressure in a mouse model of hyperoxic neonatal lung injury. Neonatology 109 (1), 6–13.
Reyburn, B., Martin, R.J., Prakash, Y.S., MacFarlane, P.M., 2012. Mechanisms of injury to the preterm lung and airway: implications for long-term pulmonary outcome. Neonatology 101 (4), 345–352.
Rezzonico, R., Mortola, J.P., 1989. Respiratory adaptation to chronic hypercapnia in newborn rats. J. Appl. Physiol. 67 (1), 311–315.
Ribeiro, A.P., Mayer, C.A., Wilson, C.G., Martin, R.J., MacFarlane, P.M., 2017. Intratracheal LPS administration attenuates the acute hypoxic ventilatory response: role of brainstem IL-1beta receptors. Respir. Physiol. Neurobiol. 242, 45–51.
Rourke, K.S., Mayer, C.A., MacFarlane, P.M., 2016. A critical postnatal period of heightened vulnerability to lipopolysaccharide. Respir. Physiol. Neurobiol. 232, 26–34.
Royce, S.G., Nold, M.F., Bui, C., Donovan, C., Lam, M., Lamanna, E., Rudloff, I., Bourke, J.E., Nold-Petry, C.A., 2016. Airway remodeling and hyperreactivity in a model of bronchopulmonary dysplasia and their modulation by IL-1Ra. Am. J. Respir. Cell Mol. Biol.
Samarasinghe, T.D., Sands, S.A., Skuza, E.M., Joshi, M.S., Nold-Petry, C.A., Berger, P.J., 2015. The effect of prenatal maternal infection on respiratory function in mouse offspring: evidence for enhanced chemosensitivity. J Appl Physiol. Appl. Physiol. 119 (3), 299–307.
Schaffer, Ta.W., Marla, 2011. Upper airway structure: function, regulation, and development. Fetal and Neonatal Physiology 1. Elsevier, pp. 919–929.
Silva, D.M., Nardiello, C., Pozarska, A., Morty, R.E., 2015. Recent advances in the mechanisms of lung alveolarization and the pathogenesis of bronchopulmonary dysplasia. Am. J. Physiol. Lung Cell Mol. Physiol. 309 (11), L1239–1272.
Sinha, S.K., Donn, S.M., 2006. Fetal-to-neonatal maladaptation. Semin. Fetal Neonatal Med. 11 (3), 166–173.
Steggerda, J.A., Mayer, C.A., Martin, R.J., Wilson, C.G., 2010. Effect of intermittent hypercapnia on respiratory control in rat pups. Neonatology 97 (2), 117–123.
Stevens, T.P., Dylag, A., Panthagani, I., Pryhuber, G., Halterman, J., 2010. Effect of cumulative oxygen exposure on respiratory symptoms during infancy among VLBW infants without bronchopulmonary dysplasia. Pediatr. Pulmonol. 45 (4), 371–379.
Stoll, B.J., Hansen, N.I., Bell, E.F., Walsh, M.C., Carlo, W.A., Shankaran, S., Laptook, A.R., Sanchez, P.J., Van Meurs, K.P., Wyckoff, M., Das, A., Hale, E.C., Ball, M.B., Newman, N.S., Schibler, K., Poindexter, B.B., Kennedy, K.A., Cotten, C.M., Watterberg, K.L., D'Angio, C.T., DeMauro, S.B., Truog, W.E., Devaskar, U., Higgins, R.D., H. Eunice Kennedy Shriver National Institute of Child and N. Human Development Neonatal Research, 2015. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA 314 (10), 1039–1051.
Stryker, C., Camperchioli, D.W., Mayer, C.A., Alilain, W.J., Martin, R.J., MacFarlane, P.M., 2018. Respiratory dysfunction following neonatal sustained hypoxia exposure during a critical window of brain stem extracellular matrix formation. Am. J. Physiol. Regul. Integr. Comp. Physiol. 314 (2), R216–R227.
Subramanian, S., Dostal, J., Erokwu, B., Han, F., Dick, T.E., Strohl, K.P., 2007. Domperidone and ventilatory behavior: Sprague-Dawley versus Brown Norway rats. Respir. Physiol. Neurobiol. 155 (1), 22–28.
Sward-Comunelli, S.L., Mabry, S.M., Truog, W.E., Thibeault, D.W., 1997. Airway muscle in preterm infants: changes during development. J. Pediatr. 130 (4), 570–576.
Takeda, K., Okamoto, M., de Langhe, S., Dill, E., Armstrong, M., Reisdorf, N., Irwin, D., Koster, M., Wilder, J., Stenmark, K.R., West, J., Klemm, D., Gelfand, E.W., Nozik-Grayck, E., Majka, S.M., 2009. Peroxisome proliferator-activated receptor-g agonist treatment increases septation and angiogenesis and decreases airway hyperresponsiveness in a model of experimental neonatal chronic lung disease. Anat. Rec. 292 (7), 1045–1061.
Tiono, J., Surate Solaligue, D.E., Mizikova, I., Nardiello, C., Vadasz, I., Bottcher-Friebertshauser, E., Ehrhardt, H., Herold, S., Seeger, W., Morty, R.E., 2019. Mouse genetic background impacts susceptibility to hyperoxia-driven perturbations to lung maturation. Pediatr. Pulmonol.
Velten, M., Heyob, K.M., Rogers, L.K., Welty, S.E., 2010. Deficits in lung alveolarization and function after systemic maternal inflammation and neonatal hyperoxia exposure. J. Appl. Physiol. 108 (5), 1347–1356 (1985).
Vento, M., Asensi, M., Sastre, J., Garcia-Sala, F., Pallardo, F.V., Vina, J., 2001. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 107 (4), 642–647.
Vogel, E.R., Britt Jr, R.D., Trinidad, M.C., Faksh, A., Martin, R.J., MacFarlane, P.M., Pabelick, C.M., Prakash, Y.S., 2015. Perinatal oxygen in the developing lung. Can. J. Physiol. Pharmacol. 93 (2), 119–127.
Vollsaeter, M., Clemm, H.H., Satrell, E., Eide, G.E., Roksund, O.D., Markestad, T., Halvorsen, T., 2015. Adult respiratory outcomes of extreme preterm birth. A regional

cohort study. Ann. Am. Thorac. Soc. 12 (3), 313–322.
Wai, K.C., Kohn, M.A., Ballard, R.A., Truog, W.E., Black, D.M., Asselin, J.M., Ballard, P.L., Rogers, E.E., Keller, R.L., G. Trial of Late Surfactant Study, 2016. Early cumulative supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. J. Pediatr. 177 97-102 e102.
Walsh, M.C., Yao, Q., Gettner, P., Hale, E., Collins, M., Hensman, A., Everette, R., Peters, N., Miller, N., Muran, G., Auten, K., Newman, N., Rowan, G., Grisby, C., Arnell, K., Miller, L., Ball, B., McDavid, G., H. National Institute of Child and N. Human Development Neonatal Research, 2004. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics 114 (5), 1305–1311.
Wang, H., Jafri, A., Martin, R.J., Nnanabu, J., Farver, C., Prakash, Y.S., MacFarlane, P.M., 2014. Severity of neonatal hyperoxia determines structural and functional changes in developing mouse airway. Am. J. Physiol. Lung Cell Mol. Physiol. 307 (4), L295–301.
Warner, B.B., Stuart, L.A., Papes, R.A., Wispe, J.R., 1998. Functional and pathological effects of prolonged hyperoxia in neonatal mice. Am. J. Physiol. 275 (1 Pt 1), L110–117.
Weber, M.A., Klein, N.J., Hartley, J.C., Lock, P.E., Malone, M., Sebire, N.J., 2008. Infection and sudden unexpected death in infancy: a systematic retrospective case review. Lancet 371 (9627), 1848–1853.
Welsford, M., Nishiyama, C., Shortt, C., Weiner, G., Roehr, C.C., Isayama, T., Dawson, J.A., Wyckoff, M.H., Rabi, Y., F. International Liaison Committee on Resuscitation Neonatal Life Support Task, 2019. Initial oxygen use for preterm newborn resuscitation: a systematic review with meta-analysis. Pediatrics 143 (1).
Wenninger, J.M., Olson, E.B., Wang, Z., Keith, I.M., Mitchell, G.S., Bisgard, G.E., 2006. Carotid sinus nerve responses and ventilatory acclimatization to hypoxia in adult rats following 2 weeks of postnatal hyperoxia. Respir. Physiol. Neurobiol. 150 (2-3), 155–164.
Whitehead, G.S., Burch, L.H., Berman, K.G., Piantadosi, C.A., Schwartz, D.A., 2006. Genetic basis of murine responses to hyperoxia-induced lung injury. Immunogenetics 58 (10), 793–804.
Willis, G.R., Fernandez-Gonzalez, A., Anastas, J., Vitali, S.H., Liu, X., Ericsson, M., Kwong, A., Mitsialis, S.A., Kourembanas, S., 2018. Mesenchymal stromal cell exosomes ameliorate experimental bronchopulmonary dysplasia and restore lung function through macrophage immunomodulation. Am. J. Respir. Crit. Care Med. 197 (1), 104–116.
Wright, C.J., Kirpalani, H., 2011. Targeting inflammation to prevent bronchopulmonary dysplasia: can new insights be translated into therapies? Pediatrics 128 (1), 111–126.
Wyatt, C.N., Wright, C., Bee, D., Peers, C., 1995. O2-sensitive K+ currents in carotid body chemoreceptor cells from normoxic and chronically hypoxic rats and their roles in hypoxic chemotransduction. Proc. Natl. Acad. Sci. U. S. A. 92 (1), 295–299.
Wyckoff, M.H., Aziz, K., Escobedo, M.B., Kapadia, V.S., Kattwinkel, J., Perlman, J.M., Simon, W.M., Weiner, G.M., Zaichkin, J.G., 2015. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Reprint). Pediatrics 136 (Suppl 2), S196–218.
Yao, L., Shi, Y., Zhao, X., Hou, A., Xing, Y., Fu, J., Xue, X., 2017. Vitamin D attenuates hyperoxia-induced lung injury through downregulation of Toll-like receptor 4. Int. J. Mol. Med. 39 (6), 1403–1408.
Yee, M., Buczynski, B.W., O'Reilly, M.A., 2014. Neonatal hyperoxia stimulates the expansion of alveolar epithelial type II cells. Am. J. Respir. Cell Mol. Biol. 50 (4), 757–766.
Yee, M., Chess, P.R., McGrath-Morrow, S.A., Wang, Z., Gelein, R., Zhou, R., Dean, D.A., Notter, R.H., O'Reilly, M.A., 2009. Neonatal oxygen adversely affects lung function in adult mice without altering surfactant composition or activity. Am. J. Physiol. Lung Cell Mol. Physiol. 297 (4), L641–649.
Yee, M., Cohen, E.D., Domm, W., Porter Jr, G.A., McDavid, A.N., O'Reilly, M.A., 2018. Neonatal hyperoxia depletes pulmonary vein cardiomyocytes in adult mice via mitochondrial oxidation. Am. J. Physiol. Lung Cell Mol. Physiol. 314 (5), L846–L859.