Title: The impact of preterm adversity on cardiorespiratory function

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New Findings

We review the influence of prematurity on the cardiorespiratory system and examine the common sequel of alterations in oxygen tension, and immune activation in preterm infants. We explore the neonatal animal models of hypoxia, hyperoxia and infection that contribute to our understanding of stress on neurodevelopment and cardiorespiratory homeostasis. Finally, we highlight some of the important physiological pathways that have a modulatory role on the cardiorespiratory system in early life.

Abstract

Preterm birth is one of the leading causes of neonatal mortality. Babies that survive early life stress associated with immaturity, have significant prevailing short- and long-term morbidities. Oxygen dysregulation in the first few days and weeks after birth is a primary concern as the cardiorespiratory system slowly adjusts to extra-uterine life. Infants exposed to rapid alterations in oxygen tension, including exposures to hypoxia and hyperoxia, have altered redox balance and active immune signalling leading to altered stress responses that impinge on neurodevelopment and cardiorespiratory homeostasis. In this review, we explore the clinical challenges posed by preterm birth followed by an examination of the literature on animal models of oxygen dysregulation and immune activation in the context of early life stress.

Introduction

Preterm birth is the leading cause of infant death worldwide (Lawn and Kinney, 2014). The rate of preterm birth is approximately 6-12% in USA and Europe, and some common risk factors include increasing maternal age, assistive reproductive techniques, multiple birth and obstetrical interventions in the form of Caesarean sections (Lantos and Lauderdale, 2011, Institute of Medicine Committee on Understanding Premature and Assuring Healthy, 2007, Frey and Klebanoff, 2016). Testament to improved obstetric and neonatal care, survival of preterm infants born after 22 weeks of gestational age has risen dramatically in the 21st century and continues to do so in recent years (Santhakumaran et al., 2018). The improved survival rates of this immature population bring about new uncertainties and provide new impetus to address ongoing clinical questions and treatment strategies in terms of early life stress. The growth in observational and interventional clinical research studies in the preterm population, supported by improved translational preclinical animal models, have contributed to a wealth of knowledge, awareness and improved evidence-based practice. Examples of improved clinical practice include antenatal steroid use, delayed cord clamping, surfactant administration, targeted oxygen saturation limits and titrated oxygen use. Yet significant challenges remain, to improve both survival and the quality of life of the smallest of preterm infants (Manuck et al., 2016). In this review, we discuss cardiorespiratory complications arising from preterm birth that lead to oxygen dysregulation. We explore increased vulnerability associated with variable patterns of early life oxygen insufficiency, as revealed by animal models of oxygen dysregulation. We examine the interplay between oxygen insufficiency and subsequent immune activation and putative mechanisms underpinning interactions between these physiological stressors. Finally, we will highlight gaps in the literature regarding gram-positive immune activation and the study of intrinsic sex differences in response to early life stress.

Preterm Physiology

Preterm birth is a primary risk factor for infant morbidity (e.g. respiratory infection and bronchopulmonary dysplasia (BPD)) and long-term disability (e.g. cerebral palsy, sensory and cognitive deficits) worldwide with huge emotional and financial costs (Frey and Klebanoff, 2016, O'Shea et al., 2009). While it is true that those born the earliest are at greater risk of adverse outcomes, babies born late preterm still have significant difficulty, with

approximately one third of these infants requiring intensive care (McIntire and Leveno, 2008), rehospitalisation in early childhood (Colin et al., 2010) and long-term respiratory deficits (Kotecha and Kotecha, 2012, Kotecha et al., 2012). Preterm infants face numerous challenges due to their anatomical and physiological immaturity, such as under-developed lungs and defence mechanisms (e.g. antioxidants), immature sensory networks, poor respiratory and upper airway motor co-ordination, immature myocardial function and persistent patent ductus arteriosus (Figure 1). Birth normally triggers a rapid sequence of physiological adaptations to sustain life outside of the uterus, inflating the lungs to oxygenate the blood and establish a new homeostatic environment (Hillman et al., 2012). However, preterm birth interrupts normal neurodevelopmental processes that are temporally programmed. Consequently, the first steps toward independence are often burdened with complications and failure to establish an efficient cardio-respiratory system. Many preterm infants will present with signs, such as, grunting, nasal flaring, tachypnoea and chest retractions that require immediate management and are indicators of respiratory insufficiency such as surfactant deficiency, airway obstruction and diaphragm dysfunction or non-respiratory conditions such as sepsis. We will briefly outline some of the cardiorespiratory challenges of the preterm transition.

Cardiorespiratory function in preterm infants

Lung development begins early in the embryonic phase, however it does not reach the end phase (alveolar) until after 37 weeks of gestational age (GA) at which time there is increased surface area and density of mature Type II pneumocytes producing surfactant (Reuter et al., 2014). Infants born preterm (i.e. <37 weeks' GA) often have fluid on the lung in addition to greater surface tension within the lungs, higher pulmonary dead space (V_D) and V_D: tidal volume ratio leading to increased collapsibility and decreased area for efficient gas exchange (Ghafoor et al., 2003, Dassios et al., 2015, Dassios et al., 2017, Helve et al., 2007, Helve et al., 2004, Janer et al., 2010). The most immature infants will have the least developed lung structures. Some research suggests that preterm birth can arrest development meaning that infants have blunted lung growth and smaller pulmonary surface area, though this may be related to respiratory complications of bronchopulmonary dysplasia (Greenough et al., 2005, May et al., 2011, Margraf et al., 1991). The chest wall of the preterm infant has a poorly developed collagen matrix, which contributes to reduced outward recoil of the chest wall and

increased tendency for the lungs to collapse. Preterm infants generally maintain their lung volume above resting functional residual capacity and prevent atelectasis by maintaining a high respiratory rate, laryngeal adduction during exhalation to increase the resistance to airflow, diaphragmatic muscle tone during expiration and reducing the expiratory time (Stark et al., 1987). The diaphragm is the main inspiratory pump muscle and works particularly hard in preterm infants while accessory muscles such as the external intercostal muscles work primarily to stabilise the thoracic cavity rather than increase tidal volume. The inspiratory muscles of preterm infants are composed of fewer slow oxidative myosin heavy chain (MHC) type 1 fibres compared with their term counterparts making the former more susceptible to fatigue when loaded (Sieck et al., 1991). A similar developmental profile is apparent in neonatal rodents (O'Connell et al., 2013).

Infants are primarily nasal breathers with high inter-breath variability especially in the preterm, indicative of their poor respiratory control and collapsible upper airway structures (Pandit et al., 2000, Beck et al., 2011, Duara et al., 1991, Gauda et al., 1987). This leaves the preterm infant vulnerable to both central and obstructive apnoeas that are commonly reported (Lemke et al., 1998, Upton et al., 1992, Fairchild et al., 2016). Apnoeas in preterm infants can be profound as a result of their low respiratory reserve capacity, giving rise to bradycardia, temporary absence of reflexes coupled with their high metabolic demands (Fyfe et al., 2014, Gerhardt and Bancalari, 1984). Apnoeas are commonly preceded by periods of hypoventilation (Adams et al., 1997, al-Saedi et al., 1997, Poets and Southall, 1991). Though the carotid body is likely anatomically mature at birth (Hervonen and Korkala, 1972), it takes time for the preterm to establish hypoxic and CO_2 thresholds after birth, usually occurring over a period of hours-to-days of life (Williams et al., 1991, Darnall, 2010) but this may be delayed in infants with recurrent apnoea (Katz-Salamon, 2004). The poor control of breathing is most evident during feeding, which requires a co-ordinated suck-swallow-breath mechanism. There is evidence of increased apnoeic episodes during feeding in infants born preterm (Thoyre and Carlson, 2003), which may be potentiated in bottle-fed babies as a result of increased vacuum with sucking (Jenik et al., 2012). In addition, increased respiratory muscle activation has been observed during feeding desaturation in preterm infants compared to term infants indicating an increased work-of-breathing and thoraco-abdominal asynchrony that will likely contribute to respiratory fatigue (Kwon et al., 2018). Overall, immature lung

and skeletal muscle form along with poor neural control contribute to poor ventilation in the preterm infant.

The respiratory system works in tandem with the cardiovascular system. Adequate oxygen transport and delivery is dependent on an efficient cardiovascular system and ability to carry and offload oxygen where it is required. After birth, cord clamping is a necessary intervention, though the timing is important. Delayed cord clamping, for at least 1 minute after birth, is essential to ensure sufficient transfer of placental blood to the baby increasing its blood volume and stabilising the cardiorespiratory system, in turn minimising need for transfusions (McAdams et al., 2018, Ersdal et al., 2016, Ersdal et al., 2014, Finn et al., 2019). In the preterm infant, adult haemoglobin will be at lower concentration than term infants, with preterm infants still circulating fetal haemoglobin. Preterm neonates have oxyhaemoglobin dissociation curves that are severely shifted to the right making these infants prone to severe hypoxia with minor drops in the provided FiO_2 (Dassios et al., 2015). Anaemia is common in preterm infants due to phlebotomy losses, breakdown of fetal haemoglobin and an immature haemopoietic system, for example low production of erythropoietin, and blood transfusions to reverse anaemia are necessary to prevent hypoxia (Bishara and Ohls, 2009, Saito-Benz et al., 2018, Whitehead et al., 2018). The physiological transition from fetal circulation to the post-natal circulation requires a complex series of events to divert blood flow from the right ventricle of the heart to the lungs and minimise shunts to the systemic circulation via the foramen ovale and the ductus arteriosus. At this time, adequate oxygen delivery to the lungs is important to prevent shunting in the pulmonary system, raising right ventricular afterload. The structural formation of blood vessels, particularly capillaries in preterm brains are weak and can easily rupture. Weak blood vessels and immature structural network can contribute to serious acute trauma of metabolically active neural tissue such as intraventricular haemorrhage and periventricular leukomalacia (Ballabh, 2010, Ballabh et al., 2004, Volpe, 2009).

Clinical approaches to preterm respiratory care

Treatment strategies have been revised over the years to maximise therapeutic value while limiting associated risks that compound the problems faced by preterm infants (Stoll et al 2015). As a result of both the immature anatomy and physiology, preterm infants often

struggle to inflate their lungs following delivery and in that situation neonatologists intervene within the first minutes to stabilise (Wyckoff et al., 2015, Kilmartin et al., 2018). Neonatal resuscitation has been reviewed elsewhere by Roehr and Bohlin (2011) who highlight that CPAP and early surfactant administration have been demonstrated to be a safe and effective strategy for resuscitation. Yet many unanswered questions remain in the immediate management: how much oxygen to give, how much pressure to use and how best should it be delivered? Despite significant research to date, the optimal protocol for oxygen supplementation during resuscitation of preterm infants remains to be determined (Lara-Canton et al., 2019). In recent years, neonatologists have moved from resuscitation with supplemental oxygen to resuscitation in room air and titrating supplemental oxygen over the next few minutes in an effort to reduce the oxidative and inflammatory burden caused by hyperoxia (Vento et al., 2009, Kapadia et al., 2017, Lui et al., 2018). The initial period after birth has been termed the 'golden hour' and implementation of the revised Golden Hour process, which encourages use of standardised evidence-based approaches and collaboration has had positive implications for preterm outcomes (Reynolds et al., 2009, Sharma, 2017). Although these practices are implemented widely, adherence could be improved (Shah et al., 2018).

After delivery room resuscitation, a significant proportion of preterm infants require on-going respiratory support in the NICU (Fairchild et al., 2016). Methods of respiratory support have evolved to limit the incidence of long-term lung disease such as BPD (Fischer and Bührer, 2013, Subramaniam et al., 2016). Steroid use postnatally has not been as successful as antenatal treatment in the maturation of the lung and prevention of disease and therefore postnatal administration is no longer recommended routinely due to the many long-term adverse effects of the drug (Halliday, 2017). Non-invasive ventilation such as continuous positive airway pressure (CPAP), Bilevel Positive Airway Pressure (BiPAP), high-frequency oscillatory ventilation, volume targeted ventilation (VTV) and high-flow nasal cannula have been successful in limiting damage of the airways; yet more studies are needed to directly compare different support systems to determine the best device for provision of respiratory support during preterm development and in the prevention of extubation failure (Cummings and Polin, 2016, Roberts and Hodgson, 2017, Manley et al., 2013, Victor et al., 2016, Rong et al., 2016, Zhu et al., 2017, Klingenberg et al., 2017). The preterm infant's respiratory function

and nutritional status are interlinked. Feeding intolerance can limit the energy necessary for growth and repair and is discussed in reviews by (Bozzetti et al., 2017, Su, 2014). A multicentre randomized single-blind controlled trial called ENTARES is currently underway to examine the impact of nasal continuous positive airway pressure and heated humidified high-flow nasal cannula on enteral nutrition (Cresi et al., 2019).

Oxygen supplementation in the most commonly used therapy in the NICU, yet the optimal oxygen targets in extremely preterm infants are not well defined. Supplemental oxygen clearly plays an important role in maintaining adequate oxygenation, reported to decrease apnoeic events, offset the severity of desaturation associated with apnoea and lessen the number of serious life-threatening events in preterm infants (Samuels et al 1994, Sekar and Duke 1991, Watkin et al 1996). The NEoProm meta-analysis study recruited nearly 5000 extremely preterm infants and set out to compare the impact of targeting differential oxygen status (SpO_2 85-89% versus 91-95%) on the primary outcome measure of composite death or major disability in these infants at 18-24 months. The study reported no difference in its primary outcomes, yet reported that the lower SpO_2 target range was associated with higher risk of death and necrotising enterocolitis, but a lower risk of retinopathy of prematurity (Zahari et al., 2016, Askie et al., 2017, Askie et al., 2018, Schmidt et al., 2013, Schmidt et al., 2016). At the moment, based on the evidence available, SpO_2 should be targeted at the higher level of 91-95% and should not be exceeded (Bizzarro, 2018, Deschmann and Norman, 2017, STOPROP, 2000). Retinopathy of prematurity is one of the major clinical side effects of supplemental oxygen therapy, but in some cases it is viewed as a necessary risk given the long-term benefits of maintaining adequate oxygenation. Yet, the danger of both hypoxia and hyperoxia means neonatologists and their vulnerable patients are walking a fine line since both stressors can induce fundamental cellular and molecular changes that are not easily observed clinically in the acute setting but have potential for long-lasting deleterious outcomes. We will discuss the impact of variable patterns of hypoxia and hyperoxia on cardiorespiratory physiology in the context of animal models in later sections.

Not only is it unclear how much oxygen should be delivered, the method of measuring oxygen sufficiency remains a challenge. The introduction of non-invasive oxygen saturation measurement in 1980's has been a welcome addition to neonatal care but it is not perfect

(Sola et al., 2005). Some causes for concern with the increased reliance on this method is the possibility of 'missed' oxygen desaturations as a result of a) varied algorithms used by different manufacturers that can often average data over periods of 10s, missing short apnoeas, b) saturation may appear normal despite anaemia, and c) habituation of care staff to alarms mean that they often disregard or mute alarms without action. Risks of inadvertent hyperoxia also exist and are not detectable using SpO_2 measurements due to the very nature of the oxygen dissociation curve, wherein large changes in partial pressure of oxygen (PO_2) above 100mmHg are not detectable since haemoglobin is fully saturated. Anderson et al. (2017) published a detailed review on 'adequate oxygenation' highlighting that current monitoring and interventions target oxygen delivery (inspired oxygen, oxygen saturation, oxygen carrying capacity and blood flow), but do not consider oxygen consumption. The authors along with other groups (Tataranno et al., 2015, Kenosi et al., 2014, Kenosi et al., 2018, Kenosi et al., 2015) recommend additional studies to test the use of cutaneous oxygen saturation combined with NIRS measurement of tissue oxygen saturation to determine a reference value for oxygen adequacy and as a useful tool for early identification of vulnerable infants based on brain metabolism (Garvey et al., 2018).

Preterm infants are at high risk of respiratory conditions such as apnoea of prematurity (AOP), respiratory distress syndrome (RDS) and BPD in addition to respiratory infection, wheezing hospital re-admission and decreased exercise capacity (Haataja et al., 2016, Paranjothy et al., 2013, Haataja et al., 2018, Leps et al., 2018, Farrell et al., 2015). Oxygen dysregulation is associated with developmental impairments in childhood. Di Fiore et al., (2019) reported that preterm infants with increased oxygen and frequent intermittent hypoxia (IH) events during just the first 3 days of age were commonly on asthma medication at 2 years and total apnoea days were associated with neurodevelopment impairments (Janvier et al., 2004). Raffay et al., (2019) reported an association between frequent, longer, and less severe IH events as well as oxygen supplementation and respiratory pressure support within the first 26 days of life and incidence of BPD at 36 weeks' postmenstrual age. There is growing evidence to suggest sex-specific developmental trajectory and thereby sex-dependent responses to treatment and long-term outcomes, with male sex recognised as a significant factor in poor respiratory outcomes in preterm infants (Wiswell et al., 1990, Farrell and Wood, 1976). Males are reported to require prolonged respiratory support and increased evidence of airway

obstruction compared to females (Bairam et al., 2018, Bentsen et al., 2017). A recent review by Kotecha et al., (2018) summarises the evidence for increased risk of male sex on adverse respiratory outcomes in preterm infants. Sex has often been excluded as a factor in the analysis of clinical data and often disregarded in preclinical data with most studies either focusing on males exclusively, or not sexing animals at all. There is increased focus on sexual dimorphism particularly in relation to developmental stress. The importance of studying both sexes is now more widely recognised revealing greater physiological insights into stress responses and recovery mechanisms.

In summary, establishing and maintaining adequate oxygenation in preterm infants remains one of the major responsibilities and challenges within neonatal intensive care units. Efforts are made to facilitate efficient gas exchange across the alveoli, adequate perfusion of the lungs and appropriate delivery of oxygen to tissues where it is required whilst minimising potential iatrogenic harm. It is imperative that we strive to understand the impact of oxygen dysregulation on cardio-respiratory development and the impact that oxygen dysregulation has on vulnerability in both male and female preterm infants, with the aim of developing targeted therapies. In addition, despite progress, much work remains to gather contemporary normative data across the range of preterm ages, to optimise timing, delivery and withdrawal of treatments as well as identification of infants particularly 'at risk'. Novel preventative strategies need to be identified to support cardiorespiratory stability in the NICU, offsetting potential stressors. Much of the normative data currently in use was gathered in an era without the use of prenatal corticosteroid administration, continuous positive airway pressure, exogenous surfactant replacement, refinements in the use of supplemental oxygen, and a return to delayed cord clamping. Long-term retrospective and prospective studies of the current spectrum of preterm survivors also need to be conducted to fully assess the persistence of respiratory disease in the preterm population in the context of modern therapeutic approaches.

Animal models of postnatal stress

Postnatal stressors

Anatomical and physiological immaturity can present life-threatening stressors in the preterm infant such as hypoxia, acidosis, hypoglycaemia, and cold stress. Additionally, preterm infants

are exposed to multiple iatrogenic stressors owing to the negative side effects of therapeutic strategies (e.g. hyperoxia, volutrauma, barotrauma and painful procedures) and/or the hospital environment (e.g. nosocomial infection via compromised immune barrier, bright lights and noise). *Physiological* stressors are stimuli that challenge homeostasis and typically activate sensory receptors, which initiate adaptive responses. As we have learned, the respiratory system of the preterm infant is not fully developed until the end of gestation and even at this point the circuitry is plastic, with sensory inputs undergoing a period of resetting, with continued maturation of the neuromechanical breathing network based on sensory feedback. *Psychological* stressors such as parental separation mainly activate cortical and limbic circuits but can also elicit visceral responses. A large amount of work has been carried out in models of altered maternal-offspring interaction particularly examining dysfunction of higher brain functions such as cognition, memory and learning and affective disorders such as anxiety and depression (Aisa et al., 2007, Bolton et al., 2017, Jin et al., 2018, Francis et al., 1999). However, there is also a growing body of literature on cardio-respiratory function in animal models of dysfunctional maternal-offspring interaction building on the early work by Hofer (1970), with recent publications continuing to support the significant physiological impact of maternal separation (Genest et al., 2007, Kinkead et al., 2005, Kinkead et al., 2009). As highlighted by Kovacs et al (2005), physiological and psychological stressors are not mutually exclusive and should be viewed in their complexity, relevant to both the clinical setting and those stressors used experimentally.

Stressors such as hypoxia, hyperoxia and inflammation impact physiological function depending on the timing, pattern (acute/chronic), and severity/intensity of stimulus as well as the developmental age (critical windows) at which the stimulus is encountered and the intrinsic make-up of the individual, such as sex. Stressors may act independently through distinct pathways or interact in a hyper- or hypo-additive manner through priming/sensitisation, or preconditioning/desensitisation by means of convergence on common end pathways such as the hypothalamic pituitary adrenal axis (HPA), autonomic nervous system, immune activation or redox modulation. The hypothalamic pituitary adrenal (HPA) axis acts to maintain homeostasis by regulating metabolism including the immune response and mitochondrial function (Kasahara and Inoue, 2015). Ascending neurons from the nTS to the corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP)

producing cells of the PVN in the hypothalamus mediate the neuroendocrine response i.e. the release of glucocorticoids (cortisol in humans, cortisone in rodents) along the HPA axis. Cortisol is released into the circulation from the adrenal glands, however the majority in circulation becomes bound to corticosteroid-binding globulin (CBG or transcortin) and is not biologically active.

A stress hyporesponsive period is evident in rats from post-natal (P)3-P14, with evidence of blunted release of the 'stress' hormone corticosterone, in response to a mild stressor (Rosenfeld et al., 1996, Levine, 2001). This period of development in rats is similar to the development period of 20-40 weeks' gestational age in humans (Clancy et al., 2001). Humans are suggested to be hyporesponsive to stress in the first year and perhaps extending throughout childhood (Gunnar and Quevedo, 2007, Gunnar and Fisher, 2006). However, during this stress hyporesponsive period the ability to respond to significantly stressful events remains. Stressors can induce acute responses and/or persistent long-term adaptations that are mediated through neuronal plasticity, eliciting persistent changes in neuronal connectivity and/or activity. Perinatal programming is the term used for the long-lasting impact of environmental stressors experienced either in utero or during neonatal life. These effects may persist throughout life and may even be transgenerational through epigenetic mechanisms (Khalyfa et al., 2017, Nanduri et al., 2017a, Nanduri et al., 2018, Nanduri and Prabhakar, 2013, Nanduri et al., 2017b). Many adult disorders should be viewed as beginning in early life and could be reduced by interventions that build resilience, decrease exposure to adversity and therapies that promote recovery (Shonkoff et al., 2009) .

Animal models of early life oxygen dysregulation/stress have clearly demonstrated long-lasting alterations in cardio-respiratory function (Mayer et al., 2013, Mayer et al., 2014, Stryker et al., 2018, Reeves and Gozal, 2006, Soukhova-O'Hare et al., 2008), as well as memory and sensorimotor deficits as a result of neural impairments (Juliano et al., 2015, Goussakov et al., 2019). Exploring stress responses during early life and (mal)adapatations to prevalent stressors will contribute to our understanding of vulnerability and resilience developed in preterm infants. Some of the key changes observed in response to early life stressors prioritise short-term survival and implement adaptations for the prevailing environmental conditions, albeit at the expense of other important but energy costing developments and as such can cause aberrant changes awry from the normal developmental trajectory. Another possibility

is that developmental damage to tissues with important functional roles gives rise to dysfunctional circuits and behaviours expressed in the long-term. Herein, we review some of the recent data on cardiorespiratory function in animal models of neonatal oxygen dysregulation and then examine possible interactions with the immune system.

Hypoxic response in the newborn

Certain cell types are exquisitely sensitive to changes in PO_2 and can initiate fast adaptive responses to a hypoxic stimulus; these are known as oxygen sensors. The glomus cells of the carotid body are established as the primary PO_2 sensors ideally located at the carotid bifurcation, they send afferent signals via the carotid sinus nerve, a branch of the glossopharyngeal nerve, into the central respiratory control network. Other candidate sites have been put forward as oxygen sensors such central astrocytes (Funk and Gourine, 2018, Czeisler et al., 2019), unidentified cells of the spinal cord (Wilson et al., 2015), as well as centrally acting AMP-activated protein kinase (AMPK) (Evans et al., 2016). The hypoxic ventilatory response in new-born infants and mammals is biphasic; characterised by a short rise in minute ventilation followed by hypoxic ventilatory depression (Bissonnette, 2000). Adrenal chromaffin cells in neonates are also particularly sensitive to hypoxia; until the maturation of splanchnic innervation, these cells release catecholamines upon stimulation (Salman et al., 2014). The new-born rat often responds to hypoxia by decreasing metabolism (Mortola, 1993, Mortola and Feher, 1998) and a similar case is likely for new-born human infants (Cross et al 1958). The hypothalamus is likely an important site for mediating hypoxic-induced hypometabolism (Mortola, 1993, Mortola and Feher, 1998, Tattersall and Milsom, 2009). This response enhances the new-born's ability to survive severe and often repeated hypoxic episodes (Mortola et al 1990), though hypoxia particularly within the first few days of life in rats can have significant impact on normal transitional adaptations (Massaro et al 1990).

Oxidative Stress

All cells in the body can respond to hypoxia through stabilisation of Hypoxia-inducible Factor (HIF) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) transcription factors and their nuclear translocation to initiate gene transcription. The pattern, intensity and duration of the hypoxia influences the balance of HIF-1 and HIF-2 activation as well as the activation of NFκB (Xu et al., 2015, Prabhakar and Semenza, 2012). In hypoxic conditions, HIF-

1 upregulates enzymes such as membrane bound NADPH oxidase (NOX) and cytosolic xanthine oxidase (XO) and downregulates HIF-2, increasing reactive oxygen species (ROS) production and decreasing antioxidant capacity. Increased NOX, XO and production of inflammatory mediators coupled with decreased antioxidant status contributes to an altered redox state and possibly oxidative stress. Oxidative stress occurs when the ROS burden overwhelms the antioxidant capacity required to buffer their harmful effects. Fluctuating levels of oxygen generate ROS, such as singlet oxygen, superoxide and hydroxyl radicals. ROS mediates cell signalling, activating inflammatory pathways such as NFκB, but is also capable of causing direct tissue damage and depletion of antioxidant resources in the short- and long-term. It has been reported that antioxidant capacity increases in preterm infants with gestational age (Rogers et al., 2000). Dye et al (2017), demonstrated that PD14 rats have equivalent levels of glutathione, glutathione reductase and glutathione peroxidase to weaned rats at P21. However, following exposure to ozone PD14 rats have sex-dependent decreased availability of SOD, glutathione peroxidase and glutathione reductase. As such neonatal rats, and perhaps preterm infants, may not be able to replenish antioxidants quickly. Interestingly, work by Prabhakar and colleagues present evidence of neonatal intermittent hypoxia (nIH)-induced SOD2 (superoxide dismutase2) gene methylation which decreases anti-oxidant reserve, an effect that persists long-term (Dylag et al., 2017, Nanduri and Prabhakar, 2013).

Animal model of neonatal intermittent hypoxia

Intermittent hypoxia is the most common pattern of hypoxia in preterm infants particularly those with AOP, whereby the infants have repeated pauses in their breathing often resulting in episodes of hypoxia and re-oxygenation. Neonatal animal models of IH (nIH) emulate many aspects of AOP with bradycardia-associated desaturations in blood oxygen (Julien et al., 2008, Mayer et al., 2015). We have compiled a summary table of studies exploring the effects of nIH on cardio-respiratory parameters (Table 1) and a figure to illustrate common findings (Figure 2). It is evident that a variety of paradigms have been employed, most studies did not examine potential sex differences, and only a small proportion of studies controlled for litter size. Exposure to nIH consistently causes blunted somatic growth in animals, indicative of conservation of energy (Julien et al., 2008, McDonald et al., 2015, Gozal et al., 2002, Reeves et al., 2006). Central dysregulation in respiratory control, illustrated by enhanced apnoeic frequency and blunted autoresuscitation is evident in nIH-exposed rodents (Julien et al., 2008,

Gozal et al., 2002). In the short-term, nIH also produces a state of autonomic dysregulation manifest as enhanced sympathetic activity and increased circulating catecholamine concentrations as a result of stimulated adrenal chromaffin cells (Souvannakitti et al., 2009). Long-term nIH treated rats exhibit reduced vagal projection to atrial ganglia and enhanced sympathetic chemoreflexes (Soukhova-O'Hare et al., 2006). Neonatal IH-induced sympathetic over-activation drives disease states such as hypertension and potentiates activation of the HPA axis, which we discuss below in respect of the inflammatory response.

Animal model of neonatal intermittent hyperoxia

Preterm infants commonly treated with supplemental oxygen, coupled with the lack of continuous monitoring for hyperoxia can inadvertently result in episodes of intermittent hyperoxia. Few studies have examined the physiological effects of intermittent hyperoxia exposure in the context of cardiorespiratory function (Table 1). Bavis et al., (2007) report that intermittent hyperoxia (60% inspired oxygen) did not alter baseline breathing but blunted hypoxic ventilatory response. In agreement with Bavis et al 2007, Logan et al., (2016) reported that new-born rats exposed to milder intermittent hyperoxia (30% inspired oxygen) demonstrated hypo-activation of the carotid body peripheral chemoreceptors during normoxia and also a blunted hypoxic ventilatory response at P14-15. These studies indicate divergent phenotypes of intermittent hypoxia compared to intermittent hyperoxia.

Animal model of neonatal intermittent hypoxia/hyperoxia

Whilst teasing out the impact of neonatal intermittent hypoxia and intermittent hyperoxia is important mechanistically, we are mindful of the need for more clinically informed models. The reality is that preterm infants are exposed to intermittent oxygen stress with a combination of hypoxia, normoxia and inadvertant hyperoxia resulting from therapeutic oxygen supplementation. Dylag et al., (2017) developed a mixed model exposing neonatal rats to one week of intermittent hypoxia with a hyperoxic overshoot, reporting long-term upregulation of NOX in the rat lung and increased airway resistance during early life. Recently Bavis et al., (2019) carried out an extensive study of the respiratory effects of exposure to intermittent hypercapnic hypoxia against the background of either normoxia or hyperoxia compared to control conditions. Bavis et al (2019) report that intermittent hypercapnic hypoxia along with intermittent hyperoxia (40% FiO_2) decreased chemo-afferent activity

without a change in carotid body size compared to control, however the intermittent hypercapnic hypoxia treatment with background of normoxia increased chemo-afferent discharge under basal conditions and increased carotid body size (Table 1). Another study, using a different pattern of neonatal intermittent hypoxia-hyperoxia, reported long-term blood-brain-barrier leakiness, which could be indicative of poor vascular development and oxidative stress (Morken et al., 2013). Capillaries within the rat cortex do not have an adult-like appearance until PD14-21 indicating a period of maturational development in the first two weeks that render them increasingly vulnerable to ROS. The variable pattern of oxygenation during early life has been shown to significantly alter redox balance and respiratory sensitivity. More research is needed to elucidate both the short- and long-term implications of this stressor and the mechanisms underlying dysfunction.

Late onset infection

Preterm infants are at increased risk of infectious diseases due to their physiological immaturity, exposure to adversity and prolonged hospital stays. 70% of late-onset infections (LOI) occur in preterm infants (Vergnano et al., 2011). In a large cohort of extremely preterm infants derived from the NICHD network (Stoll et al., 2002, Stoll et al., 2015), those that survived beyond 3 days post-partum were commonly diagnosed with LOI. Late onset infection is defined as infection occurring after the first 48-72hours of life (Vergnano et al., 2011). Although the incidences of LOI have decreased over the years (8% at 28 weeks' GA and 40% at 24 weeks' GA) it remains a significant problem that leads to up to 18% mortality (Stoll et al., 2015, Tsai et al., 2014, Stoll et al., 2002, Hornik et al., 2012). An infant's skin, respiratory tract, gastrointestinal tract, conjunctivae, umbilicus or bloodstream may become colonised. The mode of infection includes vascular catheters, indwelling lines or nosocomial infection. The improvements in the incidence of LOI likely reflect improved hand-hygiene, skin care, human breast milk supplementation, improved practices for catheter insertion and care, and timely removal of invasive devices. Increased apnoeic events and the need for increased respiratory support is one of the main presenting symptoms of infection (Fairchild et al., 2016, Hofstetter et al., 2008). Other symptoms can include brady/tachycardia, poor feeding, change in skin colour, jaundice, diarrhoea and seizures. Infection in preterm infants diverts energy away from important neurodevelopmental processes in order to protect the host and fight infection. LOI is normally confirmed clinically with elevated C-reactive protein in plasma and

confirmation of bacterial strain with culture. Confirmation of infection with lab culture can take time, so often infants are administered antibiotics such as vancomycin and/or gentamicin while awaiting results and symptoms are treated to stabilise the infant. Late onset hospital acquired infection in preterm babies is an urgent unmet clinical need with the growing emergence of resistant 'superbugs'. Both antibiotic overuse and the emergence of superbugs are endangering the effectiveness of antibiotic treatment (Zea-Vera and Ochoa, 2015, Rasigade et al., 2012). It is important to identify infants most at risk of infection and implement novel preventative strategies or targeted therapies to avoid long-term morbidity of this especially vulnerable population.

Innate immune system

The immune system is a sensory system that interfaces between the environment and host physiology. The innate immune system is activated by recognition of pattern-associated molecular patterns (PAMPS e.g. lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid (LTA)) present on the surface of bacteria (Kimbrell et al., 2008, Lotz et al., 2004, Schroder et al., 2003, Guha and Mackman, 2001) and damage-associated molecular patterns (DAMPS; Heat shock proteins, HMGB1 and surfactant A) released by the host under stress conditions such as hypoxia (Klune et al., 2008, Agrawal et al., 2013, Fang et al., 2011). PAMPS and DAMPS activate pattern recognition receptors (e.g. toll-like receptors (such as transmembrane TLR-1/2, TLR-2/6 and TLR-4), CD-14, NOD-2, peptidoglycan recognition protein and C-reactive protein). TLR activation can also stimulate the release of soluble TLR's that can act in negative feedback fashion (ten Oever et al., 2014).

Gram-positive bacteria account for nearly half of LOI's (Vergnano et al., 2011). Organisms include coagulase-negative *Staphylococcus* and *Staphylococcus aureus*. Gram-positive proteins signal through distinct receptors different to gram-negative bacteria (e.g. E-coli). The cardiorespiratory effects of acute inflammatory activation by gram-positive bacteria are largely unknown with the majority of studies focussed on gram-negative endotoxins such as LPS. LTA and PGN are cell wall components of gram-positive bacteria suggested to activate TLR-2 leading to increased BBB permeability and activation of the HPA axis (Mayerhofer et al., 2017). LTA and PGN were reported to act synergistically to mediate multiple organ dysfunction syndrome in adult rats; shock was associated with a large upregulation of iNOS

(De Kimpe et al., 1995). TLR-2 involves CD14 modulation and is dependent on MYD88 adapter protein. Yet LPS, the gram-negative bacterial protein can also potentiate the effect of LTA (Wray et al., 2001). While previously it was considered that the neonate mounted a weak immune response, a study by Kollmann et al. (2009) revealed an important insight. The authors directly compared the immune cell response to both TLR-1/2 and TLR-4 ligands and found that adult and neonatal cells have qualitatively different responses to activation and not necessarily less of a response in the neonate when examined as a function of cytokine production. Similarly, in a study comparing human new-born and adult monocytes derived from blood samples, the authors describe skewed cytokine profiles in both groups in response to TLR agonists (Angelone et al., 2006). TLR-2 and TLR-4 are mainly expressed in monocytes; TLR-2 has a relatively stable expression across development whereas TLR-4 increases with age (Sadeghi et al 2007). Sex-specific TLR-2 and TLR-4 expression following viral infection in mice influences survival, higher expression of TLR-2 had a beneficial role in females (Roberts et al., 2012). TLR-2 is altered by both the maternal and neonatal environment (Yu et al., 2018, Lauener et al., 2002) and nutritional status such as vitamin D (Ojaimi et al., 2013). LPS has been a useful tool in understanding the role of inflammation on physiological function. LPS potently activates the innate immune response across development (McDonald et al., 2016, Rana et al., 2012, Spencer et al., 2010, Fan et al., 2013). The effects of LPS are primarily mediated through the TLR-4 receptor.

Activation of immune receptors evokes a plethora of indirect and direct effects on cardiorespiratory control. Pattern recognition receptors are located on surveiling immune cells such as macrophages (peripheral nervous system) and microglia (central nervous system), but also non-immune epithelial and even muscle cells. Boyd et al., (2006) have demonstrated the presence of TLR-2, TLR-4, TLR-5, and TLR-9 in mouse whole skeletal muscles, including diaphragm, as well as in differentiated myotubes from C2C12 or primary cultures. TLR-4 has also been confirmed in human limb muscle and Zong et al. (2013) reported muscle fatigue mediated through HMGB1 activation of TLR-4. TLR-4 has been reported to regulate muscle metabolism (Frisard et al., 2010). LPS activation of TLR-4-induced catabolism was described in murine myotubes (Doyle et al., 2011) and similar findings were reported using C2C12 cells (Zhang et al., 2017). Li et al. (2018) demonstrated that both TLR-4 knockout and NF-κB inhibition ameliorated LPS-exacerbated ventilator-induced diaphragm

dysfunction, due to direct action on the muscle. Effective respiratory skeletal muscle contraction is necessary to ventilate the lungs; catabolism and muscle fatigue of the diaphragm mediated through TLR's would be problematic to an unstable preterm system. Systemic inflammation communicates via cytokines and neurotransmitters to the autonomic nervous system (ANS) to regulate homeostasis. Indeed, peripheral inflammation can be signalled to the brain via interaction with the BBB and production of IL-1β through the induction of prostaglandin E_2 (PGE_2), via vagal afferent signalling from the gut/liver/lungs or transport of cytokines through a leaky BBB (Kiernan et al., 2016, Hofstetter et al., 2007)). Endotoxins such as LPS can also enter the CNS from the periphery to activate microglia (Fan et al., 2013). Evidence from clinical and preclinical studies demonstrate that neuro development and immune function in early life is strongly influenced by gastrointestinal maturation and colonisation, microglia acting in the CNS and the HPA axis, which will be discussed below.

Gastrointestinal maturation and signalling to the brain

As mentioned previously poor nutrition can limit energy necessary for growth and repair, though nutrition is not just about what we eat/drink. Extremely preterm infants are born with immature gastrointestinal systems that have yet to be colonised. Increased intestinal permeability and poor colonisation can alter gut-brain signalling which can impact on neurodevelopment. Intestinal mucosal permeability or 'leaky gut', which can occur in preterm infants allows bacteria, bacterial toxins, digestive metabolites and small molecules to 'leak' into the bloodstream, this 'leakiness' threatens immune activation (Ma et al., 2018, Saleem et al., 2017). Our intestinal microbiome has an influence on nutrition, intestinal function and absorption. There is also growing evidence for an important role of the microbiome in overall health and wellbeing, particularly evident in animal models of disease. A number of recent papers have highlighted modulating effects of the microbiome on the cardiorespiratory system (Lucking et al., 2018, O'Connor et al., 2019, Adnan et al., 2017, Ganesh et al., 2018, Durk et al., 2019, Yang et al., 2017). Clinical studies investigating the role of the microbiota in preterm infants are growing at pace (Azad et al., 2013, Berrington et al., 2014, Fouhy et al., 2019, Grier et al., 2017, Groer et al., 2014, Xu et al., 2018). A healthy microbiome becomes established during birth and increases in diversity over the childhood years, as reviewed by Milani et al. (2017). A diverse and balanced microbiome is beneficial to our digestive system

as a result of its actions on mucosal barrier function and our neurodevelopment through gut-brain signalling. There is an association between neonatal factors, intestinal microbiota and intestinal barrier maturation (Ma et al., 2018, Fouhy et al., 2019). A review by Codagnone et al., (2018) presents the most recent evidence suggesting infant microbiota can be significantly altered as a result of postnatal stressors. The preterm infant population are at risk of altered microbiome diversity as a result of caesarean section, higher rates of formula feeding, invasive procedures, oxygen dysregulation and pre- and post-natal antibiotic exposure (Pammi et al., 2017, Dahl et al., 2018, Yee et al., 2019, Penders et al., 2006, Azad et al., 2013, Lucking et al., 2018). Dysbiosis in the immature infant gut is associated with pathogenesis of LOI's and inflammatory processes such as necrotising enterocolitis (NEC) (Berrington et al., 2014, Stewart et al., 2017). Alteration in circulating short-chain fatty acids, which is likely a result of poor colonisation, is just one consequence of prematurity. Importantly short-chain fatty acids have been demonstrated to play a role in the maturation of microglia, immune cells of the CNS (Erny et al., 2015). Healthy preterm infants born before 33 weeks and breast-fed have significantly lower short-chain fatty acids compared to infants born between 33 and 37 weeks of gestational age (Favre et al., 2002). Short-chain fatty acids were also found to be lower in formula-fed preterm infants. Short-chain fatty acids such as propionate cross the mucosal barrier and bind to FFAR3 expressed on sympathetic ganglia and enteric nerves while butyrate binds to GPR109A expressed on microglia and potentially on enteric glial cells (Nohr et al., 2013) may have an important role in gut-brain signalling. The use of probiotics as a therapeutic strategy in the NICU is limited based on current evidence (Costeloe et al., 2016), however meta-analysis data indicate that probiotics are effective at decreasing mortality, NEC and LOI (Athalye-Jape and Patole, 2019). In extremely preterm infants, parenteral nutrition is often required to prevent rapid essential fatty-acid deficits (Koletzko et al., 2005, van den Akker et al., 2010). In Ireland, lipid 1g/kg/day is currently set out in the Health Services Executive guidelines for preterm parenteral nutrition increasing to 4g/kg/day over the first 4 days (HSE, 2018) these guidelines in line with those of The European Society for Paediatric Gastroenterology Hepatology and Nutrition (Lapillonne et al., 2018). These lipid formulations do not include common short-chain fatty acids such as propionate and butyrate and deficits may have a significant impact on neurodevelopment in the preterm infant.

There is growing interest in the potential role of the gut-brain axis in modulating cardiorespiratory physiology (Lucking et al., 2018, O'Connor et al., 2019, Adnan et al., 2017,

Ganesh et al., 2018, Durk et al., 2019, Yang et al., 2017). In a model of gestational stress employed using intermittent restraint and bright light exposure, significant correlations were observed in adult offspring between altered gut microbiota composition and respiratory frequency, and gestational stress also increased responsiveness of the large intestine to sympathetic drive (Golubeva et al., 2015). Lower systolic blood pressure and pulse pressure, blunted ventilatory responsiveness to hypercapnia and disrupted brainstem neurochemistry was observed in rats following chronic broad-spectrum antibiotic intervention (O'Connor et al., 2019). A recent study by Giri et al., (2019) reported that mice raised in a germ-free environment with the absence of a microbiome and consequently short-chain fatty acids had an impaired adrenal catecholamine response to hypoglycaemia. Dysbiosis may influence excitation of cells in the nTS, a central processing site in the brain for autonomic function. Autonomic ganglia such as nodose ganglia express TLR's that recognise PAMPs are also likely to influence the bi-directional communication along the gut- brain axis via the vagus nerve (Hosoi et al., 2005). IL-1β has been shown to cause a vagal-dependent decrease in hypoxic ventilatory response in neonatal rat pups (Balan et al., 2011). These observations support a modulatory role for the microbiome and gastrointestinal integrity on immune activation and cardiorespiratory control. Future studies focusing on gut-brain signalling and its influence on autonomic control in neonatal animal models and preterm infants are needed.

Microglia in the CNS

Microglia are the prevailing immune cells of the CNS. They are present from early in embryonic development and exhibit a developmental, regional specific and sex-dependent profile (regulated both hormonally and genetically) (Hanamsagar and Bilbo, 2016, Schwarz and Bilbo, 2012). Microglia have important roles in development, including synaptogenesis, apoptosis, synaptic pruning, neuronal progenitor cell switching which are important for refining neural networks. Microglia have been a recent focus of research and could be important players in the sex-specific modulation of cardiorespiratory networks. Microglia densely populate certain regions of the brain such as hippocampus an important part of the HPA axis, but are also expressed throughout the brainstem and there is evidence to suggest that they modulate cardiorespiratory function (MacFarlane et al., 2016, Baldy et al., 2016). MacFarlane et al., (2016) reported that inhibition of microglia with minocycline, during sustained hypoxia, prevents decrease of 5-HT in the nTS, an important nucleus for cardio-

respiratory and autonomic regulation. This suggests a negative impact of glia in neuromodulation during hypoxic stress. Activation of macrophages or microglia stimulate phagocytosis and/or release of pro- (e.g. IL-1β, IL-6 TNF-α) and anti-inflammatory cytokines (e.g. IL-10) to produce a measured response. Several immune cytokines including IL-1β, IL-6, PGE_2 and LPS itself interact within hypothalamic and medullary regions such as the paraventricular nucleus (PVN), nucleus of the solitary tract (nTS) and rostro-ventrolateral medulla (RVLM). Fractalkine is a chemokine primarily released by neurons in the brain that binds to its receptor CX3R1 expressed exclusively on microglia, inducing pro-inflammatory cytokine release. Fractalkine has been reported to cause tachycardia and hypotension when microinjected into the PVN (Ruchaya et al., 2014). Activation of the immune system in early life has been associated with long-lasting psychological dysregulation such as anxiety but also altered immune responsiveness (Boissé et al., 2004, Spencer et al., 2006a, Spencer et al., 2005). Sex differences have been reported in both the expression and state of activation of glia. For example, adult females at rest have more primed and ramified microglia in mPFC compared to males (Bollinger et al., 2016). Glia express a range of steroid hormone receptors including both oestrogen and progesterone receptors, that could be important in the determination of sex-specific activation as well as glucocorticoid receptors that respond to stress (Domercq et al., 2013, Madalena and Lerch, 2017, Sierra et al., 2008). In light of the increased collective understanding of glia, the brain is no longer considered 'immune privileged' as was once previously thought. Microglia present in the CNS can be activated by common postnatal stressors such as hypoxia, carry out neuromodulatory role during development and are a possible source of sex differences. Further studies are required to reveal the extent microglia contribute to cardiorespiratory control in preterm and neonatal animals.

Immune-HPA axis

Cortisol has an important developmental role in human infants particularly in the maturation of the lungs and regulation of blood pressure (Bolt et al., 2001, Ng et al., 2004). Adrenal hyporesponsiveness and low cortisol were associated with hypotension in preterm infants during the first days of life (Ng et al., 2004). Metabolic stressors common in preterm infants including hypoxia and infection can also stimulate the HPA axis and the sympathetic adrenal-medullary axis to release glucocorticoids and catecholamines (Karrow, 2006, Zacharowski et

al., 2006, Seidler and Slotkin, 1985, Snyder et al., 2018). Cortisol is an agonist for glucocorticoid receptors which are widely expressed in liver, muscle, lung, adipose tissue and immune cells. There is also evidence to show that glucocorticoids can also be produced locally in organs such as lymph, brain and skin (Taves et al., 2011). Glucocorticoid receptors are present in the cytosol or are expressed on the cell membrane (Strehl et al., 2011). Glucocorticoid receptors have a number of splice variants and a variety of gene binding sites that may control cell-specific effects (Oakley and Cidlowski, 2013, John et al., 2011, Biddie et al., 2011). Glucocorticoid receptors in the brain mediate negative feedback to inhibit further activation of the HPA axis but also decrease CBG production in the liver. The role of glucocorticoids in innate immune response is affected by modulation of gene transcription mediated through glucocorticoid receptor activation. Glucocorticoid receptor activation has many beneficial actions with the capacity to inhibit pro-inflammatory cytokines, upregulate anti-inflammatory cytokines and alter mitochondrial respiration to reduce ROS (Kasahara et al., 2015, Long et al., 2005, Gerö and Szabo, 2016, Kasahara and Inoue, 2015). Glucocorticoids and glucocorticoid receptors exist in conjunction with accessory proteins such as hsp90 hsp70, and the FKBP52 (Pratt et al., 2006, Ratajczak et al., 2003) and have significant cross-talk with transcription factors NF-κB, AP-1, PPARα to modulate inflammation. Glucocorticoids however can also sensitise the initial inflammatory response through upregulation of NOD-like receptors that are part of the inflammasome (Busillo et al., 2011). Further evidence also suggests that glucocorticoids can increase sympathetic release of noradrenaline and activate β-adrenergic receptors associated with increased IL-1β and microglial priming, these may contribute to enhanced inflammatory response. The control of inflammation and sympathetic tone by the HPA axis is an important contributor to cardio-respiratory function.

Inflammation and Hypoxia in early life

Animal models of early-life infection have revealed important insights into immune function. Boisse et al., (2004) illustrate long lasting effects of neonatal immune challenge such that P14 Sprague Dawley rat pups treated with LPS exhibit a blunted fever response to subsequent LPS in adulthood. A similar study was carried out using viral immune challenges during early life and again at adulthood. Animals administered again at adulthood exhibited a blunted fever, though interestingly if the two stimuli were different no long-term effect on the immune system was observed (Ellis et al., 2006). Further studies identified a critical window for early

715 life infection such that days P14 and P21 attenuated adult fever in response to LPS, but
716 injections given on days P7 and P28 did not, however later time points were associated with
717 changes in behaviour (Spencer et al., 2006b). Spencer et al., (2007) also demonstrated that
718 LPS administration in P14 animals had an exacerbated response to a colitis-inducing agent,
719 2,4,6-trinitrobenzenesulfonic acid that was associated with augmented immune
720 responsiveness. Sex-dependent responses to immune challenge are also reported. Male rats
721 challenged with LPS at P4 had greater mortality compared to females, and those males that
722 survived the LPS challenge had lower weight gain at juvenile age (Hocker et al., 2019). Females
723 expressed lower concentrations of cyclooxygenase compared to males during blunted febrile
724 response in adulthood, perhaps indicating differential regulation despite a similar phenotype
725 (Spencer et al., 2006a, Kentner et al., 2010). These studies indicate that the nature of the
726 stimulus as well as the developmental period and sex of the host have important influences
727 on the long-term inflammatory responses. Martin (2009) posits that the immune system is
728 primarily upregulated during acute stress but in the face of chronic stress the immune system
729 is downregulated for energy conservation. The HPA axis can be epigenetically modified by
730 stress at multiple levels including DNA methylation of glucocorticoid receptors at the level of
731 the hippocampus (Weaver et al., 2004), and hypomethylation of CpG residues of the AVP gene
732 within the hypothalamus (Murgatroyd, 2014, Murgatroyd et al., 2009) with knock on effects
733 on the inflammatory process. Exposure to CIH in adult rats has been reported to activate and
734 sensitise the HPA axis to future stressors (Mifflin et al 2008). Exposure to nIH has been shown
735 to increase plasma ACTH and corticosterone in rats at postnatal day 2, 8, 10, 12 and 14 along
736 with hyperglycaemia (Chintamaneni et al 2013). Sex-dependent responses are also evident
737 when nLPS was coupled with an adult restraint stress in Wistar rats, which caused prolonged
738 peak corticosterone secretion in both sexes compared to control groups that did not receive
739 nLPS; only treated males exhibited elevated TNFα concentrations in the hippocampus (Walker
740 et al., 2010). Importantly, this study by Walker et al (2010) illustrates that physiological early
741 life stress can interact with psychogenic stressors later in life to alter immune function.
742 Physiological stress such as early life oxygen dysregulation, inflammation and ROS generation
743 could alter response to early life infection in a time- and sex-dependent manner.
744
745 Hypoxia and inflammation are inextricable linked (Koeppen et al., 2011, Nizet and Johnson,
746 2009, Rius et al., 2008, van Uden et al., 2008, Crifo and Taylor, 2016). There are many redox-

sensitive pathways, but one of the most studied in recent years is the NFκB-dependent pathway, which plays an important role in the innate immune response. Although tightly cross-linked to the HIF-1 pathway, NFκB can also be activated directly by hypoxia when oxygen sensitive prolyl hydroxylases (PHD) are disinhibited by Iκ β kinase (IKK-β) paving the way for NFκB transcription of inflammatory cytokines. Inflammation and hypoxia stabilise HIF-1 via distinct signalling pathways (Jantsch et al., 2011).

The pro-inflammatory nature of nIH has been demonstrated by increased serum cytokines and cytokine expression in the cerebellum (Darnall et al., 2017). In reverse, when LPS is administered at P2, rats exhibited spontaneous bouts of IH, attenuated hypoxic ventilatory response and blunted carotid body responsiveness to hypoxia that was associated with elevated dopamine levels and increased mRNA for inflammatory cytokines (Master et al., 2016). This suggests that early life infection can alter sensory input to the central respiratory network destabilising breathing. Recently, Hocker et al. (2019) revealed that one bout of LPS at P4 caused long-lasting impairments in the respiratory motor plasticity system. Long term facilitation of respiratory motor output in the adult was impaired via the serotonin dependent pathway (Q) but was reversible by anti-inflammatory drug ketoprofen administered during adulthood. The adenosine dependent pathway (S) was also impaired but could be stimulated via adenosine agonists (Hocker et al., 2019). Motor plasticity is likely an important adaptive response of the respiratory system in the face of physiological stressors such as hypoxia. The impact of specific cytokines such as IL1β on the respiratory system has been demonstrated by Hofstetter et al. (2007) in P9 mice pups causing apnoea, irregular breathing patterns and autoresuscitation failure through the activation of Prostaglandin E2 acting on EP3R receptors in respiratory centres. The proposed mechanism of action is via cytokine interaction with the blood brain barrier. However, LPS administered to P7 rat pups, 3 hours prior to hypoxia exposure did not alter hypoxic ventilatory response, but blunted hypoxic induced tachycardia (McDonald et al., 2016). This suggests that there may be critical windows wherein interactions between stimuli can differ. There is evidence to suggest that hypoxia and LPS together exacerbate the inflammatory response with crosstalk between HIF and TLR-4 signalling. One-week old rats treated with LPS, 4 hours prior to hypoxic-ischaemic injury exhibited significant cerebral infarction that was associated with an increase in both CD14 and TLR-4 mRNA expression (Eklind et al., 2001). Hypoxia (6 hours) and LPS administered together in adult rats

exacerbated acute lung injury by increasing cytokine production in a TLR-4-dependent manner, suggesting cross-talk between TLR-4 and the HIF-1α pathway (Wu et al., 2018). In support of this finding, Yao et al., (2013) found that LPS exposure in cultured microglia cells from P0 Wistar rats exhibited upregulation of TLR-4 receptor and gene expression of IL-1β was enhanced by hypoxia. Similar findings were observed in cultured human periodontal ligament cells (Jian et al., 2014) and murine dendritic cells prepared from bone marrow precursors (Jantsch et al., 2011). A study by Thompson et al., (2017) provided evidence that hypoxia and inflammation together potentiate sickness behaviours and increase mortality, however when hypoxia preconditioning was performed (7 days at 10% O_2), mice exhibited marked protection from *S. aureus* infection. Therefore, it remains unclear what the impact of early life hypoxia is on subsequent infections. It is feasible that similar to the blunting of the inflammatory response evident in response to a second immune challenge later in life (Boisse et al., 2004, Spencer et al., 2006a), hypoxia can also blunt the innate immune response in the long-term. Polke et al. (2017) reported that in cultured human bronchial epithelial cells, hypoxia and HIF-1α suppress the release of inflammatory cytokines. The influence of hypoxia on subsequent immune activation is likely dependent on pattern, intensity and timing and may be sex-dependent. A study by Kuhlicke et al., (2007) indicated a role for HIF-1-dependent upregulation of TLR-2 and TLR-6 in murine dendritic cells exposed to hypoxia, which would have important implications if subsequently faced with a gram-positive bacterial challenge.

Summary

The ontogeny of our integrated physiological network begins during embryogenesis and becomes fine-tuned throughout gestational and neonatal development. Maternal psychogenic stress, smoking, infection, and hypertension as well as multiple offspring, placental insufficiency and fetal intra-uterine growth restriction can lead to premature delivery and a sequel of post-natal stressors that can tamper with the programmed development of the integrated physiological network in the short- and long-term. Current translational and clinical research aims to understand the physiology of the preterm infant and impact of the environment on these vulnerable babies to minimise the risk to preterm infants and develop effective therapeutic strategies to enable infants to thrive.

Hypoxia in the preterm has long been identified as a major source of dysfunction that has been primarily managed with oxygen therapy through various modes of delivery. In neonatal animal models of oxygen dysregulation, somatic growth and cardiorespiratory control are altered. Both hypoxia, hyperoxia and variable patterns of intermittent oxygenation have been demonstrated to increase the release of ROS. ROS contributes to redox modulation of genes and cell pathways as well as cell damage and the activation of immune signalling cascades. Infection is also a major source of morbidity and mortality within the preterm populations that often occurs in babies with antecedent or on-going oxygen dysregulation. In the context of oxygen dysregulation and subsequent infection, the interplay between oxidative stress and inflammation in male and female preterm babies remains poorly understood.

Important differences between sexes are increasingly being highlighted prompting new investigations of the physiology underlying these differences and sex-specific therapies to better treat male and female babies. Intrinsic differences in expression and activation of cells such as microglia, neuronal pathways and neurochemistry are increasingly apparent between sexes in terms of responses to physiological stressors, as well as X chromosomal-linked and hormonal driven changes. Epidemiological evidence suggests that males are more vulnerable to acute stressors and poorer respiratory outcomes, whereas females are at increased risk of chronic immune conditions

The integrated autonomic output of the cardiorespiratory system will be influenced by direct effects of hypoxia, as well as modulatory influences along the gut-brain axis from the microbiome/immune system, central modulation by activated glia cells and the prevailing hormonal concentrations determined by the activation of the HPA axis. This short review highlights current knowledge on early life oxygen dysregulation, inflammation and cardiorespiratory performance. Much work remains to explain the mechanisms underlying chronic disturbances in males and females born prematurely. Continued translational and clinical research can ensure those born early receive the best support that limits harm and maximises quality of life.

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Publication	*Species*	*Age of exposure*	*Sex*	*Litter Size Controlled*	*Paradigm*	*Nadir FiO_2*	*Peak FiO_2*	*Age at time of experiments*	*Outcome measured*	*Significance*
Julien et al., 2008	*Rat, SD*	*P1-P10*	*10 Males & 9 females pooled*	*12*	***Intermittent Hypoxia*** *21% O_2 to 5% O_2 in 100 s and then returned to 21% O_2 in 140 s, followed by normoxia during 6 min. This 10-min cycle was repeated six times, followed by 1 h of normoxia and repeated 24 h a day during 10 consecutive days*	*5%*	*21%*	*P10*	*Body Mass* WBP *f_R (B)* *$\dot{V}_E$ (B)* *Metabolism (B)* *HVR* *V_{LTF}* *Apnoea*	↓ ↓ → → ↑M →F ↓ ↑
Julien et al., 2010	*Rat, SD*	*P1-P10*	*Males only*	*12*	***Intermittent Hypoxia*** *21% O_2 to 5% O_2 in 100 s and then returned to 21% O_2 in 140 s, followed by normoxia during 6 min. This 10-min cycle was repeated six times, followed by 1 h of normoxia and repeated 24 h a day during 10 consecutive days*	*5%*	*21%*	*3-4 Months*	*Body Mass* WBP *f_R (B)* *$\dot{V}_E$ (B)* *$\dot{V}_E/\dot{V}_{O_2}$ (B)* *MAP (B)* *HVR* *$\dot{V}_E$* *MAP* *Splanchnic LTF*	*↓P21 → P60* ↑ → → ↑ → ↑ ↓
Julien et al., 2011	*Rat, SD*	*P3-P12*	*Males only*	*12*	***Intermittent Hypoxia*** *21% O_2 to 5% O_2 in 100 s and then returned to 21% O_2 in 140 s, followed by normoxia during 6 min. This 10-min cycle was*	*5%*	*21%*	*P12*	*Body Mass nIH + water* *WBP* *f_R (B) nIH + water* *f_R (B) nIH + caffeine*	↓ ↓ ↑

					repeated six times, followed by 1 h of normoxia and repeated 12 h a day during 10 consecutive days				*$\dot{V}_E$ (B) nIH + water* *$\dot{V}_E$ (B) nIH + caffeine* *$\dot{V}_E/\dot{V}_{O_2}$ nIH + water* *$\dot{V}_E/\dot{V}_{O_2}$ nIH + caffeine* *Apneoas nIH + water* *HVR nIH + water*	→ ↑ → → → ↑
Mayer et al., 2015	*Rat, L*	*P5-P15*	*Male*	*-*	***P0-P5 normoxia followed by Intermittent Hypoxia*** *Every 5min,8h/day for 10days* ***Pre-treated P0-P5 sustained Hypoxia (11%) followed by Intermittent Hypoxia*** *Every 5min,8h/day for 10days*	*5%*	*21%*	*P16*	*Petrosal activity (B) nIH* *Petrosal activity (B) SH + nIH* *Petrosal activity (H) nIH* *Petrosal activity (H) SH + nIH* *nTS activity nIH* *nTS activity SH + nIH*	→ ↓ → ↓ → ↑
Peng et al., 2004	*Rat, SD*	*P0*	*undefined*	*-*	***Intermittent Hypoxia*** *nadir of 5% O_2 during hypoxia within 68–75 s and 21% O_2 during normoxia within 70–85 s. Nine episodes of IH per hour for 16 h.*	*5%*	*21%*	*P2*	*Carotid Body Activity* <u>WBP</u> *$\dot{V}_E$ (B)* *f_R (B)* *$\dot{V}_E$ (H)* *f_R (H)* *$\dot{V}_E/\dot{V}_{O_2}$ (H)*	↑ ↑ ↑ ↑ ↑ →
McDonald et al., 2015	*Rat, W*	*P0-P22*	*Male & Female groups*	*-*	***Intermittent Hypoxia*** *90 s of hypoxia (5% O_2 at the nadir) followed by 210 s of*	*5%*	*21%*	*P22* *P42*	*Body Mass* *HCT*	*↓M ↓F* →

					normoxia (21% O_2) i.e., 12 cycles per hour				*Resp. Muscle Function P22* *Resp. Muscle Function P42*	*↓M ↓F* *↓M ↑F*
McDonald et al., 2016	*Rat, W*	*P0-P22*	*Male & Female groups*	*-*	***Intermittent Hypoxia** –nIH* *90 s of hypoxia (5% O_2 at the nadir) followed by 210 s of normoxia (21% O_2) i.e., 12 cycles per hour for 21 days* ***Intermittent Hypoxia** –nIH + aIH* *90 s of hypoxia (5% O_2 at the nadir) followed by 210 s of normoxia (21% O_2) i.e., 12 cycles per hour for 21 days* *Repeat exposure for 21 days at 13 weeks*	*5%*	*21%*	*Adult IH* *13-16* *weeks*	*Body Mass nIH* *Body Mass nIH + aIH* *HCT nIH* *HCT nIH* *Resp. Muscle Function nIH* *Resp. Muscle Function nIH + aIH*	*↓M →F* *→M →F* *→M →F* *→M →F* *→M →F* *↓M ↓F*
Gozal et al., 2002	*Rat, SD*	*P0-P5*	*undefined*	*-*	***Intermittent Hypoxia*** *10% O_2 (90 s) alternating with 21% O_2 (90 s), 12 h/day*	*10%*	*21%*	*P5*	*Body Mass* *Gasp duration* *Autoresuscitation*	*↓* *↓* *↓*
Reeves et al., 2006a	*Rat, SD*	*P1- P30*	*Male*	*8*	***Intermittent Hypoxia*** *every 90 s for the 12-h/day for 30 days*	*10%*	*21%*	*P30*	*Body Mass* *WBP* *$\dot{V}_E$ (B)* *f_R (B)* *$\dot{V}_E/\dot{V}_{CO_2}$ (B)*	*↓* *↑* *↑* *↑*
Reeves et al., 2006b	*Rat, SD*	*P0-P5,* *-P10,* *-P15,*	*Male*	*8*	***Intermittent Hypoxia*** *every 90 s for the 12-h/day for 30 days*	*10%*	*21%*	*P10* *P15* *P30*	*Body Mass* *$\dot{V}_E$ (B)* *f_R (B)*	*↓* ↑all ↑P15&P30 only

		-P30.							*HVR* *$\dot{V}_E/\dot{V}_{CO_2}$ (B)*	↑P10, P15 &P30 ↑P30
Soukhova-O'Hare et al., 2006a	*Rat, SD*	*P1-P30*	*Male*	*-*	***Intermittent Hypoxia*** *8% O_2 (90 s) alternating with 21% O_2 (90 s), 12 h/day and 21% O_2 during the remaining 12 h.*	*8%*	*21%*	*3-5 months*	*Body Mass* *MAP* *Baroreflex* *Vagal Innervation*	↓ → ↓ ↓
Soukhova-O'Hare et al., 2006b	*Rat, SD*	*P1-P30*	*Male*	*-*	***Intermittent Hypoxia*** *8% O_2 (90 s) alternating with 21% O_2 (90 s), 12 h/day and 21% O2 during the remaining 12 h.*	*8%*	*21%*	*5-7 months*	*Body Mass* *MAP* *Renal sympathetic nerve activity (B)* *Renal sympathetic nerve activity (H)* *Baroreflex*	→ → → ↑ ↓
Soukhova-O'Hare et al., 2008	*Rat, SHR*	*P4-P30*	*Male*	*-*	***Intermittent Hypoxia*** *10% O2 (90 s) alternating with 21% O2 (90 s), 12 h/day and 21% O2 during the remaining 12 h.*	*10%*	*21%*	*6 months*	*Body mass* *Systolic BP* *Diastolic BP* *Concentric LV hypertrophy*	↓ ↑ ↑ ↑
Souvannakitti et al., 2009	*Rat, SD*	*P0-P5*	*undefined*	*-*	***Intermittent Hypoxia*** *15-s 5% O_2 followed by 5-min 21% O_2; 8 h/day) for 5 days*	*5%*	*21%*	*P5*	*Catecholamines (H)* *Ca^{2+} release(H)* *MDA*	↑ ↑ ↑
Souvannakitti et al., 2010	*Rat, SD*	*P0-P5*	*undefined*	*-*	***Intermittent Hypoxia*** *15-s 5% O_2 followed by 5-min 21% O_2; 8 h/day) for 5 days*	*5%*	*21%*	*P5*	*Nicotine evoked Catecholamines* *nAChR gene expression in adrenal medulla cells*	↓ ↓

Chu et al., 2015	*Mouse, C57BL/6 J*	*P0-P28*	*Male*	*6*	***Intermittent hypoxia*** *Alternating cycles of 8% and 21% FiO2 with 120-s cycle duration for 6 h per day*	*8%*	*21%*	*3 months*	*Body Mass* *Systolic BP* *Diastolic BP* *HR* *HRV* *Baroreflex* *Vasodilation to Ach* *ACE* *ROS*	*↓ week 1 and 4 →after 6weeks* ↑ → → ↓ ↓ ↓ ↑ ↑
Pawar et al., 2008	*Rat, SD*	*P1* *P1-P3* *-P10*	*undefined*	*-*	***Intermittent hypoxia*** *15s 5% O_2 followed by 5-min 21% O_2, 9 cycles per hour, for 8 h/day*	*5%*	*21%*	*P1* *P3* *P10* *2months*	*Carotid Body Hypoxic response* *Carotid Body LTF* *TH-positive glomus cells*	*↑all* → ↑
Nanduri et al., 2012	*Rat, SD*	*P1-P10*	*Male and female grouped*	*-*	***Intermittent Hypoxia*** *15-s 5% O_2 followed by 5-min 21% O_2; 9 cycles per hour, 8 h/day, for 10 days*	*5%*	*21%*	*P40-50*	*Body Mass* *Carotid Body Activity* *MDA* *Catecholamine secretion adrenal chromaffin cells* <u>Gene Expression</u> *Dnmt1* *Dnmt3b* *SOD2 methylation* *Duox2* *Resp. Variability*	*↓* *↑* *↑* *↑* *↑* *↑* *↑* → *↑*

									HVR *Apnoeas* *MAP*	↑ ↑ ↑
Darnall et al., 2017	*Rat, SD*	*P2-12*	*Male and female pooled*	*10*	***Intermittent Hypoxia*** *6 decreases in chamber oxygen concentration per hour (3 min, allowing ~ 7 min of room air exposure between Events) alternating with an hour of normoxia*	*8%*	*21%*	*P13* *P18* *P20-22*	*CXCL1* *IL-1β* *Neuronal specific enolase* *Creatinine (Cr)* *NAA/Cho* *Tau/Cr* *Glycine/Cr*	↑ *P13* ↑ *P13 Cerebellum* ↑*P18 medulla* ↓brainstem ↓brainstem ↓brainstem ↓brainstem
Douglas et al., 2003	*Mouse, CD-1*	*P2/P3-P30*	*Male and female pooled*	*-*	***Intermittent Hypoxia*** *2min 6-7.5% O_2 followed by 3 min 21% O_2, 8 hours per day*	*6%*	*21%*	*P30*	*Body Mass* *Na/H exchanger 1* *Na/H exchanger 3* *Cl/HCO_3 exchanger* *Na/HCO_3 cotransporter*	↓ ↓*cerebellum* ↓*cerebellum* ↓*hippocampus* ↓*cerebellum*
Farahani et al., 2007	*Mouse, CD-1*	*P2-P30*	*Male and females pooled*	*8*	***Intermittent Hypoxia*** *4 min 11% O_2, 4 min 21% O_2,*	*11%*	*21%*	*P9, P16, P23, P30*	*Body Mass* *Lung/Body Mass* *Heart/Body Mass*	↓*P9-30* → *P9, P16,* ↑ *P23, P30* ↑*P9, P16, P23, P30*
Kanaan et al., 2006	*Mouse, CD-1*	*P2- P16 - P30*	*undefined*	*-*	***Intermittent Hypoxia*** *4 min 11% O_2, 4 min 21% O_2,*	*11%*	*21%*	*P16* *P30*	*Body Mass* *Haematocrit*	↓*P16, P30* ↑*P30*

									Capillary Density *Myelination*	↑*P16, P30* ↓*P30*
Cai et al., 2011	*Mouse,* *C57BL/6*	*P2-P10*		*Yes # not reported*	***Intermittent Hypoxia*** *20.9% O_2/8.0% O_2 alternation cycles (and in some cases, 20.9% O_2/5.7% O_2 alternation cycles) lasting 120 s (i.e. 30 episodes per hour) for 6 h a day*	*8%* *5.7%*	*20.9%* *20.9%*	*P10* *P30*	*Myelination* *Mature oligodendrocytes* *Neurofilament components*	*P10*↓*striatum, cerebellum* → *Pons, spinal cord* ↓*P10* ↓*P10*
Cai et al 2012	*C57BL/6*	*P2 to P10*	*undefined*	*Yes # not reported*	***Intermittent Hypoxia*** *20.9% O_2/8.0% O_2 alternating cycles lasting 120 s (i.e. 30 episodes per hour) for 6 h a day* *20.9% O_2/5.7% O_2 alternation cycles lasting 120 s (i.e. 30 episodes per hour) for 6 h a day*	*8%* *5.7%*	*20.9%* *20.9%*	*P7-P10*	*Body Mass* *Heart Rate* *f_R* *Myelination*	→*all* ↑ *IH5.7* →*IH8* →*all* ↓*IH8*
Fan et al., 2005	*Mouse,* *CD-1*	*P2- P8* *-P15* *-P29*	*Male and female groups*	*-*	***Intermittent Hypoxia*** 21% O_2 for 4 min and 11% O_2 for another 4 min, 24 hours per day	*11%*	*21%*	*P9* *P16* *P30*	*Body Mass* *Heart Mass* *Haematocrit* *Gene expression*	↓*all* →*all* ↑ P9, P16 →P30 ↑375 & ↓440 genes P9 ↑440 & ↓795 genes P16 ↑150 & ↓68 genes P30
Pozo et al., 2012	*Rat, SD*	*P1-P7*	*undefined*	*10*	***Intermittent Hypoxia dispersed (nIHd)***	*5%*	*21%*	*4-8 Weeks*	*Body Mass nIHd*	↓

					dispersed hypoxia exposures consisted of 45 s of hypoxia (nadir of 5% O_2; FiO_2 60%) followed by 4 min and 15 s of 21% O_2 continuously over 8 h for 7 days ***Intermittent Hypoxia clustered*** *(nIHc)* *45 s of hypoxia (nadir of 5% O_2) followed by 90 s of 21% O_2. These 135 s duration cycles occurred over three periods of 72 min duration per day interspersed with 2.2 h of RA exposure for 7 days*				*Body Mass nIHc* *HR nIHd* *HR nIHc* *MAP nIHd* *MAP nIHc*	↓ ↓ ↓ → ↓
Mayer et al., 2013	*Rat, L*	*P5-P15*	*Male*	-	*P0-P5 normoxia followed by* ***Intermittent Hypoxia*** *Every 5min, 8h/day for 10days* *Pre-treated P0-P5 Hypoxia (11%) followed by Intermittent Hypoxia Every 5min, 8h/day for 10days*	*5%*	*21%*	*P16*	*Body Mass nIH* *Body Mass SH + nIH* <u>WBP</u> *F_R (B) nIH* *F_R (B) SH + nIH* *$\dot{V}_E$ (B) nIH* *$\dot{V}_E$ (B) SH + nIH* *$\dot{V}_E/\dot{V}_{O_2}$ nIH* *$\dot{V}_E/\dot{V}_{O_2}$ SH + nIH* *HVR nIH* *HVR SH + nIH*	→ ↓ → → → ↑ → → → ↓
Douglas et al., 2010	*Mouse, CD-1*	*P2-P12* *P2-P16*	*Male and female pooled*	*8*	***Intermittent Hypoxia/ Hypercapnia (8%)***	*11%*	*21%*	*P16*	*Body Mass* *Haematocrit* *Neuronal Cell Death*	↓*P16* ↑*P16* ↑*P10*

					4 min 11% O_2/8% CO_2, 4 min 21% O_2 8% CO_2, 24 hours per day				*Mitochondrial Function* *Mitochondrial Superoxide Production*	*↓P16* *↑P16*
Dylag et al., 2017	*Mouse, C57BL/6*	*P0—P7*	*undefined*	-	***Intermittent Hypoxia (IH)*** *10% O_2 (1 min) followed by return to normoxia on 10-min repeating cycles 24 h/d from birth to P7.* ***Intermittent Hyperoxia (IHyper)*** *Transient 50% O_2 followed by return to normoxia on 10-min repeating cycles 24 h/d from birth to P7.* ***Intermittent Hypoxia and Intermittent Hyperoxia (IHHyper)*** *10% O_2 (1 min) followed by a transient exposure to 50% FIO_2, on 10-min repeating cycles 24 h/d from birth to P7.*	*10%* *21%* *10%*	*21%* 50% 50%	*P21*	*Resp Resistance* *Airway Responsiveness **IH*** *Airway Responsiveness **IHyper*** *Airway Responsiveness **IHHyper*** *SOD 1 **IHyper*** *SOD 3 **IHyper*** *NOX1 **IH*** *NOX2 **IHHyper***	*→all* *→* *↑* *↑* *↓* *↓* *↓* *↑*
Logan et al., 2016	*Rat, SD*	*P0-P4* *P6-P7* *P13-P15*	*Male & female pooled*	-	***Intermittent hyperoxia*** *5 cycles per hour, 24hr per day* ***Intermittent hyperoxia*** *5 cycles per hour, 24hr per day*	*21%* *21%*	*30%* *60%*	*P4* *P6-7* *P14-15* *4-6months*	*Body Mass IHyper30* *Body Mass IHyper 60* *HVR IHyper30* *HVR IHyper 60* *Chemo-afferent activity (B) IHyper 30* *Chemo-afferent activity (B) IHyper 60*	*↑P4, P6-7* *↓P4, P6-7* *→P6-7, ↓P14-15* *↑P6-7↓P14-15* *→P4, ↓P13-14* *↓P4, ↓P13-14*

									Chemo-afferent activity (H) IHyper 30 *Chemo-afferent activity (H) IHyper 60*	*→P4, P13-14* *↓P4, →P13-14*
Bavis et al., 2007	*Rat, SD*	*P0-P14*	*Male and female or male only*		***Intermittent hypercapnia*** *(ICO_2)(<0.4 and 7.5% at 1-h intervals 24 h per day)* ***Hyperoxia with intermittent hypercapnia*** *($HyperICO_2$) (<0.4 and 7.5% at 1-h intervals 24 h per day)* ***Intermittent hyperoxia (IHyper)*** Oxygen switched 1-h intervals 24 hr per day	*21%* *21%*	*21%* *60%*	*6-10 weeks*	*Body Mass* *WBP* *$\dot{V}_E$ (B)* *fR (B)* *$\dot{V}E/\dot{V}O_2$ (B)* *$\dot{V}_E$ (H)* *f_R (H)* *$\dot{V}E/\dot{V}CO_2$ (H)*	*↑all* *→all* *→all* *→all* *→ ICO_2, $HyperICO_2$, ↓IHyper* *↑ ICO_2, →$HyperICO_2$, ↓IHyper* *→ ICO_2,, $HyperICO_2$ ↓ IHyper*
Bavis et al., 2019	*Rat, SD*	*P0-P13/14*	*Male and Female pooled*	*-*	***Intermittent hypoxia (10%) /Hypercapnia (5%) with background normoxia*** ***Intermittent Hypoxia (10%) /Hypercapnia (6%)/hyperoxia (30%) with background normoxia (21%)*** ***Intermittent Hypoxia (10%) /Hypercapnia (5%) with background hyperoxia (30%)***	*10%* *10%* *10%*	*21%* *30%* *30%*	*P13-14*	*Body Mass* *$\dot{V}E$ (B)* *f_R (B)* *$\dot{V}E$ (H)* *Hypoxic O_2 consumption* *Chemo-afferent activity (B)*	*↓a,b,c,d* →a,b,c,d →a,b,c,d →a, b, c, d ↑a,b →c,d ↑a →b, c ↓d

					Intermittent Hypoxia (10%) /Hypercapnia (6%)/ hyperoxia with background hyperoxia (30%)	10%	*40%*		*Chemo-afferent activity (H)* *CB size*	*→a, b →c ↓d* ↑a, →b, c, d
Morken et al., 2013	*Rat, SD*	*P0-P14*	*undefined*	*-*	***Intermittent Hypoxia Hyperoxia*** *Hyperoxia (50% O_2) interrupted by three consecutive two-minute episodes of hypoxia (12% O_2) every sixth hour.*	*12%*	*50%*	*P14* *P28*	*Perivascular Albumin leakage* *mean, axial and radial diffusivity*	*→P14 ↑ P28* *↑ P14 →P28*

Table Legend

Table 1

A summary of publications examining the effects of intermittent hypoxia, intermittent hyperoxia and/or intermittent hypoxia and hyperoxia on cardio-respiratory function. The table outlines the strain, age and sex used in the study and a description of the experimental paradigm indicating both the peak and nadir % FiO_2 experienced by the animals in the study. The table also indicates the major cardio-respiratory related findings from each study comparing treated animals to control (sham) animals in each case.

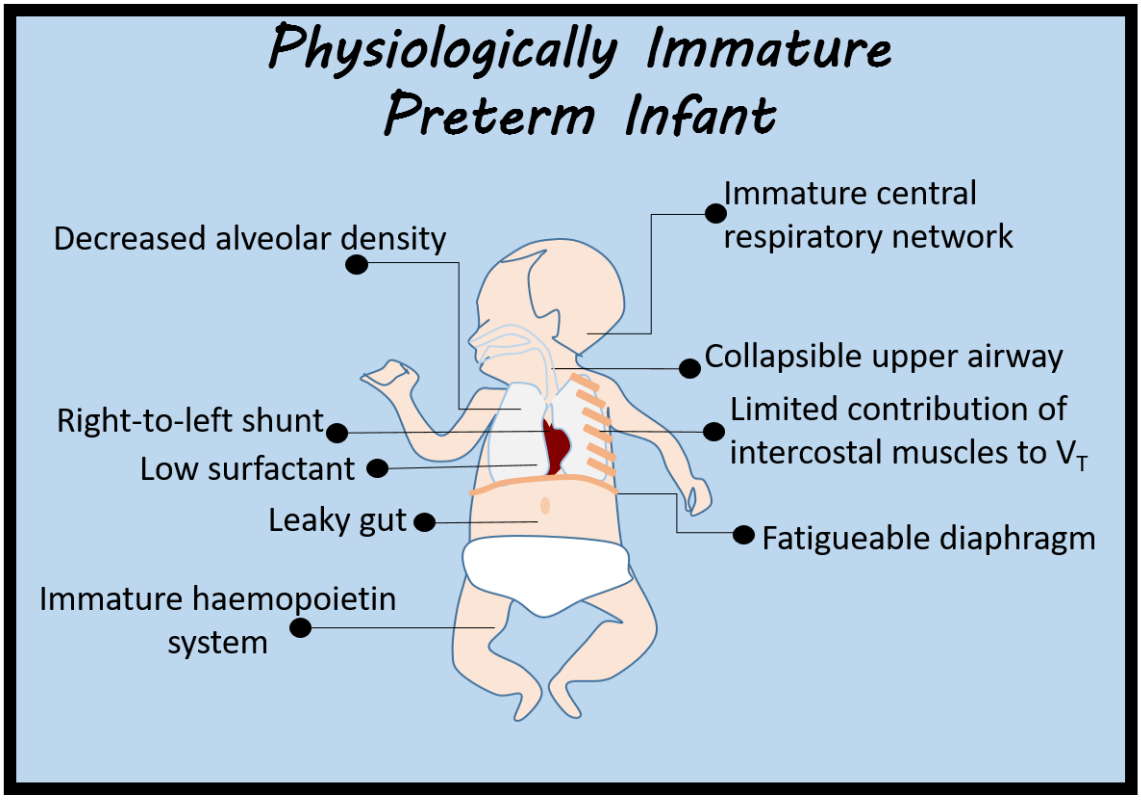
Physiologically Immature Preterm Infant
Decreased alveolar density
Immature central respiratory network
Collapsible upper airway
Right-to-left shunt
Limited contribution of intercostal muscles to V_T
Low surfactant
Leaky gut
Fatigueable diaphragm
Immature haemopoietin system

Figure 1

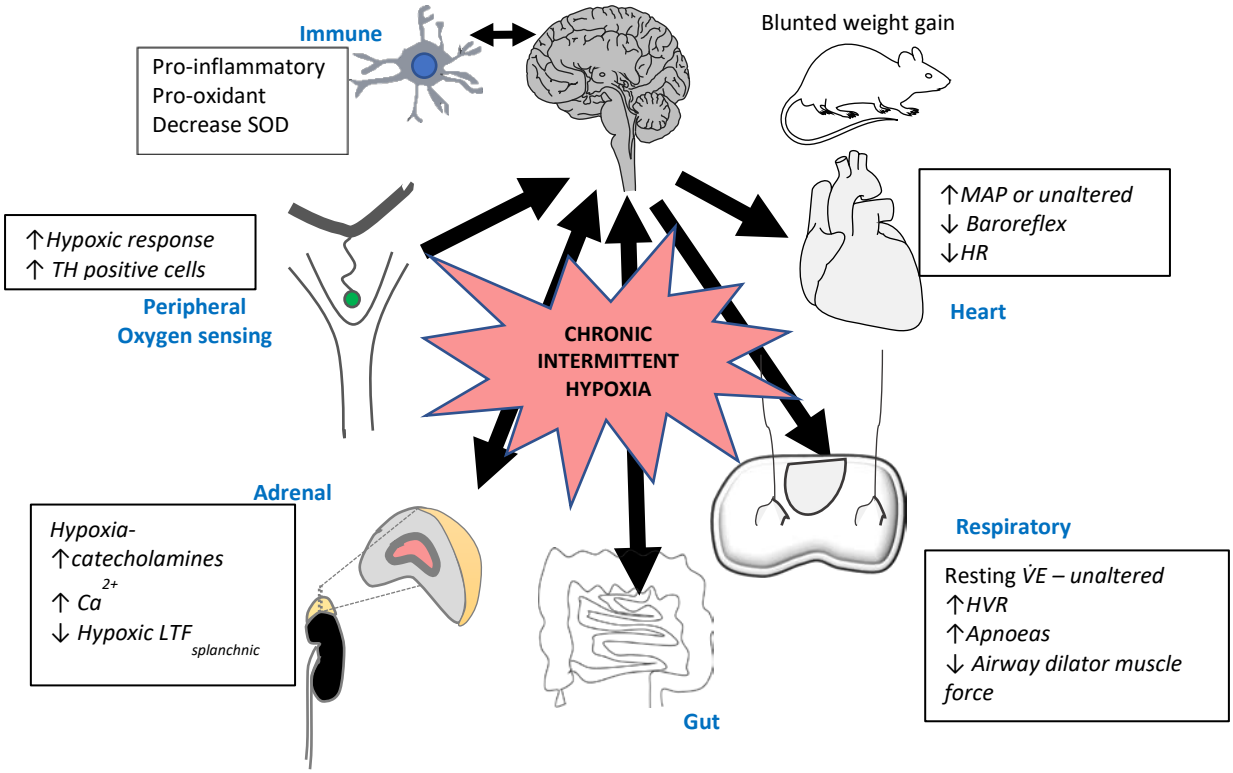
Immune
Pro-inflammatory
Pro-oxidant
Decrease SOD
Blunted weight gain
↑Hypoxic response
↑ TH positive cells
Peripheral
Oxygen sensing
↑MAP or unaltered
↓ Baroreflex
↓HR
Heart
CHRONIC
INTERMITTENT
HYPOXIA
Adrenal
Hypoxia-
↑catecholamines
↑ Ca2+
↓ Hypoxic LTF splanchnic
Respiratory
Resting V̇E – unaltered
↑HVR
↑Apnoeas
↓ Airway dilator muscle force
Gut

Figure 2

Legends

Figure 1

Preterm infants fail to reach the maturity of a term infant, which hinders their transition to life outside of the uterus. An efficient cardio-respiratory system is vital to sustain life. As illustrated above, this system is often compromised in preterm infants and those that are born earliest have the poorest outcomes, both in the short- and long-term.

Figure 2

Animal models of neonatal intermittent hypoxia have revealed significant dysfunction at several key sites that can alter cardiorespiratory physiology. The illustration captures the wide-ranging impact of oxygen dysregulation during early life. If translated to the preterm infant, these phenotypes would contribute significantly to the sequel of short- and long-term morbidity.