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REVIEW

The fetal circulation, pathophysiology of hypoxemic respiratory failure and pulmonary hypertension in neonates, and the role of oxygen therapy

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Neonatal hypoxemic respiratory failure (HRF), a deficiency of oxygenation associated with insufficient ventilation, can occur due to a variety of etiologies. HRF can result when pulmonary vascular resistance (PVR) fails to decrease at birth, leading to persistent pulmonary hypertension of newborn (PPHN), or as a result of various lung disorders including congenital abnormalities such as diaphragmatic hernia, and disorders of transition such as respiratory distress syndrome, transient tachypnea of newborn and perinatal asphyxia. PVR changes throughout fetal life, evident by the dynamic changes in pulmonary blood flow at different gestational ages. Pulmonary vascular transition at birth requires an interplay between multiple vasoactive mediators such as nitric oxide, which can be potentially inactivated by superoxide anions. Superoxide anions have a key role in the pathophysiology of HRF. Oxygen (O_2) therapy, used in newborns long before our knowledge of the complex nature of HRF and PPHN, has continued to evolve. Over time has come the discovery that too much O_2 can be toxic. Recommendations on the optimal inspired O_2 levels to initiate resuscitation in term newborns have ranged from 100% (pre 1998) to the currently recommended use of room air (21%). Questions remain about the most effective levels, particularly in preterm and low birth weight newborns. Attaining the appropriate balance between hypoxemia and hyperoxemia, and targeting treatments to the pathophysiology of HRF in each individual newborn are critical factors in the development of improved therapies to optimize outcomes.

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INTRODUCTION

Hypoxemic respiratory failure (HRF) is a deficiency of oxygenation associated with insufficient ventilation. HRF can occur in neonates owing to parenchymal lung disease, such as meconium aspiration syndrome, pneumonia or respiratory distress syndrome, secondary to lung hypoplasia as in congenital diaphragmatic hernia, or as a consequence of pulmonary vascular remodeling in the absence of lung disease (idiopathic pulmonary hypertension). HRF may be associated with unsuccessful cardiovascular transition when pulmonary vascular resistance (PVR) fails to decrease at birth, leading to persistent pulmonary hypertension of newborn (PPHN).[1–3]

In the United States, the incidence of respiratory failure requiring mechanical ventilation is estimated at ~18 per 1000 live births.[4] HRF is associated with considerable mortality (between 10% and 15%) and morbidity, including hospitalization and disability.[5,6] Oxygen (O_2) supplementation is an important component of HRF management. O_2 therapy has evolved from its early use to current approaches, based on our increasing understanding of HRF. This article discusses the etiology and pathophysiology of HRF in neonates, as well as the evolution of O_2 therapy in the management of this condition. It is part of a series summarizing presentations and discussions from a roundtable discussion focused on HRF in neonates (see the Introduction to this issue).

FETAL CIRCULATION AND PVR

In fetal life there are two sources of preload to the left ventricle: (1) the primary source, oxygenated blood from the placenta to the umbilical vein through the foramen ovale, with 85% O_2 saturation and (2) deoxygenated blood returning from the lung, with ~45% O_2 saturation.[7–9] However, pulmonary blood flow is low in the fetus, with the lungs receiving only about one-fifth of combined cardiac ventricular output at term gestation.[7] Because of the low volume of pulmonary venous return, the combination of these two sources of preload in the left ventricle results in a 65% blood O_2 saturation that circulates to the fetal brain and coronary circulation. The O_2 level in blood to the brain is higher than that circulating to the lower half of the body (~55% O_2 saturation) including umbilical arteries.[7,10]

The dynamic nature of the pulmonary circulation and the O_2 gradient across the placenta maintains O_2 delivery to the fetal brain in a narrow window. Maternal arterial blood in the pregnant ewe has an arterial partial pressure of oxygen (PaO_2) of 90 to 100 mm Hg. There is a large partial pressure of oxygen (PO_2) gradient across the placenta, with a PO_2 of 32 to 35 mm Hg in the umbilical vein, protecting the fetus from exposure to high O_2 levels. Left ventricular and ascending aorta blood perfusing the brain has a PO_2 of 25 to 28 mm Hg (65% O_2 saturation). Administering 100% O_2 to the ewe raises PaO_2 to >400 mm Hg but the umbilical venous PO_2 increases only to 40 to 50 mm Hg and fetal ascending aorta PaO_2 increases to only 30 to 35 mm Hg (Figure 1).[7] The reciprocal, complementary relationship between oxygenated flow across foramen ovale and deoxygenated blood flowing from the pulmonary veins to the left ventricle can partly explain this O_2-buffering effect. Maternal

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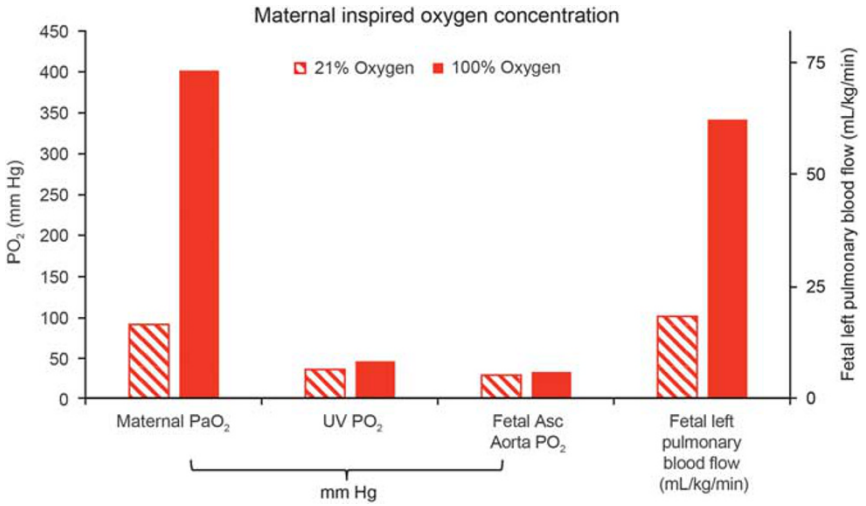

Figure 1. Protective role of placenta and fetal pulmonary circulation from maternal hyperoxia: administering 100% oxygen (solid bars) to the ewe raises maternal PaO_2 by over 300 mm Hg compared with 21% oxygen (hatched bars) but the umbilical venous (UV) PO_2 increases by only 10 to 15 mm Hg, whereas the fetal ascending arterial PO_2 increases by only 5 mm Hg but markedly increases pulmonary blood flow compared with 21% oxygen. Copyright Drs Satyan Lakshminrusimha and Ola D Saugstad. PaO_2, arterial partial pressure of oxygen; PO_2, partial pressure of oxygen.

hyperoxemia increases fetal left pulmonary arterial blood flow from 20 ± 10 to 68 ± 18 mL/min,[11] possibly by increasing pulmonary arterial PO_2. This hyperoxic effect in turn increases pulmonary venous return of desaturated blood entering the left ventricle, thereby lowering the O_2 levels to the brain. Thus, even though the mother's PaO_2 is increased by 300 mm Hg, the PaO_2 in the ascending aorta of the fetus only increases by 5 to 7 mm Hg.[7] Furthermore, pulmonary vasodilation reduces right-to-left shunt across the foramen ovale. In a human study, fetuses that had a high pulmonary foramen ovale shunt (that is, a bigger component of left ventricular input from umbilical venous return) had a low pulmonary venous return. The opposite was true for fetuses that had a low pulmonary foramen ovale shunt, and a high pulmonary venous return.[12] Thus, the placenta and pulmonary circulation play a vital role in reducing O_2 toxicity to the fetal organs.

During fetal life, when the placenta is the organ of gas exchange, placental vascular resistance is low and fetal PVR is high. Blood flow is diverted from the pulmonary artery to the aorta and umbilical arteries toward the placenta.[3,13] As previously mentioned, PVR is known to change throughout fetal life as demonstrated by the varying levels of blood circulating to the lungs during different gestation stages (Figure 2).[3,14] At 20 weeks (canalicular stage), when the fetus is immature, only 13% of combined ventricular output circulates to the lungs. The cross-sectional area of pulmonary vasculature is low in the canalicular stage, resulting in high PVR. At 30 weeks (saccular stage), an increase in pulmonary blood vessels leads to a decrease in PVR and 25% to 30% of combined ventricular output goes to the lungs. At 38 weeks' gestation (alveolar stage, pre-birth), active vaso-constriction drops the amount of combined ventricular output circulating the lungs to ~19% to 23% in spite of an increase in pulmonary vasculature. The decrease in pulmonary blood flow at this gestational age is secondary to the fact that pulmonary vasculature develops sensitivity to O_2, leading to fetal hypoxic pulmonary vasoconstriction and elevation of PVR.[3,14,15]

The U-shaped curve of PVR in the last half of gestation is mimicked by regional data on the use of inhaled nitric oxide (iNO), as a vasodilator, in babies born at various gestational ages (as a surrogate for the incidence of moderate-to-severe PPHN). This pattern was especially apparent prior to the National Institutes of Health 2010 Consensus Development Conference Statement indicating insufficient evidence to recommend routine use of iNO in preterm infants,[16] but continues to be reflected in variations in local practices. Of note, data from California show that the use of iNO is lowest ~30 to 33 weeks' gestational age,[17] reflective of the low PVR that occurs at this time in fetal development. A similar pattern of iNO use was observed among neonatal level III patients given invasive ventilation in the Australia and New Zealand Neonatal Network in 2013 (18% at <24 weeks, 5.5% at 30 to 33 weeks and 17.7% at 37 to 43 weeks postmenstrual age at birth.[18]

TRANSITION FROM *IN UTERO* TO BIRTH: FACTORS TO CONSIDER IN PPHN

Ventilation of the lungs at birth reduces PVR, and the removal of the low vascular resistance placenta from the systemic circulation at birth increases systemic vascular resistance (Figure 2).[3] The mode of delivery affects PVR. A vaginal birth is associated with a rapid reduction in fetal PVR, whereas birth by elective cesarean section slows reduction in PVR, as does the use of delayed (or late) cord clamping.[3,19,20]

With the increasing use of delayed cord clamping, it is important to assess whether this technique affects the pulmonary vascular transition at birth. In clinically normal, full-term, newborn infants ($N=32$) early cord clamping (<10 s after birth, $n=10$) resulted in a rapid decline in the pulmonary artery to aortic pressure ratio, whereas late cord clamping (3 to 5 min until umbilical pulsations stop, $n=22$), resulted in a slow decline.[20] However, there is no evidence of increased respiratory distress or neonatal intensive care unit admission among term infants following late cord clamping.[21] In fact, there may be a trend toward higher incidence of PPHN associated with early cord clamping and lower hematocrit presumed to be due to the absence of placenta transfusion.[22] This may be as a result of increased hemoglobin levels in the blood following placental transfusion that contribute to an increased O_2 carrying capacity.

THE PATHOPHYSIOLOGY OF HRF

Nitric oxide (NO), a cellular signaling molecule, is a powerful vasodilator that modulates pulmonary vascular tone.[23] It is one of the most volatile molecules in the body, avidly combining with superoxide anion to form peroxynitrite,[3,24–26] which causes

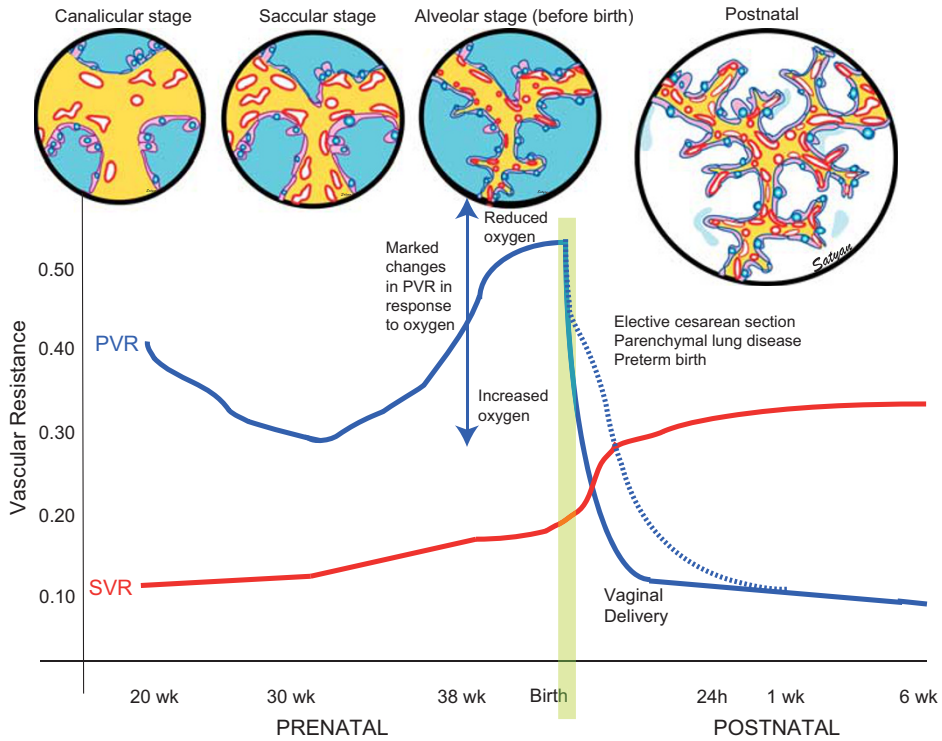

Figure 2. Changes in pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) during gestation. During the canalicular phase of lung development, high PVR is caused by low density of the vasculature. In the saccular stage, broad intersaccular septae contain the double capillary network and, with increasing vascular density, PVR decreases. In the alveolar phase, despite the rapid increase in the number of small pulmonary arteries, high PVR is maintained by active vasoconstriction. The dashed line represents the delay in decrease of PVR observed following elective C-section. SVR markedly increases after occlusion of the umbilical cord and removal of the low-resistance placental circuit from the systemic circulation.[3] Copyright Dr Satyan Lakshminrusimha.

pulmonary vasoconstriction.[27] A key factor determining the bioavailability of NO in a tissue is the local concentration of superoxide anions. Minimizing the superoxide anion concentration may enhance the effect of endogenous NO.

The superoxide anion concentration is dependent on its rate of production and the activity of various superoxide dismutases (SOD).[24] Extracellular SOD, an enzymatic scavenger of extracellular superoxide highly expressed in the lungs and vascular smooth muscle, can reduce superoxide levels and contribute to the modulation of vascular O_2 levels.[24,28,29] Increased superoxide anions have been demonstrated in PPHN induced by antenatal ductal ligation in fetal lambs. Vascular adventitia provides an active source of superoxide anions and can inactivate NO.[30] Exogenous NO delivered from the adventitial side does not cause vasodilation;[31,32] and in remodeled vessels, the thickened, superoxide anion-producing adventitia may further blunt the effect of NO.[33]

In the fetal lamb model of PPHN, which in many ways resembles a human infant with PPHN, there is an increase in the expression of genes that induce pulmonary vasoconstriction and a reduction in those that induce vasodilation.[34] Superoxide is twofold higher and hydrogen peroxide is fourfold higher in the pulmonary arteries of lambs with PPHN compared with controls without PPHN, and both enhance pulmonary vasoconstriction.[33,35] Superoxide anions also inactivate NO to produce peroxynitrite, which is a potent vasoconstrictor and cytotoxic agent.[24,36] Peroxynitrite formation is also increased when ventilated PPHN lambs are exposed to 100% O_2. Administration of catalase or allopurinol, which reduces production of reactive O_2 species, reduced pulmonary hypertension in young pigs induced by hypoxanthine and xanthine oxidase.[37] Furthermore, the administration of intratracheal recombinant human SOD was shown to reduce superoxide levels and improve oxygenation in PPHN lambs.[36] Similarly, administration of catalase or allopurinol, which reduces production of reactive O_2 species, reduced pulmonary hypertension induced by hypoxanthine and xanthine oxidase in young pigs.[37] Hydrogen peroxide has a possible role in downregulating extracellular SOD activity and further contributing to the pathogenesis of PPHN. This is evident from increased pulmonary arterial hydrogen peroxide, which decreases extracellular SOD activity in PPHN. Thus, removal of hydrogen peroxide by catalase or other scavengers may restore extracellular SOD function, thereby facilitating vasodilation.[38]

COMMON ETIOLOGIES IN HRF AND PPHN

Transient tachypnea of newborn has been associated with HRF and PPHN. For example, following elective cesarean section, newborns with transient tachypnea of newborn who have hypoxemia may be placed on high concentrations of inspired O_2 (~100%) by hood or low-flow nasal cannula (without any positive pressure). In these cases absorption atelectasis can develop, resulting in increasing O_2 requirements and respiratory failure (Figure 3). Furthermore, the formation of reactive oxygen species from the high alveolar O_2 concentrations can increase pulmonary vascular reactivity thereby contributing to PPHN.[3,19] The term 'malignant transient tachypnea of newborn' has been used to describe severe respiratory morbidity and subsequent mortality in newborns delivered by elective cesarean section who developed PPHN.[19,39] One possible strategy when managing these newborns (and to prevent malignant transient tachypnea of newborn) may be early use of positive pressure to inflate and recruit the lungs versus merely administering high amounts of O_2 without positive pressure.

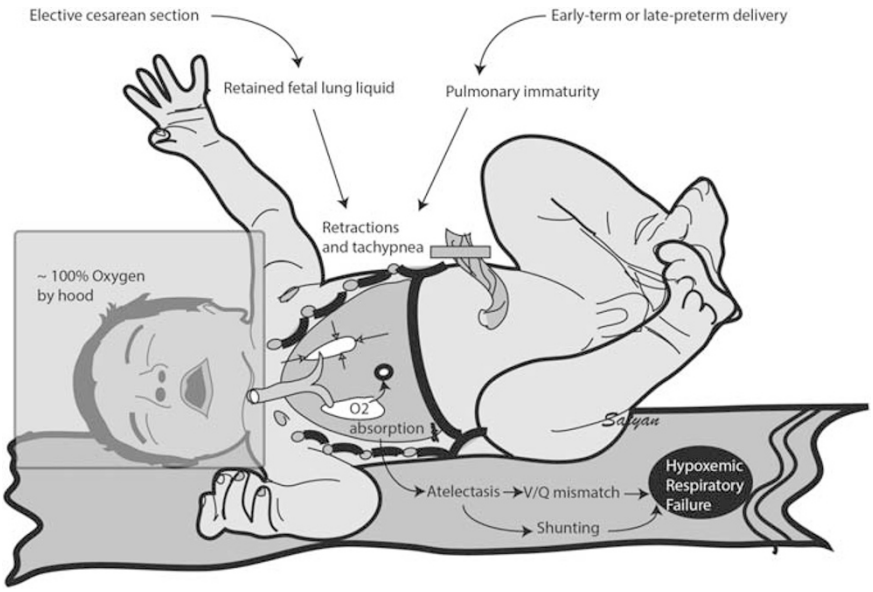

Figure 3. Absorption atelectasis—administration of high concentration of inspired oxygen without positive pressure in an infant with respiratory distress can lead to nitrogen washout and alveolar collapse. Atelectasis can result in V/Q mismatch, shunting and hypoxemic respiratory failure with PPHN. Copyright Drs Bobby Mathew and Satyan Lakshminrusimha. Modified from Polin RA, Yoder MC. *Workbook in Practical Neonatology,* 5th edn. St Louis, MO: Saunders; 2014.

Perinatal asphyxia is another well-known predisposing factor for PPHN. Perinatal asphyxia can interfere with pulmonary transition during birth, thereby impeding the decrease in PVR and increasing the risk for PPHN.[3,40] Various mechanisms cause respiratory failure in asphyxia, including fetal hypoxemia, ischemia, meconium aspiration, ventricular dysfunction and acidosis, all of which can increase PVR.[3,40]

In asphyxiated term neonates, hypothermia has been established as an effective neuroprotective strategy,[41] which could potentially exacerbate PPHN. In addition to direct effects, hypothermia affects blood gas parameters including pH and partial pressure of carbon dioxide.[42] Partial pressure of carbon dioxide is known to affect vascular tone,[43] raising potential concerns that therapeutic hypothermia may increase the risk of PPHN. In a randomized controlled trial, infants (gestational age $\geqslant 36$ weeks) with moderate or severe hypoxic–ischemic encephalopathy, were assigned to standard therapy at either 37 °C (control group, $n = 106$) or to whole-body cooling (hypothermia group, $n = 102$) at 33.5 °C. Of the infants in the control group 22% had PPHN, whereas 25% of infants in the hypothermia group had PPHN ($P =$ not significant).[44] Pooled analyses of other randomized trials have not shown an increase in the incidence of PPHN in neonates undergoing hypothermia.[45] The effect of the degree of hypothermia on PPHN was also examined in a subsequent study that compared the temperature and duration of cooling in the same patient population ($N = 364$).[46] In this study, whole-body hypothermia at 32 °C, compared with 33.5 °C, changed the rate of PPHN from 25% to 34% (not significant); however, the need for iNO therapy changed from 24% (33.5 °C) to 34% (32 °C) ($P < 0.05$) and extracorporeal membrane oxygenation from 4% (33.5 °C) to 9% (32 °C) ($P < 0.05$).[46] Thus, although standard hypothermia at 33.5 °C does not worsen PPHN, it is important to avoid deeper hypothermia ($\leqslant$32 °C). Frequent blood gas monitoring is mandatory in these patients, which can be done either by the α-stat (reporting blood gases at patient's temperature) or pH-stat (reporting at 37 °C) methods.[42] It is important to be aware of the method used, as it is possible to hypoventilate or hyperventilate a neonate, which can have positive or negative consequences on pulmonary and cerebral circulation. For example, an infant on whole-body hypothermia with a $PaCO_2$ of 49 mm Hg at 33.5 °C (α-stat) may be reported as 54 mm Hg at 37 °C (pH-stat). If the clinicians use same $PaCO_2$ parameters (such as 45 to 50 mm Hg) for both methods, the α-stat method results in better preservation of cerebral circulation but can reduce pulmonary blood flow. Similarly, hypothermia shifts the O_2 dissociation curve to the left, and decreases PaO_2 at a given peripheral oxygen saturation. Careful attention to gas exchange is therefore vital during therapeutic hypothermia.

The primary goal of PPHN treatment is to improve O_2 delivery to the tissues and decrease PVR by selective pulmonary vasodilation.[47,48] Various techniques have been employed including intubation, ventilator support and hyperventilation to induce hypocarbia and alkalosis, the latter producing a direct vasodilatory effect on pulmonary vasculature.[47] Intravenous bicarbonate and tromethamine have also been used when ventilation does not produce sufficient alkalization to achieve the desired (alkaline) pH, as acidosis can act as a pulmonary vasoconstrictor.[47,48] However, such therapies are associated with increased need for extracorporeal membrane oxygenation and neurodevelopmental concerns, and are no longer recommended.[49] Previous therapies have also included intravenous dilators such as prostacyclin and tolazoline; however, these can produce non-selective effects on the systemic circulation, leading to hypotension.[48] A more detailed discussion on the evolving knowledge in O_2 therapy is provided below. Further discussion regarding current and investigational therapeutic approaches for PPHN is provided in the articles that follow within this publication.

THE EVOLUTION OF O_2 USE IN NEONATES

O_2 therapy for neonatal conditions such as asphyxia, HRF and PPHN, was in use well before their complex etiologies and pathologies were known. The use of O_2 in the delivery room increased following the description in 1861 of cerebral palsy in newborns with asphyxia,[50–52] and again after the introduction of the Apgar score in the mid-1950s.[53]

Ongoing investigation has served to increase our understanding of both the life-giving and toxic nature of O_2 therapy (Figure 4).[54–59] One important discovery was that O_2 was toxic based on its ability to generate free O_2 radicals.[60] Hypoxanthine, a

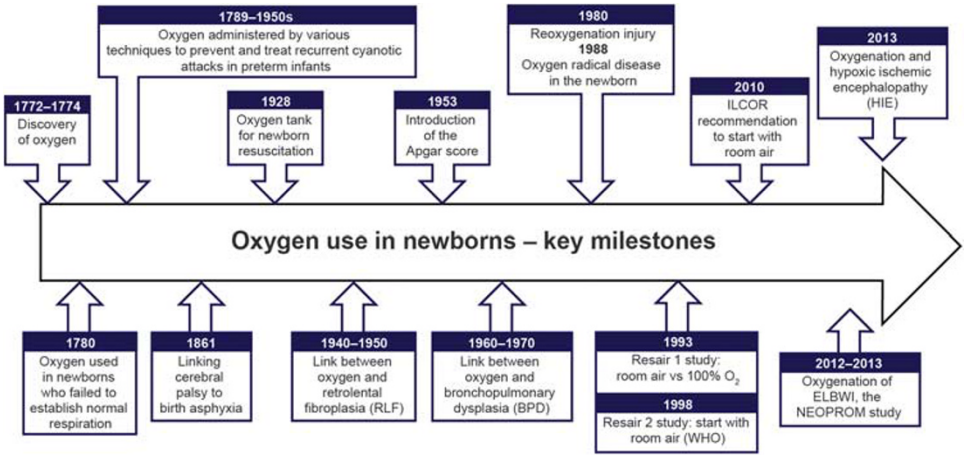

Figure 4. Key milestones in oxygen use from its discovery as a gas in the atmosphere to its use in neonatology. ELBWI, extremely low birth weight infants; ILCOR, International Liaison Committee on Resuscitation; NEOPROM, NEOnatal oxygenation PROspective Meta-analyses; WHO, World Health Organization.[72] Copyright Dr Satyan Lakshminrusimha and Ola D Saugstad.

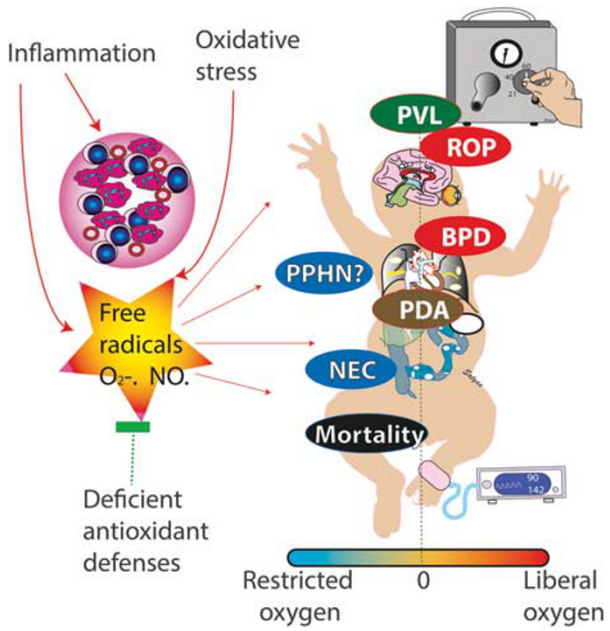

Figure 5. 'Oxygen radical disease' in preterm neonates manifesting as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), periventricular leukomalacia (PVL) and mortality are presented in the form of a 'diagrammatic forest plot'. NO, nitric oxide; PPHN, persistent pulmonary hypertension of newborn. Copyright Drs Satyan Lakshminrusimha and Ola D Saugstad.

free radical generator and breakdown product of adenosine triphosphate, has been shown to accumulate in hypoxic newborns.[61] Oxidation of hypoxanthine to uric acid results in the generation of free radicals.[62] A study in dogs showed that resuscitation with O_2 increased hypoxanthine levels exponentially in the first 12 min.[63] Experiments in rabbits established that antioxidant enzyme activities were low in fetal life, and that these increased during late gestation as important preparations for birth. Premature birth may affect the ability to tolerate hyperoxic exposure,[64] which forms a basis of the concept of O_2 radical disease in the newborn.[65] Investigation into the existence of O_2 radical disease in neonatology established that oxidative stress and inflammation were closely associated, and that factors, other than O_2, could generate oxidative stress in preterm newborns (Figure 5).[65–67]

Resuscitation of term and near-term babies (~ ⩾36 weeks)

Although earlier approaches to ventilation often included use of 100% O_2, results of the Resair 1 pilot study and Resair 2 clinical study ($N = 591$) in the 1990s demonstrated the feasibility of resuscitating asphyxiated newborns with room air just as efficiently as with 100% O_2.[68,69]

Subsequent meta-analyses showed that neonatal mortality was reduced by ~30% when room air (21% O_2) was used instead of 100% O_2 to resuscitate term or late preterm babies.[70–72] One explanation for this finding may be related to the results from another study, in which term neonates resuscitated with 100% O_2 exhibited biochemical findings reflective of prolonged oxidative stress even after 4 weeks of postnatal life, compared with neonates resuscitated with room air. In addition, there was an increase in markers of myocardial and kidney injury in neonates resuscitated with 100% O_2 compared with those who received air (Figure 6).[73,74] These findings led to a worldwide change in oxygenation and resuscitation practices in neonates. In 2010, the International Liaison Committee on Resuscitation recommended using air (21%) rather than 100% O_2, when resuscitating term or near-term newborns in need of positive pressure ventilation at birth.[75]

The potential adverse effects of resuscitating with 100% O_2 were demonstrated in a study in which infants ⩾36 weeks' gestation with perinatal acidemia and hyperoxemia on their admission blood gas had a higher incidence of hypoxic–ischemic encephalopathy than those without hyperoxemia (58% vs 27%; $P = 0.003$).[76] The effect of 100% O_2 has also been shown in newborn lambs with PPHN delivered by cesarean section. Resuscitation with 100% O_2 did not enhance pulmonary vasodilation compared with 21% and 50% O_2. In fact, 100% O_2 impaired the subsequent response to iNO in these lambs (Figure 7).[77,78] Thus, although hypoxia markedly increased PVR, hyperoxemia did not confer significant additional pulmonary vasodilation in lambs with PPHN.[77]

Resuscitation of preterm and/or low birth weight babies (<32 weeks)

A few meta-analyses have investigated the issue of the optimal O_2 concentration for resuscitation of preterm and/or low birth

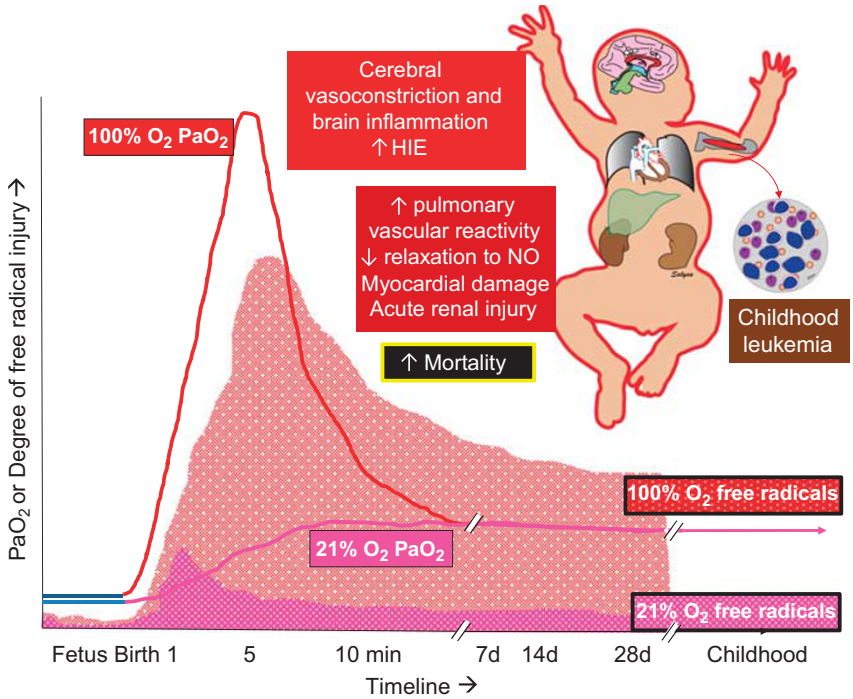

Figure 6. Consequences (short- and long-term) of 100% oxygen resuscitation in term neonates: the course of events following resuscitation of neonates with 21 or 100% oxygen. The blue lines represent fetal PaO_2 levels; the red line and pink line represent postnatal PaO_2 levels with 100 and 21% oxygen resuscitation, respectively. The shaded red and pink areas represent the degree of free radical injury following 100% and 21% oxygen resuscitation. Short-term and long-term consequences of 100% oxygen resuscitation are shown in the figure. Copyright Drs Saugstad and Lakshminrusimha. PaO_2, arterial partial pressure of oxygen.

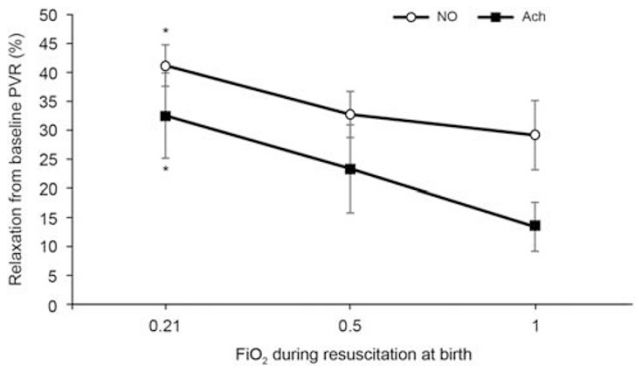

Figure 7. The effect of initial resuscitation with 21%, 50% and 100% O_2 in newborn lambs with acute PPHN induced by thromboxane analog on subsequent pulmonary vasodilation by inhaled nitric oxide (20 ppm) and infusion of acetylcholine. The decrease in PVR in response to inhaled nitric oxide and acetylcholine, as a percent of baseline, was significantly higher in PPHN lambs resuscitated with 21% O_2 compared with 100% ($^*P < 0.05$).[79,80] Ach, acetylcholine; FiO_2, fraction of inspired oxygen; NO, nitric oxide; PPHN, persistent pulmonary hypertension of newborn; PVR, pulmonary vascular resistance.

weight babies. A systematic review and meta-analysis of six randomized controlled trials ($N = 484$) determined the effect of using lower (21% to 50%) versus higher (>50%) O_2 concentrations for delivery room transition support of preterm newborns (born before 32 weeks' gestation) on mortality and morbidity. Lower O_2 concentrations were associated with reduced risk of death (pooled risk ratio 0.65, 95% confidence interval: 0.43 to 0.98), but this effect disappeared when four trials with allocation concealment were included. Thus, there was no strong evidence that using lower versus higher O_2 concentrations for delivery room transition support for preterm infants conferred benefits or harm.[79]

A systematic review and meta-analysis of 10 randomized studies in 677 newborns ⩽32 weeks' gestation showed the relative risk for mortality as 0.62 (95% confidence interval: 0.37 to 1.04, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.88$) for those receiving low (0.21 to 0.30, $n = 321$) versus high (0.60 to 1.0, $n = 356$) initial fraction of oxygen. There was no significant association for bronchopulmonary dysplasia (BPD) or intraventricular hemorrhage when comparing low and high initial fraction of oxygen. These findings suggest that premature babies (⩽32 weeks' gestation) in need of stabilization in the delivery room should be given an initial fraction of oxygen of 0.21 to 0.30.[80] More recently, the TO_2RPIDO study reported a higher mortality in babies < 29 weeks' gestation who were resuscitated with air (21%) compared with 100% O_2,[81] The Canadian neonatal intensive care units have reported higher risk of severe neurologic injury or death among preterm infants ⩽27 weeks' gestation following a change in practice to initiating resuscitation with either 21% O_2 or an intermediate O_2 concentration.[82] These findings demonstrate the difficulty in establishing guidelines, particularly for the most premature infants <32 weeks of gestational age.

O_2 saturation levels in premature newborns (<28 weeks' gestation), beyond delivery, have been assessed in the NEOnatal oxygenation PROspective Meta-analyses (NEOPROM), a collaborative study examining the effect of low and high O_2 saturation levels. NEOPROM assessed data from SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), the three BOOST II (Benefits of Oxygen Saturation Targeting) studies and the COT (Canadian Oxygen Trial) study in extremely low birth weight newborns ($N = 4911$) at < 28 weeks' gestation. O_2 targets in the low saturation group were 85% to 89%, versus 91% to 95% in the high O_2 group. To date, NEOPROM are the largest meta-analyses

in preterm newborns < 28 weeks' gestation at birth.[83] Findings from the meta-analysis of these studies showed the relative risk for mortality and necrotizing enterocolitis was increased, whereas severe retinopathy of prematurity (ROP) was decreased, in low compared with high O_2 saturation ranges in these extremely low birth weight infants. Overall, there was an 18% increased risk of mortality in the low saturation target.[83] The recommendation from this study was that functional O_2 saturation should be targeted at 90% to 95% in newborns with a gestational age of < 28 weeks until 36 weeks' postmenstrual age.[83]

A more recent meta-analysis of NEOPROM accounted for the risk of bias of each included study, as well as the quality of evidence for each outcome. In this analysis, preterm newborns (<28 weeks' gestation at birth) administered a 91% to 95% O_2 target had a lower mortality before hospital discharge, compared with those managed within an 85% to 89% O_2 target. In addition, necrotizing enterocolitis occurred less frequently in the 91% to 95% O_2 group. However, there was no difference in death or disability at 24 months, BPD, ROP, neurodevelopmental outcomes, or hearing loss at 24 months. Based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria, the quality of evidence for the outcomes in this analysis was graded as moderate to low.[84]

Findings from NEOPROM present an 'oxygen dilemma,' in that, if O_2 saturation targets are kept high, mortality and necrotizing enterocolitis is reduced but other complications may arise (for example, ROP, BPD), and vice versa when O_2 targets are low. Thus, identifying the optimum O_2 concentration in extremely small (low birth weight or preterm (<28 weeks)) newborns remains an important question to be addressed. The current available data make it difficult to recommend appropriate guidelines, particularly in newborns with a gestational age <28 weeks. The recent *post hoc* analysis of the SUPPORT trial showed that increased mortality in infants randomized to the low peripheral oxygen saturation target group was predominantly due to the high rate of death before discharge among small-for-gestational-age infants. The leading causes of mortality in preterm small-for-gestational-age infants were respiratory distress syndrome and BPD, which may have been accompanied by PH and HRF.[85] These results suggest that O_2 saturation targeting among preterm infants may even benefit from a 'precision-medicine' individualized approach based on growth (small-for-gestational-age vs appropriate-for-gestational-age infants), pulmonary (respiratory distress syndrome, BPD and PPHN) and ophthalmological (presence of pre-threshold ROP) status.

CONSIDERATIONS WHEN INTERPRETING CLINICAL TRIAL FINDINGS THAT TARGET O_2 SATURATION LEVELS

For clinicians, interpreting results from clinical trials that target precise O_2 saturation levels can be challenging. A potential consideration for future such trials may be to include a third group (in addition to high and low O_2 saturation targets or alarm limits), to reflect real-world clinical practice with a wider gap between lower and higher O_2 saturation alarm limits that can be effectively achieved by bedside nurses. This type of study design might suggest a medium mean between no increased mortality and less ROP.

But to date, no study has provided definitive evidence and recommendations for the optimum O_2 saturation targets in preterm newborns (< 28 weeks' gestation at birth). This poses an important question that remains to be addressed.

It is likely that there will be more genomic studies in this area in the future. One such study used a hypoxia mouse model to assess how hyperoxic reoxygenation, following hypoxia, affected transcriptional changes in the newborn lung.[86] Findings from this study suggest that acute hyperoxia induces hypoxia-inducible factor 1 targets (or example, *Vegfc*, *Adm* and *Aqp1*) irrespective of the reoxygenation regimen. In addition, hyperoxic reoxygenation mediated ~70% of gene expression changes, particularly pathways regulating cell growth and survival (for example, mTOR signaling pathway). Effects included upregulation of genes involved in inflammation, inhibition of cell growth, angiogenesis and stress; whereas there was downregulation of genes involved in oxidative phosphorylation. Thus, adenosine triphosphate production may be impacted or reduced when newborns are resuscitated with 60% to 100% O_2.[86]

SUMMARY

The newborn period presents a unique time during which there is reduced protection from oxidative stress and reduced oxidative phosphorylation. Failed circulatory transition at birth, pulmonary parenchymal lung disease, pulmonary alveolar/vascular hypoplasia and asphyxia are key factors in HRF and PPHN. Excessive O_2 has a role in the exacerbation of PPHN and possibly of hypoxic to ischemic encephalopathy. A better understanding of hemodynamic, biochemical and histologic changes in HRF and PPHN will enhance our ability to develop new therapeutic strategies.

The challenge remains as to how best to approach resuscitation with O_2, particularly in preterm newborns. Attaining the balance between hypoxia and hyperoxia is critical to prevent iatrogenic toxicity and optimize outcomes. There should be consideration of the varied pathophysiology of HRF to design appropriate treatments and to effectively employ those currently available.

CONFLICT OF INTEREST

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