Oxygen Targets in Neonatal Pulmonary Hypertension

Individualized, "Precision-Medicine" Approach

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KEYWORDS

- Oxygen saturation • Alveolar oxygen • Pulmonary vascular resistance
- Superoxide anions

KEY POINTS

- Alveolar oxygen tension is the primary determinant of pulmonary vascular resistance.
- Hypoxemia (preductal $Pa_{O_2} \leq 49$ mm Hg or $Sp_{O_2} \leq 89\%$) is associated with hypoxic pulmonary vasoconstriction.
- Hyperoxemia (preductal $Pa_{O_2} > 100$ mm Hg or $Sp_{O_2} \geq 99\%$) can lead to oxidative stress.
- Maintaining preductal Sp_{O_2} between 90% and 97% and Pa_{O_2} between 50 and 80 mm Hg results in low pulmonary vascular resistance in most patients with pulmonary hypertension.
- Every patient is unique, and optimal oxygen targets may vary between one patient to another and within a given patient based on changing pathophysiology.

INTRODUCTION

Oxygen is a specific and potent pulmonary vasodilator. At the microvascular level, hypoxic pulmonary vasoconstriction (HPV) is physiologically protective mechanism that limits blood flow to a diseased alveolus, thereby preserving optimal ventilation–perfusion (V/Q) matching.[1,2] With global hypoxia or when several segments of the lung suffer from alveolar hypoxia due to heterogeneous parenchymal lung disease, pulmonary vascular resistance (PVR) increases, resulting in pulmonary hypertension (PH). Primary vascular pathology resulting in pulmonary vasoconstriction and remodeling can also lead to PH without parenchymal lung disease.[3]

The etiology of PH varies with age.[3] Persistent PH of the newborn (PPHN) or acute PH (aPH) among late preterm, term, and post-term infants is secondary to a variety of

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causes such as birth asphyxia, meconium aspiration syndrome (MAS), pneumonia, respiratory distress syndrome (RDS), and congenital diaphragmatic hernia (CDH).[4] Among preterm infants, it is secondary to delayed transition or RDS during the first week or due to bronchopulmonary dysplasia (BPD) in the postneonatal period.[5] The underlying cause of PH, gestational age, and critical antenatal and postnatal determinants play key roles in determining the optimal oxygen target range and likely contribute to intersubject variability regarding the pulmonary vascular response to hypoxia.

GOALS OF OXYGEN THERAPY

Supplemental oxygen is commonly used in diverse clinical settings, including intensive care units (ICUs), hospital wards and as chronic therapy in outpatients. The primary purpose of oxygen therapy is to optimize oxygen delivery to the tissues while minimizing concerns regarding oxidative stress due to excessive supplemental oxygen.[6] Inadequate tissue oxygen delivery promotes anaerobic metabolism leading to lactic acidosis and reduces adenosine triphosphate (ATP) production from glucose. In patients with PH, oxygen therapy increases alveolar P_{AO_2} and prevents HPV.[1] Reduction of PVR in these patients reduces right ventricular afterload. Among neonates, infants, and children, optimal oxygenation is necessary to promote growth. Supplemental oxygen and prevention of sleep-associated hypoxemia improve growth in infants with BPD.[7]

Although arterial Pa_{O_2} is the gold standard for assessing oxygenation, it is invasive, requires arterial access, and can only be assessed intermittently. Oxygen saturation assessment by pulse oximetry (SpO_2) provides a continuous, noninvasive assessment of oxygenation but has limitations requiring periodic Pa_{O_2} assessment, and these limitations will be discussed later in this article. In each individual patient, evaluation of Fi_{O_2}, Pa_{O_2}, SpO_2, and regional oxygenation (rSO_2) by near-infrared spectroscopy (NIRS) provides information assesses oxygenation from different angles.[8] In order to identify an optimal oxygen target, we have to determine the lower and upper limits using physiologic principles and clinical outcomes.

Lower Limit of Oxygen Target Range

Two physiologic factors determine the lower limit of oxygenation: oxygen delivery to tissues and increasing PVR due to HPV, with detrimental effects of high PVR on cardiac output.

Oxygen consumption versus delivery and the "critical point"

To maintain aerobic metabolism and generate ATP, cells need a constant supply of oxygen. Hypoxia (inadequate delivery of oxygen to tissues) should be differentiated from hypoxemia (low Pa_{O_2} levels). For example, a normal fetus is relatively hypoxemic (by postnatal standards) but is not hypoxic. Oxygen delivery to the tissues (DO_2) can be mathematically calculated as follows:

DO_2 = Arterial oxygen content (CaO_2) × Cardiac output (typically, 231 ± 38 mL/kg/min in term neonates)[9]; Cardiac output = stroke volume × heart rate.

CaO_2 = Hemoglobin (Hb) × SaO_2 × 1.39 mL + (Pa_{O_2} × 0.003); in term infants with Hb of 15 g/dL, SaO_2 of 95%, and Pa_{O_2} of 60 mm Hg, CaO_2 = 15 × 0.95 × 1.39 + (60 × 0.003) = 19.8 + 0.18 = 19.98 mL O_2/100 mL of blood. These calculations suggest that DO_2 may be approximately 35 to 46 mL/kg/min (20 mL/100 mL × 230 mL/kg/min) in neonates. It is clear from this equation that Hb and SaO_2 along with blood flow play a more important role than Pa_{O_2} in determining DO_2.[6]

Under physiologic circumstances, the DO_2 exceeds oxygen consumption by the tissues (Vo_2, typically ~4 mL/100 mL of blood) by four- to fivefold (Fig. 1). When DO_2 decreases (secondary to reduced heart rate, stroke volume, blood flow, Hb, or SaO_2), compensatory mechanisms such as changes in Hb affinity, capillary recruitment, and hypoxic systemic regional vasodilation try to support normal Vo_2.[6] The point at which these compensatory mechanisms fail to meet tissue oxygen requirements is termed critical oxygen delivery point (DO_2-crit). Below this point, a decrease in DO_2 results in a fall in Vo_2 and serum lactate increases with a rapid decrease in rSO_2 (see Fig. 1).[6] The precise DO_2-crit in humans is not known. In adult human volunteers, a reduction in Hb to 4.8 ± 0.2 g/dL and DO_2 from 14 ± 2.9 to 7.3 ± 0.1 mL/kg/min did not result in lactic acidosis suggesting that DO_2-crit is lower than this value.[10] In one postoperative adult patient with severe anemia, the investigators estimated the DO_2-crit to be approximately 4.9 mL/kg/min while fully ventilated, sedated, and paralyzed.[11,12] To our knowledge, there are no studies evaluating DO_2-crit in human neonates. Mathematical translation of DO_2-crit to a Pao_2 or SaO_2 value is difficult as cardiac output and Hb vary among patients.

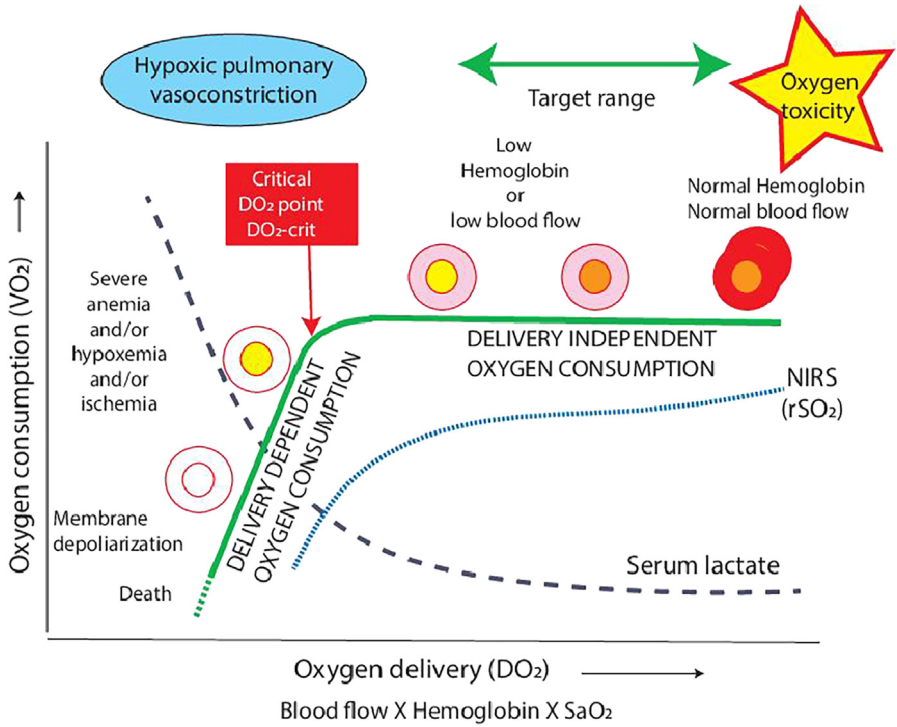

Fig. 1. The oxygen consumption (Vo_2) versus delivery (DO_2) curve. The horizontal portion of the curve depicts "delivery-independent oxygen consumption" as decrease in DO_2 does not impact Vo_2 and metabolism remains aerobic without lactic acidosis (*black hyphenated line*). However, during this phase with decreasing DO_2, regional oxygen saturation (rSO_2) measured by near-infrared spectroscopy (NIRS) decreases due to increased oxygen extraction with decreasing DO_2. Once oxygen delivery falls below the critical point (DO_2-crit), oxygen consumption decreases, and this sloped portion of the curve represents "delivery-dependent oxygen consumption." Lactic acid rapidly increases and rSO_2 markedly decreases during this phase. (Image Courtesy of Dr. Satyan Lakshminrusimha. Modified from references.[65,66])

Fetal hemoglobin and oxygen delivery

Newborn infants (both preterm and term) have high proportion of fetal hemoglobin (HbF). The oxygen dissociation curve of HbF is shifted to the left compared with hemoglobin A (HbA) (**Fig. 2**). HbF has higher affinity to oxygen compared with HbA. Hence, it is often assumed that oxygen delivery is decreased in newborns due to the presence of HbF.[13] However, during severe hypoxemia, HbF delivers more oxygen to the tissues (see **Fig. 2**).[13,14] Peripheral, but not cerebral fractional oxygen extraction, correlates with HbF in neonates.[15–17] Maintaining high HbF may be a protective factor against retinopathy of prematurity (ROP) in preterm infants.[18] Promoting placental transfusion at birth in infants at risk for PPHN or hypoxic ischemic encephalopathy (HIE) may potentially benefit tissue oxygen delivery by increasing HbF.[19] Although the presence of HbF significantly alters the relationship between Pa_{O_2} and Sp_{O_2}, its impact on oxygen saturation targets in PPHN is not known.

Pulmonary vascular resistance, "change point" for hypoxic pulmonary vasoconstriction

The site of HPV is not clear but is considered to be the precapillary pulmonary arteriole (**Fig. 3**).[2] In neonatal animal models, pulmonary veins may also contribute to PVR and HPV.[20,21] The primary determinant of oxygen tension in these vessels is alveolar P_{AO_2} (see **Fig. 3**).[22] However, P_{AO_2} within each region of the lung cannot be measured and, in the absence of shunts, correlates well with preductal Pa_{O_2}. Hence, preductal Pa_{O_2}

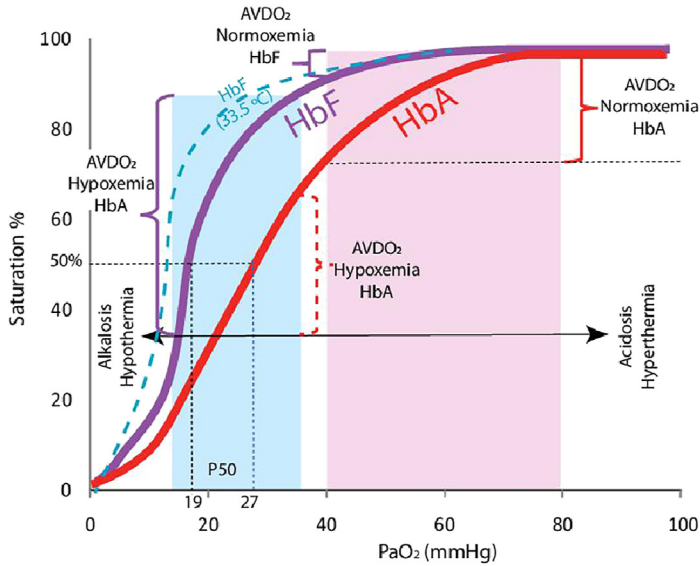

Fig. 2. Impact of hemoglobin type, temperature, and pH on hemoglobin–oxygen dissociation curve and arterio-venous oxygen difference ($AVDO_2$). Hemoglobin A (HbA) is shown by the red line, fetal hemoglobin (HbF) by the purple line, and HbF during whole body hypothermia by the purple-dashed line. The pink zone refers to the "normoxemic" arterial Pa_{O_2} of 80 mm Hg and venous P_{O_2} of 40 mm Hg. The blue zone refers to hypoxemic arterial Pa_{O_2} of 35 mm Hg and venous P_{O_2} of 15 mm Hg. P50 is the partial pressure of oxygen at 50% oxygen saturation and is 19 mm Hg for HbF and 27 mm Hg for HbA. (*Modified from* Polin R, Abman SH, Rowitch DH, Benitz WE. *Fetal and Neonatal Physiology, 2-Volume Set.* Vol 2: Elsevier; 2021, Chapter 109 – Developmental erythropoiesis by Timothy M. Bahr and Robin K. Ohls.)

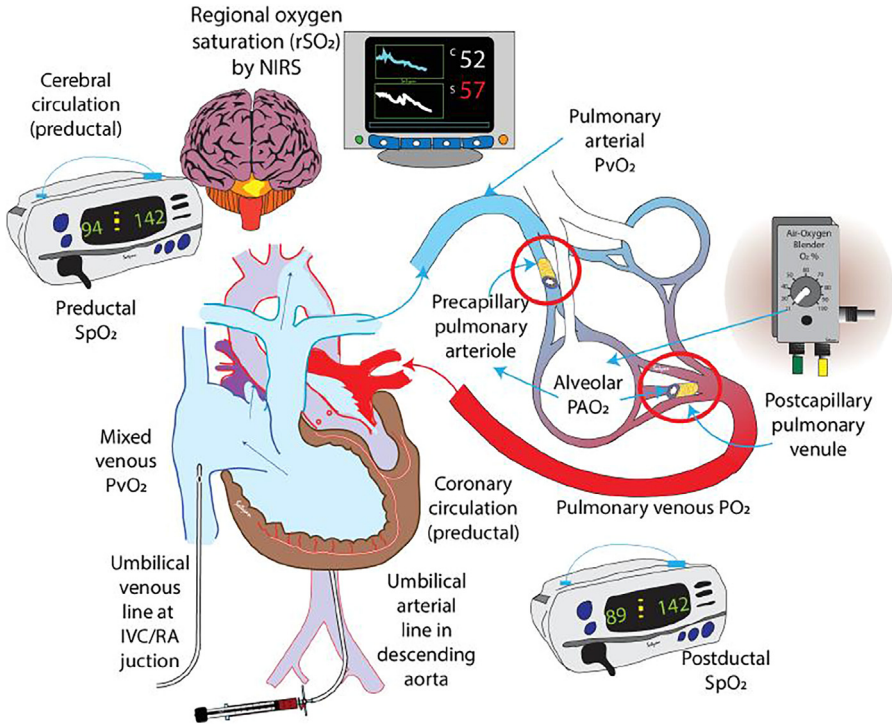

Fig. 3. Site of hypoxic pulmonary vasoconstriction (HPV) and different measures of oxygenation in neonates. The precapillary pulmonary arterioles and possibly the postcapillary venules are thought to be the sensing site for HPV (red circles). The oxygen tension in these vessels is determined mainly by alveolar P_{AO_2} and to a lesser extent by pulmonary arterial (or mixed venous) P_{O_2}. Clinically, preductal and postductal Pa_{O_2} and SpO_2 can be measured along with cerebral regional SO_2 (rSO_2). Of these values, preductal P_{O_2} (or SpO_2) correlates closely with alveolar P_{AO_2}. (*Modified from* Chandrasekharan et al.[8] Image courtesy of Dr Satyan Lakshminrusimha.)

to PVR relationship is studied in translational studies. Pulmonary arterial P_{O_2} (similar to mixed venous P_{O_2}) also plays a role in determining HPV.[22]

In 1966, Rudolph and Yuan instrumented newborn calves to measure PVR and ventilated them with different Fi_{O_2} and plotted Pa_{O_2} against PVR. When Pa_{O_2} decreased below 45 to 50 mm Hg, there was an increase in PVR.[23] The Pa_{O_2} (or SpO_2) value below which PVR increases is called the "change point" (**Fig. 4**). Studies in control lambs demonstrated a similar change point of 52.5 ± 1.7 mm Hg.[24,25] In lambs with PPHN induced by antenatal ductal ligation, the change point was higher at 59.6 ± 15.3 mm Hg (see **Fig. 4**).[24] Using preductal SpO_2 (instead of Pa_{O_2}), in lamb models of PPHN induced by asphyxia, and meconium aspiration or antenatal ductal ligation, the change point was approximately 90% (**Fig. 5**A). PVR was lowest with preductal SpO_2 between 90% and 97%.[26] Rawat and colleagues randomized term lambs with asphyxia induced by umbilical cord occlusion and meconium aspiration and PPHN into preductal SpO_2 target groups of 85% to 89%, 90% to 94%, 95% to 99% and inspired oxygen of 100%.[27] Pulmonary blood flow was significantly lower in the 85% to 89% SpO_2 target group. PVR was lowest in the 95% to 99% target group, but these lambs achieved median SpO_2 of 95% (IQR: 93%–97%). These

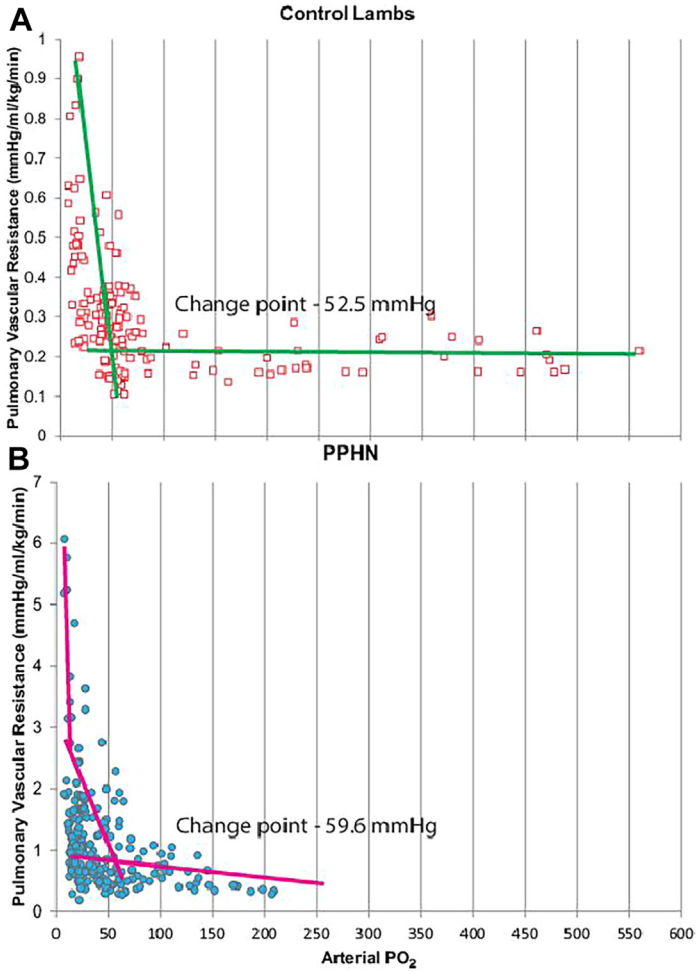

Fig. 4. Change point in the Pa_{O_2} and PVR relationship. Data from control lambs (*A*) and lambs with PPHN induced by antenatal ductal ligation (*B*). Pa_{O_2} values are low and PVR is high in lambs with PPHN. (*Modified from* Refs.[24,25])

results suggest that preductal SpO_2 in the low-to-mid 90s is associated with lowest PVR in animal models of PPHN.

Clinical observations

There are no clinical trials in newborn infants to determine the lower limit of oxygen target range in PPHN. However, among preterm infants, in the multinational NeOProM randomized controlled trials, targeting SpO_2 in the 85% to 89% range is associated with higher mortality compared with 91% to 95%.[28–30] Some of these trials excluded infants with PPHN and PH was not a prespecified outcome. Among centers that increased their SpO_2 target range from 88% to 92% to 90% to 95% or from 85% to 94% to 88% to 94% and 90% to 95% in response to NeOProM study results showed a decline in the incidence of PH among preterm infants.[31,32] Cardiac catheterization studies among infants with BPD suggest that targeting SpO_2 in the 92% to 94% range reduces pulmonary arterial pressures.[33,34] These clinical observations suggest that

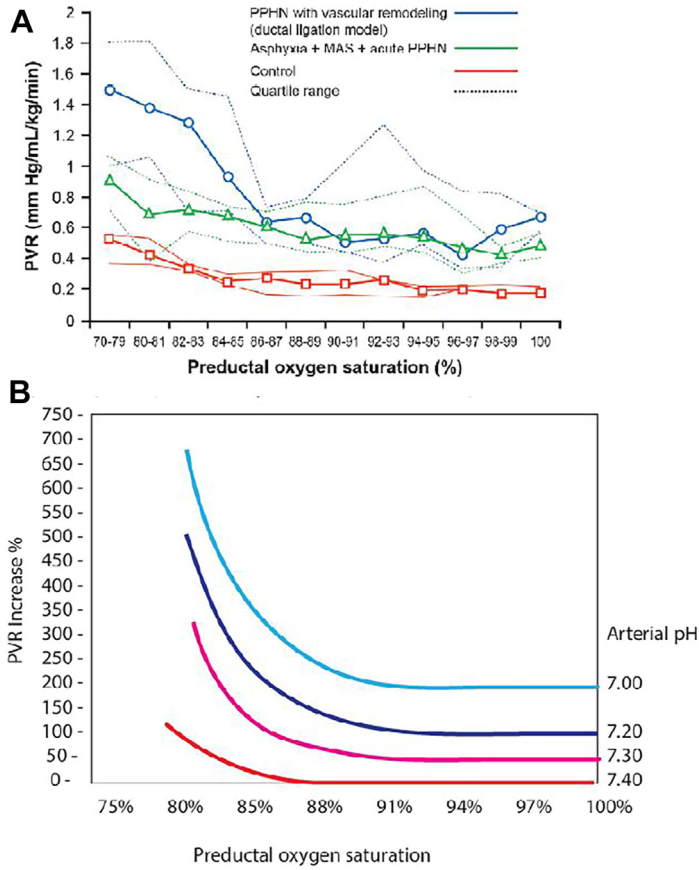

Fig. 5. Oxygen saturation and pulmonary vascular resistance (PVR). (*A*) Preductal SpO_2 plotted against PVR in three models of neonatal lambs. Red squares—control lambs delivered by elective cesarean section; green triangles—asphyxia by umbilical cord occlusion with meconium aspiration syndrome and PPHN; blue circles—PPHN induced by antenatal ductal ligation. In all three models, preductal SpO_2 between 90% and 97% is associated with low PVR. (*B*) Hypothetical figure showing the relationship between PVR, SpO_2 and pH. Acidosis exacerbates hypoxic pulmonary vasoconstriction (HPV). As pH decreases, the change point (SpO_2 below which PVR increases) increases and the degree of HPV markedly increases.[23,26,67]

the proposed target of 90% to 97% SpO_2 based on animal models of PPHN may be reasonable based on limited clinical data.

Arterial pH and lower limit of SpO_2/Pao_2 target. Acidosis exacerbates HPV (Fig. 5B). The degree of HPV and the Pao_2 change point both increase with lower pH.[23] Studies in newborn calves have shown that when pH less than 7.25, hypoxia induced by ventilation with 10% oxygen markedly increases PVR. However, when pH is greater than 7.3, 10% oxygen ventilation results in minimal increase in PVR compared with 100% oxygen ventilation (Fig. 6). A secondary analysis of data from studies in asphyxiated lambs with meconium aspiration shows that combination of hypoxemia (preductal $Pao_2 < 50$ mm Hg) and acidosis (pH < 7.25) results is marked exacerbation of HPV (Fig. 7). These studies show the importance of maintaining pH greater than 7.25 in the

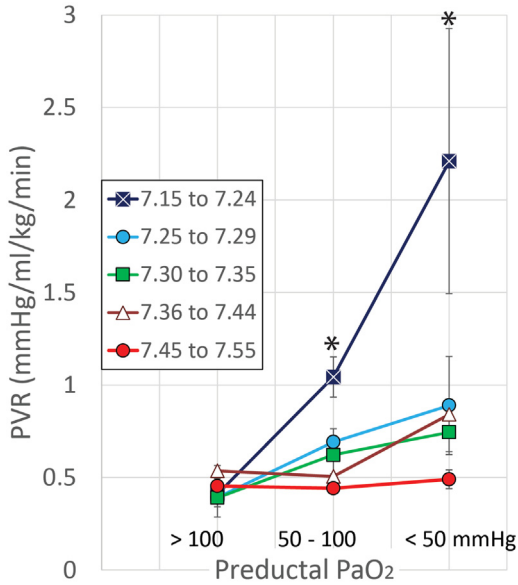

Fig. 6. Effect of ventilation with 10% (blue zones) and 100% oxygen (pink zones) on PVR (triangles plotted on primary vertical axis) and Pa_{O_2} (circles plotted on secondary vertical axis) in newborn calves. Although Pa_{O_2} levels with 10% oxygen ventilation are low (blue circles), the pulmonary vascular resistance (PVR) is low when pH is approximately 7.35 and high when it is < 7.25. (*Data from* Rawat et al.[27])

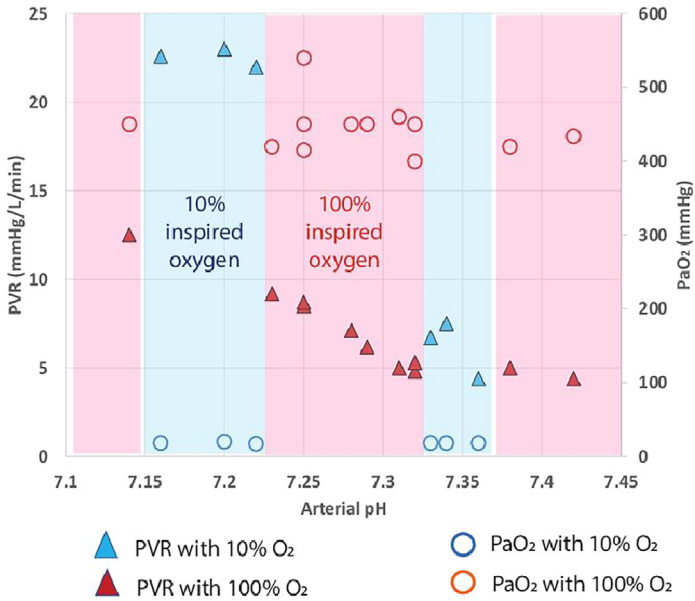

Fig. 7. Effect of pH on hypoxic pulmonary vasoconstriction. Pooled data from 30 lambs with acute MAS and asphyxia ventilated with varying Fi_{O_2} from 0.21 to 1.0 sorted by pH and right carotid arterial Pa_{O_2}. Data are shown as mean ± SEM. Arterial pH < 7.25 markedly increases HPV. (*Data derived from* Rudolph et al.[23])

presence of hypoxemia in PPHN. The European Pediatric Pulmonary Vascular Disease Network recommends preductal SpO_2 between 91% and 95% and avoid hypoxemia (SpO_2 < 85%) or hyperoxemia (SpO_2 > 97%) with a pH greater than 7.25 during management of suspected or established PPHN.[35]

Other factors influencing the lower limit of oxygen target

Two key factors that determine the lower limit of oxygen target are the critical DO_2 point and the "change-point" for HPV (see **Figs. 1** and **4**). For most newborn infants, the change point for HPV is probably higher than the critical DO_2 point and is the main determinant of the lower limit of Pa_{O_2} or SpO_2 target range. Based on the previous discussion with animal data, this limit seems to be a preductal SpO_2 of approximately 89% to 90% (see **Fig. 5**A) or a preductal Pa_{O_2} of 45 to 50 mm Hg (slightly higher in PPHN). A couple of exceptions to this lower limit are explained as follows.

Fi_{O_2} versus Pa_{O_2} versus SpO_2. The limit for SpO_2 during the management of PPHN is partly dependent on Fi_{O_2} and Pa_{O_2}. Infants showing signs of aPH on echocardiogram need adequate alveolar P_{AO_2} to minimize HPV.[2] Balancing the risk of pulmonary free radical injury with the risk of HPV may result in specific limits of SpO_2 in each patient and also at different times in a given patient (precision medicine approach). For example, in a patient with MAS and labile oxygenation due to PPHN, we recommend preductal SpO_2 range of 90% to 97%. If this patient is being ventilated with Fi_{O_2} of 0.85 and has preductal SpO_2 of 90%, it may be better to tolerate the current settings to minimize the risk of free radical injury to the lung (the risk of free radical injury outweighs the benefit of slightly higher P_{AO_2}, Pa_{O_2}, or SpO_2 on pulmonary vasculature). In contrast, if this patient is on Fi_{O_2} of 0.3 and experiencing severe PH and has preductal SpO_2 of 90%, it may be appropriate to increase Fi_{O_2} to 0.4 to achieve SpO_2 in the 93% to 97% range to minimize the risk of HPV (the benefit of higher P_{AO_2}, SpO_2, or Pa_{O_2} on pulmonary vasculature outweighs the risk of oxidative stress). In this circumstance, increasing the lower limit of SpO_2 to 93% is justified.

Occult hypoxemia, skin pigmentation, and lower SpO_2 limit

During the COVID-19 pandemic, concerns were expressed on the accuracy of pulse oximetry among Black adults and individuals with dark skin pigmentation.[36] Occult hypoxemia defined as SpO_2 greater than 90% (or 92% in some studies) when arterial blood gas and SaO_2 by co-oximetry was below 88% (or 85% in some studies) was noted to be more common among Black adults compared with White adults. Similar concerns have been expressed among preterm infants[37] and children.[38] The incidence of occult hypoxemia was 56.3% among White and 69.8% among Black children when the SpO_2 values were 88% to 91%. At the current recommended SpO_2 range of 92% to 96%, occult hypoxemia was observed in 13.4% of White and 29.3% of Black children. Maintaining SpO_2 greater than 96% eliminated the difference in the incidence of occult hypoxemia between White and Black children (2.5% and 2.6%, respectively).[38] These findings suggest that the lower limit of SpO_2 target range may need to be higher in Black children.[39] Prospective trials evaluating the impact of skin pigmentation on pulse oximetry in the NICU are currently under investigation (Siefkes and colleagues, Racial disparities in accuracy of pulse oximetry, RO3HD106138). Evaluation of other factors associated with race that might influence SpO_2 in addition to skin pigmentation (such as hemoglobinopathies) will be required along with new technologies that can correct for variations in skin pigmentation. The higher incidence of neonatal conditions that are associated with hypoxemia (PPHN and necrotizing enterocolitis) among Black children and conditions associated

with hyperoxemia (ROP) among White children may potentially be due to impact of skin pigmentation on pulse oximetry.[39]

Anemia and hemoglobin type

Oxygen delivery to the tissues is based on arterial oxygen content (CaO_2) and both low Hb and low SaO_2 decrease CaO_2. Neonates with anemia may have less tolerance for a lower target SpO_2. In the SUPPORT trial, death before discharge in the lower SpO_2 target (85%–89%) arm was greater than the higher target (90%–94%), but this difference in survival was only evident after the first few postnatal weeks.[40] It has been speculated that decrease in Hb levels with time and switch from HbF to HbA with transfusions might have contributed to higher mortality after the first 2 weeks in the 85% to 89% target SpO_2 arm.[41] However, there was no difference in mortality or neurodevelopmental outcomes in a study on different transfusion thresholds among preterm infants.[42] We recommend maintaining Hb levels $\geq$ 12 g/dL during management of severe PPHN to optimize DO_2 and minimize lactic acidosis.

Upper Limit of Oxygen Target Range

Compared with physiologic factors determining the lower limit of oxygen target range (HPV and critical DO_2), the upper limit of oxygen target range is based on the risk of oxygen toxicity such as development of ROP and BPD in preterm infants. There are no similar conditions associated with oxygen toxicity in late-preterm and term infants. Evidence for oxygen toxicity at term gestation mainly comes from observational studies and animal models.

Oxygen toxicity and lung

We speculate that free radical formation is mainly mediated by partial pressure of oxygen as it creates a gradient for diffusion into mitochondria. The lung is exposed to the highest P_{O_2} among all the organs in the body and is subject to free radical injury. High inspired oxygen, especially ~100% can increase free radical formation in the lungs,[43] increase pulmonary arterial contractility,[44] and impair inhaled nitric oxide (iNO)-mediated pulmonary vasodilation.[24] Interestingly, the inhibition of iNO-mediated decrease in PVR is related to high F_{IO_2} and not to hyperoxemia (high Pa_{O_2}), as lambs in this study had PPHN and low Pa_{O_2} levels (40 $\pm$ 5 mm Hg) despite 100% inspired oxygen. The increased pulmonary arterial contractility was reversed by both in vitro[43] and in vivo treatment with superoxide dismutase[45] suggesting that it may be mediated by superoxide anion formation. The American Heart Association (AHA) and American Thoracic Society (ATS) caution that extreme hyperoxia (F_{IO_2} > 0.6) may be ineffective owing to extrapulmonary shunt in PPHN and aggravate lung injury.[46]

The use of higher SpO_2 targets (90%–94% vs 85%–89%) is associated with increased incidence of ROP among preterm infants.[28,30,47] Among preterm infants with pre-threshold ROP randomization to 96% to 99% SpO_2 (compared with 89%–94%) prolonged duration of oxygen need (46.8 vs 37%), hospitalization at 50 weeks postmenstrual age (12.7 vs 6.8%), and diuretic use (35.8 vs 24.4%). Pneumonia and exacerbations of BPD were more common in the supplemental oxygen arm (13.2 vs 8.5%).[48] Although these findings suggest that pulmonary toxicity of SpO_2 targets in the high 90s in preterm infants, we do not have similar data in late preterm and term infants.

Oxygen toxicity and the brain

Hypoxia causes cerebral vasodilation, and hyperoxia is associated with cerebral vasoconstriction.[49,50] Among term infants with perinatal acidosis, it is important to avoid high Pa_{O_2} (especially >100 mm Hg) as it has been associated with increased incidence

of HIE (58% vs 27%).[51] Among the neonates with signs suggestive of moderate-to-severe HIE during the first six postnatal hours, those with hyperoxemia (defined as Pa_{O_2} > 100 mm Hg) had a higher incidence of abnormal brain MRI findings consistent with HIE (79% vs 33%) compared with those with $Pa_{O_2} \leq$ 100 mm Hg.[51] Although causation cannot be implied, this association suggests that perinatal asphyxia combined with postnatal hyperoxemia may potentially increase secondary free-radical mediated injury in HIE. Hence, high preductal SpO_2 (~99–100%) should be avoided, and periodic arterial blood gas evaluation may need to be conducted in infants with perinatal acidosis and HIE.

Additional factors influencing oxygen target range

a. Underlying lung disease: The phenotype of aPH secondary to pulmonary vasoconstriction is commonly managed with preductal SpO_2 range of 90% to 97% with a pH greater than 7.25. Management of PPHN associated with CDH and preterm PH (with RDS or BPD) may need different target SpO_2 levels.
   i. CDH: The European guidelines for management of PPHN in CDH recommend preductal SpO_2 of 80% to 95% in the delivery room, greater than 70% (if slowly improving) in the first two postnatal hours and 85% to 95% in the neonatal intensive care unit (NICU).[52] Postductal SpO_2 of greater than 70% is tolerated provided organs are well perfused as indicated by a pH greater than 7.2, lactate less than 5 mM/L, and urine output greater than 1 mL/kg/h. Several institutional protocols (personal communication with medical directors of multiple NICUs in the US and Canada) in the United States follow similar guidelines. However, these guidelines are not based on randomized controlled trials. The lungs in infants with CDH are hypoplastic and minimizing volutrauma and oxygen toxicity by gentle ventilation[53,54] and hence slightly lower SpO_2 targets are acceptable. However, each individual patient must be carefully evaluated before determining SpO_2 targets. A preductal SpO_2 of 88% may be acceptable in an infant with CDH with a pH greater than 7.30 but requiring high Fi_{O_2} of greater than 0.8. However, the same SpO_2 of 88% is not acceptable if the CDH infant has lactic acidosis, pH less than 7.25, Fi_{O_2} less than 0.5 and has echocardiographic evidence of severe PPHN. This infant needs a higher Fi_{O_2} and preductal SpO_2 greater than 90%.
   ii. BPD: The AHA/ATS guidelines for PH management recommend SpO_2 of 92% to 94% during management of BPD-PH.[46] More recently, the European guidelines for management of PH associated with BPD recommend SpO_2 of $\geq$93% for suspected PH and $\geq$95% for confirmed PH associated with BPD.[55] There is no upper limit for SpO_2 target mentioned in these guidelines. Targeting very high SpO_2 (99%–100%) may be associated with lung toxicity. There are no clinical trials evaluating optimal SpO_2 targets in BPD-PH. We recommend SpO_2 of 92% to 95% in preterm infants with PH and BPD-PH.[56]

b. Therapeutic hypothermia (TH): Approximately 25% of infants undergoing TH for moderate to severe HIE are also diagnosed with PPHN.[57] The presence of lung disease such as MAS, severe birth asphyxia requiring chest compressions and epinephrine in the delivery room, and need for high Fi_{O_2} greater than 0.5 before onset of TH increase the risk of PPHN.[58] Hypothermia and HbF shift the hemoglobin–oxygen dissociation curve to the left (see **Fig. 2**). In the presence of aPH during TH, a preductal Pa_{O_2} corrected for body temperature of 60 to 80 mm Hg is recommended.[59] Achieving this Pa_{O_2} might need higher preductal SpO_2 range of 93% to 98%. Based on the previous discussion, it is important to avoid SpO_2 of 99% to 100% and Pa_{O_2} greater than 100 mm Hg in term infants with perinatal acidosis.[51]

c. Gestational age: Although several trials have evaluated optimal SpO_2 targets among preterm infants, there are no randomized trials in term infants. One single-center study (POST-IT trial) is currently recruiting patients.[39] The risk of ROP and lung toxicity with BPD exacerbations clearly set an upper limit among preterm infants that should be lower than late preterm and term infants.[56] Pending future trials, it may be prudent to recommend 92% to 95% targets for PH in preterm infants and 90% to 97% SpO_2 in late preterm/term infants. Among preterm infants greater than 6 weeks of age with associated BPD and PH, SpO_2 range of 92% to 95% is probably appropriate, although a range of 92% to 97% may be considered based on ROP status. A few exceptions to these general guidelines are listed in the summary section.

STUDIES IN OLDER INFANTS, CHILDREN, AND ADULTS

There are few trials evaluating optimal SpO_2 targets in postneonatal age groups (Fig. 8). These trials include infants with bronchiolitis,[60] pediatric ICU patients[61] requiring ventilation with supplemental oxygen or acute respiratory distress syndrome

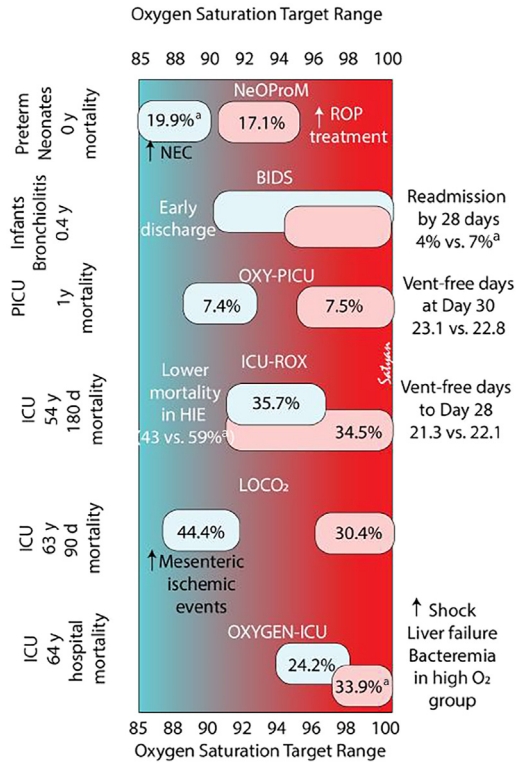

Fig. 8. Graphic representation of a few trials conducted in different age groups comparing low versus high SpO_2 target range. The blue ovals represent the range and mortality in the lower oxygen target group, and the pink ovals represent similar data from the higher target group. **Preterm neonatal data are *from* Askie and colleagues.[28] Data for infants with bronchiolitis are from Cunningham and colleagues.[60] PICU data are from the OXY-PICU trial by Peters and colleagues.[68] Adult studies included were ICU-ROX trial,[69] $LOCO_2$ trial,[70] and Oxy-ICU trial.[71]** [a]Significant difference between low and high SpO_2 target groups.

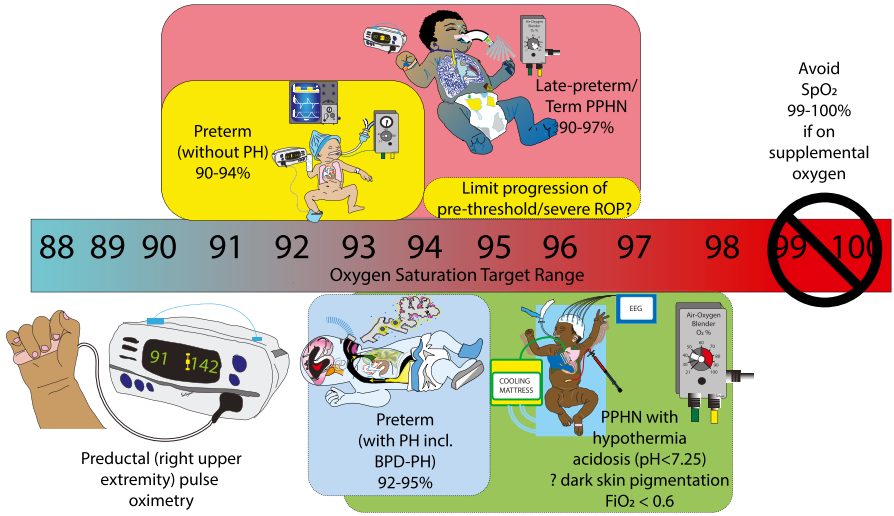

Fig. 9. Precision medicine approach to oxygen saturation targets in PPHN. Optimal preductal SpO_2 range based on gestational age and physiologic status is shown. BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; ROP, retinopathy of prematurity. (Image Courtesy of Dr. Satyan Lakshminrusimha.)

(ARDS) and adults admitted to ICU (see **Fig. 8**). For adult patients with ARDS, SpO_2 of 88% to 95% and a Pa_{O_2} of 55 to 80 mm Hg are recommended.[62] At the peak of COVID-19, several pregnant women with SARS CoV-2 infection developed ARDS.[63] Societies recommended higher targets (≥95%) in pregnant women with ARDS secondary to COVID-19 to optimize fetal oxygen delivery, although some investigators have suggested lower targets (92%–96%).[64]

SUMMARY

There are no randomized clinical trials guiding optimal SpO_2 targets in the management of PH in neonates. Based on available evidence from animal studies and expert opinion, we recommend preductal SpO_2 target of 90% to 97% in the management of acute PPHN in late preterm and term infants. Preterm infants without PH can be managed between 90% and 94% and those with PH between 92% and 95%. Targeting slightly higher range at 93% to 98% may be prudent in the following situations with acute severe PPHN: (1) when Fi_{O_2} is less than 0.6 and risk of lung toxicity is low, (2) pH less than 7.25, (3) TH, (4) lactic acidosis, and (5) probably in patients with dark skin pigmentation. High SpO_2 (99%–100%) values should be avoided in most patients on supplemental oxygen (**Fig. 9**). In conclusion, every neonate with PPHN must be approached individually (precision medicine approach) and a SpO_2 target range determined based on current pathophysiological status. More translational studies and clinical trials are desperately needed to evaluate optimal SpO_2 and Pa_{O_2} range in neonatal PH.

Best Practice Box

- In term infants with PPHN, preductal oxygen saturation between 90% and 97% is recommended based on its association with low PVR based on animal studies.
- In preterm infants (without pulmonary hypertension), saturation targets between 90% and 94% are associated with lower mortality but higher incidence of ROP in multicenter trials.

- Preterm infants with BPD-PH, slightly higher SpO_2 targets between 92% and 95%, are recommended to prevent episodes of hypoxemia.
- In the presence of acidosis (pH < 7.25), whole-body hypothermia, in infants with dark pigmentation and when the risk of lung oxygen toxicity is low (due to Fio_2 < 0.6), it may be prudent to consider preductal SpO_2 between 93% and 98% to minimize the risk of occult hypoxemia and hypoxic pulmonary vasoconstriction.
- Further studies are needed to evaluate short-term echocardiographic changes and long-term neurodevelopmental outcomes with various SpO_2 targets in PPHN.

DISCLOSURE

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