Title

Oxygen Targets in Neonatal Pulmonary Hypertension: Individualized, Precision-Medicine Approach.

Journal

Clinics in Perinatology, 51(1)

Authors

Lakshminrusimha, Satyanarayana

Abman, Steven

Publication Date

2024-03-01

DOI

10.1016/j.clp.2023.12.003

Peer reviewed

HHS Public Access

Author manuscript

Clin Perinatol. Author manuscript; available in PMC 2025 March 01.

Published in final edited form as:

Clin Perinatol. 2024 March ; 51(1): 77–94. doi:10.1016/j.clp.2023.12.003.

Oxygen Targets in Neonatal Pulmonary Hypertension – Individualized, "Precision-Medicine" Approach

Satyan Lakshminrusimha, MD FAAP [Professor and Chair],
Department of Pediatrics, University of California, UC Davis Children's Hospital, 2516 Stockton Blvd, Sacramento CA 95817, USA

Steven H. Abman, MD [Professor and Director]
Department of Pediatrics, The Pediatric Heart Lung Center, University of Colorado Anschutz Medical Campus, Mail Stop B395, 13123 East 16th Avenue, Aurora, CO 80045, USA

Keywords

oxygen saturation; alveolar oxygen; pulmonary vascular resistance; superoxide anions

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 pulmonary hypertension of the newborn (PPHN) or acute pulmonary hypertension (aPH) among late preterm, term and post-term infants is secondary to a variety of 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 inter-subject variability regarding the pulmonary vascular response to hypoxia.

Corresponding author: Satyan Lakshminrusimha, MD FAAP, slakshmi@ucdavis.edu, Phone: (916) 734-5178.

Disclosure: The authors have no conflict of interest to disclose

Goals of oxygen therapy

Supplemental oxygen is commonly used in diverse clinical settings, including intensive care units, 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 ATP production from glucose. In patients with PH, oxygen therapy increases alveolar PAO_2 and prevents HPV.[1] Reduction of PVR in these patients reduces right ventricular (RV) afterload. Among neonates, infants and children, optimal oxygenation is necessary to promote growth. Supplemental oxygen and prevention of sleep-associated hypoxemia improves growth in infants with BPD.[7]

Although arterial PaO_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 PaO_2 assessment and these limitations will be discussed later in this manuscript. In each individual patient, evaluation of FiO_2, PaO_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 physiological principles and clinical outcomes.

LOWER LIMIT OF OXYGEN TARGET RANGE

Two physiological 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 vs. 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 PaO_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 + (PaO_2 × 0.003); in term infants with a Hb of 15 g/dL, SaO_2 of 95% and PaO_2 of 60 mmHg, 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 35–46 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 PaO_2 in determining DO_2.[6]

Under physiological circumstances, the DO_2 exceeds oxygen consumption by the tissues (VO_2, typically ~4 mL/100 mL of blood) by 4–5-fold (figure 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, 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. (figure 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, 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.

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 to HbA (figure 2). HbF has higher affinity to oxygen compared to HbA. Hence, it is often assumed that oxygen delivery is decreased in newborns due to presence of HbF.[13] However, during severe hypoxemia, HbF delivers more oxygen to the tissues (figure 2).[13 14] Peripheral, but not cerebral fractional oxygen extraction (FOE) correlates with HbF in neonates.[15 16,17] 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 PaO_2 and SpO_2, its impact on oxygen saturation targets in PPHN are 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 (figure 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 PAO_2 (figure 3).[22] However, PAO_2 within each region of the lung cannot be measured and in the absence of shunts, correlates well with preductal PaO_2. Hence, preductal PaO_2 to PVR relationship is studied in translational studies. Pulmonary arterial PO_2 (similar to mixed venous PO_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 FiO_2 and plotted PaO_2 against PVR. When PaO_2 decreased below 45–50 mmHg, there was an increase in PVR.[23] The PaO_2 (or SpO_2) value below which PVR increases is called the “change point” (figure 4). Studies in control lambs demonstrated a similar change point of 52.5±1.7 mmHg.[24 25] In lambs with PPHN induced by antenatal

ductal ligation, the change point was higher at 59.6±15.3 mmHg (figure 4).[24] Using preductal SpO_2 (instead of PaO_2), in lamb models of PPHN induced by asphyxia, and meconium aspiration or antenatal ductal ligation, the change point was approximately 90% (figure 5A). PVR was lowest with preductal SpO_2 between 90 to 97%.[26] Rawat et al randomized term lambs with asphyxia induced by umbilical cord occlusion and meconium aspiration and PPHN into preductal SpO_2 target groups of 85–89%, 90–94%, 95–99% and inspired oxygen of 100%.[27] Pulmonary blood flow was significantly lower in the 85–89% SpO_2 target group. PVR was lowest in the 95–99% target group, but these lambs achieved median SpO_2 of 95% (IQR – 93 to 97%). These 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 85–89% range is associated with higher mortality compared to 91–95%.[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 88–92% to 90 to 95%, or from 85–94% to 88–94% and 90–95% in response to NeOProM study results showed a decline in the incidence of pulmonary hypertension among preterm infants.[31,32] Cardiac catheterization studies among infants with BPD suggest that targeting SpO_2 in the 92–94% range reduces pulmonary arterial pressures.[33,34] These clinical observations suggest that the proposed target of 90–97% 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 (figure 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<7.25, hypoxia induced by ventilation with 10% oxygen markedly increases PVR. However, when pH is >7.3, 10% oxygen ventilation results in minimal increase in PVR compared to 100% oxygen ventilation (figure 6). A secondary analysis of data from studies in asphyxiated lambs with meconium aspiration shows that combination of hypoxemia (preductal PaO_2 <50 mmHg) and acidosis (pH <7.25) results is marked exacerbation of HPV (figure 7). These studies show the importance of maintaining pH >7.25 in the presence of hypoxemia in PPHN. The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) recommends preductal SpO_2 between 91 and 95% and avoid hypoxemia (SpO_2 < 85%) or hyperoxemia (SpO_2 > 97%) with a pH > 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 (figures 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 PaO_2 or SpO_2 target range. Based on the previous discussion with animal data, this limit appears to be a preductal SpO_2 of approximately 89–90% (figure 5A) or a

preductal PaO_2 of 45–50 mmHg (slightly higher in PPHN). A couple of exceptions to this lower limit are explained below.

FiO_2 vs. PaO_2 vs. SpO_2:

The limit for SpO_2 during the management of PPHN is partly dependent on FiO_2 and PaO_2. Infants showing signs of acute pulmonary hypertension on echocardiogram need adequate alveolar PAO_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 90–97%. If this patient is being ventilated with FiO_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 PAO_2, PaO_2 or SpO_2 on pulmonary vasculature). In contrast, if this patient is on FiO_2 of 0.3 and experiencing severe PH and has preductal SpO_2 of 90%, it may be appropriate to increase FiO_2 to 0.4 to achieve SpO_2 in the 93–97% range to minimize the risk of HPV (the benefit of higher PAO_2, SpO_2, or PaO_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 > 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 to 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 92–96%, occult hypoxemia was observed in 13.4% of White and 29.3% of Black children. Maintaining SpO_2 >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 et al, 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 (retinopathy of prematurity – 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 85–89% 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 ≥ 12g/dL during management of severe PPHN to optimize DO_2 and minimize lactic acidosis.

UPPER LIMIT OF OXYGEN TARGET RANGE

Compared to physiological 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 bronchopulmonary dysplasia (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 PO_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 iNO-mediated pulmonary vasodilation.[24] Interestingly, the inhibition of iNO-mediated decrease in PVR is related to high FiO_2 and not to hyperoxemia (high PaO_2), as lambs in this study had PPHN and low PaO_2 levels (40±5 mmHg) 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 ($FiO_2 > 0.6$) may be ineffective owing to extrapulmonary shunt in PPHN and aggravate lung injury.[46]

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 96–99% SpO2 (compared to 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] While these findings suggest 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 PaO_2 (especially >100 mmHg) 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 6 postnatal hours, those with hyperoxemia (defined as PaO_2>100 mmHg) had a higher incidence of abnormal brain MRI findings consistent with HIE (79% vs. 33%) compared to those with $PaO_2 \leq 100$ mmHg.[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 acute PH secondary to pulmonary vasoconstriction is commonly managed with preductal SpO_2 range of 90–97% with a pH >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, > 70% (if slowly improving) in the first two postnatal hours and 85 to 95% in the NICU.[52] Postductal SpO_2 of >70% is tolerated provided organs are well perfused as indicated by a pH >7.2, lactate <5 mM/L and urine output >1 ml/kg/h. Several institutional protocols (personal communication) in the US 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 >7.30 but requiring high FiO_2 of >0.8). However, the same SpO_2 of 88% is not acceptable if the CDH infant has lactic acidosis, pH < 7.25, FiO_2 < 0.5 and has echocardiographic evidence of severe PPHN. This infant needs a higher FiO_2 and preductal SpO_2 >90%.

   ii. **BPD**: The AHA/ATS guidelines for PH management recommend SpO_2 of 92–94% during management of BPD-PH.[46] More recently, European guidelines for management of PH associated with BPD recommend SpO_2 of ≥93% for suspected PH and ≥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 92–95% 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 FiO_2 >0.5 prior to onset

of TH increase the risk of PPHN.[58] Hypothermia and HbF shift the hemoglobin-oxygen dissociation curve to the left (figure 2). In the presence of acute PH during TH, a preductal PaO_2 corrected for body temperature of 60–80 mmHg is recommended.[59] Achieving this PaO_2 might need higher preductal SpO_2 range of 93–98%. Based on the previous discussion it is important to avoid SpO_2 of 99–100% and PaO_2 > 100 mmHg in term infants with perinatal acidosis.[51]

c. **Gestational age**: While 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 sets 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 92–95% targets for PH in preterm infants and 90–97% SpO_2 in late preterm/term infants. Among preterm infants > 6 weeks of age with associated BPD and PH, SpO2 range of 92=95% is probably appropriate although a range of 92–97% may be considered based on ROP status. A few exceptions to these general guidelines are listed in the conclusion section below.

Studies in older infants, children and adults

There are few trials evaluating optimal SpO_2 targets in postneonatal age groups (figure 8). These trials include infants with bronchiolitis,[60] pediatric intensive care unit (PICU) patients[61] requiring ventilation with supplemental oxygen or acute respiratory distress syndrome (ARDS) and adults admitted to ICU (figure 8). For adult patients with ARDS, SpO_2 of 88 to 95% and a PaO_2 of 55–80 mmHg is 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 authors have suggested lower targets (92–96%).[64]

CONCLUSION

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 90–97% in the management of acute PPHN in late preterm and term infants. Preterm infants without PH can be managed between 90–94% and those with PH between 92 and 95%. Targeting slightly higher range at 93–98% may be prudent in the following situations with acute severe PPHN: (a) when FiO_2 is <0.6 and risk of lung toxicity is low, (b) pH < 7.25, (c) therapeutic hypothermia, (d) lactic acidosis, and (e) probably in patients with dark skin pigmentation. High SpO_2 (99–100%) values should be avoided in most patients on supplemental oxygen (figure 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 PaO_2 range in neonatal PH.

REFERENCES

1. Sylvester JT, Shimoda LA, Aaronson PI, Ward JP. Hypoxic pulmonary vasoconstriction. Physiol Rev. 2012;92(1):367–520. [PubMed: 22298659]
2. Moudgil R, Michelakis ED, Archer SL. Hypoxic pulmonary vasoconstriction. Journal of applied physiology. 2005;98(1):390–403. [PubMed: 15591309]
3. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).
4. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California. Pediatrics. 2017;139(1).
5. Mirza H, Mandell EW, Kinsella JP, McNamara PJ, Abman SH. Pulmonary Vascular Phenotypes of Prematurity: The Path to Precision Medicine. The Journal of pediatrics. 2023;259:113444. [PubMed: 37105409]
6. Nichols D, Nielsen ND. Oxygen delivery and consumption: a macrocirculatory perspective. Crit Care Clin. 2010;26(2):239–253, table of contents. [PubMed: 20381718]
7. Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. Pediatrics. 1996;98(4 Pt 1):779–783. [PubMed: 8885961]
8. Chandrasekharan P, Rawat M, Lakshminrusimha S. How Do We Monitor Oxygenation during the Management of PPHN? Alveolar, Arterial, Mixed Venous Oxygen Tension or Peripheral Saturation? Children (Basel). 2020;7(10).
9. Hudson I, Houston A, Aitchison T, Holland B, Turner T. Reproducibility of measurements of cardiac output in newborn infants by Doppler ultrasound. Arch Dis Child. 1990;65(1 Spec No):15–19. [PubMed: 2407197]
10. Lieberman JA, Weiskopf RB, Kelley SD, et al. Critical oxygen delivery in conscious humans is less than 7.3 ml O2 × kg(−1) × min(−1). Anesthesiology. 2000;92(2):407–413. [PubMed: 10691227]
11. van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? Anesthesia and analgesia. 1992;75(5):818–821. [PubMed: 1416137]
12. Leone BJ, Spahn DR. Anemia, hemodilution, and oxygen delivery. Anesthesia and analgesia. 1992;75(5):651–653. [PubMed: 1416114]
13. Polin R, Abman SH, Rowitch DH, Benitz WE. Fetal and Neonatal Physiology, 2-Volume Set. Vol 2: Elsevier; 2021.
14. Wimberley PD. Fetal hemoglobin, 2,3-diphosphoglycerate and oxygen transport in the newborn premature infant. Scand J Clin Lab Invest Suppl. 1982;160:1–149. [PubMed: 6182604]
15. Wardle SP, Yoxall CW, Crawley E, Weindling AM. Peripheral oxygenation and anemia in preterm babies. Pediatric research. 1998;44(1):125–131. [PubMed: 9667382]
16. Wardle SP, Yoxall CW, Weindling AM. Determinants of cerebral fractional oxygen extraction using near infrared spectroscopy in preterm neonates. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2000;20(2):272–279. [PubMed: 10698064]
17. Pritisanac E, Urlesberger B, Schwaberger B, Pichler G. Fetal Hemoglobin and Tissue Oxygenation Measured With Near-Infrared Spectroscopy-A Systematic Qualitative Review. Frontiers in pediatrics. 2021;9:710465. [PubMed: 34485197]
18. Stutchfield CJ, Jain A, Odd D, Williams C, Markham R. Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants: a pilot prospective cohort study. Eye (Lond). 2017;31(10):1451–1455. [PubMed: 28548651]
19. Katheria AC, Clark E, Yoder B, et al. Umbilical cord milking in nonvigorous infants: a clusterr-andomized crossover trial. American journal of obstetrics and gynecology. 2023;228(2):217 e211–217 e214.
20. Gao Y, Raj JU. Role of veins in regulation of pulmonary circulation. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2005;288(2):L213–L226. [PubMed: 15640520]

21. Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. Physiol Rev. 2010;90(4):1291–1335. [PubMed: 20959617]
22. Lumb AB, Thomas CR. Nunn's Applied Respiratory Physiology: Chapter 6. Pulmonary Circulation. 9 ed: Elsevier Health Sciences; 2020.
23. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. The Journal of clinical investigation. 1966;45(3):399–411. [PubMed: 5904557]
24. Lakshminrusimha S, Swartz DD, Gugino SF, et al. Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension. Pediatric research. 2009;66(5):539–544. [PubMed: 19680165]
25. Lakshminrusimha S, Russell JA, Steinhorn RH, et al. Pulmonary hemodynamics in neonatal lambs resuscitated with 21%, 50%, and 100% oxygen. Pediatric research. 2007;62(3):313–318. [PubMed: 17622960]
26. Lakshminrusimha S, Konduri GG, Steinhorn RH. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates. Journal of perinatology : official journal of the California Perinatal Association. 2016;36 Suppl 2:S12–19.
27. Rawat M, Chandrasekharan P, Gugino SF, et al. Optimal Oxygen Targets in Term Lambs with Meconium Aspiration Syndrome and Pulmonary Hypertension. American journal of respiratory cell and molecular biology. 2020;63(4):510–518. [PubMed: 32609558]
28. Askie LM, Darlow BA, Finer N, et al. Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. JAMA : the journal of the American Medical Association. 2018;319(21):2190–2201. [PubMed: 29872859]
29. Lakshminrusimha S, Manja V, Mathew B, Suresh GK. Oxygen targeting in preterm infants: a physiological interpretation. Journal of perinatology : official journal of the California Perinatal Association. 2015;35(1):8–15. [PubMed: 25357098]
30. Manja V, Saugstad OD, Lakshminrusimha S. Oxygen Saturation Targets in Preterm Infants and Outcomes at 18–24 Months: A Systematic Review. Pediatrics. 2017;139(1).
31. Laliberte C, Hanna Y, Ben Fadel N, et al. Target oxygen saturation and development of pulmonary hypertension and increased pulmonary vascular resistance in preterm infants. Pediatric pulmonology. 2019;54(1):73–81. [PubMed: 30461218]
32. Kanaan U, Srivatsa B, Huckaby J, Kelleman M. Association of unit-wide oxygen saturation target on incidence of pulmonary hypertension in very low birthweight premature infants. Journal of perinatology : official journal of the California Perinatal Association. 2018;38(2):148–153. [PubMed: 29048404]
33. Abman SH, Wolfe RR, Accurso FJ, Koops BL, Bowman CM, Wiggins JW Jr.Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics. 1985;75(1):80–84. [PubMed: 3838113]
34. Abman SH. Monitoring cardiovascular function in infants with chronic lung disease of prematurity. Archives of disease in childhood Fetal and neonatal edition. 2002;87(1):F15–18. [PubMed: 12091282]
35. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2019;38(9):879–901. [PubMed: 31495407]
36. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial Bias in Pulse Oximetry Measurement. The New England journal of medicine. 2020;383(25):2477–2478. [PubMed: 33326721]
37. Vesoulis Z, Tims A, Lodhi H, Lalos N, Whitehead H. Racial discrepancy in pulse oximeter accuracy in preterm infants. Journal of perinatology : official journal of the California Perinatal Association. 2021.

38. Andrist E, Nuppnau M, Barbaro RP, Valley TS, Sjoding MW. Association of Race With Pulse Oximetry Accuracy in Hospitalized Children. JAMA Netw Open. 2022;5(3):e224584. [PubMed: 35357460]
39. Siefkes H, Sunderji S, Vaughn J, et al. Factors to Consider to Study Preductal Oxygen Saturation Targets in Neonatal Pulmonary Hypertension. Children (Basel). 2022;9(3).
40. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. The New England journal of medicine. 2010;362(21):1959–1969. [PubMed: 20472937]
41. Vali P, Underwood M, Lakshminrusimha S. Hemoglobin oxygen saturation targets in the neonatal intensive care unit: Is there a light at the end of the tunnel? (1). Can J Physiol Pharmacol. 2019;97(3):174–182. [PubMed: 30365906]
42. Kirpalani H, Bell EF, Hintz SR, et al. Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants. The New England journal of medicine. 2020;383(27):2639–2651. [PubMed: 33382931]
43. Lakshminrusimha S, Steinhorn RH, Wedgwood S, et al. Pulmonary hemodynamics and vascular reactivity in asphyxiated term lambs resuscitated with 21 and 100% oxygen. J Appl Physiol (1985). 2011;111(5):1441–1447. [PubMed: 21799125]
44. Lakshminrusimha S, Russell JA, Steinhorn RH, et al. Pulmonary arterial contractility in neonatal lambs increases with 100% oxygen resuscitation. Pediatric research. 2006;59(1):137–141. [PubMed: 16326983]
45. Lakshminrusimha S, Russell JA, Wedgwood S, et al. Superoxide dismutase improves oxygenation and reduces oxidation in neonatal pulmonary hypertension. American journal of respiratory and critical care medicine. 2006;174(12):1370–1377. [PubMed: 17008638]
46. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015.
47. Manja V, Lakshminrusimha S, Cook DJ. Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. JAMA pediatrics. 2015;169(4):332–340. [PubMed: 25664703]
48. STOP-ROP. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000;105(2):295–310. [PubMed: 10654946]
49. Rosenberg AA. Regulation of cerebral blood flow after asphyxia in neonatal lambs. Stroke; a journal of cerebral circulation. 1988;19(2):239–244.
50. Rosenberg AA. Cerebral blood flow and O2 metabolism after asphyxia in neonatal lambs. Pediatric research. 1986;20(8):778–782. [PubMed: 3737291]
51. Kapadia VS, Chalak LF, DuPont TL, Rollins NK, Brion LP, Wyckoff MH. Perinatal asphyxia with hyperoxemia within the first hour of life is associated with moderate to severe hypoxic-ischemic encephalopathy. The Journal of pediatrics. 2013;163(4):949–954. [PubMed: 23759422]
52. Reiss I, Schaible T, van den Hout L, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology. 2010;98(4):354–364. [PubMed: 20980772]
53. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. Journal of pediatric surgery. 2002;37(3):357–366. [PubMed: 11877648]
54. Gupta A, Rastogi S, Sahni R, et al. Inhaled nitric oxide and gentle ventilation in the treatment of pulmonary hypertension of the newborn--a single-center, 5-year experience. Journal of perinatology : official journal of the California Perinatal Association. 2002;22(6):435–441. [PubMed: 12168118]
55. Hansmann G, Sallmon H, Roehr CC, et al. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatric research. 2021;89(3):446–455. [PubMed: 32521539]
56. Gentle SJ, Abman SH, Ambalavanan N. Oxygen Therapy and Pulmonary Hypertension in Preterm Infants. Clinics in perinatology. 2019;46(3):611–619. [PubMed: 31345551]
57. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England journal of medicine. 2005;353(15):1574–1584. [PubMed: 16221780]

58. Lakshminrusimha S, Shankaran S, Laptook A, et al. Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy-Antecedent Characteristics and Comorbidities. The Journal of pediatrics. 2018;196:45–51 e43. [PubMed: 29502880]
59. Afzal B, Chandrasekharan P, Tancredi DJ, Russell J, Steinhorn RH, Lakshminrusimha S. Monitoring Gas Exchange During Hypothermia for Hypoxic-Ischemic Encephalopathy. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2019;20(2):166–171. [PubMed: 30720647]
60. Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. Lancet. 2015;386(9998):1041–1048. [PubMed: 26382998]
61. Chang I, Thomas K, O'Neill Gutierrez L, et al. Protocol for a Randomized Multiple Center Trial of Conservative Versus Liberal Oxygenation Targets in Critically Ill Children (Oxy-PICU): Oxygen in Pediatric Intensive Care. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2022;23(9):736–744. [PubMed: 35699737]
62. Capellier G, Barrot L, Winizewski H. Oxygenation target in acute respiratory distress syndrome. J Intensive Med. 2023.
63. Lim MJ, Lakshminrusimha S, Hedriana H, Albertson T. Pregnancy and Severe ARDS with COVID-19: Epidemiology, Diagnosis, Outcomes and Treatment. Seminars in fetal & neonatal medicine. 2023:101426. [PubMed: 36964118]
64. Eid J, Stahl D, Costantine MM, Rood KM. Oxygen saturation in pregnant individuals with COVID-19: time for re-appraisal? American journal of obstetrics and gynecology. 2022;226(6):813–816. [PubMed: 34922921]
65. Vali P, Lakshminrusimha S. The Fetus Can Teach Us: Oxygen and the Pulmonary Vasculature. Children (Basel). 2017;4(8).
66. Vali P, Underwood M, Lakshminrusimha S. Hemoglobin oxygen saturation targets in the neonatal intensive care unit: Is there a light at the end of the tunnel? (1). Can J Physiol Pharmacol. 2018:1–9.
67. Rudolph AM. Congenital diseases of the heart: Clinical-physiological considerations. 3 ed. West Sussex: John Wiley and Sons Ltd; 2009.
68. Peters MJ, Jones GAL, Wiley D, et al. Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. Intensive care medicine. 2018;44(8):1240–1248. [PubMed: 29868973]
69. Investigators I-R, the A, New Zealand Intensive Care Society Clinical Trials G, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. The New England journal of medicine. 2020;382(11):989–998. [PubMed: 31613432]
70. Barrot L, Asfar P, Mauny F, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. The New England journal of medicine. 2020;382(11):999–1008. [PubMed: 32160661]
71. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2016;316(15):1583–1589. [PubMed: 27706466]

Synopsis:

Oxygen is a specific pulmonary vasodilator. Hypoxemia causes pulmonary vasoconstriction and normoxia leads to pulmonary vasodilation. However, hyperoxia does not enhance pulmonary vasodilation but causes oxidative stress. There are no clinical trials evaluating optimal oxygen saturation or PaO_2 in pulmonary hypertension. Data from translational studies and case series suggest that oxygen saturation of 90–97% or PaO_2 between 50 to 80 mmHg is associated with the lowest pulmonary vascular resistance. Underlying cause of pulmonary hypertension, body temperature, hemoglobin content and type, skin pigmentation, pH and FiO_2 influence oxygen target range necessitating an individualized, precision-medicine approach during the management of pulmonary hypertension.

BEST PRACTICES

1. In term infants with PPHN, preductal oxygen saturation between 90 to 97% is recommended based on its association with low PVR based on animal studies.
2. In preterm infants (without pulmonary hypertension), saturation targets between 90–94% are associated with lower mortality but higher incidence of ROP in multicenter trials.
3. Preterm infants with BPD-PH, slightly higher SpO2 targets between 92–95% is recommended to prevent episodes of hypoxemia.
4. 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 93–98% to minimize the risk of occult hypoxemia and hypoxic pulmonary vasoconstriction.
5. Further studies are needed to evaluate short-term echocardiographic changes and long-term neurodevelopmental outcomes with various SpO_2 targets in PPHN.

Key points:

1. Alveolar oxygen tension is the primary determinant of pulmonary vascular resistance.
2. Hypoxemia (preductal $PaO_2 \leq 49$ mmHg or $SpO_2 \leq 89\%$) is associated with hypoxic pulmonary vasoconstriction.
3. Hyperoxemia (preductal $PaO_2 > 100$ mmHg or $SpO_2 \geq 99\%$ can lead to oxidative stress.
4. Maintaining preductal SpO_2 between 90 to 97% and PaO_2 between 50 to 80 mmHg results in low pulmonary vascular resistance in most patients with pulmonary hypertension.
5. Every patient is unique and optimal oxygen targets may vary between one patient to another and within a given patient, based on changing pathophysiology.

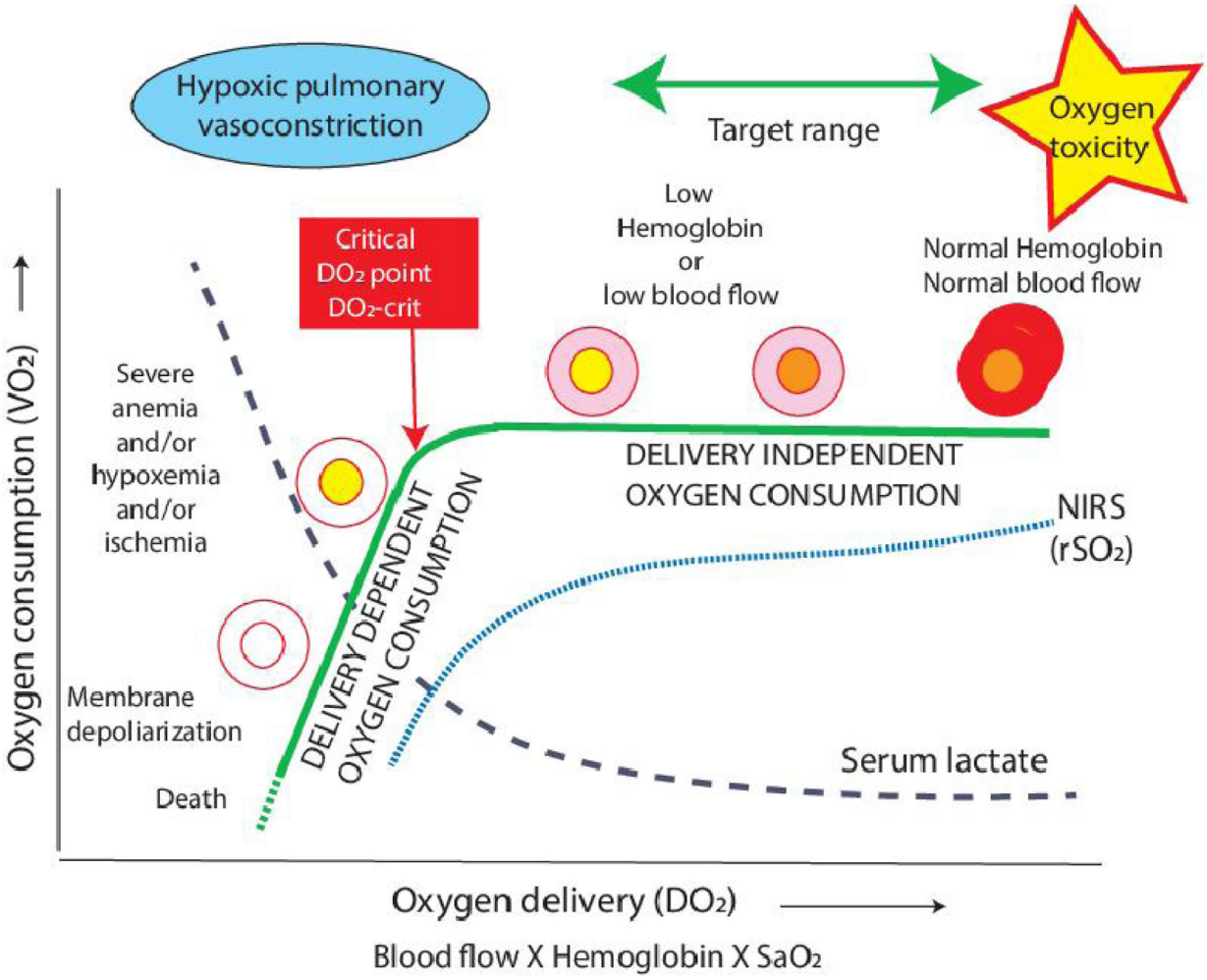

Figure 1.

The oxygen consumption (VO_2) vs. 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 DO2, regional oxygen saturation (rSO2) measured by near-infrared spectroscopy (NIRS) decreases due to increased oxygen extraction with decreasing DO2). 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 rSO2 markedly decreases during this phase. **Image Courtesy of Dr. Satyan Lakshminrusimha. Modified from references**[65,66]

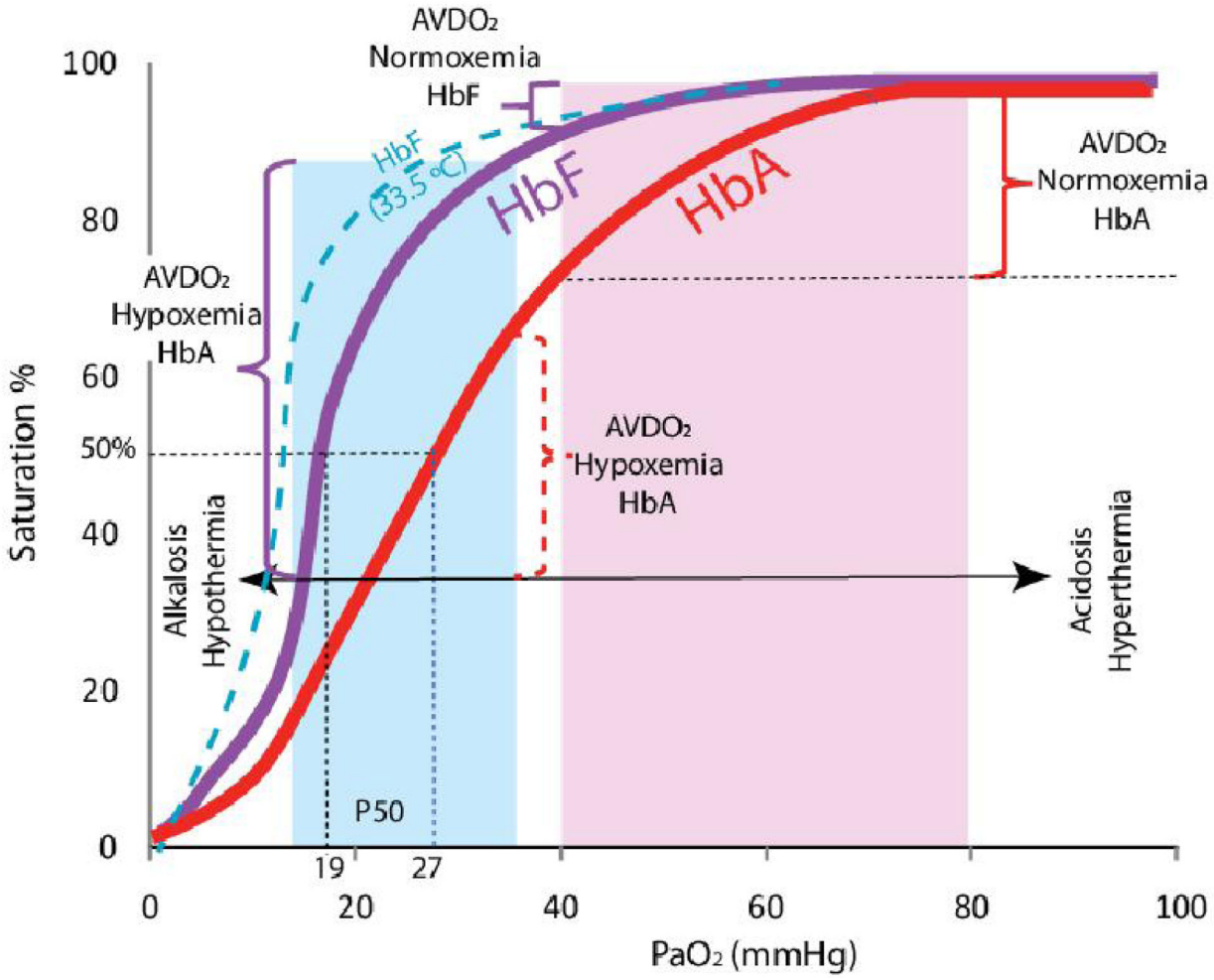

Figure 2.

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 dashed purple line. The pink zone refers to the "normoxemic" arterial PaO_2 of 80 mmHg and venous PO_2 of 40 mmHg. The blue zone refers to hypoxemic arterial PaO_2 of 35 mmHg and venous PO_2 of 15 mmHg. P50 is the partial pressure of oxygen at 50% oxygen saturation and is 19 mmHg for HbF and 27 mmHg 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.**

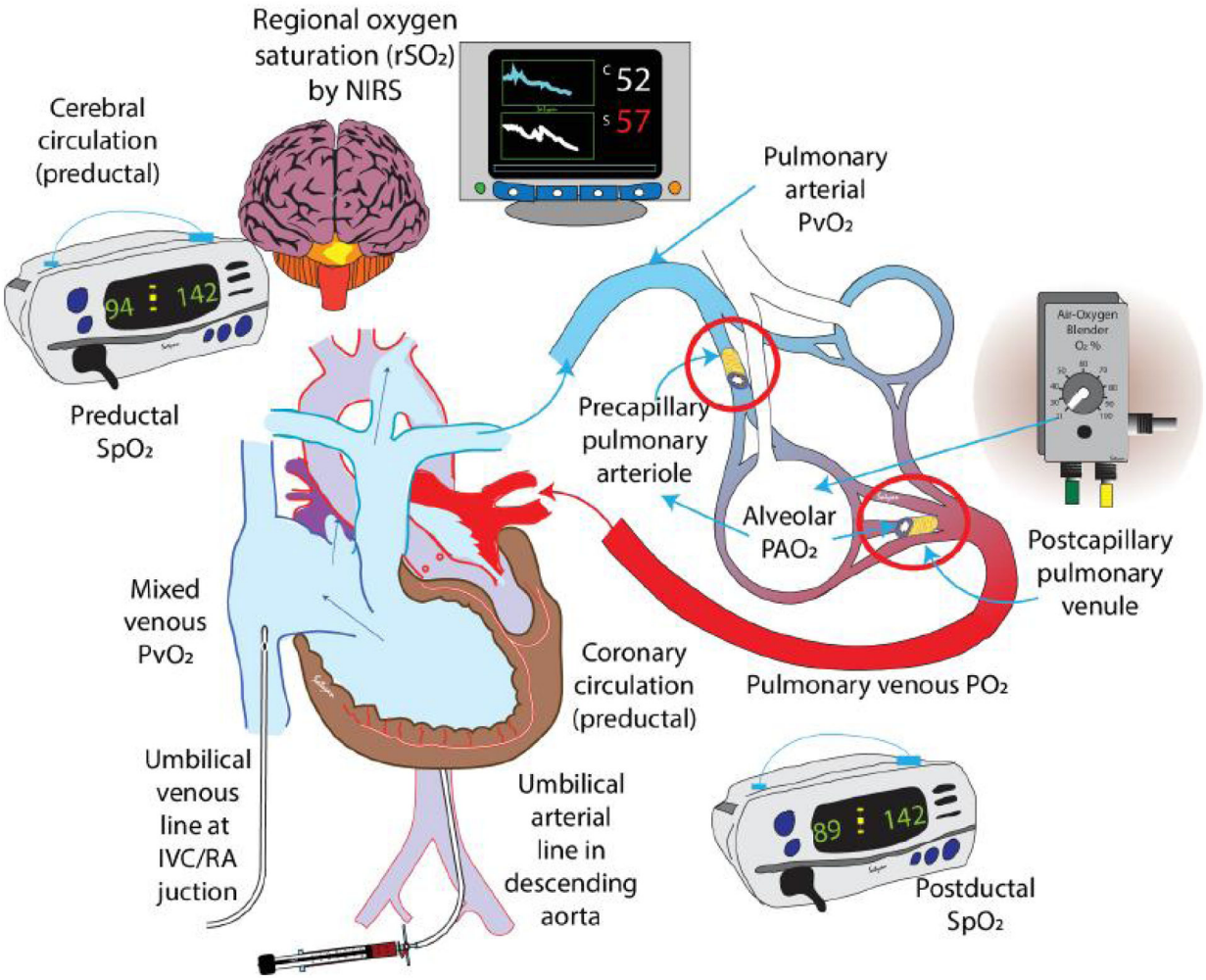

Figure 3.

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 PAO_2 and to a lesser extent by pulmonary arterial (or mixed venous) PO_2. Clinically, preductal and postductal PaO_2 and SpO_2 can be measured along with cerebral regional SO_2 (rSO_2). Of these values, preductal PO_2 (or SpO_2) correlates closely with alveolar PAO_2. Modified from Chandrasekharan et al.[8] **Image Courtesy of Dr. Satyan Lakshminrusimha..**

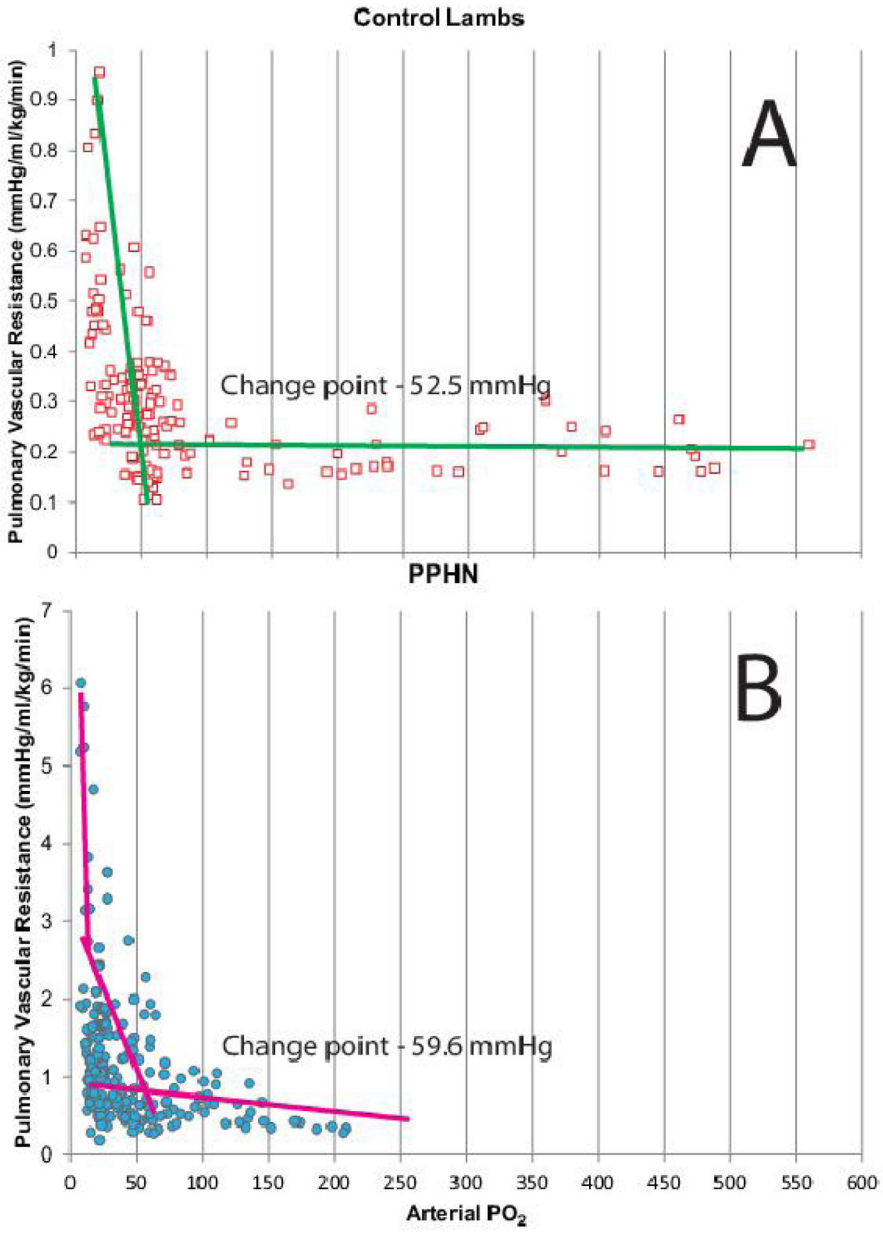

Figure 4.

Change point in the PaO_2 and PVR relationship. Data from control lambs (A) and lambs with PPHN induced by antenatal ductal ligation (B). PaO2 values are low and PVR is high in lambs with PPHN**. Modified from references**[24,25]

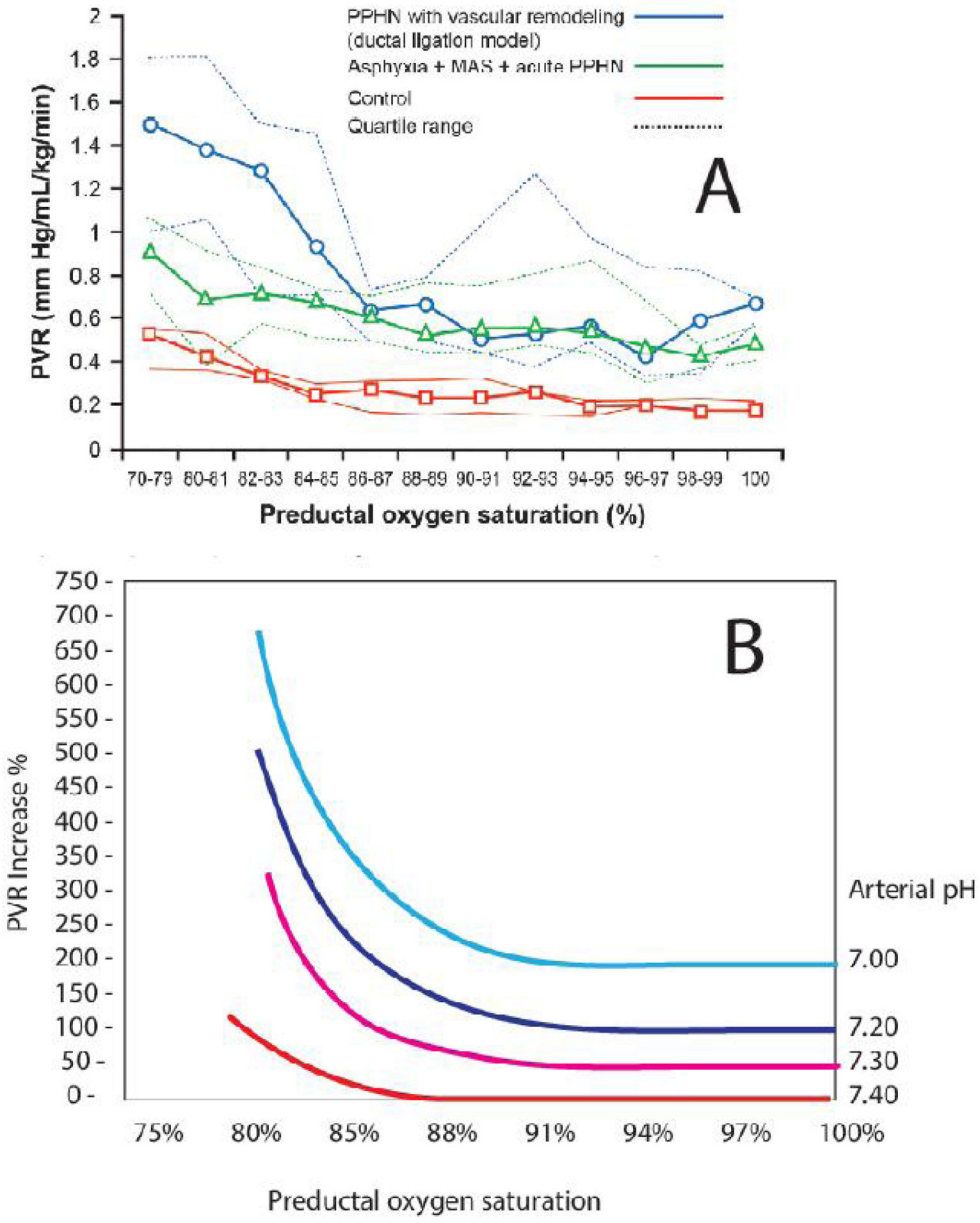

Figure 5.

Oxygen saturation and pulmonary vascular resistance (PVR). **A**. Preductal SpO2 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 (SpO2 below which PVR increases) increases and the degree of HPV markedly increases.[23,26,67]

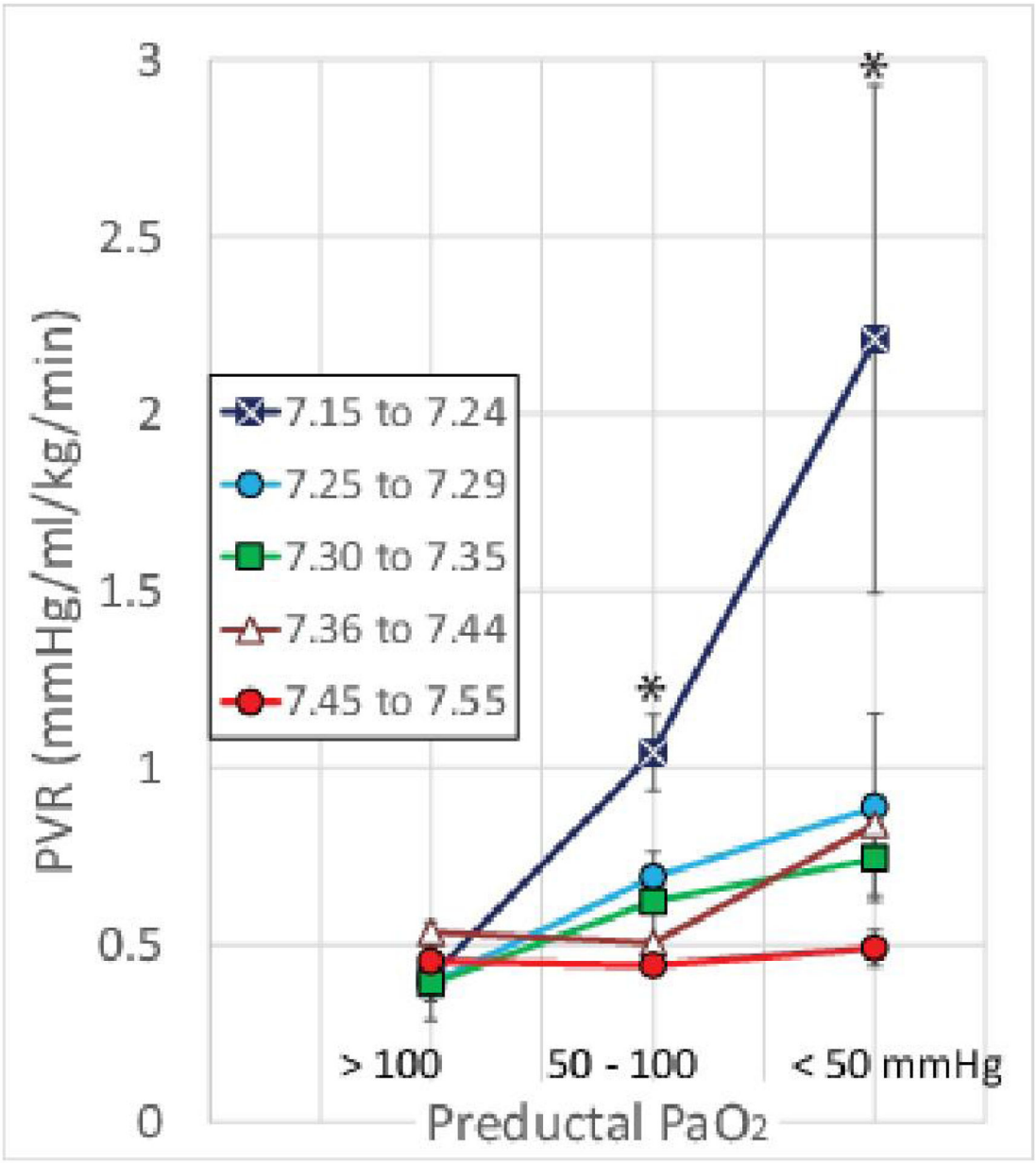

Figure 6.

Effect of ventilation with 10% (blue zones) and 100% oxygen (pink zones) on PVR (triangles plotted on primary vertical axis) and PaO2 (circles plotted on secondary vertical axis) in newborn calves. Although PaO2 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 derived from Rudolph et al[23]

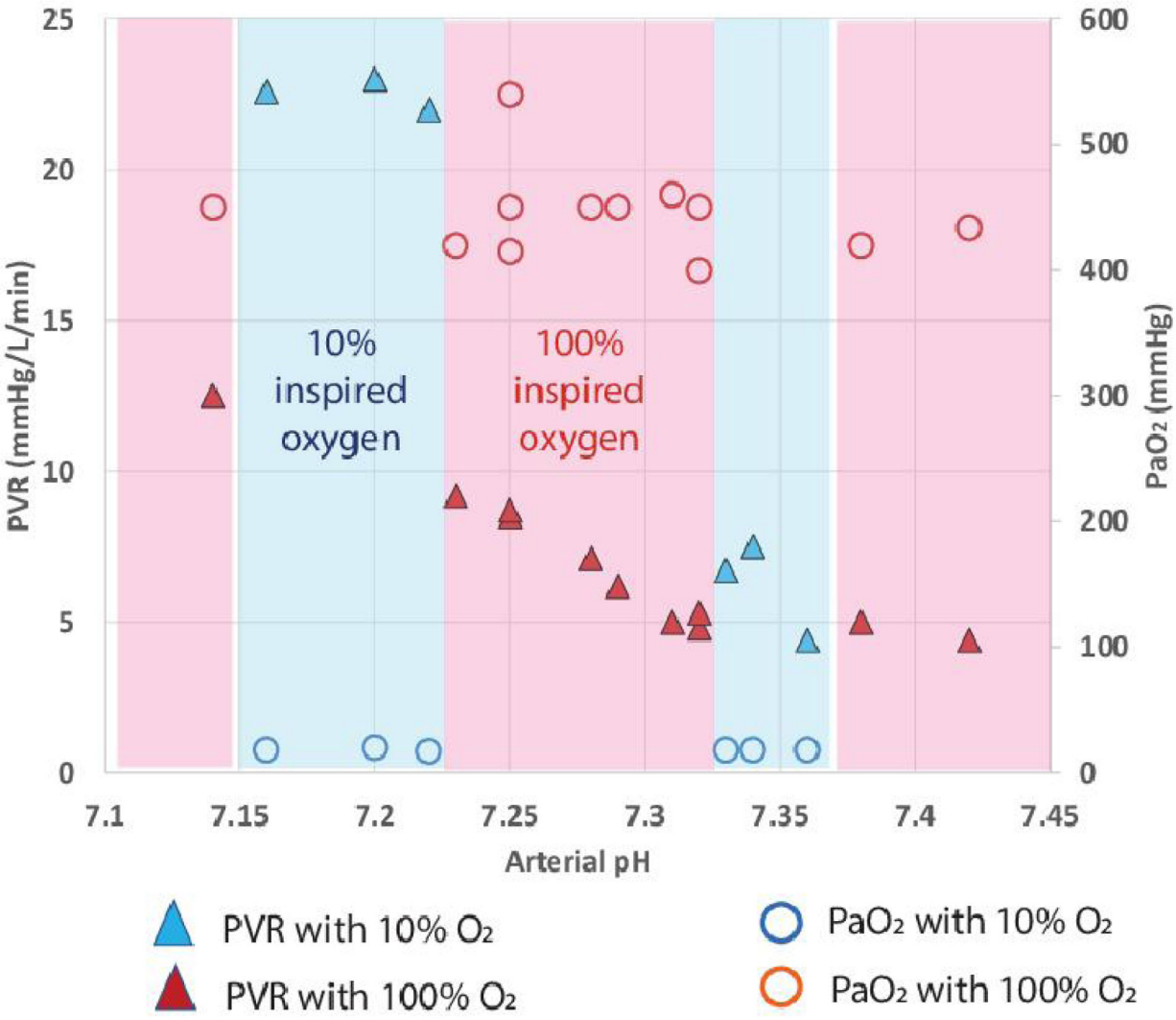

Figure 7.

Effect of pH on hypoxic pulmonary vasoconstriction. A. **Data from Rawat et al**[27] – pooled data from 30 lambs with acute MAS and asphyxia ventilated with varying FiO2 from 0.21 to 1.0 sorted by pH and right carotid arterial PaO2. Data are shown as mean ± SEM. Arterial pH < 7.25 markedly increases HPV.

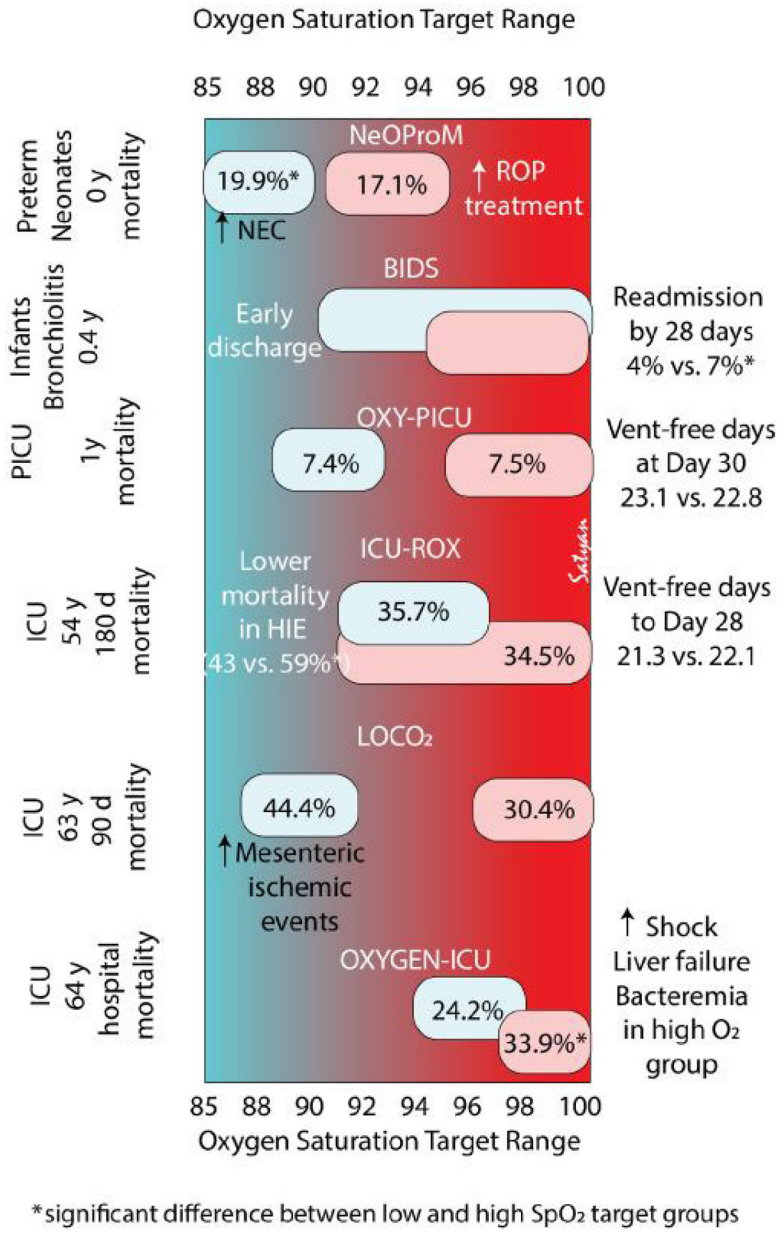

Figure 8.

Graphic representation of a few trials conducted in different age groups comparing low vs. high SpO2 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 et al.[28] Data for infants with bronchiolitis is from Cunningham et al.[60] PICU data are from the OXY-PICU trial by Peters et al.[68] Adult studies included were ICU-ROX trial[69], $LOCO_2$ trial[70] and Oxy-ICU trial.[71]**

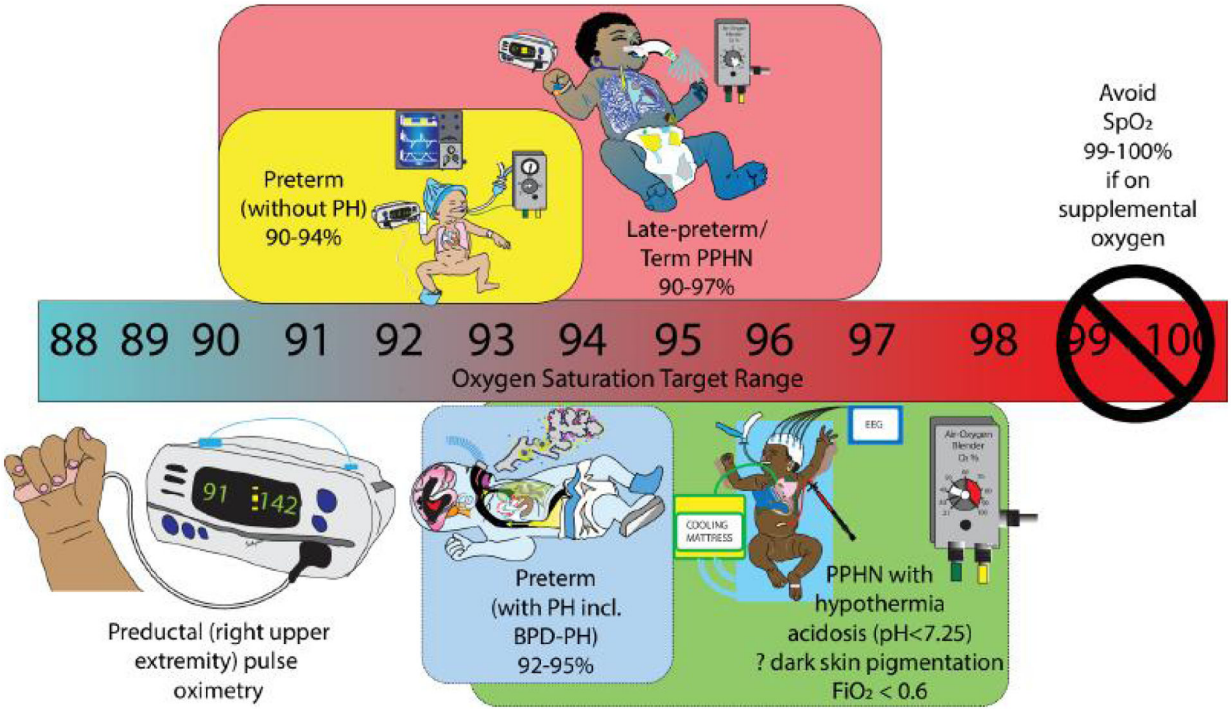

Figure 9.

Precision-medicine approach to oxygen saturation targets in PPHN. Optimal preductal SpO_2 range based on gestational age and physiological status are shown.

Image Courtesy of Dr. Satyan Lakshminrusimha.