

Review

How Do We Monitor Oxygenation During The Management of PPHN? Alveolar, Arterial, Mixed Oxygen Tension or Peripheral Saturation?

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Abstract: Oxygen is a pulmonary vasodilator and plays an important role in mediating circulatory transition from fetal and postnatal period. Alveolar oxygen tension (PAO₂) and pulmonary arterial PO₂ are the main factors that influence hypoxic pulmonary vasoconstriction (HPV). Inability to achieve adequate pulmonary vasodilation at birth leads to persistent pulmonary hypertension of the newborn (PPHN). Supplemental oxygen is the mainstay of PPHN management. However, optimal monitoring of oxygenation to achieve low pulmonary vascular resistance (PVR) and optimize oxygen delivery to vital organs is not known. Noninvasive pulse oximetry measures peripheral saturations (SpO₂) and ranges 91-95% are recommended during acute PPHN management. However, for a given SpO₂, there is wide variability in arterial oxygen tension, especially with variations in hemoglobin type (transfusions), pH and body temperature. This review evaluates the role of alveolar, preductal, postductal, and mixed venous oxygen tension and SpO₂ in the management of PPHN. Translation and clinical studies suggest maintaining an arterial oxygen tension of 50-80 mmHg to help decrease PVR and optimize pulmonary vasodilator management. Nevertheless, there are no randomized clinical trials evaluating outcomes in PPHN based on targeting SpO₂ or PO₂. However, most critically ill patients have umbilical arterial catheters and postductal arterial oxygenation may not be an accurate assessment of oxygen delivery to vital organs or factors influencing HPV. The mixed venous oxygen tension from umbilical venous catheter blood gas may assess pulmonary arterial PO₂ and potentially predict HPV. It is crucial to conduct randomized controlled studies with different PO₂/SpO₂ ranges and compare outcomes in PPHN.

Keywords: oxygenation; PPHN; oxygen tension

1. Introduction:

Persistent pulmonary hypertension of the newborn (PPHN) occurs when there is impaired pulmonary vascular transition during birth due to disruption of pulmonary vasodilator mechanisms. Impaired transition from fetal to neonatal circulation leads to elevated pulmonary vascular resistance (PVR), right-to-left shunts at patent foramen ovale (PFO) and/or patent ductus arteriosus (PDA) leading to hypoxemia [1]. Both term and preterm neonates are at risk for PPHN [2-5]. The course of preterm neonates in the neonatal intensive care unit (NICU) is further complicated by the development of bronchopulmonary dysplasia (BPD) and can potentially be associated with pulmonary hypertension (PHT) [6-8]. The incidence of PPHN in neonates are often underestimated but is thought to be around 1.8 to 2/1000 live births [1,5,9]. In infants with PPHN, several studies report poor long-term neurodevelopment outcomes and higher early mortality rates despite

pulmonary vasodilator therapies [1,10,11]. At birth, with the initiation of spontaneous breathing or with positive pressure ventilation (PPV) and with adequate lung inflation, the pulmonary blood flow (PBF) increases by 8 to 10-fold along with a decrease in PVR. As the fetus grows in a relatively hypoxemic environment, increase in oxygen tension seems to play a significant role in decreasing PVR at birth [12]. Optimal oxygenation is necessary to meet tissue demand, especially in vital organs such as brain and heart and to prevent hypoxic pulmonary vasoconstriction (HPV). This review intends to discuss the role of oxygen tension (PO_2) and pulse oximetry (SpO_2) during the management of PPHN. With lack of clinical evidence on optimal oxygenation in PPHN, this review discusses data from both term and preterm translational models associated with high PVR in the perinatal period.

2. Discussion:

Understanding the relationship of fetal oxygenation, PVR, PBF in both the fetus and newborn is critical to managing a neonate with PPHN.

2.1 Relation of PO_2 and fetal PVR: The fetus develops with placenta serving as an organ of gas exchange. The highest PO_2 within the fetal circulation is approximately 32-35 mmHg in the umbilical vein. There is a further decrease in PO_2 to 25-28 mmHg in the ascending aorta supplying the developing brain and myocardium [13-15]. The placenta protects the fetus from maternal hyperoxia and hypoxia [14,15]. As observed in translation studies, during maternal hyperoxia/hypoxia, the distribution of blood in the placenta, channeling of blood to and from the fetal liver by ductus venosus, and alteration of PVR (increase/decrease) avoids excessive fluctuations in fetal PO_2 [16]. The relationship of fetal PVR to PO_2 is dependent on the gestational age of the fetus [17]. At term gestation, PVR changes dramatically in response to fetal PO_2 [18].

2.2 Gestational age, fetal PVR, and PO_2 : The changes in PVR to PO_2 in relation to gestational age (GA) were studied in fetal ovine model [19]. Ovine fetuses at different gestational ages of 0.6 (103-104/term ~150d), 0.74 (112-119d), 0.80 (121-130d), and 0.90 (132-138d) were exposed to hypoxia or hyperoxia by adjusting the oxygen exposure to the ewe. Pulmonary vasoconstriction and vasodilation were observed at term gestation when exposed to low and high PO_2 . Hypoxia and hyperoxia did not have a significant effect on PVR at 0.6 and 0.74 gestation. In humans, maternal hyperoxia did not alter fetal PBF at 20-26 weeks GA but increased PBF and reduced atrial and ductal shunting at 31 to 36 weeks [20]. Extrapolating from these findings, the pulmonary vascular response to PO_2 seems to increase with advancing gestational age.

2.3 Effect of PO_2 on PVR at birth: During the normal transition, spontaneous breath initiated by the newborn infant ventilates the lung and increases alveolar oxygen tension, which increases PBF reducing PVR, successfully switching from fetal to neonatal circulation [21]. Multiple factors such as mode of delivery (vaginal delivery results in more rapid reduction in PVR compared to an elective cesarean section), maturity, antenatal glucocorticoids, temperature (hypothermia increases PVR), mode of cord clamping and asphyxia (related to higher PVR), could affect transition at birth [22]. These factors affect the balance between the vasoconstrictors (endothelin-1, thromboxane), and vasodilators (prostacyclin and endothelium derived nitric oxide), which exert their effects on the pulmonary artery smooth muscle cells (PASMC). Despite these factors, oxygen (O_2) seems to play a greater role in the regulation of PVR by having a direct effect on PASMC. Oxygen stimulates the

increased production of pulmonary endothelial nitric oxide (NO), which is a potent pulmonary vasodilator birth [22].

2.4 Oxygen and hypoxic pulmonary vasoconstriction (HPV): A fundamental difference between pulmonary blood vessels and systemic vessels is their ability to constrict in response to hypoxia [23]. Regional HPV diverts blood away from underventilated alveoli and promotes ventilation-perfusion (V/Q) matching. HPV is mediated by PO₂ surrounding the precapillary pulmonary arteriole (figure 1) and is influenced both by mixed venous (pulmonary arterial) PVO₂ and alveolar PAO₂ [24]. The stimulus for HPV is dictated by the equation $P(\text{stimulus})\text{O}_2 = \text{PVO}_2^{0.375} \times \text{PAO}_2^{0.626}$. Based on this equation, it is clear that alveolar PAO₂ is the predominant factor determining the severity of HPV. Acidosis exacerbates HPV in neonatal animal models [15].

2.5 Supplemental oxygen and PO₂ during the transition: Oxygen supplementation is the most common resuscitative measure for newborns in the delivery room. American Academy of Pediatrics Neonatal Resuscitation Program (AAP NRP), recommend that supplemental O₂ be started at concentrations of 21% O₂ in term and 21-30% O₂ in preterm neonates and to titrate based on prespecified preductal saturations [25]. Given the ease and universal use of pulse oximetry, preductal oxygen saturations (SpO₂) could be the most efficient way of targeting oxygenation in the delivery room and the neonatal intensive care unit (NICU). However, for a given saturation range, the achieved PO₂ could vary widely and the extremes of SpO₂ have low accuracy [26]. In a newborn, requiring resuscitation, hypoperfusion could also decrease the accuracy of SpO₂.

2.6 Oxygen tension in spontaneous air breathing infants: The concept of normoxemia in a transitioning newborn is not well defined. A healthy newborn, who transitioned from placenta to lungs as an organ of gas exchange, sees a rise in arterial oxygen tension (PaO₂) by 30 – 40 mmHg from fetal values. The higher alveolar and arterial PaO₂ along with ventilation plays a greater role in decreasing PVR and increase in PBF. In a study using transitional ovine model (near term gestation comparable to human term neonates), the use 21% O₂ lead to PaO₂ values of 50 – 60 mmHg [12]. The observed decrease in PVR (0.24 - 0.0013 mmHg/ml/kg/min) from fetal life occurred at a PaO₂ of 52.5 ± 1.7 mmHg, also known as the change point [12]. In human neonates, who were spontaneously breathing room air, 176 samples of arterial blood gas were analyzed [27]. The analysis showed that 80% of the PaO₂ was between 40 – 80 mmHg and the average PaO₂ was 64 mmHg. A recent study, defined normoxemia with a PaO₂ range of 50 – 80 mmHg [28]. Based on these observations, the PaO₂ in normal neonates mostly ranges between 50 – 80 mmHg.

2.7 Oxygen tension and PPHN: In a neonate with PPHN secondary to failed transition or underlying lung pathology, the elevated pulmonary pressures often lead to shunting of blood from pulmonary to the systemic circulation, leading to profound and labile hypoxemia despite PPV and supplemental oxygen. Adequate oxygenation remains the cornerstone of PPHN management in both term and preterm neonates.

2.8 Alveolar PO₂ and its effect on PPHN: The alveolar PO₂ (PAO₂), which takes into account the inspired O₂ concentration and arterial oxygenation and carbon dioxide tension, is a major determinant of HPV [29]. In the presence of parenchymal lung injury and or immature lungs, alveolar hypoxia could exacerbate pulmonary vasoconstriction. Studies done four decades ago, using ovine models, have shown that alveolar hypoxia leads to significant HPV leading to redistribution of pulmonary circulation to both lungs exacerbating ventilation-perfusion mismatch [30].

Parameters	O ₂ (%)	PaCO ₂ (mmHg)*	PaO ₂ (mm Hg)*	PVR (mmHg/ml/kg/min)*	PAO ₂ (mmHg) calculated
Control	21	42±2	57±6	0.28±0.01	37.5
PPHN	21	44±3	23±2	1.6±0.2	69.0
PPHN	50	39±3	36±8	1.0±0.1	265.3
PPHN	100	47±5	40±5	1.0±0.1	601.3

*mean and standard error of mean

In a term model of PPHN, use of 21% leads to normal PAO₂ but low PaO₂ and mixed venous PVO₂ compared to non-PPHN controls, and high PVR. Increasing calculated PAO₂ by increasing inspired oxygen led to a decrease in PVR (table 1). [12]. Although alveolar hypoxia worsens PPHN, hyperoxia (> 300 mmHg) did not have any additional vasodilator effect. Exposure to hyperoxia may not be sustained and could blunt the vasodilator response to inhaled nitric oxide (iNO) [31]. One concern with alveolar PAO₂ is that it is calculated using mathematical equations and in heterogenous lung disease, different areas of the lung may have different PAO₂ values. In a meconium aspiration model of ovine PPHN, increase in PaO₂ and PAO₂ were necessary to achieve adequate decrease in PVR.

2.9 Arterial oxygen tension and its effect on PPHN:

Preductal arterial oxygenation (PaO₂) is typically used to assess the severity (based on oxygenation index), management, and response to therapy of PPHN. In neonates with PPHN, despite adequate ventilation and supplemental oxygen, a preductal PaO₂ of <40 mmHg reflects hypoxemia. Secondary to shunting across the ductus, there is a pre and post ductal SpO₂ difference, secondary to difference in PaO₂. No clinical studies to date have studied the effect of maintaining various levels of PaO₂ in the management of PPHN. As mentioned previously, a preductal PaO₂ of > 52.5 ± 1.7 mmHg decreased PVR in ovine models without PPHN, while a PaO₂ of > 59.6 ± 15.3 mmHg was required to decrease the PVR (0.72 -0.0028 mmHg/ml/kg/min) in a PPHN model [12]. In a preterm RDS model, a PaO₂ of > 58 mmHg was required to see a change in PVR (1.34 (0.86 – 2.24) mmHg/ml/kg/min) [17].

Similarly, the change point for preductal PaO₂ was 45 ± 0.1 mmHg in a model of asphyxia with meconium aspiration syndrome.

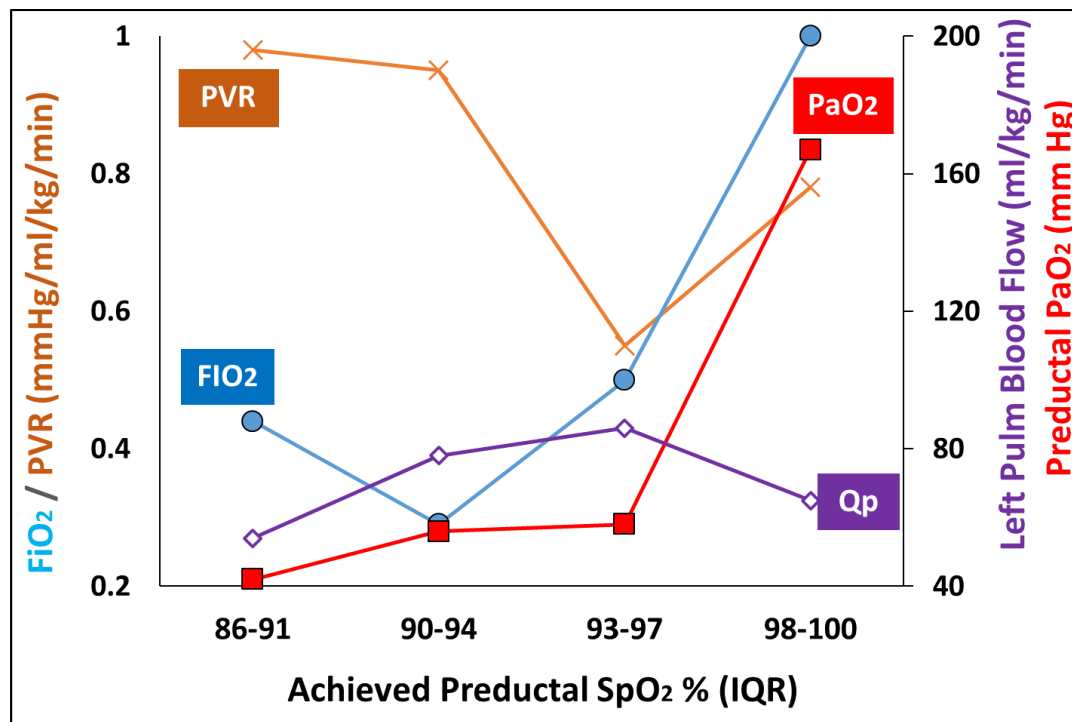


Figure 1: A graph depicting the relationship of oxygen, PVR, left pulmonary blood flow, arterial oxygenation and SpO₂ is illustrated in a meconium aspiration model with PPHN. [32] The pulmonary vascular resistance (PVR-brown cross), pulmonary blood flow (Qp - purple open circles), FiO₂ (blue circles) and PaO₂ (red squares) at different preductal saturation (SpO₂) ranges. Preductal SpO₂ in the mid-90s was associated with lowest PVR, higher pulmonary blood flow, lower supplemental oxygen in this model. For detailed statistical analysis, please refer to Rawat et al [32]. Copyright MR/SL.

Recently, we have shown that in a model of asphyxia and meconium aspiration with PPHN, within the first 6 hours post-resuscitation, targeting a preductal SpO₂ of 95-99%, with a corresponding PaO₂ of 58±19 mmHg was associated with the lowest PVR (0.55±0.15 mmHg/ml/kg/min), with an inspired oxygen requirement of 68±18 % [32]. In this study, the SpO₂ range of 90-94 % had a similar PaO₂ (56±11 mmHg), but the corresponding PVR was much higher with a significantly lower inspired oxygen requirement (30±17 %) [32]. These results shown in figure 2 outline the importance of alveolar PAO₂ in addition to arterial PaO₂ in mediating lower PVR. While the PaO₂ in the 90-94% target SpO₂ group and 95-99% target SpO₂ group were identical, the difference in FiO₂ contributed to the drop in PVR were different (Figure 1).

With the available data, preductal PaO₂ has a high utility in neonate PPHN as it dictates the amount of oxygen delivered to the brain and coronary circulation. In summary, targeting preductal arterial oxygenation in the clinically accepted range of normoxemia (50-80 mmHg), could help in managing PPHN by optimizing oxygen delivery, but is not the only factor determining PVR. Providing adequate FiO₂ to maintain optimal alveolar PAO₂ is also important in mediating pulmonary vasodilation. Avoiding extremely high PaO₂ (> 100 mmHg) and PAO₂ (> 300 mmHg) may potentially

facilitate response to other pulmonary vasodilators, reducing high cumulative oxygen and its toxicity [12,29,31]. The optimal PaO₂ range during acute phase of PPHN warrants further clinical trials focusing on both short-term and long-term outcomes.

3.0 Postductal PaO₂ (PDPaO₂) and PPHN: Given the easy access path in neonates, a high umbilical arterial catheter (UAC), with its tip in the thoracic portion of the descending aorta, is the most commonly placed arterial access in the NICU [33]. When blood gas is obtained from the UAC, it usually reflects PDPaO₂ unless the ductus arteriosus is closed. Labile hypoxemia, in the presence of shunting from pulmonary to systemic circulation, could present with pre and post ductal PaO₂ gradient of 10 – 20 mmHg, which often goes in hand with pre and post ductal SpO₂ difference and is characteristic of PPHN. In the absence of shunting, a PDPaO₂ could reflect preductal PaO₂. In a clinical trial comparing the blood gas to saturation values, out of 800 arterial blood gas samples collected, 88% of the samples were postductal, which reflects the extensive use of PDPaO₂ to evaluate and guide therapy when supplemental oxygen is needed [27].

3.1 Mixed venous oxygen tension (PvO₂) and management of PPHN: The mixed venous PO₂ typically refers to oxygen tension in the pulmonary artery [34]. Since umbilical venous catheters (UVC) are commonly placed in the NICU, the blood gas obtained from a UVC is used as a proxy for mixed venous gas [35]. The PVO₂ could assess the tissue oxygenation in neonates. In a clinical study involving 22 neonates with respiratory failure requiring mechanical ventilation, PVO₂ had an inverse relationship with arterial-venous oxygen content difference ($r = -0.528$) and fractional oxygen extraction ($r = -0.592$). The position of UVC (high in the right atrium or near PFO vs. low in the inferior vena cava) could affect the PVO₂ measurements and may not accurately reflect the pulmonary arterial PO₂ especially if they are also being used to infuse fluids.

In our lab in a meconium aspiration model and a preterm RDS model, a PVO₂ demonstrated a change point of 25 and 32 mmHg [36,37] (figure 1). The utility of PVO₂ from the UVC during the management of PPHN requires further exploration.

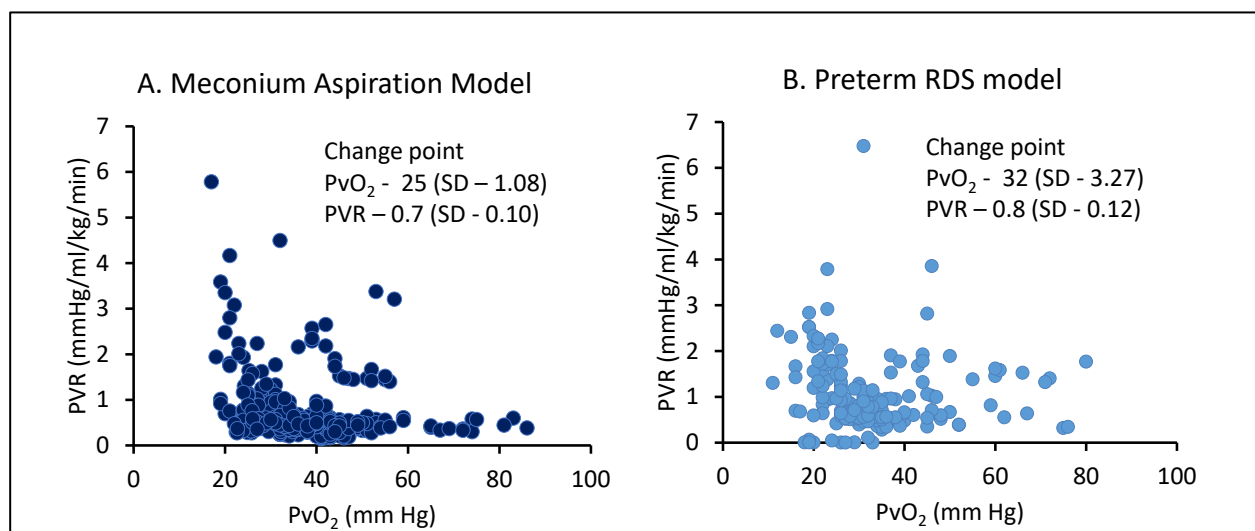
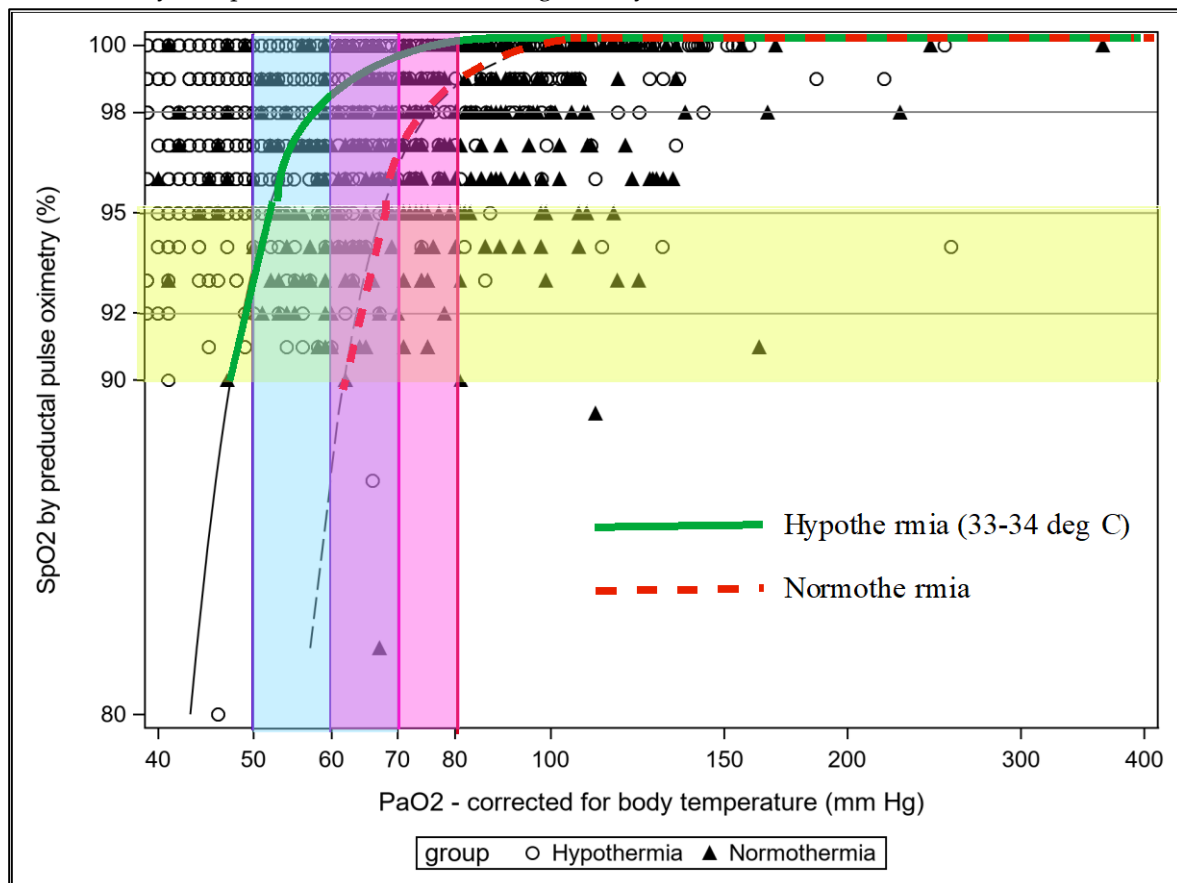


Figure 2. The scatterplot between PVR and PVO₂ is shown in a) meconium aspiration model and b) preterm RDS model. There was no correlation between PVR and PVO₂ in both the models. The PVO₂ was obtained from the main pulmonary artery blood gas. The MCMC model using SAS 9.4 (NC) estimated change point. Copyright MR/PC/SL.

3.2 Effect of transfusion, acidity (pH) and temperature on relationship between SpO₂ and PaO₂ in PPHN:

The influence of transfusion, temperature and acidity (pH) on SpO₂ and PaO₂ could be explained by oxygen dissociation curve. Oxygen dissociation curve (ODC) explains the relationship between oxygen saturation of the hemoglobin (plotted in y-axis) and oxygen tension (plotted in x-axis), which is essential for oxygen absorption in the lungs and delivery to the tissues [38]. A right shift in the curve is associated with release of O₂ to the tissues and a left shift is associated with O₂ absorption from the lungs. Fetal hemoglobin (HbF) is the predominant type during fetal and neonatal period. Secondary to high affinity of HbF to O₂ the ODC is shifted to the left in neonates and this could lead to higher oxygen saturation for lower PaO₂. Thus for a PaO₂ of approximately 40 mmHg, the SpO₂ could be between 85 – 93% , and for a SpO₂ of 97% the PaO₂ could be > 100 mm Hg [27]. Factors such as blood transfusions affect the ODC. The packed red blood cell transfusion that predominantly has HbA (adult hemoglobin), could alter the oxygen affinity moving the ODC to the right affecting the relation between SpO₂ and PaO₂ [38]. PPHN, respiratory failure and carbon dioxide retention with low pH could move the ODC right with lower affinity of Hb to O₂, which affects the SpO₂ for a given PaO₂. Lastly, temperature affects the blood gas analysis unless it is corrected [39].



The solubility of a gas increases with lower temperature and it is important to analyze blood gas with

Figure 3: The relation between SpO₂ (y-axis) and PaO₂ (x-axis) in hypothermia and normothermia is shown. In normothermia and hypothermia, the relation between SpO₂ and PaO₂ alters and it is safe to target a PaO₂ of 50-80 mmHg. Copyright SL.

temperature correction. In infants undergoing whole body hypothermia for moderate to severe hypoxic ischemic encephalopathy (HIE), uncorrected PaO₂ may not be reliable and could lead to

hypo/hyperoxemia [39] (figure 2). Thus, it is important that blood transfusions, pH and temperature be taken into account while managing an infant with PPHN. Periodically checking arterial blood gases and trying to maintain PaO₂ at or slightly above 50 mmHg may also help in the management of PPHN by avoiding HPV.

4.0 Conclusion:

In the management of PPHN, arterial oxygen tension plays an essential role in diagnosis, assess severity, guide treatment, facilitate specific pulmonary vasodilator therapy, evaluate the response to therapy, and to escalate care if needed. Since an UAC placement is standard of care, the disadvantage of having PDPaO₂ could be a limitation, especially in severe PPHN with labile hypoxemia with ductal shunts. Preductal oxygenation dictates oxygen delivery to brain and heart. Hypoxic pulmonary vasoconstriction is associated with low alveolar oxygen tension and mixed venous oxygen tension. While SpO₂ provides a continuous, non-invasive assessment of preductal oxygenation, periodic blood gas evaluation is warranted especially in the presence of hypothermia or acidosis. Further clinical trials are warranted to assess the utility of preductal, postductal, and umbilical venous PO₂ in addition to preductal SpO₂ in the management of PPHN.

Author Contributions: PC conceptualized, wrote the first draft, reviewed revised, provided data from RDS model, did the statistical analysis and accepted the final draft. MR conceptualized, provided data and calculations from meconium aspiration model with PPHN, reviewed, revised and accepted the final draft. SL conceptualized, provided data from PPHN model, hypothermia model, reviewed, revised and accepted the final draft.

Funding: PC - RO3 HD096510, SL RO1 HD072929

Acknowledgments: We thank Sylvia Gugino, Carmon Koenigsnecht, Justin Helman, and Lori Nielsen for their valuable contributions at the Center for Developmental Biology of the Lung, University at Buffalo.

Conflicts of Interest: "The authors declare no conflict of interest."

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