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Oxygen therapy in preterm infants with pulmonary hypertension

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Abstract

Premature neonates <34 weeks gestation can present with early-onset, late-onset and bronchopulmonary dysplasia (BPD) associated pulmonary hypertension (PHT), with clinical, echocardiographic, and histological features similar to term infants with PHT. Changes in pulmonary vascular resistance (PVR) in response to oxygen are diminished in preterm infants compared to term. Studies from preterm lambs and human infants with BPD have shown that PaO_2 > 30–55 mm Hg promote pulmonary vasodilation. Targeting saturations of 80–85% by 5 min, 85–95% by 10 min during resuscitation and 90–95% during the postnatal course are appropriate targets for routine management of preterm infants. Among preterm infants with PHT, avoiding hypoxia/hyperoxia by titrating supplemental oxygen to maintain saturations in low to mid 90s with alarm limits at 90 and 97% seems to be a reasonable approach pending further studies. Further high quality evidence generated from randomized trials is required to guide oxygen therapy in preterm PHT.

Keywords

Preterm pulmonary hypertension; supplemental oxygen; oxygen saturation target; bronchopulmonary dysplasia associated pulmonary hypertension

Introduction:

Premature neonates are at risk of developing pulmonary hypertension (PHT). Several factors including immature lungs, high alveolar-arterial (A-a) gradient, impaired oxygenation, and low vascular response to vasodilator mediators lead to elevated pulmonary vascular resistance (PVR) resulting in PHT.[1] Other factors that could lead to the development of pulmonary hypertension (PHT) in preterm infants include hypoplasia of the lung due to prolonged rupture of membranes, oligohydramnios, fetal growth restriction and genetic factors[2–5]. The extrauterine development of premature lungs, especially under the influence

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of positive pressure ventilation leads to abnormal development of alveolar capillary unit leading to bronchopulmonary dysplasia (BPD), which can be associated with PHT. The vascular remodeling that occurs in later stages may not be restricted to pulmonary arteries but could also involve the veins occasionally leading to pulmonary venous stenosis, which further complicates the management of PHT. This review intends to evaluate the role of oxygen in the development and management of PHT in preterm neonates throughout the course of hospitalization in the neonatal intensive care unit (NICU) and after discharge.

Discussion:

Preterm pulmonary hypertension

Preterm PHT has a biphasic presentation. Early PHT is often associated with respiratory distress syndrome (RDS), which could present clinically as increased oxygen requirement despite rescue surfactant therapy and adequate ventilator support.

The acute early PHT has clinical, echocardiographic, and histologic features similar to term infants with persistent pulmonary hypertension of the newborn (PPHN). Early PHT usually presents in the first four weeks after birth, most often in the first few postnatal days, especially in the presence of risk factors[4, 6].

Late-onset PHT is often associated with BPD and presents with need for increased concentrations of inspired oxygen, lability, and extrauterine growth restriction. The actual prevalence of early or late PHT remains unknown secondary to heterogeneity of reported data, timing of screening, screening methods (echocardiogram vs. cardiac catheterization), etc. A recent meta-analysis reported 20% prevalence of PHT in infants with BPD[7]. Also, infants with severe BPD were 2.7 times at risk of developing PHT, and PHT in this population increased mortality by 4.7 times[7].

Effect of oxygen on fetal PVR and pulmonary blood flow (PBF)

The fetus develops in a relatively low oxygen environment where the placenta serves as an organ of gas exchange[1, 8, 9]. The relative hypoxemia along with other mechanical factors (fluid-filled lungs compressing the capillary unit) and vasoconstrictor mediators (endothelin-1, thromboxane) maintain the high fetal PVR thus diverting the blood flow to the brain[10, 11]. The fetal PBF based on studies in lambs could range from 10–11% of combined ventricular output[9, 12]. The changes in PVR with gestational age (GA) were studied in fetal lambs in utero[12]. Fetal lambs 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 by reducing the inspired oxygen to the pregnant ewe[12] or hyperoxia (ventilation with 100% oxygen)[13]. Hypoxic pulmonary vasocontriction (HPV) and oxygen induced pulmonary vasodilation were observed at term gestation. Hypoxia and hyperoxia did not have a significant effect on PVR at 0.6 and 0.74 gestation. In human fetuses, maternal hyperoxygenation does not alter fetal PBF at 20–26 weeks GA but increases PBF and reduces atrial and ductal shunting at 31 to 36 weeks[14]. These data suggest that pulmonary vascular response to oxygen increases with gestational age.

The percentage of combined ventricular cardiac output to the fetal lungs is relatively low (13%) at 20 weeks GA in human infants[15]. Subsequently, pulmonary blood flow increases to 25% of combined ventricular output by 30 weeks GA[16]. Extremely preterm infants born at 22–25 weeks gestation have low PBF with poor response to oxygen and are at risk for PHT. Interestingly, vasodilator response to inhaled nitric oxide (iNO) is more pronounced at an earlier gestation compared to response to oxygen in lambs although response to iNO also appears to increase with advanced GA[17].

Factors associated with preterm PHT

Factors such as premature prolonged rupture of membrane (PPROM), oligohydramnios, pulmonary hypoplasia, fetal growth restriction increase the risk of PHT in preterm infants (figure 1)[2, 4, 5]. In premature neonates born following PPROM, an increase in erythrocyte malondialdehyde levels is observed suggesting oxidative stress[18]. Preterm infants born after PPROM presenting with hypoxemic respiratory failure (HRF) demonstrate low nitrite and nitrate levels in airway samples suggesting a deficiency of nitric oxide. This deficit appears to be due to low nitric oxide generation[3] and not inactivation by reactive oxygen species[19]. At least two percent of all premature neonates with PPROM and oligohydramnios are at risk of early PHT[2, 3, 5]. Prospective cohort studies in premature neonates have shown that maternal factors such as placental insufficiency, pregnancy induced hypertension (PIH) and intrauterine growth restriction are associated with PHT[20, 21]. Preterm neonates with oligohydramnios and growth restriction showed improved oxygenation and pulmonary hemodynamics to iNO therapy[22]. Oxidative stressors during intrauterine life secondary to placental insufficiency including PIH could affect vascular endothelial growth factors, cord blood placental growth factor, granulocyte – colony stimulating factor as seen in a cord blood metabolomics evaluation and has shown a strong association with late onset of PHT and BPD[23 24 25]. These findings suggest that abnormalities in reactive oxygen species and nitric oxide pathway may play a role in pathogenesis of PHT in preterm infants (figure 1).

Oxygen use during resuscitation of preterm infants:

Ventilation of the lungs remains the most important step during neonatal resuscitation and triggers an increase in PBF that establishes lungs as the site of postnatal gas exchange. Immature lungs with deficient gas exchange and the presence of a wide-open ductus arteriosus complicates transition at birth in extremely preterm infants. The use of oxygen during resuscitation of a preterm infant remains controversial[26]. The American Academy of Pediatrics (AAP), Neonatal Resuscitation Program (NRP) guidelines recently recommended starting resuscitation with 21–30% O_2 and titrating upwards based on preductal oxygen saturations (SpO_2)[27]. The recommendations were based on several large randomized control trials (RCTs) which showed no advantage of using higher oxygen concentration to initiate resuscitation[28]. Premature neonates lack antioxidant defenses and use of 100% O_2 for resuscitatation can cause oxidative injury that could be detrimental after transition[29–31]. After 2015 recommendations by the international liaison committee on resuscitation (ILCOR), an RCT from Australia and a large retrospective study from Canada showed decreased survival with initiation of resuscitation with 21% oxygen in extremely preterm infants[32–34]. Interestingly, a majority of early deaths reported in the Australian study among preterm infants were secondary to respiratory failure and poses a question as to whether

resuscitation with 21% oxygen in extremely preterm infants increase the risk of HRF, early PHT and death from respiratory failure? Including the results of this recent RCT in the latest meta-analysis, there is no conclusive evidence to support low or high oxygen use in the delivery room[35].

We have studied the effect of O_2 supplementation on pulmonary hemodynamics in lambs models of neonatal lung disease at both term and preterm gestation[36]. Term lambs ventilated with 21% oxygen decrease pulmonary arterial pressure significantly below systemic blood pressure[37, 38]. Such a gradient between the aorta and pulmonary artery is essential to switch the ductal shunt from right-to-left during fetal life to left-to-right and promote PBF (figure 2)[39]. In sharp contrast, resuscitation with 21% oxygen in a preterm (127 days/term ~ 150d) lamb model, resulted in SpO_2 below the range recommended by NRP with PaO_2 of 37 ± 10 mmHg and did not decrease PVR from fetal levels. The lack of significant decrease in pulmonary arterial pressure with 21% oxygen in preterm lambs leads to a failure to establish a pressure gradient between aorta and pulmonary artery necessary to facilitate left-to-right ductal shunt and enhanced PBF. However, if resuscitation of preterm lambs was initiated with 100% oxygen, the pulmonary pressures dropped below systemic pressures resulting in a left-to-right ductal shunt and increased PBF. These results suggest that 21% oxygen may not be adequate to mediate pulmonary transition at birth in extremely preterm infants with RDS (figure 2). This could be due to lower sensitivity of preterm pulmonary vasculature to oxygen or failure to achieve optimal oxygen levels in preterm lambs due to lung immaturity and high Alveolar-arterial gradient.

Hypoxic pulmonary vasoconstriction (HPV) and prematurity

Optimal target oxygenation in preterm newborn continues to be a subject of controversy. Reducing alveolar oxygen results in HPV, an important physiological response that facilitates ventilation-perfusion (V/Q) matching[40]. An important goal of supplemental oxygen therapy is to avoid HPV. Rudolph and Yuan evaluated term newborn calves and demonstrated that the change-point or HPV trigger-point at which the slope of a scatter-plot of PVR and PaO_2 changes is approximately 45–50 mmHg. Arterial oxygenation (PaO_2) values below this change point are associated with pulmonary vasoconstriction. We have reported that the change point in term lambs without lung disease is 52.5 ± 1.7 mmHg (preductal SpO_2 of 92 ± 0.4%)[41]. This change point in PaO_2 corresponds to a median PVR in the left lung of 0.6 (IQR: 0.35–0.72) mmHg/ml/kg/min (figure 3). Similarly, term lambs with perinatal asphyxia with meconium aspiration syndrome (MAS) had a change point preductal PaO_2 of 45 ± 0.1 mmHg (SpO_2 90 ± 4.9%) with a corresponding median left PVR of 0.6 (IQR: 0.48–0.79) mmHg/ml/kg/min. Preliminary data from our laboratory suggests that the PaO_2 change point in preterm lambs (127 d gestation) with RDS is lower at 31 ± 0.7 mmHg (SpO_2 86 ± 10%) (figure 3) with a significantly higher corresponding PVR (median – 1.34 with IQR: 0.87–2.24) mmHg/ml/kg/min. These results and figure 3 suggest that PVR is higher in preterm lambs but HPV may be triggered at a lower PO_2 compared to term lambs indicating reduced sensitivity to oxygen. In all gestational age categories, hypoxemia below the change point caused HPV and normoxemia (SpO_2 in the low to mid-90s and PaO_2 50–70 mmHg) causes vasodilation but hyperoxemia (SpO_2 > 97% and PaO_2 > 70 mmHg)

does not result in further vasodilation (figure 3). A comparison of preductal SpO_2 in preterm lambs demonstrated low PVR with saturations in the 91–96% range (figure 3D).

Oxygen tension required to achieve low postnatal PVR in preterm lambs

In term lambs without lung disease ventilated with 21% oxygen for 2–6 hours, the median PVR is 0.45 mm Hg/ml/kg/min (IQR: 0.35–0.63) and the median PaO_2 is 56 mm Hg (IQR: 46–73). The PaO_2 in preterm lambs associated with this PVR value is 58 mm Hg (IQR: 45–94). These findings suggest that the pulmonary vasodilation to oxygen in preterm lambs at 127d gestation is similar to term lambs. (inset in figure 3). We speculate that more immature lambs and extremely preterm infants (22–26 weeks gestation) may have impaired pulmonary vasodilator response to oxygen. In addition, the high A-a gradient in extremely preterm neonates may necessitate higher inspired oxygen requirement to achieve PaO_2 levels similar to term infants breathing room air (figure 2).

Oxygen levels achieved during resuscitation of extremely preterm infants

Preductal saturation ranges have been generated in preterm infants with and without respiratory support in the delivery room[42, 43]. In preterm infants < 29 weeks gestation requiring positive pressure ventilation in the delivery room, initiation of resuscitation with 30% oxygen with titration to 67 ± 23% oxygen by 5 min achieved a mean SpO_2 of approximately 62%. An individual patient analysis of eight RCTs has shown that SpO_2 of <80% by 5 min was associated with lower heart rates and intraventricular hemorrhage (IVH)[44]. Furthermore, adjusting for confounding factors such as GA, birth weight and 5 min bradycardia, the risk of death was significantly higher with the time taken to achieve a SpO_2 of 80%[44].

The current AAP NRP recommends a target SpO_2 value of 80–85% by 5 min after birth[27]. From our studies in preterm lambs, a SpO_2 value of in the mid to high-80s and a PaO_2 of > 31 ± 0.7 mmHg is required to increase the PBF to facilitate successful transition at birth[45]. The impact of delayed cord clamping on oxygen saturations in preterm infants needs further evaluation. Variability in oxygen-hemoglobin dissociation curves in preterm based on the concentration of fetal hemoglobin leads to a wide range of PaO_2 for a given SpO_2[46]. A preductal SpO_2 of 80–85% at 5 min corresponds to a PaO_2 of 30 – 35 mm Hg, and SpO_2 of 85–90% by 10 min will correspond to a PaO_2 of 42 – 55 mm Hg[46].

Until further evidence is available, using oxygen to target preductal saturations in the delivery room may help provide adequate oxygenation and induce pulmonary vasodilation in a premature neonate. Failure to achieve such pulmonary vasodilation may potentially increase the risk for PHT.

Practice points:

- Targeting saturations of 80–85% by 5 min and 85–95% by 10 min after birth of premature infants is appropriate. Inability to achieve >80% SpO2 by 5 minutes is associated with poor outcomes.
- Oxygen saturations of 85–90% and arterial oxygenation of >31± 0.7 mmHg is required to decrease PVR and increase PBF in a preterm lambs.

Research directions:

- After decades of research, the optimal initial O_2 concentration required to initiate resuscitation in a preterm infant remains unknown
- Optimal saturations during delayed cord clamping and resuscitation with an intact umbilical cord needs further evaluation.

Saturation targets and supplemental oxygen management in acute or early PHT

Pulse oximetry has become an inevitable non-invasive tool to assess oxygenation in the NICU. The optimal SpO_2 target in the management of extremely preterm infants has been a subject of debate. There have been five randomized control trials comparing low (85–89%) vs. high (91–95%) SpO_2 targets in the NICU in managing preterm infants[47–52]. These studies are collectively known as the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) studies. A prospectively planned individual participant data analysis[53], demonstrated that low SpO_2 target was associated with a higher risk of mortality and necrotizing enterocolitis but lower risk of retinopathy of prematurity[53]. Pulmonary hypertension was not a prespecified outcome and was not assessed in these studies. Some experts have speculated if some of the deaths in the low SpO_2 target group could be secondary to BPD, PHT and respiratory failure[54].

Recently, a retrospective study from Canada demonstrated a 50% decrease in the cumulative incidence of PHTand 45% lower risk of persistent high PVR among preterm infants at 36 weeks corrected GA following a policy change to increase target SpO_2 from 88–92 to 90–95%[55]. In addition, PHT developed quicker in low SpO_2 group compared to the high group[55]. Similar decrease in the incidence of PHT and use of inhaled nitric oxide (iNO) among preterm infants was observed in a NICU in Atlanta following a change from an SpO_2 target from 85–94% to 90–95%[56].

The optimal saturation range in premature neonates to manage early PHT remains unclear. With the available evidence from NeOProM trials and animal data, it may be safer to aim for a target saturations in the low to mid-90s in preterm neonates with acute PHT[57]. Lung recruitment, rescue surfactant therapy, adequate ventilation, avoiding acidosis and maintaining appropriate systemic blood pressures play a vital role in maintaining oxygenation[2]. Translational/ animal model studies have shown that exposure to brief hyperoxia is harmful to the central nervous system and may impair pulmonary vasodilation to iNO[58, 59] and prolonged exposure to hyperoxia and iNO may promote to peroxynitrite formation and lead to lung injury[60, 61].

Practice points:

- In acute PHT, lung recruitment, rescue surfactant therapy, adequate ventilation, avoiding acidosis, maintaining appropriate systemic blood pressures and targeting saturations of low to mid 90s may be prudent pending further studies.

Research direction:

- Multicenter RCTs are needed to evaluate the appropriate oxygenation to prevent and mange acute PHT

BPD associated PHT and late PHT in preterm neonates

Northway and colleagues first described Bronchopulmonary Dysplasia (BPD) as lung injury in premature neonates because of positive pressure ventilation and oxygen exposure[62]. The new BPD is defined as O_2 requirement at 28 days after birth or the need for ventilation support and O_2 requirement at 36 weeks postmenstrual age[63]. It is further classified into mild, moderate, and severe based on the O_2 requirement and ventilator support[63]. Arjaans et al. in their meta-analysis report the prevalence of PHT as 2% (CI 0% – 8%) in the absence of BPD, 6% (CI 1% – 13%) for mild BPD, 12% (CI 4 – 24) for moderate BPD, and 39% (95% CI 29% – 49)% for severe BPD. Extremely premature neonates are at high risk of developing late or BPD associated PHT[64]. BPD associated PHT is often attributed to the pulmonary vascular disease affecting the right ventricle as a result of the extrauterine lung development leading to remodeled airway and pulmonary vasculature in a premature neonate[2]. The fact that late PHT also develops in neonates without BPD suggests that there exists mechanism beyond remodeled airways and capillaries that could contribute to the pathophysiology[7]. The American Heart Association (AHA) and American Thoracic Society (ATS) recommends obtaining screening echocardiogram to assess BPD associated PHT (Class I; Level of Evidence B).[2] Cardiac catheterization is recommended to assess disease severity, left ventricular function and evaluate the presence of pulmonary vein stenosis to plan therapy for BPD associated PHT (Class I; Level of Evidence B).

Postnatal factors inflencing oxygenation in BPD associated PHT

Various causes of hypoxemia in infants with BPD and PHT are shown in figure 4 and include right-to-left shunting of blood, lung hyperinflation and or atelectasis, hypercarbia pulmonary vascular disease, decreased alveolar and vascular growth and increasing systemic to pulmonary vascular collaterals[65]. In addition gastro-esophageal reflux and recurrent aspiration, upper airway disease such as malacia and stenosis, pulmonary edema and reactive airway disease can contribute to hypoxemia in BPD[65].

Saturation targets and supplemental oxygen management in late and BPD associated PHT

The NeOProM meta-analysis evaluated the outcomes of BPD in the high (91–95%) and low (85–89%) SpO_2 targets. The BPD rates in the low SpO_2 targets were significantly lower compared to the high SpO_2 targets (relative risk 0.81, CI 0.74 – 0.90, $p<0.001$). A low SpO_2 target strategy may help reduce ventilator and oxygen-associated injury. Indeed a change in policy favoring higher SpO_2 targets was associated with an increase in BPD among hospitals within the NICHD Neonatal Research Network[66]. However, as mentioned previously two recently published studies reported a decrease in the cumulative incidence of PHT with an increase in target SpO_2 range to 90–95%.

During cardiac catherization, a vasodilator response during acute vasoreactivity testing to oxygen and other pulmonary vasodialtors is associated with better prognosis among preterm infants with BPD and PHT[67]. Evaluation of older children (median age – 5 y) with BPD showed that reduction of PaO_2 from a baseline of 78.5 ± 4.9 to 46.9 ± 2.2 mmHg by reducing FiO_2 resulted in an increase in pulmonary arterial pressure from 34.1 ± 2.6 to 45.2 ± 4.4 mmHg. Maintaining PaO_2 > 55–60 mmHg or SpO_2 > 92% blunted hypoxic pulmonary vasoconstriction[68]. However, there was little further decrease in pulmonary arterial pressure

with higher levels of supplemental oxygen to achieve PaO_2 > 70 mmHg similar to data reported from lambs (figure 3)[69].

The recommendations by ATS and AHA for treating BPD associated PHT with supplemental O_2 is to target SpO_2 between 92–95% (Class IIa; Level of Evidence C)[2]. Based on the consensus and expert opinion, the target range was chosen to avoid episodic or sustained hypoxemia that could exacerbate BPD associated PHT[2]. Maintaining a narrow range of SpO_2 target may not be practically difficult in a NICU setting[70]. The European Paediatric pulmonary vascular disease network recommends maintaining systemic arterial O_2 saturation (SaO_2) of >93% for all premature neonates and >95% SaO_2 for proven BPD associated PHT[57]. We suggest using a broader range of SpO_2 targets in the low to mid-90s with alarm limits set at 90 and 97% for BPD associated PHT.

Oxygen saturation recommendations for discharge:

A recent survey of clinical practices in BPD associated PHT, majority of the neonatologists reported 90–92% as minimum (lower limit) SpO_2 target and 65% of the neonatologists considered BPD associated PHT as an indication for home oxygen therapy[71]. Among these 65% of the neonatologists, 69% were from the university hospital settings and 56% from the non-university hospitals (p=0.03). This survey highlights wide variations in the current practice among neonatologists to screen, diagnose and manage premature neonates with BPD associated PHT. It remains unclear if home oxygen is beneficial and optimal SpO_2 targets at home in BPD associated PHT. In the US, patients are discharged home on 100% oxygen at flows ranging from 1/8 to 2 LPM without any ability to titrate FiO_2 resulting in further challenges to targeting oxygenation.

Practice points:

- Based on available evidence, consensus guidelines and expert opinions, supplemental oxygen in late onset and BPD associated PHT could be managed by targeting saturations of low to mid 90s with alarm limits at 90 and 97%.
- In a survey, majority of the neonatologists consider BPD associated PHT as an absolute indication for home oxygen therapy

Research directions:

- Lower oxygen saturation targeting in NeOPrOM study meta-analysis is associated with a lower risk of BPD. However, the impact of oxygen saturation targeting on the incidence of PHT remains unknown.
- Home oxygen therapy and target saturations in BPD associated PHT needs further research.
- Randomized trial of different oxygen saturations in the NICU and after discharge in BPD with PHT with long term follow up studies with neurodevelopmental and pulmonary outcomes are needed.

Conclusion:

Acute-onset, late-onset, and BPD associated PHT can occur in preterm neonates and often present clinically with labile hypoxemia with echocardiographic signs of elevated PVR. Autopsy reveals histological findings of remodeled lung parenchyma/vasculature similar to PPHN in term infants. As of now, the available recommendations to manage supplemental oxygen in preterm PHT are limited by scientific evidence and rely more on guidelines based on data from preterm animal models, institutional policies, practice guidelines, and expert opinions. Managing preterm neonates diagnosed with PHT with supplemental oxygen targeting saturations in the low- to mid-90s as recommended by ATS and AHA, may be a reasonable approach. Further research to generate high-quality evidence form well-planned randomized trials is needed to guide supplemental oxygen therapy and optimal oxygen saturation targets in preterm neonates with PHT.

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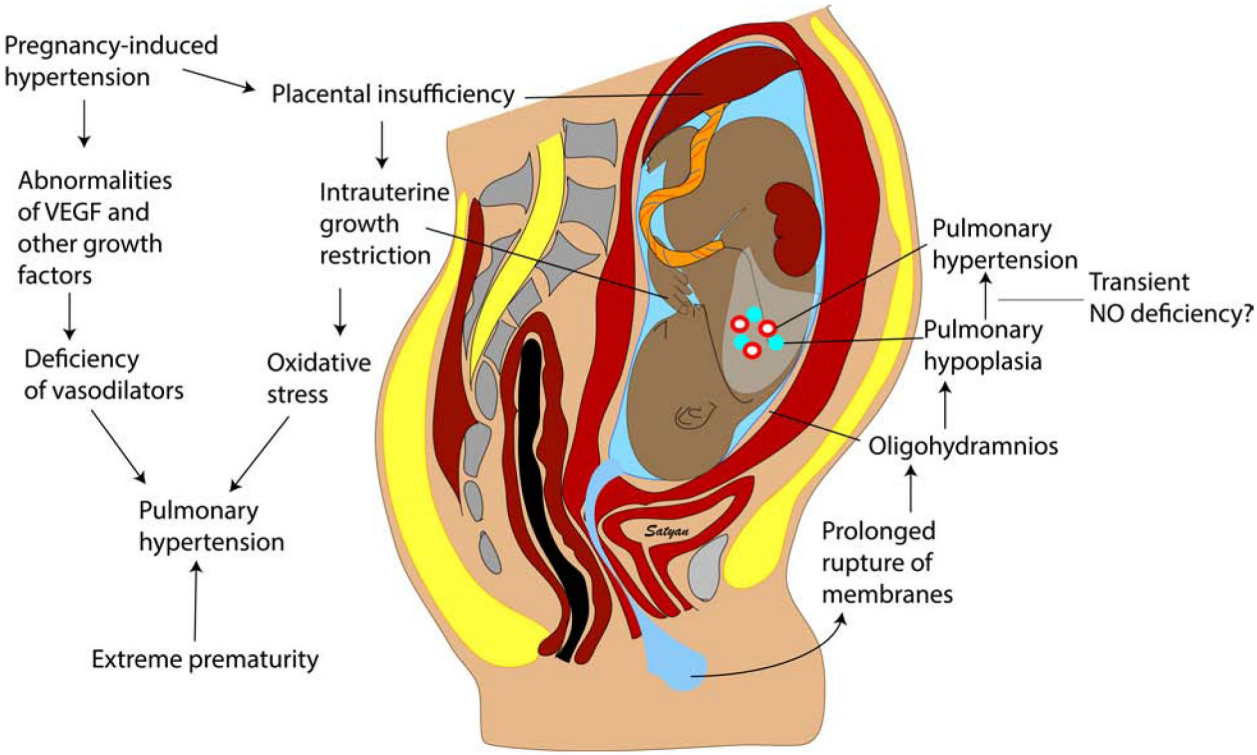

Figure 1:
Factors associated with preterm pulmonary hypertension

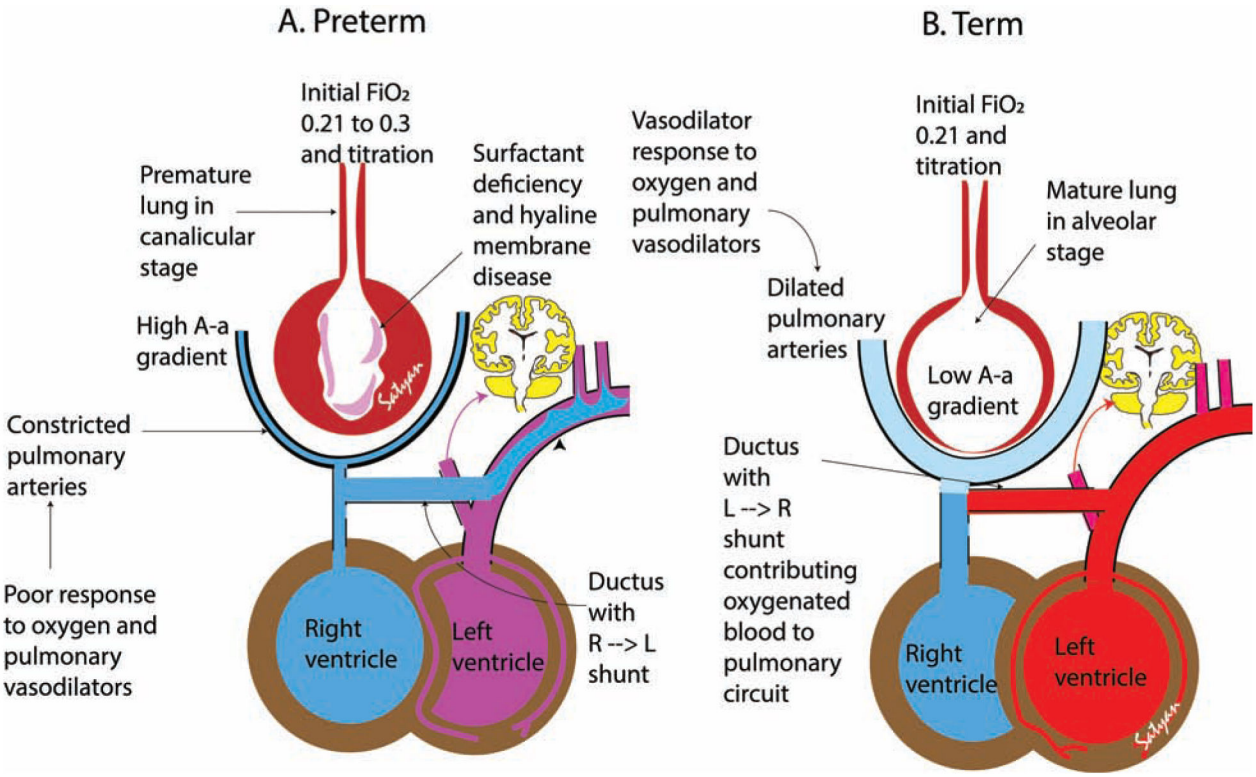

Figure 2:
Differences in pulmonary vascular transition during resuscitation in preterm compared to term neonates

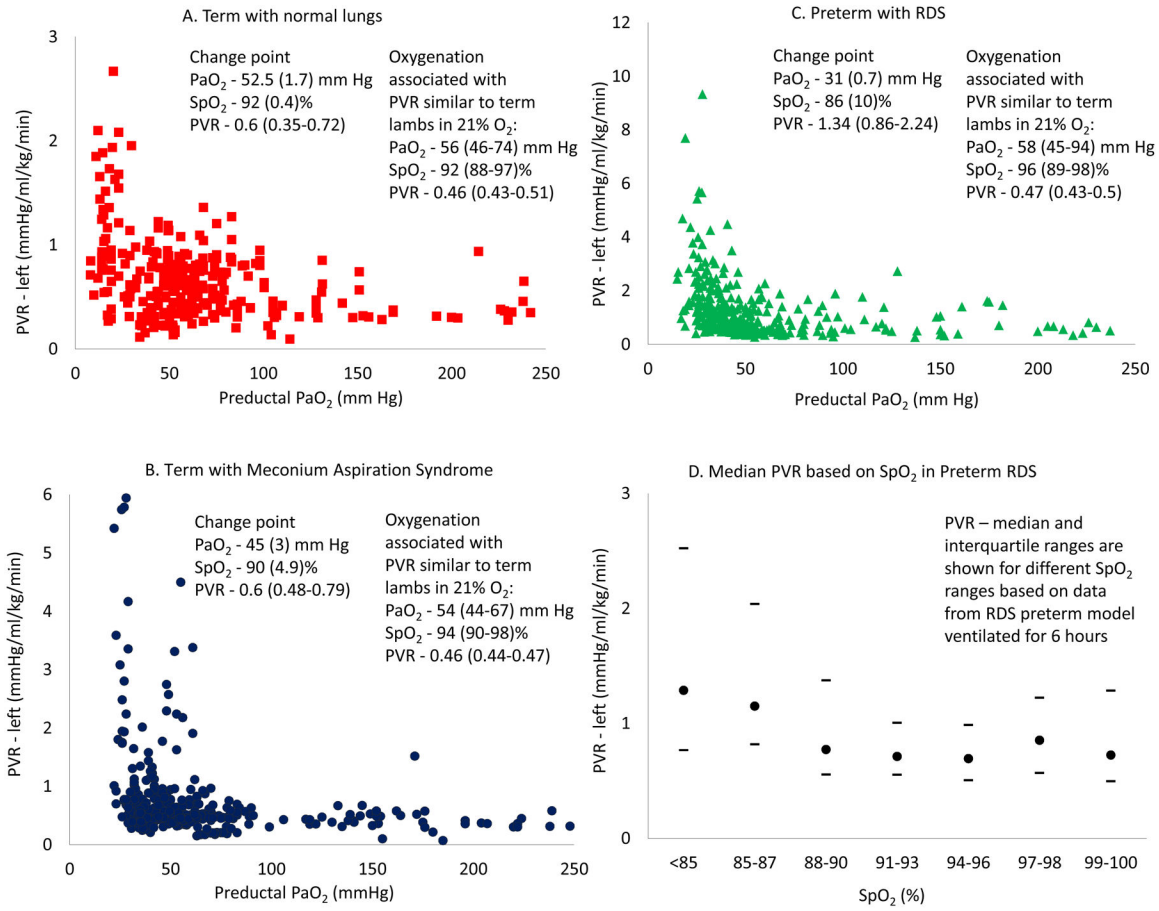

Figure 3:

Scatter plot of pulmonary vascular resistance (PVR) from left pulmonary artery and preductal PaO_2 from term lambs without lung disease (A), term lambs with asphyxia and meconium aspiration syndrome (B) and preterm lambs (127 d gestation, term ~ 150d) with respiratory distress syndrome (RDS – C). The change points or the hypoxic pulmonary vasoconstriction trigger-point (PaO_2 and corresponding SpO_2 and PVR) are shown in the inset. The second inset on the right compares the oxygenation status of each lung model at the level of PVR observed in term lambs without lung disease ventilated with 21% oxygen. Figure 3 D shows the median and the interquartile range of left PVR (y-axis) is plotted against different saturation ranges (x-axis).

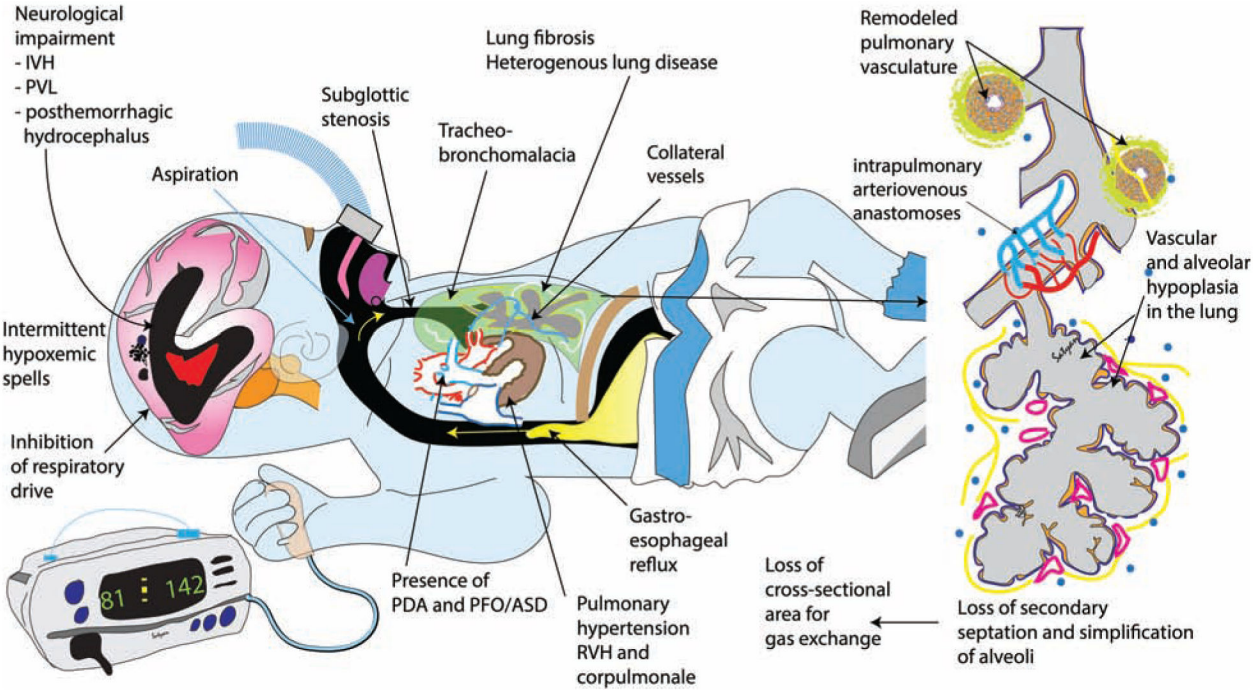

Figure 4:

Determinants of oxygenation and contributors to hypoxemia in Bronchopulmonary Dysplasia associated pulmonary hypertension.