Persistent Pulmonary Hypertension in the Modern NICU: Integrating Evidence-Based Therapies into Practice

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) happens when the normal drop in pulmonary vascular resistance (PVR) after birth doesn't occur properly, leading to a failure in circulatory transition. In the womb, the fetus naturally exists in a state of high pulmonary pressure. Oxygenated blood is delivered via the placenta through the umbilical vein. Once the baby starts breathing after birth, PVR is supposed to fall sharply, while systemic vascular resistance (SVR) rises due to placental separation. This shift increases pulmonary blood flow and gradually reverses the fetal shunting at the foramen ovale and ductus arteriosus. When this transition doesn′t happen as expected, PPHN can develop. Clinically, PPHN presents with varying levels of hypoxemic respiratory failure. Outcomes for these infants have improved significantly over the years, largely thanks to advances in supportive care—like gentle ventilation strategies, surfactant therapy, and the introduction of inhaled nitric oxide (iNO). Still, PPHN remains linked to substantial risks, including both mortality and long-term complications in survivors. Emerging therapies targeting various molecular pathways within pulmonary vascular smooth muscle cells are currently under development or in early testing. Continued research into these targeted treatments holds promise for further reducing the burden of disease and improving outcomes in newborns with PPHN.

Keywords: *Persistent Pulmonary Hypertension, Evidence-Based Therapies*

1. Introduction

During fetal life, pulmonary vascular resistance (PVR) remains high, while pulmonary blood flow (Qp) is relatively low [1]. After birth, as part of the normal circulatory transition, PVR drops and pulmonary blood flow increases significantly [2]. However, when this decrease in PVR is delayed or fails to occur properly, it results in persistent pulmonary hypertension of the newborn (PPHN)—a condition characterized by failed cardiovascular adaptation to extrauterine life [3].

PPHN remains a significant neonatal concern, often associated with high mortality and long-term morbidity in survivors. The condition affects approximately 1.8 to 2 per 1,000 live births [4, 5], and its incidence increases to around 2% in premature infants who develop respiratory distress

syndrome (RDS).

2. Pathophysiology of Persistent Pulmonary Hypertension

In the fetal state, the pulmonary circulation is naturally constricted—a condition referred to as physiological pulmonary hypertension [6]. Oxygen-rich blood from the placenta travels through the umbilical vein, reaching the fetal heart, where it is directed from the right atrium to the left atrium via the foramen ovale. This bypasses the fluid-filled lungs, which have high resistance and low blood flow.

The placenta, serving as the organ of gas exchange during gestation, receives about 30–45% of the combined cardiac output [7], whereas the lungs receive only 8–21% through the pulmonary arteries [7, 8]. Due to the high PVR, blood is preferentially shunted from the pulmonary artery into the descending aorta via the ductus arteriosus, maintaining right-to-left flow.

Several factors maintain this elevated PVR in the fetus. Physically, fluid-filled alveoli compress the pulmonary vessels, and the lack of lung expansion limits vascular development. Structurally, endothelial cells within the pulmonary arteries are more cuboidal and narrow the vessel lumen. Biochemically, the low oxygen tension in both alveoli and arterioles sustains hypoxic pulmonary vasoconstriction.

Additionally, various humoral factors contribute to high PVR. These include vasoconstrictors like endothelin-1, leukotrienes, and thromboxane, along with a relative deficiency of vasodilators such as nitric oxide (NO) and prostacyclin (PGI_2) [2, 9]. In contrast, the placental circulation has a low resistance, supported by high levels of estrogen, prostaglandins, and NO produced by the placenta.

At birth, with the initiation of breathing, alveolar oxygen levels rise and ventilation begins. This triggers a rapid and substantial fall in PVR, while systemic vascular resistance (SVR) increases due to placental separation. Pulmonary vasodilation is mediated by endothelial-derived NO via the cGMP pathway and by PGI_2 acting through the cAMP pathway. These changes result in an eight-fold rise in pulmonary blood flow, with a subsequent drop and eventual reversal of fetal shunting through the foramen ovale and ductus arteriosus.

When this critical pulmonary transition fails, PPHN develops, often presenting clinically as hypoxic respiratory failure (HRF).

3. Etiology of Persistent Pulmonary Hypertension of the Newborn

Based on etiology, PPHN can be categorized into seven broad groups (Figure 1):

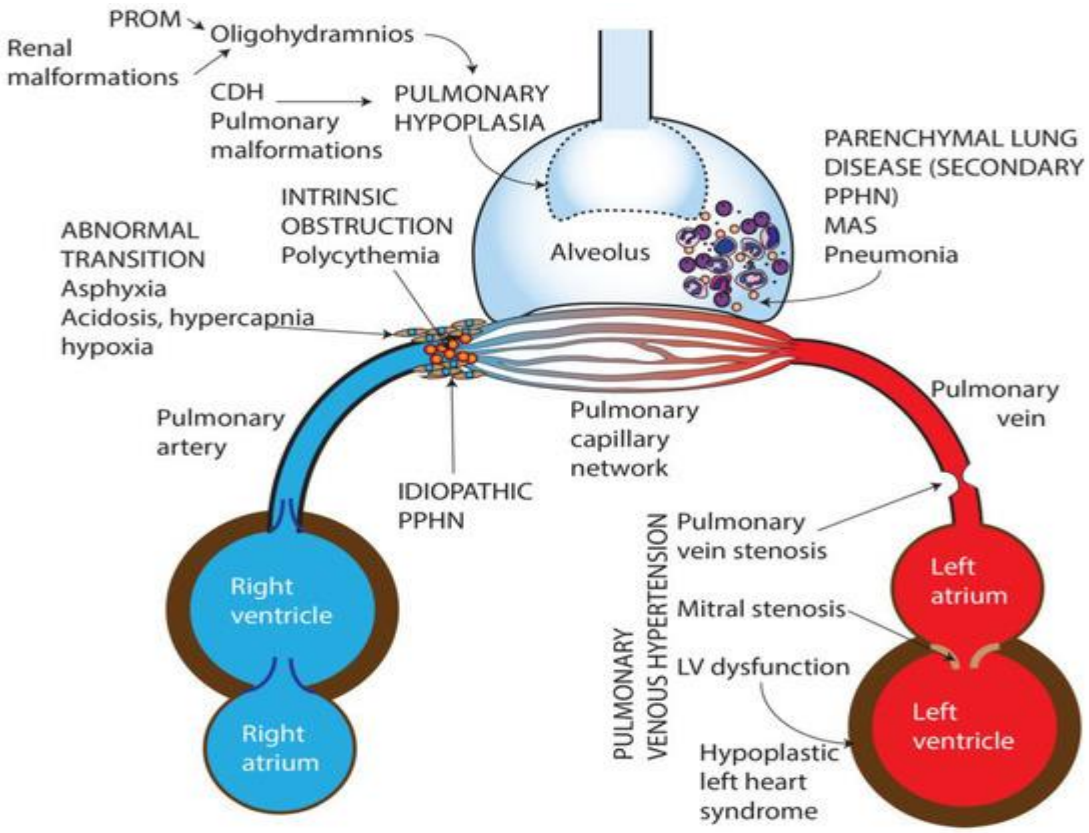

Figure 1. Causes of persistent pulmonary Hypertension in the newborn. PROM—Premature rupture of membranes, CDH—Congenital diaphragmatic hernia, MAS—Meconium aspiration syndrome, PPHN—Persistent pulmonary hypertension of the newborn, LV—Left ventricle. Copyright Satyan Lakshminrusimha.

3. Etiologies of Persistent Pulmonary Hypertension of the Newborn

PPHN can develop through several distinct mechanisms, often classified based on the underlying pathophysiology. These include:

- **Idiopathic PPHN** – where no lung disease is present, and pulmonary blood flow (Qp) is reduced due to vascular remodeling and increased vasoconstriction.
- **Abnormal circulatory transition at birth** – such as in cases of perinatal asphyxia, respiratory distress syndrome (RDS), or transient tachypnea of the newborn (TTN), which impair pulmonary vasodilation.
- **Parenchymal lung diseases**, often termed *secondary PPHN*, like meconium aspiration syndrome (MAS) or pneumonia.
- **Abnormal lung development** – such as pulmonary hypoplasia from congenital diaphragmatic hernia (CDH), oligohydramnios due to renal anomalies, or thoracic malformations.
- **Intravascular obstruction** due to increased blood viscosity, for instance in polycythemia.
- **Pulmonary hypertension in preterm infants** during the early phase of RDS [10].
- **Pulmonary venous hypertension** related to structural heart disease or left ventricular dysfunction [11].

3.1. Idiopathic PPHN

This form occurs when pulmonary vascular relaxation fails to occur after birth in infants with structurally normal lungs. Histology typically shows excessive proliferation of smooth muscle in the pulmonary vessels, extending into the smaller intra-acinar arteries. One known mechanism involves premature closure of the ductus arteriosus in utero, forcing blood through the high-resistance pulmonary circulation, leading to shear stress and vascular remodeling.

Maternal use of NSAIDs [12] or selective serotonin reuptake inhibitors (SSRIs) [13] during pregnancy has been linked to idiopathic PPHN, though newer studies show conflicting evidence [14]. Reduced nitric oxide (NO) production, as seen in conditions like urea cycle disorders [15], along with decreased NO availability and impaired response to vasodilators, may also contribute. On chest X-ray, this form has been referred to as “black lung PPHN” due to the absence of lung opacities and visible reduction in pulmonary vascularity.

3.2. Abnormal Pulmonary Transition

When the circulatory transition fails to progress normally at birth—commonly due to perinatal asphyxia—it may result in hypoxia, hypercapnia, and acidosis. These physiological changes trigger pulmonary vasoconstriction and promote right-to-left shunting. Inadequate alveolar recruitment and lung inflation physically compress pulmonary vessels, worsening the condition. Effective lung recruitment to restore functional residual capacity (FRC), combined with supportive ventilation, often reverses this state. Notably, preterm infants with severe RDS or those delivered by cesarean section without labor tend to experience a slower postnatal decline in PVR compared to term infants delivered vaginally.

3.3. Parenchymal Lung Disease

Conditions like sepsis, pneumonia, and MAS lead to significant lung inflammation and injury. This often results in surfactant dysfunction, chemical pneumonitis, and the release of inflammatory mediators that promote vasoconstriction—such as endothelin and thromboxane. The resulting ventilation–perfusion mismatch leads to hypoxemia, which exacerbates pulmonary vasoconstriction. Moreover, systemic vasodilation in sepsis, combined with high PVR, promotes persistent right-to-left shunting across the ductus arteriosus and foramen ovale.

3.4. Pulmonary Hypoplasia

Pulmonary underdevelopment can arise from conditions like CDH, thoracic abnormalities, or prolonged oligohydramnios caused by renal dysplasia or premature rupture of membranes. In these settings, both lung tissue and the vascular bed are underdeveloped. CDH is often complicated by abnormal cardiac development, especially left-sided heart dysfunction, contributing to pulmonary venous hypertension and worsening clinical severity [16, 17].

3.5. Prematurity

Extremely premature infants are at increased risk of pulmonary hypertension and hypoxic respiratory failure in the first days after birth. During the canalicular stage of lung development, the pulmonary vasculature is sparse, reducing the vascular bed's cross-sectional area. In addition, the immature vessels are less responsive to oxygen-induced vasodilation. These infants often

respond poorly to inhaled NO [18]. However, a subset of preterm neonates, particularly those with prolonged rupture of membranes and oligohydramnios, may show PPHN physiology similar to term infants and have a better response to iNO [19].

3.6. Pulmonary Venous Hypertension

Pulmonary venous hypertension can mimic pulmonary arterial hypertension in its clinical presentation, often presenting with hypoxemic respiratory failure [20]. On chest X-ray, it is characterized by increased vascular markings and pulmonary edema. The pulmonary blood flow reduction in these cases is secondary to elevated left atrial pressure from poor venous drainage (Figure 1).

This form may result from left-sided obstructive congenital heart defects such as mitral atresia, hypoplastic left heart syndrome, critical aortic coarctation, or obstructed total anomalous pulmonary venous return (TAPVR) [21]. Pulmonary vein stenosis and left ventricular dysfunction—whether due to asphyxia, infection, or CDH—may also contribute.

Echocardiography is essential for diagnosis, particularly in evaluating the direction of blood flow through fetal shunts. Importantly, inhaled NO is contraindicated in these infants as it can worsen pulmonary edema and impair oxygenation further [22].

4. Clinical Presentation

PPHN typically presents as **hypoxemic respiratory failure (HRF)**, with symptoms ranging from mild to severe depending on the extent of pulmonary hypertension and shunting. For a comprehensive list of differential diagnoses for neonatal hypoxemia, refer to **Table 1**.

One of the hallmark signs of PPHN is **labile oxygenation**, where oxygen saturation levels fluctuate widely in response to even minor stimulation. These changes are due to episodic increases in pulmonary vascular resistance (PVR), which alter pulmonary blood flow and enhance right-to-left shunting through fetal channels.

Differential cyanosis—where oxygen saturation differs between the upper and lower limbs—is a classic clinical clue. This is usually assessed by comparing **pre-ductal (right hand)** and **post-ductal (either foot)** oxygen saturation. A pre-to-post ductal saturation gradient of more than 10% is frequently observed in affected infants [23].

On physical exam, findings may be subtle. The most consistent signs are a **loud second heart sound**, due to elevated pulmonary pressures, and occasionally a **systolic murmur** of **tricuspid regurgitation**, caused by right ventricular strain.

A **chest X-ray** can be useful—not necessarily to diagnose PPHN itself, but to help identify any underlying lung pathology and monitor response to ventilator adjustments.

Table 1. Differential diagnosis of hypoxemia in newborn infants.

	Lung Disease without PPHN	Cyanotic Congenital Heart Disease	PPHN
History	Fetal distress, PROM, chorioamnionitis	Antenatal diagnosis	Often negative other than in secondary PPHN
Respiratory distress	Present	Usually absent	Often present
Oxygen saturation on pulse oximetry	Improves with supplemental oxygen	Fixed low saturations Minimal response to supplemental oxygen	Labile saturations. Differential cyanosis
Hyperoxia test *	PaO_2 often > 150 mm Hg	PaO_2 often < 100 mm Hg	PaO_2 often > 100 mm Hg
$PaCO_2$	Elevated	Normal/low	Often elevated (except in idiopathic PPHN)
Hyperoxia-Hyperventilation *	PaO_2 > 150 mm Hg	PaO_2 often < 100 mm Hg	PaO_2 improves with hyperventilation
Chest X ray	Abnormal	Abnormalities of cardiac silhouette and pulmonary vascularity	Decreased vascularity in idiopathic PPHN
Echocardiogram	Normal	Structural cardiac abnormalities	Structurally normal heart (see text for characteristic echo findings of PPHN)

* Both hyperoxia and hyperoxia hyperventilation tests are not used routinely in clinical practice due to increased availability of echocardiography in most institutions. These tests expose the infant to hyperoxia and hypocarbia with the potential to cause oxidative stress and decreased cerebral perfusion respectively.

4.1. Echocardiography

Echocardiography plays a central role in diagnosing and managing PPHN. Key findings include right ventricular hypertrophy, leftward deviation of the interventricular septum, and tricuspid regurgitation (TR). In addition, right-to-left or bidirectional shunting at the patent foramen ovale (PFO) and patent ductus arteriosus (PDA) are classic markers of the condition (see Figure 2).

Right ventricular systolic pressure (RVSP) can be estimated using the **modified Bernoulli equation**:

RVSP = $4v^2$ + right atrial pressure, where *v* is the peak velocity (in m/s) of the TR jet.

Serial echocardiograms are valuable not just for diagnosis but also for **tracking pulmonary arterial pressures**, **assessing heart function**, and **monitoring flow direction across the ductus and foramen ovale**. They are also critical for evaluating how well the infant is responding to therapeutic interventions [24].

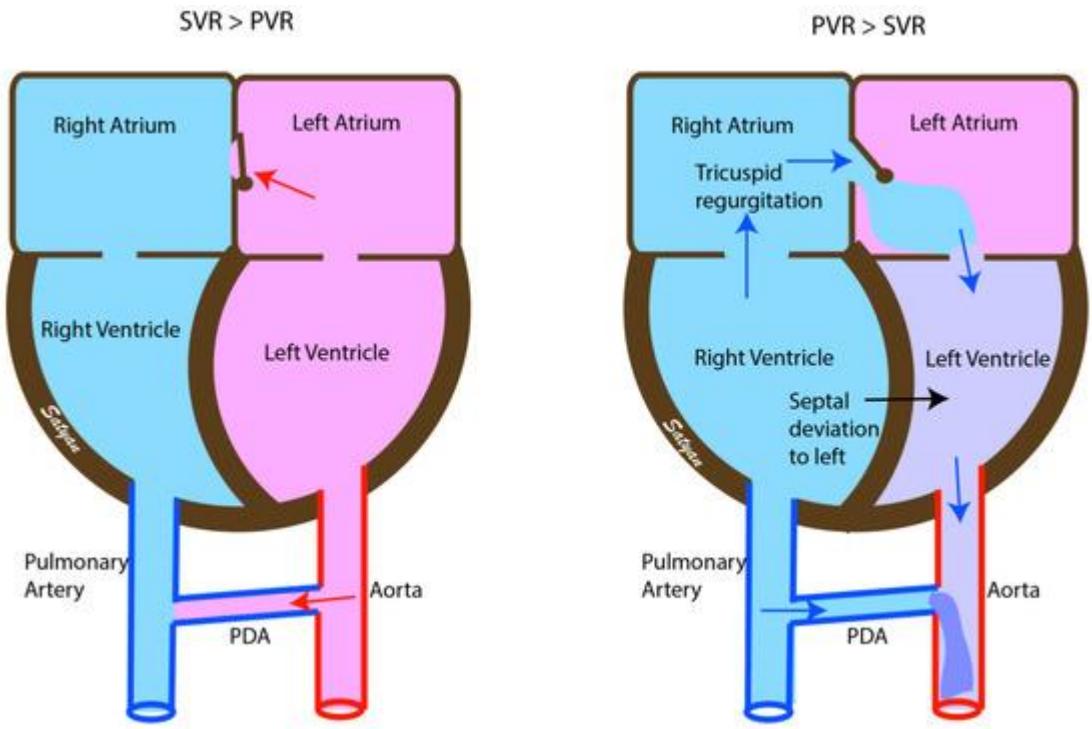

Figure 2. Echocardiographic findings in normal infants (left) and in PPHN (right). Soon after birth the pressures within the left-sided chambers of the heart are higher than in the right and the fetal shunts are reversed. The interatrial shunt and the shunt across the patent ductus arteriosus (PDA) is left to right. In infants with PPHN the pressures remain elevated in the right atrium and ventricle with right to left shunt at the atrial level and at the PDA causing desaturation (due to interatrial shunt) and differential cyanosis (due to PDA). There is right ventricular hypertrophy with bulging of the interventricular septum to the left and tricuspid regurgitation. SVR—Systemic vascular resistance, PVR—Pulmonary vascular resistance. Copyright Satyan Lakshminrusimha..

4.2. Interpretation of Shunt Direction in PPHN

Evaluating the direction of blood flow across the patent ductus arteriosus (PDA) and patent foramen ovale (PFO) provides essential diagnostic and therapeutic insights in neonates with hypoxemic respiratory failure (HRF) [25]. A left-to-right shunt across both the PDA and PFO typically indicates that pulmonary hypertension is not the primary pathology. Instead, this pattern suggests intrapulmonary shunting, often secondary to parenchymal lung disease. Management in these cases should aim to optimize lung recruitment through strategies such as increased positive end-expiratory pressure (PEEP), higher mean airway pressures, and administration of surfactant when appropriate [25].

In contrast, a right-to-left shunt at both the PDA and PFO is a classic finding in persistent pulmonary hypertension of the newborn (PPHN), reflecting elevated pulmonary vascular resistance (PVR) and extrapulmonary shunting. After ensuring optimal lung inflation, these infants are often responsive to pulmonary vasodilator therapy, with inhaled nitric oxide (iNO) being the first-line treatment [25].

A mixed shunting pattern—right-to-left at the PDA and left-to-right at the PFO—usually reflects pulmonary hypertension complicated by left ventricular dysfunction. This scenario may be seen in infants with congenital diaphragmatic hernia (CDH), perinatal asphyxia, or sepsis. In such cases, isolated use of pulmonary vasodilators may increase pulmonary venous return and exacerbate pulmonary edema, worsening oxygenation. A combined therapeutic approach using both vasodilators and inotropes, such as milrinone, is often more beneficial, as it supports left ventricular function while reducing PVR [25]. This shunt pattern may also be present in structural heart diseases, including pulmonary vein stenosis and ductal-dependent systemic circulation lesions such as hypoplastic left heart syndrome, mitral atresia, critical coarctation of the aorta, and severe aortic stenosis [25].

Finally, a left-to-right shunt at the PDA with a right-to-left shunt at the PFO may be indicative of cyanotic congenital heart disease with ductal-dependent pulmonary blood flow. This pattern is often seen in defects such as tricuspid atresia, critical pulmonary stenosis, or pulmonary atresia. It is essential to exclude structural cardiac anomalies via echocardiography before initiating pulmonary vasodilator therapy in such cases, as inappropriate treatment could worsen clinical deterioration [25].

5. Assessing Severity of HRF and Monitoring Response to Therapy

Several indices are used to assess the severity of hypoxemic respiratory failure (HRF) and evaluate response to treatment in infants with PPHN. These include both invasive and noninvasive measures of oxygenation.

5.1. Oxygenation Index (OI)

The Oxygenation Index (OI) is a widely accepted tool in neonatal intensive care settings. It is calculated as: **$OI = (FiO_2 \times \text{Mean Airway Pressure} \times 100) / PaO_2$**

This index allows categorization of HRF severity as follows:

- Mild: OI ≤ 15
- Moderate: OI 15–25
- Severe: OI 25–40
- Very Severe: OI > 40 [25]

5.2. Alveolar–Arterial Oxygen Gradient (A–a Gradient or $A–aDO_2$)

The A–a gradient quantifies the difference between the alveolar and arterial partial pressures of oxygen, offering a measure of gas exchange efficiency. It is calculated using the following formula: **$A–aDO_2 = [FiO_2 \times (Pb – PH_2O) – (PaCO_2 / R)] – PaO_2$**, where Pb is barometric pressure, PH_2O is water vapor pressure, and R is the respiratory quotient (typically ≈1.0 in infants receiving intravenous fluids and ≈0.8 with enteral feeding). In healthy neonates, the normal A–a gradient ranges between 4–20 mmHg, but in severe HRF, it may exceed 600 mmHg [25]. A convenient online calculator for this parameter is available at: http://perinatology.com/calculators/A-a%20gradient.htm.

5.3. PaO_2/FiO_2 Ratio (P/F Ratio)

The PaO_2/FiO_2 ratio (P/F ratio) is another indicator of oxygenation status and is calculated as: **$P/F\ Ratio = PaO_2 / FiO_2$**

Severity of HRF using this ratio is classified as:

- Mild: >200 to ≤300
- Moderate: >100 to ≤200

- Severe: ≤100 mmHg [25]

For both the OI and P/F ratio, preductal blood gas analysis is preferred because it better reflects oxygen delivery to vital organs such as the brain and heart. Postductal blood gases, often drawn from umbilical arterial lines, may underestimate oxygenation, leading to higher OI and lower P/F ratio readings [25].

5.4. Oxygen Saturation Index (OSI)

In clinical scenarios where arterial blood gases are not available, the Oxygen Saturation Index (OSI) offers a noninvasive alternative. It is calculated as:
OSI = (Mean Airway Pressure × FiO_2 × 100) / Preductal SpO_2
OSI has been found to correlate well with OI in neonates with HRF. A practical approximation used in clinical practice is:
OI ≈ 2 × OSI [26].

6. Management

The primary objectives in managing **persistent pulmonary hypertension of the newborn (PPHN)** are to ensure adequate lung recruitment, promote **pulmonary vasodilation**, improve oxygenation, and maintain sufficient tissue oxygen delivery—all while minimizing **oxidative stress** and the potential damage caused by free radicals.

6.1. Supportive Therapies

Basic supportive measures are essential in stabilizing infants with PPHN. It's important to maintain normothermia, correct blood glucose and calcium levels, and ensure adequate sedation and analgesia. These measures help reduce stress and oxygen demand, supporting more stable hemodynamics and respiratory function.

6.2. Lung Recruitment

One of the most common reasons for poor response to therapy in neonates with hypoxemic respiratory failure is incomplete lung recruitment. Proper use of positive end-expiratory pressure (PEEP) helps expand the lungs to functional residual capacity (FRC)—typically reflected as expansion of about 8–9 ribs on an anteroposterior chest X-ray.
Both underinflation and overinflation can worsen PVR. Atelectasis promotes intrapulmonary right-to-left shunting, leading to worsening hypoxia and hypercapnia. Conversely, overinflation may reduce venous return to the heart, causing systemic hypotension and impairing cardiac output. Hence, careful ventilation strategies that balance oxygenation and lung inflation are key.

6.3. Oxygenation

Oxygen acts as a potent pulmonary vasodilator, while hypoxia is a known trigger of vasoconstriction. Supplemental oxygen should be titrated to achieve normoxia, typically targeting a PaO_2 between 50–80 mmHg [27].
Hyperoxia (PaO_2 >100 mmHg) has not been shown to further enhance pulmonary vasodilation [28, 29]. Instead, it increases the production of oxygen free radicals, which can heighten pulmonary arterial tone and reduce responsiveness to therapies like inhaled nitric oxide (iNO) [30, 31].
Although there's no universally agreed-upon oxygen saturation target for PPHN, maintaining preductal SpO_2 between 92% and 97% strikes a balance—minimizing hypoxia while reducing

oxidative stress [32, 33]. Oxygen delivery should be assessed frequently using pulse oximetry and arterial blood gases, especially to avoid acidosis. In certain complex cases, near-infrared spectroscopy (NIRS) may offer additional insight into regional oxygen delivery, especially in infants with hypoxic-ischemic encephalopathy, although it is not standard in routine PPHN management.

6.4. Surfactant Replacement Therapy

In conditions like meconium aspiration syndrome (MAS), pneumonia, or sepsis, the pulmonary surfactant is often inactivated, contributing to V/Q mismatch and hypoxemia. Surfactant replacement therapy can significantly improve oxygenation by restoring ventilation–perfusion matching and reducing intrapulmonary shunting.

In neonates with underlying parenchymal lung disease, giving surfactant before initiating iNO has been shown to improve outcomes and reduce the likelihood of needing extracorporeal membrane oxygenation (ECMO) [34].

6.5. Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide is the only pulmonary vasodilator currently FDA-approved for treating PPHN in neonates. NO is naturally produced by endothelial cells and mediates vasodilation by increasing cyclic guanosine monophosphate (cGMP) within pulmonary smooth muscle cells (see Figure 3) [35].

When delivered via inhalation, NO diffuses from the alveoli into the adjacent pulmonary vessels, causing localized vasodilation. Since NO is rapidly inactivated by hemoglobin in the bloodstream, its effects remain limited to the lungs, with minimal systemic vasodilation.

Importantly, iNO preferentially dilates vessels near well-ventilated alveoli, reducing intrapulmonary right-to-left shunting and improving ventilation–perfusion (V/Q) matching—a phenomenon often referred to as its microselective effect.

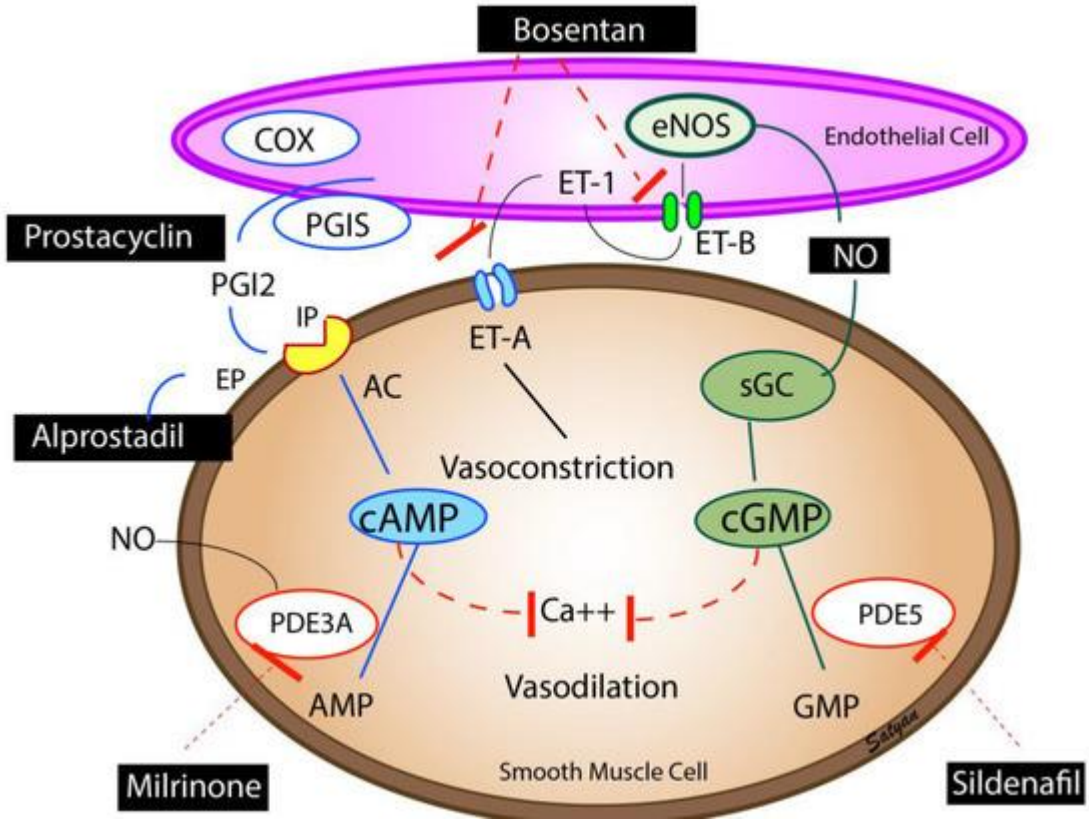

Figure 3. Pulmonary vasodilators—Endothelium-derived vasodilators: prostacyclin (PGI2), nitric oxide (NO), and vasoconstrictor (endothelin, ET-1). The enzymes, cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the synthesis of prostacyclin. Prostacyclin through (PGI2 receptor (IP) stimulates adenylate cyclase (AC) to produce cAMP. cAMP is broken down by phosphodiesterase 3A (PDE3A) in the smooth muscle cell. Milrinone inhibits PDE 3A and increases cAMP levels in pulmonary arterial smooth muscle cells and cardiac myocytes resulting in vasodilation and inotropy. Endothelin is a powerful vasoconstrictor and acts on ET-A receptors in the smooth muscle cell and increases ionic calcium concentration. A second endothelin receptor (ET-B) on the endothelial cell stimulates NO release and vasodilation. Endothelial nitric oxide synthase (eNOS) catalyzes the production of NO which diffuses from the endothelium to the smooth muscle cell and stimulates soluble guanylate cyclase (sGC) enzyme to produce cyclic guanosine monophosphate (cGMP). cGMP is broken down by the PDE5 enzyme in the smooth muscle cell. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells. cAMP and cGMP reduce cytosolic ionic calcium concentrations and induce smooth muscle relaxation and pulmonary vasodilation. NO is a free radical and avidly combines with superoxide anions to form a toxic vasoconstrictor, peroxynitrite. The bioavailability of NO in a tissue is determined by the local concentration of superoxide anions. Hyperoxic ventilation can increase the risk of formation of superoxide anions in the pulmonary arterial smooth muscle cells and limit the bioavailability of NO. Copyright Satyan Lakshminrusimha.

Inhaled nitric oxide (iNO) is typically initiated when the oxygenation index (OI) reaches between 15 and 25, indicating moderate hypoxemic respiratory failure. Evidence suggests that delaying the start of pulmonary vasodilator therapy may worsen outcomes in these infants by allowing progression of hypoxia-related injury.

The standard starting dose of iNO is 20 parts per million (ppm). Increasing the dose beyond this does not result in greater vasodilatory benefit and may raise the risk of adverse effects.

A positive clinical response to iNO is generally defined as an improvement in PaO_2 by at least 20 mmHg after treatment initiation. If an infant does not show improvement despite optimized lung recruitment, appropriate ventilation, and hemodynamic support, iNO should be discontinued. Prolonged use without benefit may lead to downregulation of the endogenous NO pathway [36] and increase the risk of oxidative injury through formation of peroxynitrite, a reactive nitrogen species [32].

Once oxygenation improves, weaning should begin. The iNO dose is typically reduced in steps of 5 ppm until a level of 5 ppm is reached, after which smaller decrements of 1 ppm are used. This gradual approach minimizes the risk of rebound pulmonary hypertension (see weaning protocol in Figure 4) [37].

Routine monitoring of methemoglobin levels and nitrogen dioxide (NO_2) concentrations is recommended at the start of iNO therapy and daily thereafter, as both can cause toxicity if elevated.

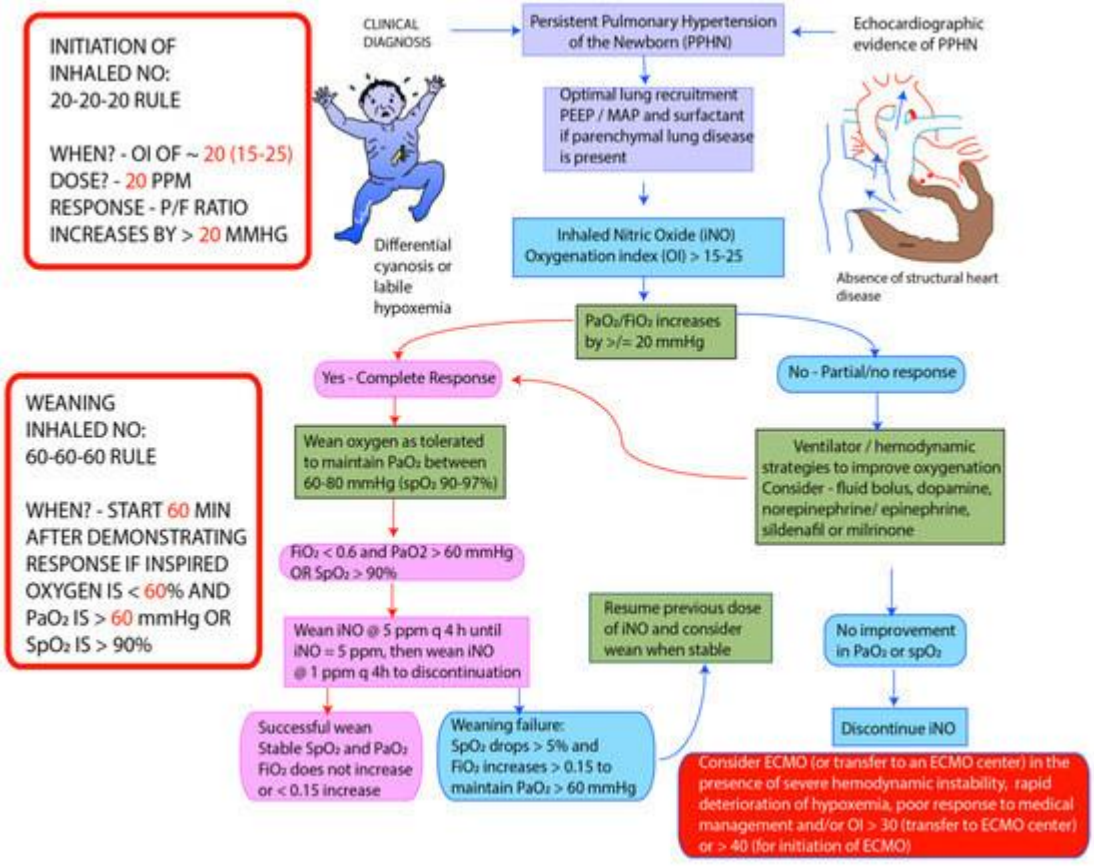

Figure 4. Guidelines for initiation and weaning iNO in PPHN/hypoxic respiratory failure (HRF) in Neonatal Intensive Care Unit (NICU) (adapted from the protocol at Women & Children's Hospital of Buffalo). The recommended starting dose of iNO is 20 parts per million (ppm). Improvement in $PaO_2 \geq 20$ mm Hg or hemoglobin saturation by pulse oximetry ≥ 5% is considered complete response. In patients who fail to respond iNO, measures needed to optimize of lung recruitment and hemodynamics need to be undertaken. iNO should be discontinued if there no response. In responders wean FiO_2 initially while maintaining PaO_2 between 60 and 80 mm Hg. Once PaO_2 is stable and FiO_2 is below 0.6, start weaning iNO by 5 ppm every 4 h till 5 ppm. Below 5 ppm wean iNO by 1 ppm every 4 h. During weaning >5% drop in pulse oximetry or sustained increase in $FiO_2 > 0.15$ to maintain $PaO_2 > 60$ mm Hg is considered weaning failure, and previous dose of iNO should be resumed. Weaning should be resumed once stable. Monitor methemoglobin levels at baseline, 2 and 8 h following initiation and every 48 h thereafter [37]. PEEP—Positive End Expiratory Pressure, MAP—Mean Airway Pressure, ECMO—Extracorporeal Membrane Oxygenation. Copyright Satyan Lakshminrusimha.

6.6. Prostaglandins

Prostacyclins are a cornerstone in the treatment of pulmonary arterial hypertension (PAH) in adults; however, their role in neonates with persistent pulmonary hypertension of the newborn (PPHN) remains experimental. Current evidence supporting their use is limited to small case series. Prostacyclins act by stimulating adenylate cyclase, thereby increasing intracellular cyclic adenosine monophosphate (cAMP) in vascular smooth muscle cells, leading to pulmonary vasodilation [38]. While intravenous prostacyclins can decrease pulmonary vascular resistance (PVR), they may also induce systemic hypotension and exacerbate ventilation-perfusion (V/Q) mismatch. In contrast, inhaled prostacyclin (PGI_2) administered via nebulization has shown potential benefits, particularly in infants unresponsive to inhaled nitric oxide (iNO) [39].

6.7. Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) enzymes regulate the degradation of intracellular cyclic mononucleotides, including cAMP and cGMP, which are pivotal in modulating vascular tone within the pulmonary circulation. Two PDE inhibitors utilized in neonatal PPHN are milrinone, a PDE3 inhibitor, and sildenafil, a PDE5 inhibitor. Milrinone increases cAMP levels in both vascular smooth muscle and cardiac myocytes, facilitating vasodilation and augmenting myocardial contractility [38]. The recommended regimen involves a loading dose of 50 µg/kg over 30 minutes, followed by a continuous infusion starting at 0.33 µg/kg/min, titrated up to 1 µg/kg/min with vigilant blood pressure monitoring due to the risk of systemic hypotension.

Sildenafil functions by inhibiting PDE5, thus reducing cGMP degradation and enhancing pulmonary vasodilation [40]. It is effective both as monotherapy and in conjunction with iNO, and is especially valuable in preventing rebound pulmonary hypertension during weaning from iNO. Hyperoxia has been shown to upregulate PDE5 expression, which may further support the role of PDE5 inhibitors in oxygen-exposed neonates [41]. Intravenous sildenafil dosing includes a loading dose of 0.42 mg/kg over 3 hours, followed by a maintenance infusion at 0.07 mg/kg/hour [42]. Oral dosing begins at 0.5 mg/kg/dose every 8 hours and can be increased to 3–8 mg/kg/day, divided every 6–8 hours. Since both agents act independently of ventilation, they may contribute to V/Q mismatch and worsen oxygenation. Systemic hypotension remains a recognized side effect, especially at the start of therapy, necessitating optimized volume status and close hemodynamic monitoring.

6.8. Inotropes

In neonates with PPHN, systemic hypotension can result from low vascular tone or cardiac dysfunction, particularly right ventricular (RV) failure due to elevated afterload. Adequate cardiac output, supported through volume expansion and inotropic therapy, is critical for improving tissue oxygen delivery and gas exchange. For infants without evidence of cardiac dysfunction, vasopressor agents such as dopamine, norepinephrine, or vasopressin are commonly used. In those with cardiac dysfunction, epinephrine or a combination of dopamine or vasopressin with milrinone is recommended. Milrinone is the inotrope of choice in cases where blood pressure is stable but cardiac output is insufficient.

Experimental studies have demonstrated that high-dose dopamine (greater than 10 µg/kg/min) can significantly increase pulmonary artery pressure in neonates with remodeled pulmonary vasculature [9]. This hypertensive response is attenuated in neonates with normal pulmonary vasculature. Dobutamine, on the other hand, may lower systemic blood pressure and increase myocardial oxygen consumption, potentially aggravating right-to-left shunting and myocardial dysfunction in PPHN. Although augmenting systemic blood pressure may temporarily reduce shunting, this strategy does not necessarily improve oxygen delivery to essential organs like the brain and may increase RV workload and subsequent decompensation. Several inotropic agents may also inadvertently raise pulmonary artery pressure, worsening the underlying hemodynamics [9, 43].

6.9. Sedation and Paralysis

Reducing environmental stress is a fundamental component of PPHN management. External stimuli can trigger sympathetic responses and worsen pulmonary vasoconstriction. Therefore, neonates should be cared for in low-stimulation environments and receive appropriate sedation, typically with agents such as fentanyl or morphine. Although the routine use of paralytic agents is discouraged, they may be necessary in cases requiring high ventilatory support to optimize gas exchange and prevent ventilator dyssynchrony [4].

6.10. Nutrition

Providing adequate parenteral nutrition is vital in supporting myocardial performance and overall recovery in neonates with PPHN. Nutritional support should include appropriate glucose, amino acid, and lipid provision, along with careful regulation of electrolyte and ionized calcium levels to sustain metabolic and cardiac function.

6.11. Acid–Base Balance

Maintaining acid–base homeostasis is critical, as acidosis can intensify pulmonary vasoconstriction. A target pH between 7.25 and 7.40 is recommended. The use of sodium bicarbonate to induce metabolic alkalosis and hyperventilation to achieve respiratory alkalosis should be avoided [4], as both approaches have been associated with adverse neurodevelopmental outcomes, including sensorineural hearing loss and long-term developmental delays [44]. A $PaCO_2$ range of 40–55 mmHg is considered optimal for balancing oxygenation and minimizing vasoconstriction.

6.12. Extracorporeal Membrane Oxygenation (ECMO)

Approximately 30–40% of neonates with PPHN may fail to respond adequately to iNO and maximal medical therapy. In such cases, extracorporeal membrane oxygenation (ECMO) serves as a critical rescue therapy. Thus, all centers treating severe HRF or PPHN should have ECMO capabilities or established referral pathways. ECMO is indicated when the oxygenation index (OI) exceeds 40 for at least two hours in three out of five arterial blood gases, or when the alveolar–arterial oxygen gradient remains ≥630 mmHg for over four hours. These thresholds

predict a mortality rate of 60–80% without ECMO. Transfer planning should begin early—ideally when OI reaches 30—even if vasodilator therapy is ongoing.
Contraindications to ECMO include gestational age below 34 weeks (due to the heightened risk of intraventricular hemorrhage), existing severe intracranial bleeding, active uncontrolled bleeding, irreversible neurological damage, and the presence of lethal chromosomal or multisystem anomalies.

7. Follow-Up

Long-term follow-up is essential for infants treated for PPHN, given the substantial risk of developmental sequelae. Research indicates that approximately 25% of survivors experience neurodevelopmental impairments, while 6–23% develop sensorineural hearing loss. Chronic respiratory symptoms may persist in up to one-quarter of affected infants. Consequently, a comprehensive post-discharge care plan should include neurology, audiology, pulmonology, and developmental follow-up to ensure early detection of complications and timely intervention.

Conclusion

Survival rates for infants with persistent pulmonary hypertension of the newborn (PPHN) have significantly improved over the past few decades, largely due to advances in neonatal care such as gentle ventilation strategies, the use of exogenous surfactant, and the introduction of inhaled nitric oxide (iNO). Despite these advances, important limitations remain. iNO, although a landmark therapy, is costly, not widely accessible in all healthcare settings, and fails to achieve satisfactory clinical improvement in approximately one-third of affected neonates.
These limitations underscore the pressing need for alternative therapeutic strategies that target different molecular mechanisms regulating pulmonary vascular tone. Several promising agents are currently under investigation, including L-citrulline, endothelin receptor antagonists, soluble guanylyl cyclase stimulators and activators, Rho kinase inhibitors, peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, and various antioxidant compounds [45].
Ongoing research into these emerging therapies is critical and may pave the way for more effective treatments that can further reduce the morbidity and mortality associated with PPHN in the future.

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