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Pathophysiology and Management of Persistent Pulmonary Hypertension of the Newborn

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a disorder of circulatory transition resulting in high pulmonary vascular resistance (PVR) with extrapulmonary right-to-left shunts causing hypoxemia. There has been a substantial gain in understanding of pathophysiology of PPHN over the last two decades, and biochemical pathways responsible for abnormal vasoconstriction of pulmonary vasculature are now better understood. Easy availability of bedside echocardiography helps in establishing early definitive diagnosis, understanding the pathophysiology and hemodynamic abnormalities, monitoring the disease process and response to the therapeutic intervention in PPHN. In addition to improvements in the general supportive management and ventilation strategies, there has been a significant advancement in specific management of PPHN targeted at deranged biochemical pathways and hemodynamic instability. When available, inhaled nitric oxide is the pulmonary vasodilator of choice. The emphasis has shifted from hyperoxygenation-hyperventilation-alkalosis to improved gentle ventilation strategies to optimize lung recruitment and allow permissive hypercapnia, early use of iNO and surfactant therapy, and avoid hypoxia-hyperoxia. These changes have led to a substantial decrease in the number of infants with PPHN requiring ECMO for respiratory disorders. Newer pulmonary vasodilators, such as antioxidants (superoxide dismutase), soluble guanylate cyclase activators and rho-kinase inhibitors, are promising but still under investigation and currently their use is limited to research studies. They may play an important role in targeting specific therapy in PPHN, especially in infants resistant to inhaled nitric oxide.

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Keywords

Persistent pulmonary hypertension of the newborn (PPHN); Inhaled nitric oxide; oxygen; Echocardiography; Term infant

Introduction

Persistent pulmonary hypertension of the newborn (PPHN), previously referred to as persistent fetal circulation, is a syndrome of impaired circulatory adaptation at birth (1). The hallmark of PPHN physiology is sustained elevation of pulmonary vascular resistance (PVR) and persistent hypoxemia after birth (2). Despite advances in understanding of perinatal pathophysiology and neonatal management strategies, its prevalence (2 per 1000 live births) has not changed significantly (2). The vast majority of infants with PPHN are born at term or near term, although around 2% cases are born prematurely (3). Mortality has not changed (5–10%) and PPHN remains as one of the leading causes of critical illness in the neonatal intensive care unit (NICU) (4).

PPHN is secondary to impaired or delayed relaxation of the pulmonary vasculature associated with a diverse group of cardiopulmonary pathologies such as meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), congenital pneumonia, hypoxic ischemic encephalopathy (HIE / perinatal asphyxia), premature prolonged rupture of membranes (pPROM), respiratory distress syndrome (RDS) and underlying or associated congenital heart disease (CHD) (5, 6). It is critical to understand the etiopathogenesis, altered physiology and impact of the interventions on the pathophysiology in order to manage these patients effectively. A physiology based approach towards PPHN is essential to decrease morbidity and mortality.

This article will review the pathophysiology and hemodynamic changes that occur in PPHN. We will also review a cardiocentric echo based approach in the management of PPHN in late preterm, term and post-term infants.

Classification of PPHN

During the sixth World Symposium of Pulmonary Arterial Hypertension (PAH) held in 2018 in Nice, France, the classification of PAH was updated (7). Due to its particular anatomic and physiologic nature, PPHN has been moved to a separate subcategory. While this classification of pediatric pulmonary hypertension is useful, a more commonly used classification of PPHN is based upon etiology – primary (idiopathic) and secondary PPHN. (Table 1)

Primary or idiopathic PPHN refers to the absence of parenchymal lung disease to explain elevated pulmonary arterial pressure and implies intrauterine pulmonary vascular remodeling. Compared to pediatric pulmonary hypertension, only around 10–20% of cases of PPHN are idiopathic and a vast majority of PPHN cases, from abnormally constricted pulmonary vasculature, are due to other acute respiratory disease processes, such as MAS, RDS, pneumonia, or CDH – this is referred to as secondary PPHN (6). Recent data from

California suggests that infection (30%), MAS (24%), idiopathic (20%) RDS (7%) and CDH (6%) are the five leading causes of PPHN (8). In these cases, it can be difficult to separate chronic intrauterine remodeling from acute pulmonary vasoconstriction due to parenchymal lung disease. A practical list of congenital and acquired causes of PPHN with mnemonics is shown in figure 1.

Pathophysiology of Persistent Pulmonary Hypertension of the Newborn (PPHN) – figure 2

The pathophysiology of PPHN is complex, multifactorial and dynamic – it evolves with time and is significantly affected by the intervention and disease process. The hallmark of the PPHN pathophysiology is increased pulmonary vascular resistance (PVR) resulting in decreased pulmonary blood flow (PBF) and hence, decreased amount of oxygenated blood returning to left side of the heart leading to hypoxia, decreased end-organ perfusion, acidosis and cyanosis (9). Hypoxemia and acidosis are potent vasoconstrictors leading to increase in PVR and worsening of PPHN. Persistently elevated PVR results in hypertrophy of right ventricle (RV) from pumping of blood against high vascular resistance. If elevated PVR persists or worsens, it may lead to impaired RV function and RV dilatation, and in severe cases it can lead to in RV failure – which may further decrease PBF and worsen hypoxemia. In severe cases of PPHN this becomes a vicious cycle until altered pathophysiology is changed (9).

RV dysfunction may impair left ventricle (LV) function because of interventricular functional independence. Poor LV function may decrease LV cardiac output and systemic blood flow leading to poor end-organ perfusion and acidosis, and hence worsening of PPHN. Severe LV dysfunction may also impair left ventricle filling due to poor compliance, which can lead to increased left atrial and pulmonary wedge pressure resulting in pulmonary venous hypertension (5).

The elevated PVR may result from: (1) abnormal pulmonary vasoconstriction, (2) structural remodeling of the pulmonary vasculature, (3) lung hypoplasia, and (4) intravascular obstruction from increased viscosity of blood as in polycythemia. PVR is often higher than the systemic vascular resistance (SVR) in infants with moderate to severe PPHN. Elevated PVR to SVR ratio resulting from one or more of the mechanisms described above leads to right-to-left shunting of blood across the ductus arteriosus and foramen ovale resulting in severe hypoxemia (11). (Figure 2). The shunt across PFO is often bidirectional, rather than right to left, even in severe cases of PPHN. In presence of pure right to left shunt, total anomalous pulmonary venous drainage should be ruled out (especially if associated with a small left atrium and absence of tricuspid regurgitation).

Hypoxemia, one of the most potent factors of pulmonary vasoconstriction, is the clinical hallmark of PPHN, and it occurs due to intrapulmonary shunting secondary to ventilation/perfusion (V/Q) mismatch and/or extrapulmonary right-to-left shunting of blood (figure 2). In some newborns, a single mechanism predominates (e.g. extrapulmonary right to left shunting in idiopathic PPHN). However, in clinical practice several of these mechanisms often contribute to hypoxemia. For instance, in infants with meconium aspiration syndrome

(MAS), obstruction of the airways by meconium decreases V/Q matching and increases intrapulmonary right-to-left shunt. Other segments of the lungs may be overventilated relative to perfusion resulting in V/Q mismatch and increase in physiological dead space. The same patient may also exhibit severe hypoxemia due to extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale (9, 12, 13). Similarly, pathophysiological changes may be seen infants with severe congenital pneumonia. On the other hand, PPHN in infants with MAS and congenital pneumonia may result from alveolar hypoxia, from inflammatory mediators, metabolic acidosis and from abnormal pulmonary vascular muscularization. Similar mechanisms may play a significant role in infants with sepsis. Infants with severe HIE may have associated PPHN both from altered or delayed transition leading to persistent high PVR, which could also be worsened by the therapeutic hypothermia. Perinatal asphyxia can also lead to myocardial ischemia leading to poor cardiac function, acidosis and low cardiac output which may contribute to PPHN (13).

On the other hand, lung hypoplasia resulting from impaired in-utero lung development or anatomical causes may be the primary cause of increased PVR and PPHN in infants with pPROM or anatomical abnormalities such as CDH (12).

Infants with CDH have abnormal cardiopulmonary vascular development leading to in-utero left ventricle hypoplasia, lung hypoplasia and increased PVR (14). In infants with PPHN, previously the primary focus was on lowering of PVR. However, now with better understanding of altered pathophysiology, the focus is shifting to managing PPHN with gentle ventilation to improve V/Q mismatch and supporting the left ventricle (such as with early introduction of a low dose of epinephrine and milrinone) to stabilize the cardiovascular hemodynamics (5, 14). The article is primarily focused on PPHN and a detailed description of impaired pathophysiology and management of CDH is out of the scope of this manuscript.

Other causes of PPHN include constriction of the fetal ductus arteriosus in utero which can occur after exposure of fetus to non-steroidal anti-inflammatory drugs (NSAIDS) or selective serotonin reuptake inhibitors (SSRI) during late gestation (15–17). There is a six-fold increase in the prevalence of PPHN after exposure to these medications during the third trimester (17). These findings have been confirmed in animal models – ductal constriction or surgical ligation in lambs produces a rapid antenatal remodeling of pulmonary vasculature resulting in increased fetal pulmonary artery pressure and profound hypoxemia after birth, similar to human infants (15,18). Similarly, in utero exposure to fluoxetine resulted in pulmonary vasculature remodeling and hypoxemia in newborn rats after birth (18).

Mechanism of pulmonary vasculature remodeling and basis of therapeutic intervention in PPHN

From animal studies there is good evidence that remodeling of the pulmonary vasculature occurs as a result of the disruption of the following one or more pathways: 1) nitric oxide-cGMP pathway, 2) prostacyclin-cAMP pathway, 3) endothelin signaling pathway and 4) oxidant stress pathway (5, 6). (Figure 3)

The nitric oxide-cGMP pathway is the best studied mechanism of PPHN and has been the basis of nitric oxide therapeutic trials in treatment of PPHN (4, 5). Nitric oxide (NO) produced by the endothelium stimulates soluble guanylyl cyclase (sGC) in the pulmonary arterial smooth muscle cell (PASMC) to produce cGMP. Both NO and cGMP produce pulmonary vasodilation. Abnormal vasodilator responses to NO secondary to impaired sGC activity are well described in animal models of neonatal pulmonary hypertension and CDH (19, 20). In fetal lambs, disruption of the NO-cGMP pathway by chronic in utero inhibition of endothelial nitric oxide synthase (eNOS) resulted in the physiologic characteristics of PPHN (21). Decreased expression of eNOS has also been reported in the umbilical venous endothelial cultures and reduced levels of NO metabolites in urine have been noted in human infants with MAS and PPHN (22–24). Because NO and cGMP both vasodilate and inhibit vascular smooth muscle growth, it is possible that the combination of diminished eNOS expression, inactivation of sGC, and reduced cGMP levels contribute to both abnormal vasoreactivity and excessive muscularization of pulmonary vessels in PPHN. Inhaled NO (iNO) therapy, exogenous nitric oxide, stimulates PASMC to produce cGMP resulting in pulmonary vasodilation.

Increased phosphodiesterase 5 (PDE5) activity results in catabolism of cGMP and limitation of NO-induced vasodilation (25). Hence, inhibition of PDE5 with the use of sildenafil is a promising strategy in the treatment of PPHN (5). Sildenafil may also augment the effect of iNO in patients with partial or poorly sustained responses to iNO. It may be particularly effective in patients following prolonged hyperoxic ventilation, which increases production of superoxide anions and stimulates PDE5 activity (25–27). Oral sildenafil has been used in infants with prolonged pulmonary hypertension associated with BPD and it is the mainstay of treatment in children with chronic pulmonary hypertension (28).

The disruption of the prostacyclin pathway can also play an important role in PPHN. Prostacyclin I_2 (PGI_2) mediates vasodilation by activating adenylate cyclase and increasing cAMP in the PASMC (29). Prostacyclin I_2 (PGI_2) analogs administered by the intravenous route are the mainstay of pulmonary vasodilator therapy in adults with PAH. Inhaled PGI_2 (epoprostenol) acts synergistically with iNO - it improves oxygenation in PPHN and prevents rebound hypertension when iNO is weaned off (30–31). Use of inhaled iloprost has also been reported in combination with iNO for intractable PPHN (32). However, as there are no randomized controlled trials evaluating the effect of prostaglandin vasodilators, their use remains limited.

cAMP levels can be enhanced through inhibition of its metabolism by phosphodiesterase 3 (PDE3A) modulation. Milrinone inhibits PDE3A activity in pulmonary arterial smooth muscle and increases cAMP, resulting in pulmonary vasodilation (33). The pulmonary vasodilatory response to milrinone is proportional to PDE3A activity in PASMCs (34). Animal studies suggest that exposure to iNO increases PDE3A activity, and that milrinone may be especially effective in promoting pulmonary vasodilation and improving oxygenation in iNO resistant PPHN (34–35). Milrinone also enhances the heart's inotropic effect through inhibition of cardiac PDE3A and is considered an inodilator (36). In some infants with PPHN, especially those with left ventricular dysfunction or hypoplasia (due to CDH, asphyxia, or sepsis), milrinone can help in augmenting left ventricle (LV) function

and induce pulmonary vasodilation. It can also be particularly helpful in infants with pulmonary venous hypertension from raised left atrial pressure secondary to impaired LV dysfunction or mitral regurgitation. Administration of iNO to infants with pulmonary venous hypertension may flood the pulmonary capillary bed and worsen pulmonary edema, resulting in clinical deterioration (5). Three case series have demonstrated the effectiveness of milrinone in improving oxygenation in iNO-resistant PPHN (33–35), and currently multicentric randomized controlled trials are underway to study the effects of milrinone in infants with CDH and pulmonary hypertension.

The disruption of the endothelial signaling pathway can also play an important role in infants with PPHN. Endothelin-1 (ET-1) synthesized by vascular endothelial cells is a potent vasoconstrictor and acts through two receptors: ET_A and ET_B. The ET_A receptor plays a critical role in vasoconstriction while the endothelin-B receptor (ET_B) receptor promotes vasodilation mediated by endothelium-derived NO (37–38). Selective blockade of the ET_A receptor causes fetal pulmonary vasodilation (39). Chronic intrauterine ET_A receptor blockade following ductal ligation decreases pulmonary arterial pressure and distal muscularization of small pulmonary arteries in utero, decreases right ventricular hypertrophy, and increases the fall in PVR at delivery in newborn lambs with PPHN (40). Thus, ET-1 acting through the ET_A receptor might contribute to the pathogenesis and pathophysiology of PPHN. Bosentan, a nonspecific ET-1 receptor blocker, has mainly been used to treat PH in adults. Two recent trials show that bosentan is well tolerated in neonates with PPHN, although its efficacy is variable, possibly due to inconsistent intestinal absorption (41–42).

Lastly, there is mounting evidence for the role of oxidant stress in the pathogenesis of PPHN. Reactive oxygen species (ROS) such as hydrogen peroxide, superoxide, and peroxynitrite cause pulmonary vasoconstriction. In animal studies, lamb PPHN model, an increase in superoxide and hydrogen peroxide in the smooth muscle and adventitia of pulmonary arteries has been demonstrated (43–44). In addition to direct inactivation of NO, ROS can decrease eNOS and sGC activity and increase PDE5 activity, resulting in decreased cGMP levels (45). Increased ROS can be secondary to: a) exposure to high concentrations of oxygen, b) reduced levels of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and c) increased activity of prooxidant enzymes such as NADPH oxidase (43). Oxidative stress can be minimized by judicious use of inspired oxygen or possibly by the use of targeted antioxidants.

Oxygen is one of the most potent pulmonary vasodilators and increased oxygenation is the primary mediator of the reduction in PVR at birth. Alveolar hypoxia and hypoxemia increase PVR and contribute to the pathophysiology of PPHN. Avoiding hypoxemia by mechanical ventilation and high concentrations of oxygen is the mainstay of PPHN management (5, 12). Furthermore, animal studies demonstrate exaggerated hypoxic pulmonary vasoconstriction with pH below 7.25, suggesting that acidosis should be avoided (46). However, exposure to extreme hyperoxia promotes formation of ROS and may lead to lung injury. The animal studies demonstrated that even brief exposure to 100% oxygen in newborn lambs increased the contractility responses of pulmonary arteries and resulted in formation of superoxide anions and reduced response to iNO (47–48).

Diagnosis of PPHN

Hypoxic respiratory failure is a hallmark feature of PPHN, but differentiating cyanotic congenital heart disease (CHD) from PPHN is critical in a hypoxemic infant (5). The initial evaluation should include a thorough history of risk factors for PPHN, a meticulous physical examination, simultaneous measurement of pre-ductal (right upper limb) and post-ductal (lower limb) oxygen saturation to check the difference between them, chest radiography, and arterial blood gas analysis. Pre- and post-ductal oxygen saturation and PaO2 measurements can help in differentiating PPHN from cyanotic CHD. Saturation differences of greater than 5%–10% or PaO2 differences of 10–20 mm Hg between right upper limb and lower limbs, with pre-ductal levels being higher than post-ductal levels, are considered significant. Hypoxemia is often labile in PPHN, unlike fixed hypoxemia seen in cyanotic CHD (4–6).

The chest X-ray is particularly helpful in diagnosing respiratory pathology (figure 4). It may help in differentiating etiology of PPHN (such as MAS, pneumonia, RDS, CDH, etc) and differentiating types of CHD (49). Hypoxemia disproportionate to the severity of parenchymal disease on chest radiography suggests idiopathic PPHN (or cyanotic heart disease). Pulmonary oligemia is seen in tetralogy of Fallot (TOF), Ebstein anomaly, critical pulmonary stenosis and pulmonary atresia due to decreased pulmonary flow. Pulmonary plethora is seen in transposition of great arteries (TGA) with intact interventricular septum, truncus arteriosus, tricuspid atresia, total anomalous pulmonary venous connection (TAPVC) and single ventricle (9, 50, 51).

The hyperoxia test may be useful in differentiating the cardiac causes from respiratory causes in cyanotic newborns. On confirmation of central cyanosis by measuring the arterial partial pressure of oxygen (PaO_2), response of PaO_2 to 100% oxygen inhalation is tested (hyperoxia test). Oxygen should be administered through a plastic hood for at least 10 minutes in order to fill the alveolar spaces completely with oxygen. In a cyanotic CHD case, the rise in PaO2 is usually no more than 10–30 mmHg and hardly ever exceeds 100 mmHg. With pulmonary diseases, PaO2 often rises greater than 100 mmHg. However, infants with massive intra-pulmonary shunt from a respiratory disease may not show a rise in PaO2 to 100 mmHg. Conversely, some infants with cyanotic defects with a large pulmonary blood flow, such as TAPVC, may demonstrate a rise in PaO2 of 100 mmHg or higher. A hyperoxia test should be interpreted in the context of the clinical picture and the degree of pulmonary pathology seen on X-ray (49–51). With the availability of bedside echocardiography, the hyperoxia test is seldom performed but can be helpful when echocardiography is not available.

Echocardiography is the gold standard to confirm the diagnosis of PPHN, monitor the response to the therapeutic interventions and rule out underlying cyanotic or critical CHD. It can help in assessing the severity of PPHN. Pulmonary artery systolic pressure (PASP) can be estimated using tricuspid regurgitation velocity or ductus arteriosus shunt when present. Serial echocardiographic assessment can help in understanding evolving pathophysiology and response to the therapeutic intervention. Echocardiographic assessment and hemodynamic evaluation can help in targeting specific intervention and they can guide the choice of appropriate pulmonary vasodilator and vasoactive therapy (9, 10, 52–54).

Detailed description of echocardiographic technique used for assessment of PPHN is out of the scope of this article, a summary of echocardiography parameters commonly used in clinical practice have been summarized in Figures 3 & 4, and Table 2. We recommend serial echocardiography (Figure 5) assessment to monitor the disease progress, changing pathophysiology and response to treatment in PPHN, especially in infants with moderate to severe PPHN with hemodynamic instability (Figure 6).

General supportive management

The severity of PPHN can range from mild hypoxemia with minimal respiratory distress to severe hypoxemic respiratory failure and cardiopulmonary instability. General management principles for the newborn with PPHN include maintenance of normal temperature, electrolytes (particularly calcium and magnesium), glucose, nutritional support, avoidance of stress, maintaining good hemostasis (Hb >140gm/L), and handling with sedation and analgesia as needed. Paralysis should be avoided if possible because it has been associated with increased mortality (5). As sepsis is difficult to rule out in critically unwell infants, empirical antibiotic therapy for pneumonia or sepsis is required. Hyperventilation and infusion of alkali were used in the past but should be avoided because of adverse effects on cerebral perfusion and increased risk of sensorineural deafness (55, 56). Alkali infusion was associated with increased use of extracorporeal membrane oxygenation (ECMO) and need for oxygen at 28 days (2). Most centers continue to avoid acidosis based on animal studies that found exaggerated hypoxic pulmonary vasoconstriction with pH less than 7.25 (2, 5). Maintaining pH greater than 7.25, preferably 7.30 to 7.40, during the acute phase of PPHN is recommended.

Oxygen saturation targets in managing infants with PPHN

The optimal PaO_2 in the management of PPHN is not clear. Wung and colleagues have suggested that gentle ventilation with avoidance of hyperoxia and hyperventilation results in good outcomes for neonates with respiratory failure (57). In lamb studies with PPHN model, decreasing PaO_2 below 45 to 50 mm Hg results in increased PVR in newborn calves and lambs, and maintaining PaO_2 above 80 mm Hg does not result in any additional decrease in PVR (47, 58). Maintaining preductal oxygen saturations in the mid-90s appears to maximize the drop in PVR in the ductal ligation model of PPHN and meconium aspiration model of PPHN (figure 7). In summary, animal studies show that hypoxemia results in pulmonary vasoconstriction and normoxemia reduces PVR, but hyperoxemia does not enhance pulmonary vasodilation. Furthermore, ventilation with 100% oxygen in PPHN lambs prevents the normal postnatal increase in eNOS expression in pulmonary arteries and increases PDE5 activity (59).Randomized studies comparing different PaO_2 targets have not been conducted in infants with PPHN. Based on the current evidence from translational studies, it appears that avoiding both hyperoxia hypoxia are critical.

Mechanical ventilation

Underinflation and overinflation of the lung will lead to elevation of PVR (figure 8A). Optimal lung recruitment (8–9 posterior-rib expansion on an inspiratory chest radiograph)

decreases PVR. Gentle ventilation strategies with optimal PEEP, relatively low peak inflation pressure or tidal volume, and a degree of permissive hypercapnia are recommended to ensure adequate lung expansion while limiting barotrauma and volutrauma (57). In newborns with severe lung disease, high-frequency (jet or oscillator) ventilation is frequently used to optimize lung inflation and minimize lung injury (60). In clinical studies, the combination of high-frequency ventilation and iNO resulted in the greatest improvement in oxygenation in PPHN associated with diffuse parenchymal lung disease, such as RDS, MAS and pneumonia, but had no benefit in idiopathic PPHN (61).

Surfactant therapy

In patients with PPHN secondary to parenchymal lung disease, early administration of surfactant and lung recruitment is associated with better outcomes and reduced risk of ECMO or death (62, 63). A recent randomized trial of surfactant+iNO compared to iNO alone in PPHN showed less progression of hypoxemia and reduced incidence of death/ ECMO with surfactant use (figure 9). Surfactant inactivation and deficiency are observed in many neonatal respiratory disorders, such as MAS, pneumonia and RDS. In infants with PPHN secondary to parenchymal lung disease, a dose of surfactant rich in surfactant protein B (such as calfactant or poractant alfa) is recommended (5).

Pulmonary vasodilator therapy

Inhaled nitric oxide (iNO)

iNO is a potent and selective pulmonary vasodilator - it is considered as the first line therapy to decrease PVR in infants with PPHN needing mechanical ventilation. It is preferentially distributed to the ventilated segments of the lung, resulting in increased perfusion of the ventilated segments, optimizing ventilation-perfusion match (microselective effect of iNO) and a marked improvement in oxygenation in term newborns with PPHN (64–66). Multicenter randomized clinical studies demonstrated that iNO therapy reduced the need for ECMO in term neonates with hypoxemic respiratory failure (66–68). iNO is the only therapy approved by the US Food and Drug Administration for clinical use in term or near-term newborn infants (>34 weeks' gestation) with hypoxemic respiratory failure with clinical or echocardiographic evidence of PPHN (5).

A dose of 20 ppm results in improved oxygenation and the most optimal decrease in pulmonary to systemic arterial pressure ratio (69) and is the typical starting dose. Higher doses are not recommended because they are associated with increased levels of nitrogen dioxide and methemoglobin (64). iNO should be initiated early in the disease process to break the vicious cycle of PPHN – it should be commenced at a dose of 20ppm if oxygenation index is around 20. An optimal response to iNO is defined as an increase in PaO_2/FiO_2 ratio of 20 mm Hg or more (20-20-20 rule for initiation of iNO). However, in presence of echocardiographic evidence of pulmonary hypertension, it should be commenced early without any delay. Methemoglobin levels should be monitored regularly - at 2 hours, 8 hours after initiation of iNO, and then once a day for the duration of iNO therapy (5), although with most modern blood gas analyses it is almost always available.

Weaning iNO is a gradual process to minimize the risk of rebound vasoconstriction and resultant pulmonary hypertension associated with abrupt withdrawal. If there is good response to iNO, weaning should start 30 minutes after initiation, if inspired oxygen concentration is below 60%, and then iNO is weaned only if PaO_2 can be maintained at 60 mm Hg or higher (or preductal oxygen saturation as measured by pulse oximetry >90%) (30-60-90 rule of weaning iNO) (5). The authors practice is to wean iNO by 5 ppm every 4 hours, and once iNO dose is 5 ppm, gradual weaning by 1 ppm every 2 to 4 hours is performed. Continuing iNO in infants unresponsive to iNO or failure to wean iNO can potentially lead to prolonged dependence on iNO due to suppression of endogenous eNOS (70).

Ideally all infants with PPHN should have an echocardiographic assessment before or soon after starting PPHN when available but it should definitely be performed in iNO non-responders or infants who deteriorate after starting iNO to rule out underlying cyanotic CHD, understand pathophysiology and assess cardiac function to guide further management.

Sildenafil

Sildenafil is a PDE5 inhibitor (figure 3) and causes pulmonary vascular dilatation by increasing cGMP levels. It should be started in infants with poor or no response to iNO or when iNO therapy is not available. Intravenous route is preferred over oral route in critically unwell infants. However, intravenous infusion may lead to systemic hypotension, so blood pressure should be monitored closely. It may be considered as a 2^{nd} line pulmonary vasodilator therapy in infants with stable blood pressure and good ventricular function, especially in the presence of a right-to-left shunt at the PFO and/or PDA levels (5). Therefore, all infants with poor response to iNO should have an echocardiographic assessment before commencing sildenafil.

In facilities without access to iNO, studies have demonstrated that oral sildenafil improves oxygenation and reduces mortality (71, 72). Neonatal clinicians should be aware of the current US Food and Drug Administration safety warning in the pediatric population based on a dose escalation pediatric trial (all infants were older than 1 year) that demonstrated a higher mortality in the high-dose group (73).

Milrinone

Milrinone is a PDE3A inhibitor and increases cAMP levels, resulting in pulmonary vascular vasodilatation (figure 3). If blood pressure is normal but there is evidence of ventricular dysfunction, a pulmonary vasodilator and an inodilator such as milrinone might be the preferred therapeutic agent in PPHN (5, 36). It may be used in infants where iNO is contraindicated, such as in the presence of LV dysfunction and evidence pulmonary venous hypertension from raised left atrial pressure or in iNO non-responders (33, 36). It can be used as an adjunct therapy (figure 10). We recommend using intravenous infusion without loading dose in neonates because of the risk of systemic hypotension. Optimal cardiac filling may help in reducing the risk of hypotension and a 10ml/kg fluid bolus may be given prior to commencing milrinone infusion, especially if decreased preload is suspected (5),

or stabilizing blood pressure with low dose of epinephrine before commencing milrinone infusion.

Prostacyclin

Alternate agents (not approved by the US Food and Drug Administration) for iNO-resistant PPHN include aerosolized prostaglandin E1 and inhaled prostaglandin I_2 (PGI_2) (74, 75). The intravenous formulation epoprostenol carries a significant risk of systemic hypotension and is often avoided in critically unwell infants with PPHN. Iloprost is a synthetic prostacyclin that can also be delivered by aerosolization or by intravenous route, and it improves oxygenation in PPHN (76).

Role of prostaglandin E1 in management of PPHN

Critically unwell infants with failing right ventricle may benefit from a patent ductus arteriosus (PDA), which can work as a “pop off” valve in cases with severely elated PVR. In infants with a constricting PDA, prostaglandin E1 will open the ductus arteriosus and keep in patent. This will decrease the RV afterload by allowing right to left shunt (5) (figure 10). In authors’ experience, prostaglandin E1 use should be guided by the echocardiography, and it would be specifically useful in infants with failing RV and a constricting ductus arteriosus.

Supporting systemic blood pressure

Hypotension in critically unwell infants with PPHN should be treated promptly and most clinicians, including the authors, would support systemic blood pressure with vasoactive medications such as epinephrine, nor-epinephrine, dobutamine, low dose dopamine or vasopressin (5, 13, 77). Maintaining systemic pressure at a reasonable level (for example around 50 mmHg in a term infant) may help in reversing shunt direction across ductus arteriosus, from right-to-left to left-to-right. This will increase pulmonary blood flow (and hence oxygenation and systemic end-organ perfusion) by increasing left ventricle cardiac output. However, the authors do not recommend using a very high dose of vasoactive medications because all of these vasoactive medications have significant adverse effects profile, especially at higher doses. Risks versus benefits should always be assessed. These medications should be weaned off as soon as possible and this can be guided by functional echocardiography. A detailed description of all the vasoactive medications is out of the scope of this article but their mechanisms and important hemodynamic effects are summarized in Table 3 along with an algorithm for PPHN management is shown in figure 11.

Role of extracorporeal membrane oxygenation (ECMO)

Hypotension associated with cardiac dysfunction and rapid deterioration with hemodynamic instability should precipitate cannulation for ECMO. We recommend considering commencing ECMO or discussion with the ECMO center early in iNO non-responders or those who continue to deteriorate despite the conventional therapy described above.

Conclusion

There has been a substantial gain in understanding of pathophysiology of PPHN over the last two decades, and biochemical pathways responsible for abnormal vasoconstriction of pulmonary vasculature are now better understood. Availability of bedside echocardiography establishes early diagnosis, provides an understanding the pathophysiology and hemodynamic abnormalities, and allows for monitoring of the disease process and response to the therapeutic intervention in PPHN. There has been a significant advances in the management of PPHN targeting biochemical pathways and hemodynamic instability. When available, inhaled nitric oxide is the pulmonary vasodilator of choice. Clinical practice has shifted from hyperoxygenation-hyperventilation-alkalosis to improved gentle ventilation strategies to optimize lung recruitment and allow permissive hypercapnia, early use of iNO and surfactant therapy, and avoid hypoxia-hyperoxia. These changes have led to a substantial decrease in the number of infants with PPHN requiring ECMO for respiratory disorders. Newer pulmonary vasodilators, such as antioxidants (superoxide dismutase), soluble guanylate cyclase activators and rho-kinase inhibitors, are promising but still under investigation and currently their use is limited to research studies. They may play an important role in targeting specific therapy in PPHN, especially in infants resistant to inhaled nitric oxide.

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Key points

1. Understanding the pathophysiology is of paramount importance in diagnosis and management of persistent pulmonary hypertension of the newborn (PPHN).
2. Echocardiography is diagnostic in PPHN – for confirming diagnosis, assessing the severity, understanding pathophysiology, guiding targeted specific therapy and monitoring response to therapy.
3. Inhaled nitric oxide (iNO) is the pulmonary vasodilator of choice. However, alternative therapy (such as sildenafil, milrinone, iloprost, etc) should be considered in iNO resistant cases.
4. Hypoxia and hyperoxia both should be avoided in managing PPHN.
5. Alkalosis and hyperventilation should be avoided and gentle lung recruitment strategy should be preferred in conjunction with early iNO, surfactant, and a “cardiocentric” approach to manage hemodynamic instability.

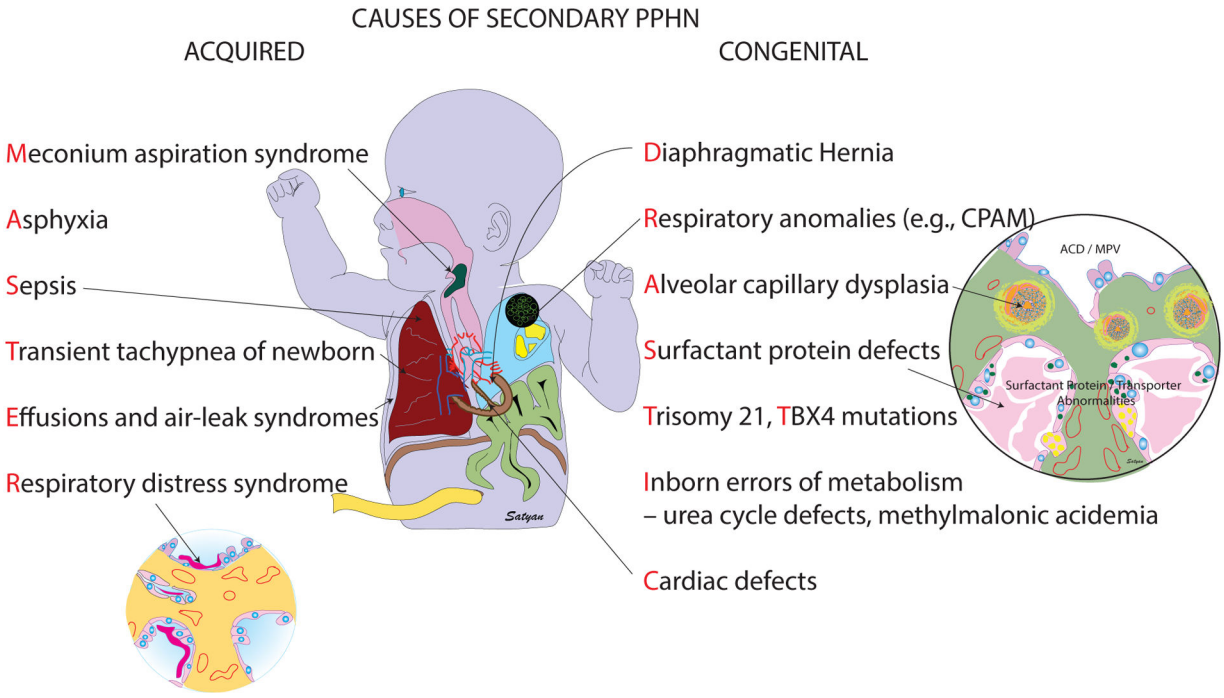

Figure 1.

Secondary causes of PPHN – acquired and congenital with mnemonics. PPHN is a MASTER of disguise and can be associated with many common perinatal conditions. Congenital causes of PPHN, if not recognized early, can be associated with DRASTIC consequences. Modified from PK R, Lakshminrusimha S, Vidyasagar D. Essentials of Neonatal Ventilation, 1st Edition: Elsevier India; 2019;with permission. CPAM – congenital pulmonary adenomatoid malformation, ACD – alveolar capillary dysplasia, MPV – malalignment of pulmonary veins, TBX4 – T-box transcription factor 4 gene mutations.

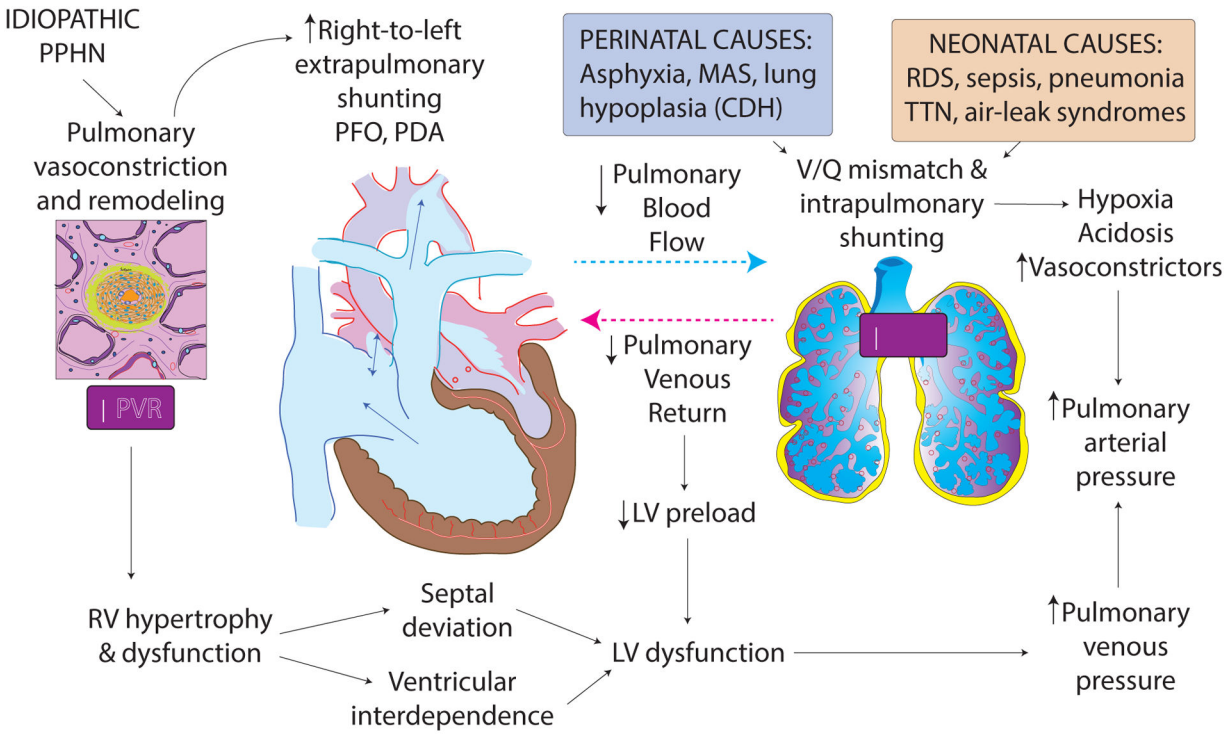

Figure 2.

Pathophysiology of extrapulmonary shunts, ventricular dysfunction and interventricular function interdependence in PPHN (10). RV – right ventricle, LV – left ventricle, MAS – meconium aspiration syndrome, CDH – congenital diaphragmatic hernia, TTN – transient tachypnea of newborn, PVR – pulmonary vascular resistance. Courtesy of Satyan Lakshminrusimha and Yogen Singh.

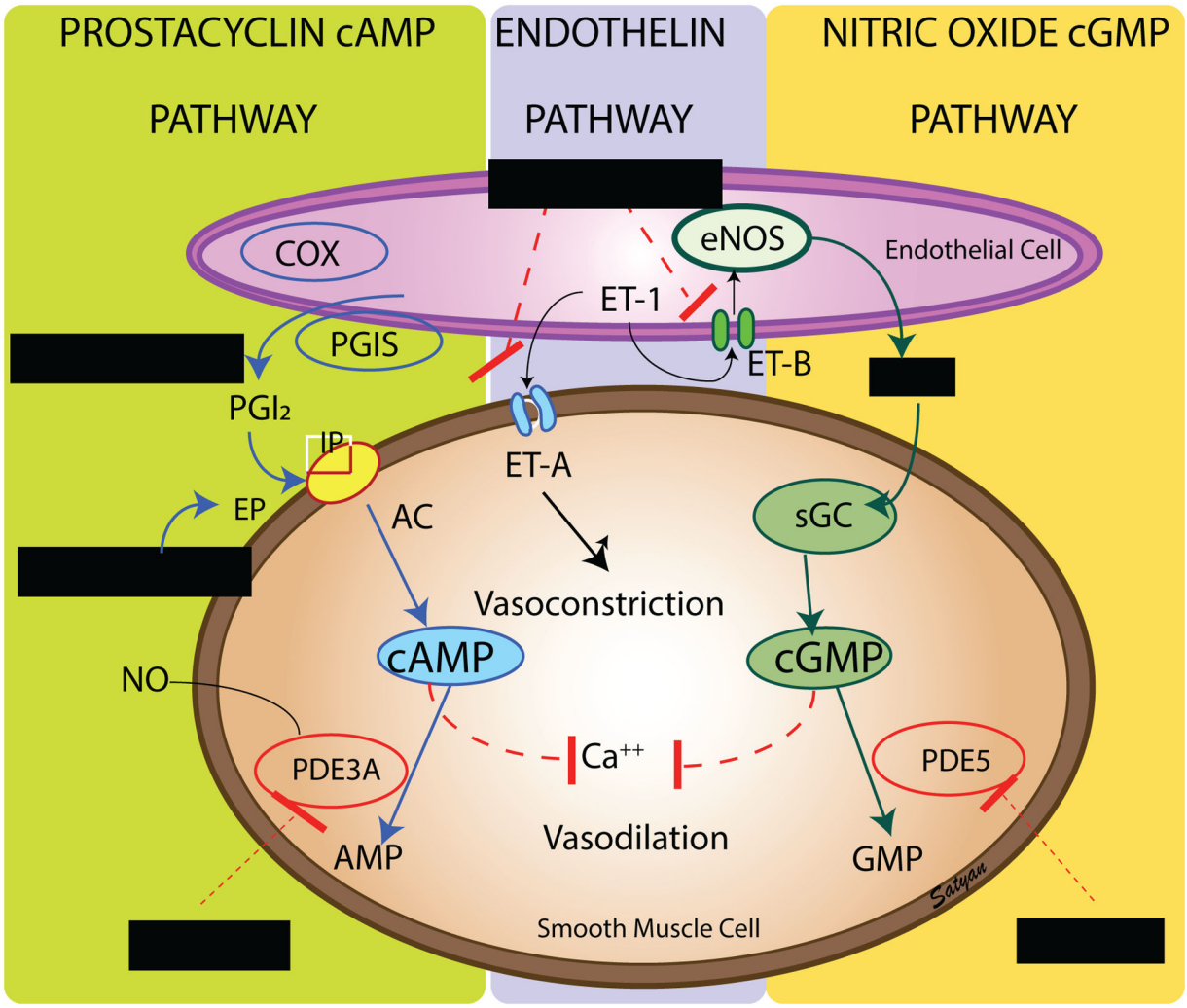

Figure 3.

Pathways of vasoactive agents in the pulmonary circulation and agents used for therapy of PPHN including endothelium derived vasodilators – prostacyclin (PGI_2) and nitric oxide (NO) and blockers of vasoconstrictors (endothelin, ET-1). The enzymes, cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor (IP) in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). Similarly, alprostadil acts on EP receptor to stimulate cAMP production. Cyclic AMP is broken down by phosphodiesterase 3A (PDE 3A) in the smooth muscle cell. Milrinone inhibits PDE 3A and increases cAMP levels in pulmonary arterial smooth muscle cells and cardiac myocytes resulting in pulmonary (and systemic) 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 nitric oxide release and vasodilation. Endothelin receptor blockers such as Bosentan are beneficial in intractable PPHN. Endothelial nitric oxide synthase (eNOS) produces NO which diffuses from the endothelium to the smooth muscle cell

and stimulates soluble guanylate cyclase (sGC) enzyme to produce cyclic guanosine monophosphate (cGMP). Cyclic GMP is broken down by PDE 5 enzyme in the smooth muscle cell. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells. Cyclic AMP and cGMP reduce cytosolic ionic calcium concentrations and induce smooth muscle cell relaxation and pulmonary vasodilation. Modified from PK R, Lakshminrusimha S, Vidyasagar D. Essentials of Neonatal Ventilation, 1st Edition: Elsevier India; 2019;with permission.

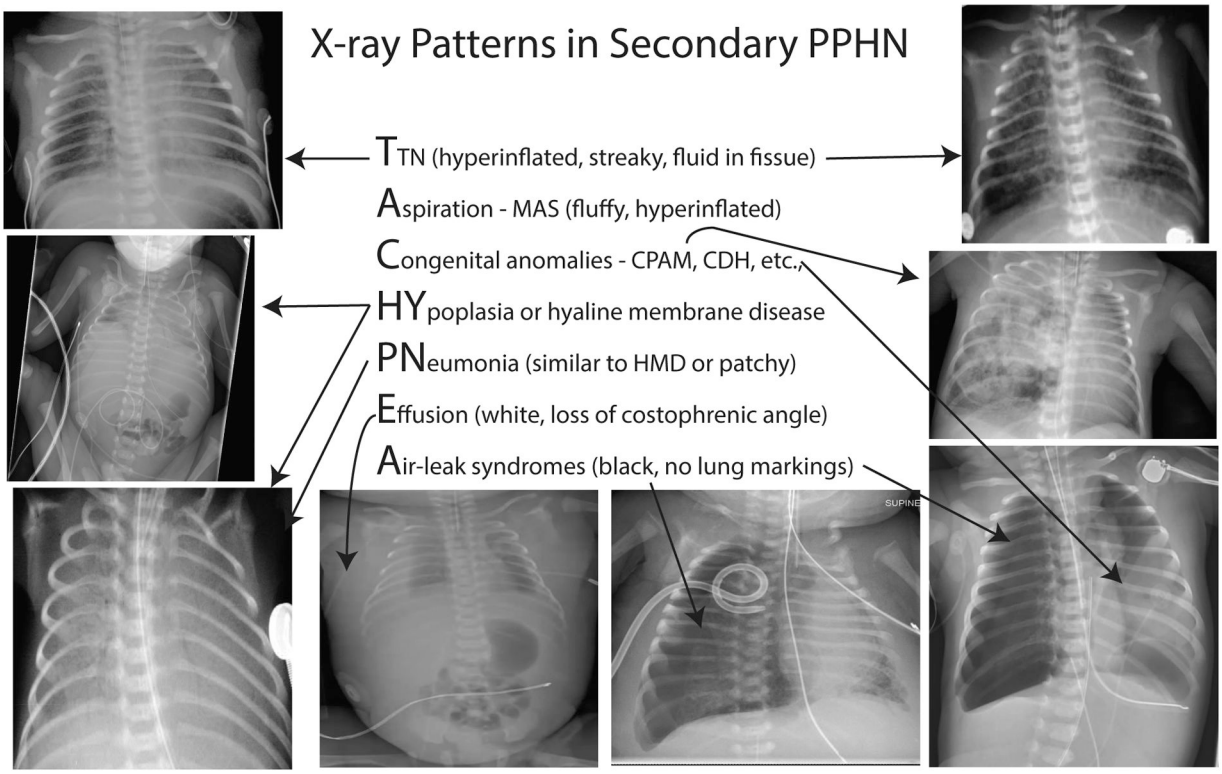

Figure 4.

X-ray patterns in secondary PPHN in term infants. A. Transient tachypnea of the newborn (TTN), B. severe lung hypoplasia secondary to prolonged oligohydramnios, C. Hyaline membrane disease (HMD) or respiratory distress syndrome (RDS) with ground glass appearance with air bronchograms, D. hydrops with pleural effusions and ascites, E. Air-leak with pneumothorax with chest tube in place, F. congenital diaphragmatic hernia (CDH) on the left and pneumothorax on the right, G. congenital cystic pulmonary adenomatoid malformation (CPAM) and H. meconium aspiration syndrome (MAS) with fluffy infiltrates and hyperexpanded lung fields. Modified from Alhassen Z, Vali P, Guglani L, Lakshminrusimha S, Ryan RM. Recent advances in pathophysiology and management of transient tachypnea of newborn. Journal of Perinatology. 2020 Aug 4:1-1.

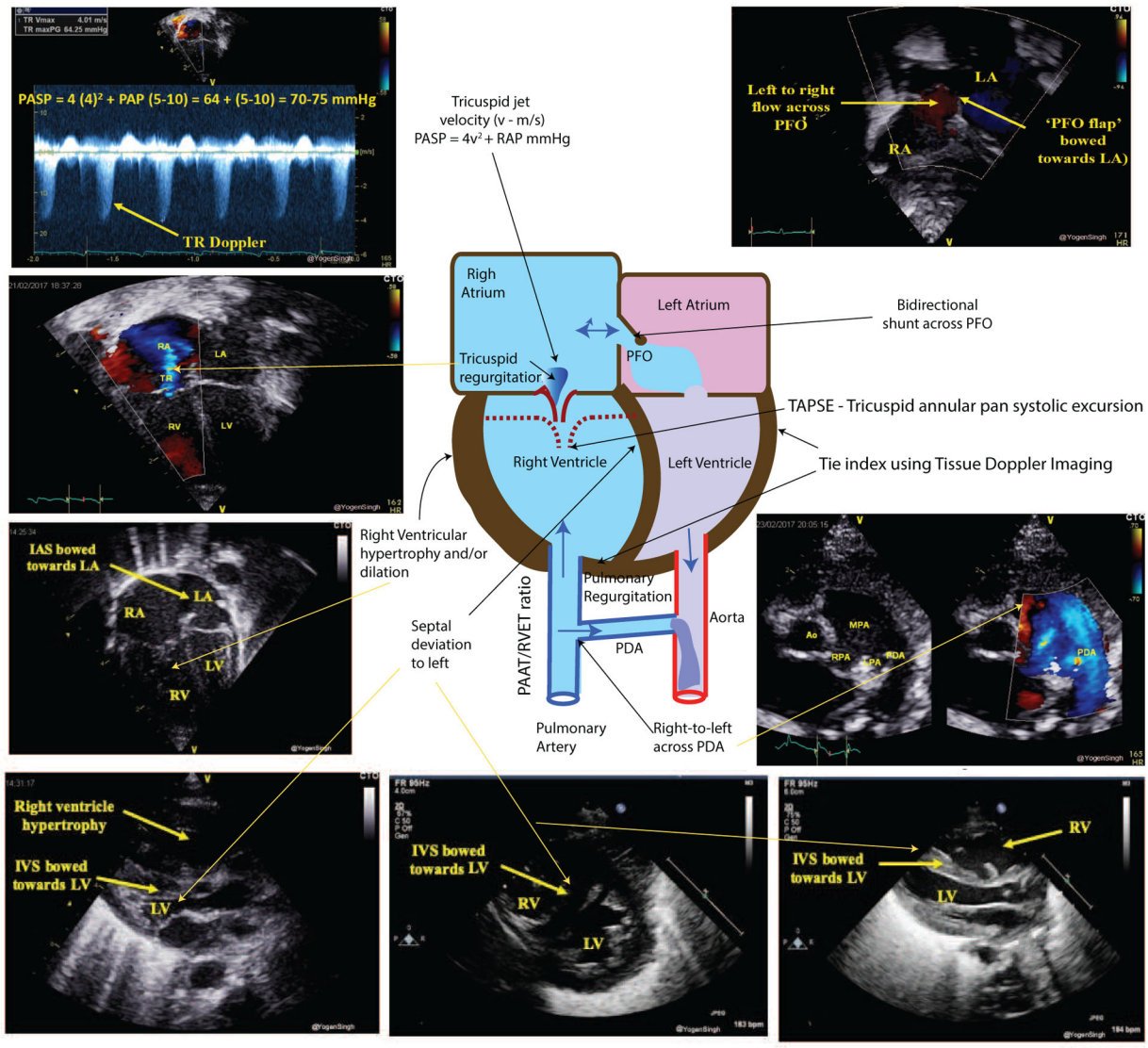

Figure 5.

Echocardiography images showing features on PPHN on 2D images. Image A). Apical 4 chamber view (A4C) showing right ventricle (RV) hypertrophy, interventricular septum (IVS) bowed towards left ventricle (LV) and inter-atrial septum bowed towards LA, Image B) Parasternal long axis view (PLAX) showing RV and IVS hypertrophy with bowing of IVS towards LV, Image C) Parasternal short axis showing significant bowing of IVS towards LV due to suprasystemic pulmonary artery pressure, and Image D) PLAX view showing RV dilatation and hypertrophy with paradoxical septal movements in an infant with PPHN and RV failure. Echocardiography images showing estimation of pulmonary artery systolic pressure (PASP) and shunts in PPHN are shown in images E–H. Image E). Apical 4 chamber showing tricuspid regurgitation (TR) jet on color flow mapping, Image F) shows Doppler assessment of TR velocity (Vmax 4m/s) which equates to an estimated PASP of around 70–75mmHg, Image H is a PSAX view showing right to left shunt across patent ductus arteriosus (PDA) suggesting suprasystemic PASP, and Image H) Subcostal view showing

bidirectional transatrial shunt across patent foramen ovale (PFO – left to right blood flow direction seen on frozen image and ‘flap of PFO’ bowed towards left atrium. TAPSE – tricuspid annular pan systolic excursion can assess right ventricular function. Tei index using tissue doppler imaging can be used to assess both right and left ventricular function. PAAT-pulmonary arterial acceleration time, RVET-right ventricular ejection time. Courtesy of Satyan Lakshminrusimha and Yogen Singh.

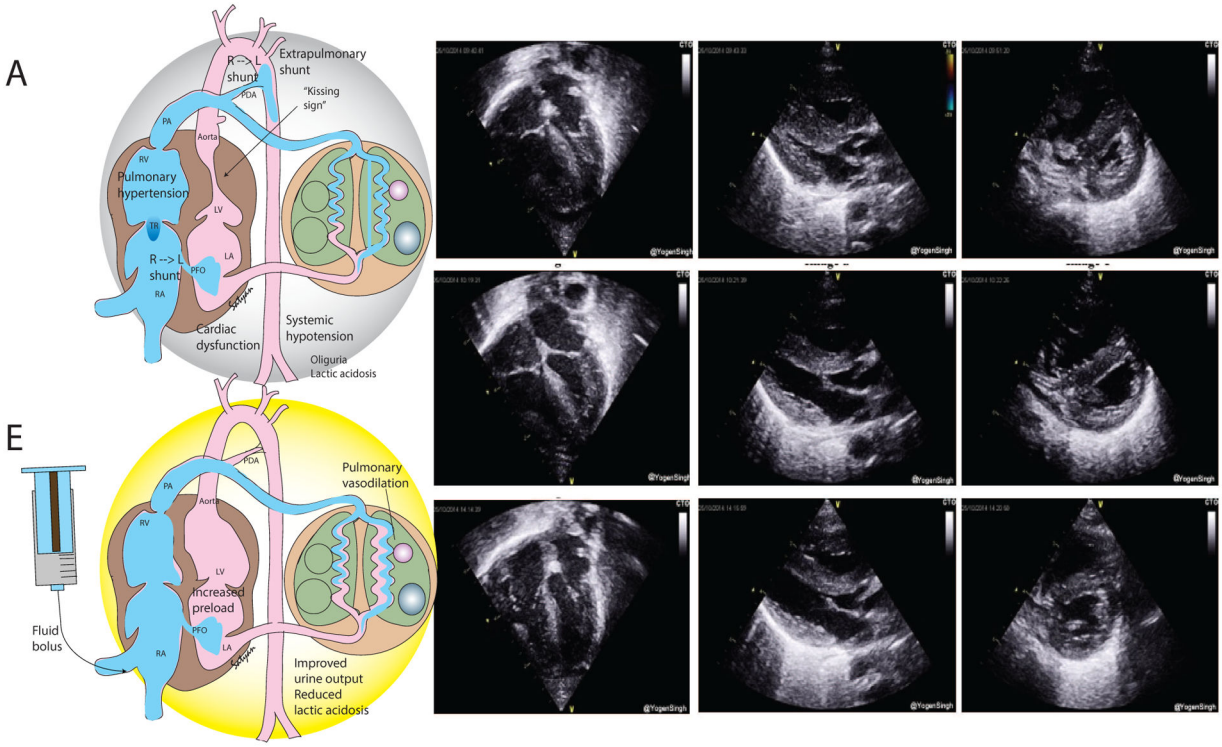

Figure 6.

Serial echocardiography assessment showing rapid improvement in clinical condition in an infant with severe secondary PPHN due to sepsis. Image A shows cardiopulmonary hemodynamics in an infant with high pulmonary vascular resistance (PVR) and low systemic vascular resistance (SVR) with intravascular hypovolemia. Images B, C and D show echocardiographic signs of PPHN and hypovolemia – right ventricle (RV) hypertrophy, bowing of interventricular septum (IVS) towards left ventricle (LV), and 'kissing sign' of hypovolemia in image C with IVS touching LV free wall in parasternal long axis view (PLAX); when infant was needing maximum intensive care support showing hypovolemia. Image E shows effect of a fluid bolus and pulmonary vasodilator therapy. Images F, G and H show significant improvement in signs within 35 minutes after echocardiography targeted intervention (30ml/kg fluid bolus) and optimizing "cardiocenteric" management. Images I, J and K, taken 5 hours after images B, C and D, showed marked improvement in PPHN echocardiography signs and hypovolemia, which was reflected in dramatic clinical improvement. Courtesy of Satyan Lakshminrusimha and Yogen Singh.

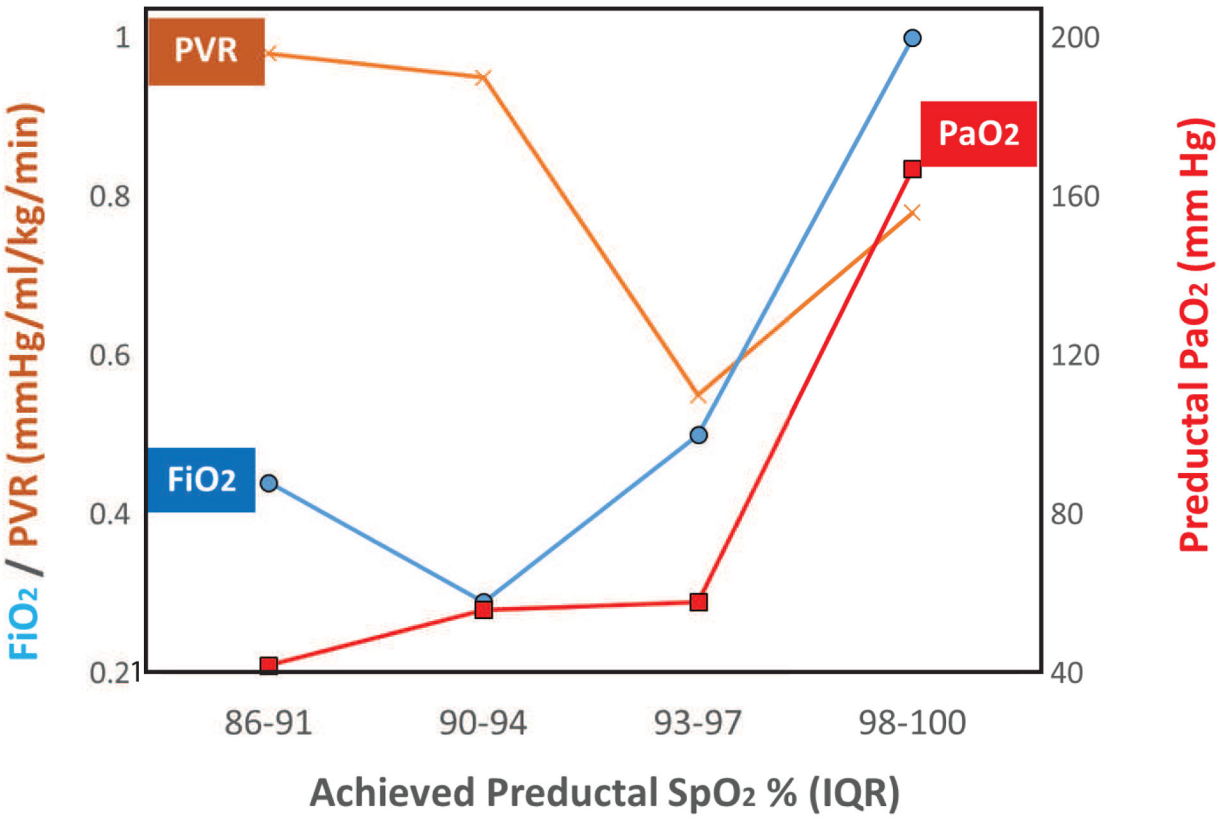

Figure 7.

Preductal oxygen saturation and pulmonary vascular resistance (PVR) in lambs with meconium aspiration and pulmonary hypertension based on Rawat et al. (78) Term lambs with asphyxia, meconium aspiration and pulmonary hypertension were randomized to preductal SpO_2 target of 85–89%, 90–94%, 95–99% and fixed inspired oxygen at 100%. The achieved SpO_2, PVR in the left pulmonary circuit (in mmHg/ml/kg/min), preductal PaO_2 (mm Hg) and FiO_2 are shown. Achieved SpO_2 interquartile range (IQR) are shown on the horizonal axis. Achieving preductal 93–97% SpO_2 resulted in lowest PVR. However, 90–94% SpO_2 was associated with lowest FiO_2 requirement. Targeting 85–89% SpO_2 was associated with high PVR. Fixed inspired FiO_2 of 1.0 resulted in median SpO_2 of 100% (IQR 96–100%) with supraphysiological PaO_2 (mean – 167 mmHg). However, despite high FiO_2 and PaO_2, no further reduction in PVR was observed compared to 93–97% achieved SpO_2. Modified from Rawat M, Chandrasekharan P, Gugino SF, Koenigsknecht C, Nielsen L, Wedgwood S, Mathew B, Nair J, Steinhorn R, Lakshminrusimha S. Optimal oxygen targets in term lambs with meconium aspiration syndrome and pulmonary hypertension. American Journal of Respiratory Cell and Molecular Biology. 2020 Oct;63(4):510-8.

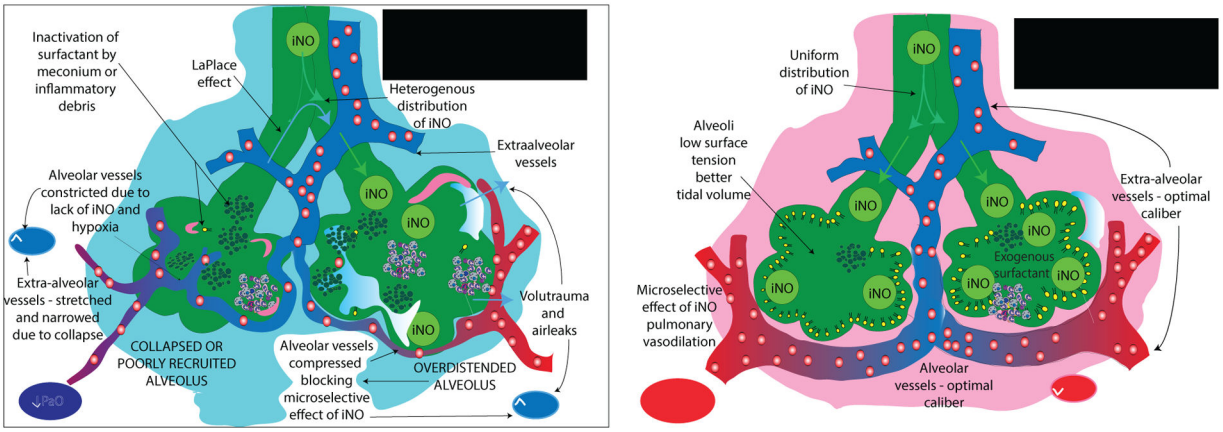

Figure 8.

Effect of lung inflation, surfactant and inhaled nitric oxide (iNO) on pulmonary vascular resistance (PVR). In conditions such as meconium aspiration syndrome and pneumonia, heterogenous lung disease with surfactant deficiency leads to collapsed and overdistended alveoli (Image A). Underinflation or collapse compresses extraalveolar pulmonary vessels and prevents their access to oxygen and iNO causing high PVR (left sided alveolus in A). Overdistended alveoli compress alveolar pulmonary vessels and prevent them from dilating in response to iNO and oxygen; overdistension increases the risk of airleak. (right sided alveolus in A). Following optimal lung recruitment and surfactant use, uniform distension of alveoli and optimal recruitment will allow oxygen and iNO to reach pulmonary vessels decreasing PVR and improving PaO_2. (Image B). Modified from Konduri GG, Lakshminrusimha S. Surf early to higher tides: surfactant therapy to optimize tidal volume, lung recruitment, and iNO response. Journal of Perinatology: Official Journal of the California Perinatal Association. 2020 Aug 13;with permission.

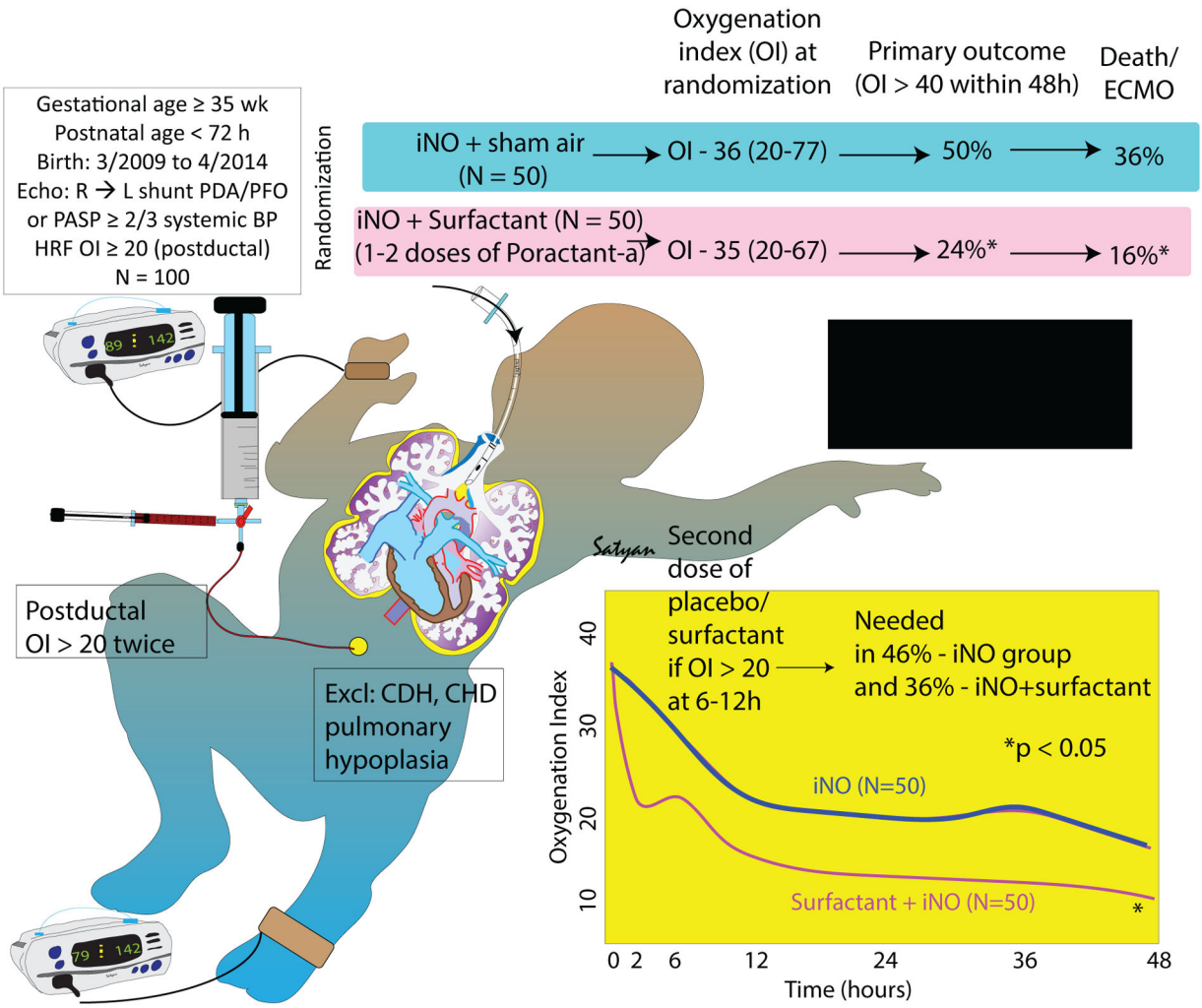

Figure 9.

Graphic abstract of randomized controlled trial of surfactant + iNO vs. iNO only in infants with PPHN by Gonzalez et al (80). Addition of surfactant to iNO resulted in reduced progression of hypoxemic respiratory failure (HRF), decreased incidence of ECMO/death and more rapid reduction in oxygenation index (OI). Courtesy of Satyan Lakshminrusimha.

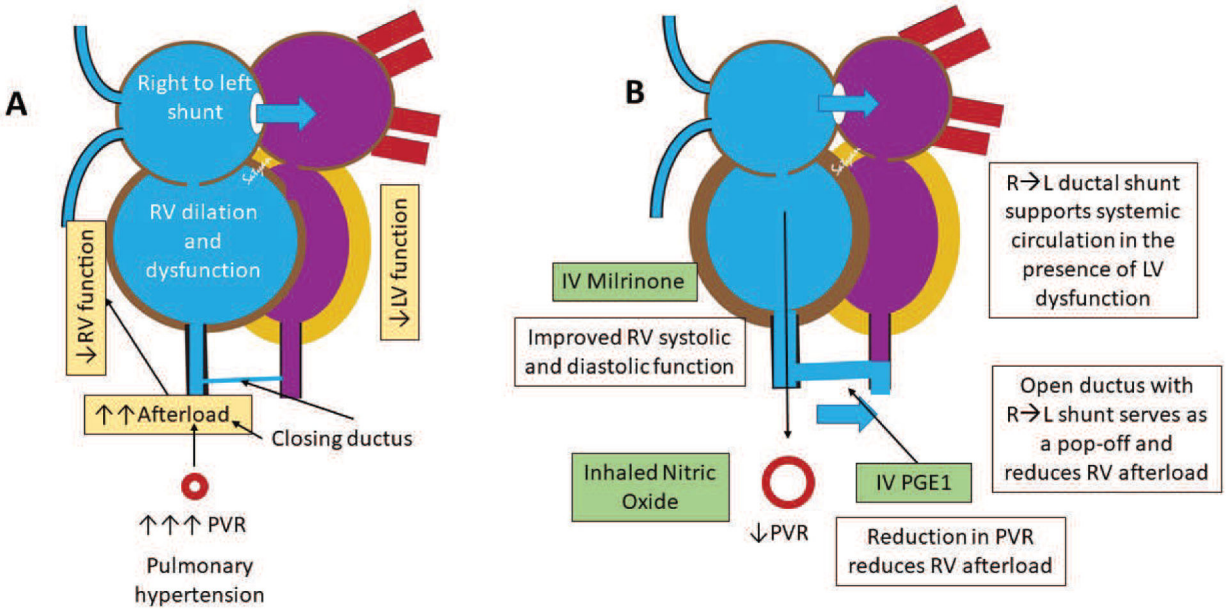

Figure 10.

Cardiac pathophysiology in PPHN. (A) In severe PPHN, the PFO and PDA shunt right-to-left with IVS bulging to the left decreasing left ventricular (LV) preload. Extremely high right ventricular (RV) afterload leads to uncoupling of RV function leading to RV dilation. An open PDA might benefit the RV by providing a pop-off mechanism to reduce RV afterload. (B) Inhaled nitric oxide reduces PVR and reduces RV afterload and milrinone can improve RV function leading to synergy with ductal patency maintained by IV prostaglandin E1 (PGE1) Modified from Lakshminrusimha and Keszler – Diagnosis and management of PPHN in Assisted Ventilation of the Neonate, Elsevier.

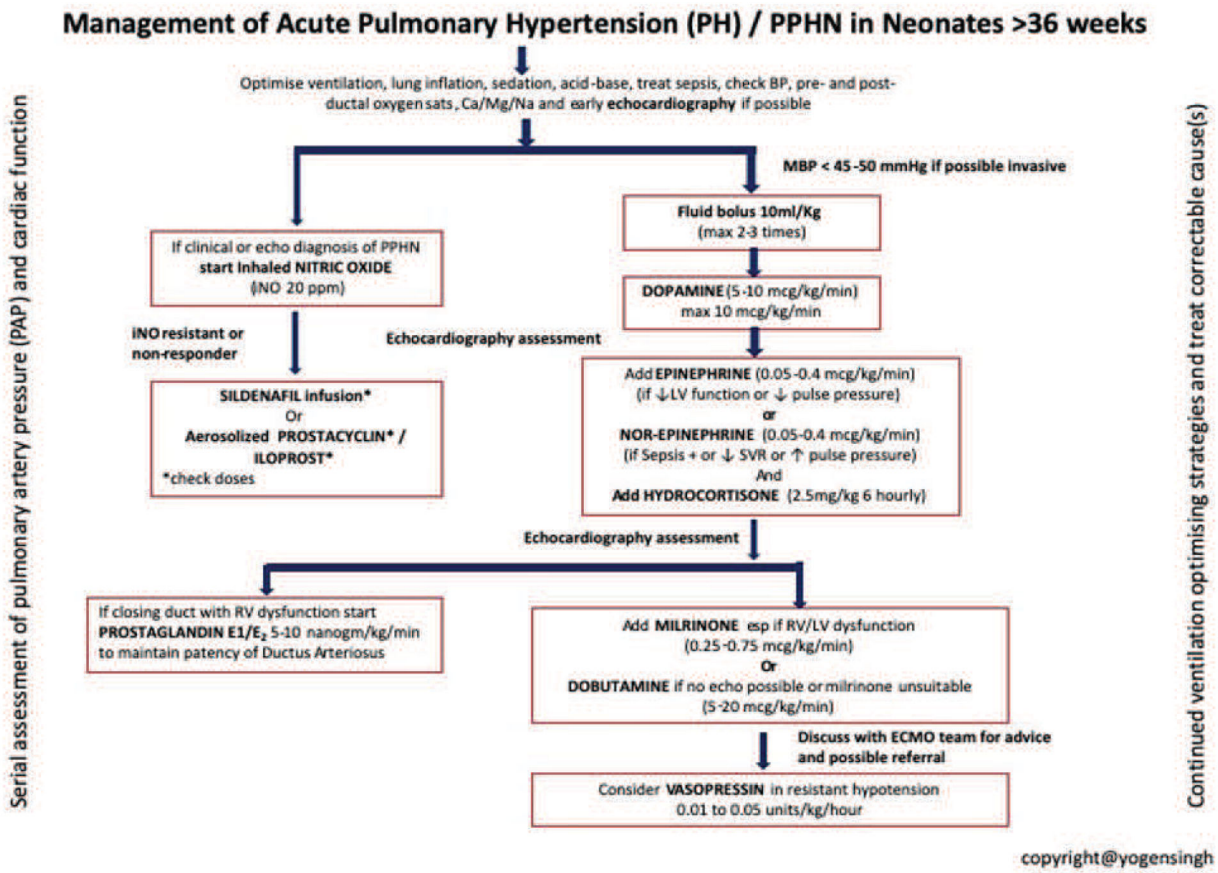

Figure 11.

An approach to management of PPHN in term or near-term infants. Courtesy of Yogen Singh.

Table 1.

Etiology of Persistent pulmonary hypertension of the newborn

A). Secondary PPHN (80–90% of all PPHN cases)	
Lung parenchymal diseases (abnormal constriction of pulmonary vasculature)	Meconium aspiration syndrome (MAS) Pneumonia / sepsis Respiratory distress syndrome (RDS)
Abnormal or delayed transition at birth (Impaired pulmonary vasculature vasodilation)	Transient tachypnea of the newborn (TTN) Perinatal stress / asphyxia Alveolar capillary dysplasia (ACD) Syndromic – Trisomy 21 Associated congenital heart disease (CHD)
Lung hypoplasia Hypoplastic pulmonary vasculature	Congenital diaphragmatic hernia (CDH) Oligohydramnios / Premature prolonged rupture of membranes Syndromic – Trisomy 21
B). Idiopathic PPHN (10–20% of all PPHN cases)	
Normal pulmonary parenchyma with abnormally remodeled pulmonary vasculature	

Table 2.

Echocardiographic parameters for assessment of PPHN (9, 10, 52–54).

Echocardiographic parameter	Comment
Disproportionately large right side of the heart with right ventricle (RV) hypertrophy and / or RV dilatation on visual inspection	In multiple views on visual inspection “eyeballing” shows cardiac asymmetry with right ride of the heart bigger than left side
Estimation of pulmonary artery systolic pressure (PASP)	By using tricuspid gradient (when present) or ductal shunt – Doppler assessment
Direction of blood flow across patent ductus arteriosus (PDA)	**Right to left shunt:** supra-systemic pulmonary artery pressure (PAP) **Left to right shunt:** sub-systemic PAP **Bidirectional shunt:** PAP equal to systemic blood pressure
Direction of blood flow across patent foramen ovale (PFO)	Often it’s bidirectional and seldom purely right to left
Flattening of interventricular septum (due to sustained high pressure in the right ventricle and flattening proportional to severity of PPHN	Helps in estimating severity of PPHN in absence of TR or PDA; can be categorized as mild, moderate and severe flattening
Assessment of right ventricle function	On visual inspection Tricuspid annular pan systolic excursion (TAPSE) Tei index using Tissue Doppler Imaging (TDI)
Assessment of left ventricle function	On visual inspection Tei index using Tissue Doppler Imaging (TDI) (note fraction shortening may be unreliable in presence of RV hypertrophy and dysfunction)
Assessment of cardiac filling (preload)	IVC size and collapsibility
Advanced echocardiography and hemodynamic evaluation	RV fractional area change PAAT and PAAT/RVET ratio Speckle tracking and strain rate Estimation of left and right cardiac output and serial assessment to see the response to therapy

Table 3:

Commonly used vasoactive medications and pulmonary vasodilators in PPHN

Name of drug	Dose	Site of action	Hemodynamic effects
Epinephrine	0.02–0.3 microgm/kg/min	β1 and β2 receptors	Inotropic effects; Decrease SVR
	0.3–1 microgm/kg/min	α1 receptors	Vasopressor effects; Increase SVR
Norepinephrine	0.1–1microgm/kg/min	α1 and α2 receptors	Vasopressor effects; Increase SVR
Milrinone	0.25–0.75 microgm/kg/min	Phosphodiesterase III inhibitor and effects at β1 & β2 receptors	Inodilator effects; Lusitropic effects; Increase contractility; Decrease SVR
Dobutamine	5–20 microgm/kg/min	β1 and β2 receptors, some effect on α receptors	Inotropic effects; Decrease SVR; Increase cardiac output
Dopamine	1–4 microgm/kg/min	Dopaminergic receptors 1 & 2	Renal and mesenteric dilatation
	4–10 microgm/kg/min	α receptors	Inotropic effects
	11–20 microgm/kg/min	β receptors	Vasopressor, increase SVR and increase PVR
Hydrocortisone	1–2.5 mg/kg; 4–6 hourly		Uncertain - enhance sensitivity to catecholamines
Vasopressin	0.018–0.12 units/kg/hour	Vasopressin 1 receptors	Increase SVR; No inotropic effect
Pulmonary vasodiators			
Inhaled nitric oxide	1–20 ppm	Selective pulmonary vasodilator	Decrease PVR
Sildenafil	IV: load of 0.42 mg/kg for 3 hours followed by 1.6 mg/kg per day as a continuous maintenance infusion	Phosphodiesterase (PDE) 5 inhibitor	Pulmonary and systemic vasodilator; Decreases PVR, decreases SVR
	Oral: 1–2 mg/kg every 6 hours		
Synthetic prostacyclin (Iloprost)	Aerosolized: 1–2.5 mg/kg every 2–4 hours	Pulmonary vasodilator acting locally	Decreases PVR
	IV 0.5 to 3 ng/kg per minute and titrated to 1–10 ng/kg per minute	Pulmonary and systemic vasodilator	Decreases SVR and hypotension
Prostacyclicn I_2 (PGI_2)	Inhaled prostaglandin I2 at a dose of 50 ng/kg per minute	Pulmonary vasodilator acting locally	Decreases SVR

SVR – systemic vascular resistance; PVR – pulmonary vascular resistance; α- alpha and β- beta receptors; IV - intravenous