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UPDATE ON PPHN: MECHANISMS AND TREATMENT

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome of failed circulatory adaptation at birth, seen in about 2/1000 live born infants. While it is mostly seen in term and near term infants, it can be recognized in some premature infants with respiratory distress or bronchopulmonary dysplasia. Most commonly, PPHN is secondary to delayed or impaired relaxation of the pulmonary vasculature associated with diverse neonatal pulmonary pathologies such as meconium aspiration syndrome, congenital diaphragmatic hernia and respiratory distress syndrome. Gentle ventilation strategies, lung recruitment, inhaled nitric oxide and surfactant therapy have improved outcome and reduced the need for extracorporeal membrane oxygenation (ECMO) in PPHN. Newer modalities of treatment discussed in this review include systemic and inhaled vasodilators like sildenafil, prostaglandin E1, prostacyclin and endothelin antagonists. With prompt recognition/treatment and early referral to ECMO centers, the mortality rate for PPHN has significantly decreased. However, the risk of potential neurodevelopmental impairment warrants close follow up after discharge for infants with PPHN.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by sustained elevation of pulmonary vascular resistance (PVR) and is often associated with normal or low systemic vascular resistance (SVR). This leads to extrapulmonary shunting from right to left across persistent fetal channels (patent ductus arteriosus, PDA and patent foramen ovale, PFO) leading to labile hypoxemia. This disorder was previously referred to as persistent fetal circulation (PFC) and is often secondary to an unsuccessful pulmonary transition at birth. This article gives a brief overview of fetal circulation and transition at birth and focuses on mechanisms of PPHN in various neonatal respiratory disorders and postnatal management of an infant with PPHN.

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Fetal Circulation

Circulation in the fetus is characterized by high PVR and low SVR. The placenta is the site of gas exchange. Pulmonary blood flow to fluid-filled lungs is low (approximately 8-10% of combined ventricular output in an ovine fetus).[1, 2] However, more recent human fetal doppler flow studies demonstrate a much higher pulmonary blood flow (13% of combined ventricular output at 20 weeks gestation, increasing to 25% at 30 weeks and 21% at 38 weeks).[3]

Numerous factors contribute to the high pulmonary vascular tone *in-utero*, such as mechanical factors (compression of the small pulmonary arterioles by the fluid-filled alveoli and a lack of rhythmic distension), the presence of low-resting alveolar and arteriolar oxygen tensions, and a relative lack of vasodilators.[4] Low oxygen tension and elevated levels of vasoconstictor mediators such as endothelin-1 (ET-1) and thromboxane play a crucial role in maintaining elevated fetal PVR.[4] Serotonin increases fetal PVR [5, 6] and the use of serotonin re-uptake inhibitors (SSRI) during pregnancy has been associated with increased incidence of PPHN.[7]

Endothelin-1 synthesized by vascular endothelial cells is a potent vasoconstrictor [8] and acts through two receptors; ET_A and ET_B (figure 1). The ET_A receptor plays a critical role in vasoconstriction while the ET_B receptor plays a significant role in vasodilation. Selective blockade of the ET_A receptor causes fetal pulmonary vasodilation.[9] Vasoconstriction induced by ET-1 is mediated by calcium.[10] Pulmonary vasodilaton to ET_B receptor stimulation is mediated by endothelium-derived nitric oxide (NO).[11, 12]

Vasoconstriction in response to low oxygen tension contributes to high PVR in the fetal lamb as it approaches term.[13, 14] Basal production of vasodilator agents such as prostacyclin (PGI_2) and NO are low in the fetus. Response to NO is dependent on activity of its target enzyme, soluble guanylate cyclase (sGC). In the ovine fetus (term gestation is 145-147d), sGC mRNA levels are low during early preterm gestation (126d) and significantly increase during late preterm and early term gestation (137d).[15] There is abundant sGC activity in the lung at late gestation and the early newborn period and gradually decreases in adult rats.[16] Low levels of pulmonary arterial sGC activity during late canalicular and early saccular stages of lung development are likely responsible for the poor response to inhaled nitric oxide (iNO) observed in preterm infants < 29 weeks GA.[17]

Transition at birth

A series of circulatory events take place at birth to ensure a smooth transition from fetal to extra-uterine life. Clamping of the umbilical cord removes low resistance placental circulation, increasing systemic arterial pressure (figure 2). Simultaneously, various mechanisms operate to rapidly reduce pulmonary arterial pressure and increase pulmonary blood flow. Of these, the most important stimuli appear to be ventilation of the lungs and an increase in oxygen tension. With initiation of respiration, the fluid-filled fetal lungs are distended with air.[4] There is improved oxygenation of the pulmonary vascular bed, further decreasing PVR.[18] There is an eight-fold increase in pulmonary blood flow, which raises left atrial pressure, closing the foramen ovale. As PVR drops lower than SVR, there is a reversal of flow across the ductus arteriosus. The increase in arterial oxygen saturation leads to closure of the ductus arteriosus and ductus venosus within the first few hours after birth. In the final phase of neonatal pulmonary vascular transition, further decline in PVR is accompanied by rapid structural remodeling of the entire pulmonary bed, from the main pulmonary arteries to the capillaries.[19]

Vascular endothelium releases several vasoactive products that play a primary role in pulmonary transition at birth. Pulmonary endothelial NO production increases markedly at the time of birth. Oxygen is believed to be an important catalyst for this increased NO production, although the precise mechanism is not clear. It increases oxidative phosphorylation and the release of red blood cell ATP which is a pulmonary vasodilator during fetal life and a potential stimulus for endothelial NO production.[20, 21] In intrapulmonary arteries isolated from near-term fetal sheep, both basal and stimulated NO release increase with escalating oxygen tension.[22] The shear stress resulting from increased pulmonary blood flow and increased oxygenation also induce endothelial nitric oxide synthase (eNOS) expression, thus contributing to NO-mediated pulmonary vasodilation after birth.[4] Nitric oxide exerts its action through sGC and cGMP (figure 1). Bloch et al report that expression of sGC is higher in late gestation and newborn rats than in adult rats[16], which may explain the better response to NO in neonates. There is a similar developmental regulation of cGMP specific phosphodiesterase 5 (PDE5) expression and activity. Expression of PDE5 in the lungs increases during gestation and in the immediate newborn period.[23, 24]

The arachidonic acid-prostacyclin pathway also plays an important role in the transition at birth. The cyclooxygenase enzyme acts on arachidonic acid to produce prostaglandin endoperoxides. Prostaglandins activate adenylate cyclase to increase cAMP concentrations in vascular smooth muscle cells. Inhibition of prostacyclin production by non-steroidal anti-inflammatory drugs (NSAIDs) during late pregnancy has been associated with PPHN although this association has been recently called into question. [25] Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) dilate fetal pulmonary vasculature by increasing cGMP through particulate guanylate cyclase (pGC) [26] and may play a role in pulmonary vascular transition at birth.

Etiology and pathophysiology of PPHN

Failure of the pulmonary circulation to undergo the normal transition after birth leads to PPHN, which is characterized by an elevated PVR/SVR ratio resulting from either vasoconstriction, structural remodeling of the pulmonary vasculature, intravascular obstruction or lung hypoplasia. There is right-to-left shunting of blood across the foramen ovale and ductus arteriosus, resulting in hypoxemia and labile oxygen saturations (figure 3).

PPHN may be idiopathic (10%) or secondary to certain neonatal pulmonary diseases which lead to delayed relaxation of the pulmonary vascular bed. Common pulmonary conditions such as congenital diaphragmatic hernia (CDH), respiratory distress syndrome (RDS), pneumonia, meconium aspiration syndrome (MAS) and transient tachypnea of the newborn (TTN) may be associated with PPHN. Some of the rare causes of severe and intractable PPHN include alveolar capillary dysplasia [27], hyaline membrane disease caused by mutations in surfactant protein B (SP-B) gene [28] and respiratory failure due to ATP binding cassette protein member A3 (ABCA3) deficiency.[29] Recently, Byers et al noted a genetic association. PPHN was significantly associated with genetic variants in corticotropin-releasing hormone (cRh) receptor 1, CRHR1 and cRh-binding protein, CRHBP.[30]

Congenital diaphragmatic hernia is often associated with intractable PPHN. A combination of pulmonary arterial hypertension, right ventricular hypertrophy and/or failure and left ventricular hypoplasia with pulmonary venous hypertension results in severe PPHN unresponsive to conventional management. Associated pulmonary hypoplasia and decreased cross-sectional area of the pulmonary vascular bed, contribute to hypoxemic respiratory failure in neonates with CDH. Lung damage is exacerbated by volutrauma and hyperoxic mechanical ventilation. A combination of gentle ventilation, reduced oxygen exposure,

inodilators and PGE1 has been shown to improve outcome in CDH (figure 4). This condition is discussed in detail in a later chapter.

Parenchymal diseases such as meconium aspiration, perinatal asphyxia, surfactant deficiency (RDS) and pneumonia interfere with normal oxygenation and ventilation of the lungs. The ensuing acidosis, hypoxia and hypercarbia can cause abnormal vasoconstriction in the lungs. Hypoxemia ensues from ventilation/perfusion (V/Q) mismatch as well as right-to-left intrapulmonary and extrapulmonary shunting of blood.

Meconium aspiration syndrome—Meconium aspiration syndrome (MAS) is the most common cause of PPHN, although its incidence has decreased in recent years due to a reduced number of post-term deliveries. Meconium staining of amniotic fluid (MSAF) occurs in 5%-24% of normal pregnancies, however only 5% of infants born with MSAF develop MAS. Meconium can partially or completely obstruct the airway and also inactivate surfactant.[31] This results in decreasing V/Q ratios and increasing intrapulmonary right-to-left shunt. Other segments of the lungs may be over-ventilated relative to perfusion, causing increased physiologic dead space and hypoxemia.

The exact mechanism of PPHN associated with parenchymal lung disease is unclear, but it is thought that pulmonary artery vasoconstriction induced by fetal and neonatal hypoxia may be a significant factor. Activation of inflammatory mediators like thromboxane A2, angiotensin II and cytokines, as well as abnormal pulmonary vascular muscularization possibly contribute to the pulmonary hypertension observed in these neonates. Levels of leukotrienes, platelet-activating factor, thromboxanes [32] and ET-1 [33] are noted to be elevated in infants with PPHN.

Asphyxia—Multiple mechanisms contribute to hypoxemic respiratory failure and PPHN in asphyxiated newborns including fetal hypoxemia, ischemia, meconium aspiration, right and left ventricular dysfunction, coagulation defects, hyperoxic resuscitation and effects of mechanical ventilation.[34] Acidosis and hypoxia increase PVR. In hypothermia trials for asphyxia, approximately 20% of asphyxiated infants in the control group and 25% in the hypothermia group were diagnosed with PPHN.[35]

Pulmonary hypertension in premature infants—Although PPHN is traditionally considered a disease of term and near-term infants, it is increasingly being diagnosed in preterm infants.[36] Some preterm infants present with PPHN in the first few days of life.[17] Preterm infants with bronchopulmonary dysplasia (BPD) may present with severe pulmonary hypertension later in the hospital course or after discharge from the Neonatal Intensive Care Unit (NICU). Preterm infants with fetal growth restriction are at high risk for developing BPD with pulmonary hypertension.[37] Pulmonary vascular disease contributes to poor outcomes in BPD.[38]

Idiopathic or “black lung” PPHN—PPHN can occur in the absence of any parenchymal disease or lung hypoplasia due to abnormal muscularization of pulmonary arterioles. There is severe hypoxemia with pulmonary vasoconstriction. Conditions such as polycythemia and hyperviscosity may also increase PVR and contribute to PPHN in the absence of parenchymal lung disease. *In-utero* closure of the ductus arteriosus due to antenatal exposure to non-steroidal anti-inflammatory drugs such as aspirin and ibuprofen has been associated with PPHN[39]. This association was brought into question in a recent study[25]. Antenatal ligation of the ductus arteriosus in fetal lambs creates a model of severe PPHN with clinical and pathological features of “black-lung” PPHN[40]. There is some evidence to suggest that the use of SSRI antidepressants after 20 weeks of gestation is associated with PPHN[7, 41]. Prenatal exposure to fluoxetine (an SSRI) induced fetal pulmonary hypertension

in rats[42]. However, another study by Andrade et al did not find any increase in the incidence of PPHN when they compared pregnant women who received an SSRI in the third trimester with control mothers[43]. Maternal physical and psychological well-being should be the primary factor dictating anti-depressant therapy during pregnancy and postpartum period.

Pathogenesis of PPHN

There is evidence suggesting that an alteration of the NO pathway contributes to PPHN. Activity and expression of eNOS and sGC in lungs is decreased[44-46] in the fetal lamb model of PPHN. In these lambs, the vascular response to NO itself is also diminished,[46] whereas the response to cGMP is normal. Thus the decreased responsiveness appears to result from decreased vascular smooth muscle sensitivity to NO at the level of sGC. Decreased expression of eNOS[47] and reduced levels of NO metabolites in urine [48] have also been noted in infants with PPHN.

Endothelin-1 through ET_A stimulation is thought to contribute to the pathogenesis of PPHN. ET-1 production is increased [49] in the lungs in the fetal lamb model of PPHN. Chronic intrauterine ET_A receptor blockade following ductal ligation decreases right ventricular hypertrophy and distal muscularization of small pulmonary arteries and increases the fall in PVR at delivery in newborn lambs with PPHN[50]. ET-1 has been shown to decrease eNOS expression and activity through ET_A receptor-mediated generation of hydrogen peroxide[51]. In addition to hydrogen peroxide, superoxide, another reactive oxygen species, may cause pulmonary vasoconstriction and play a role in the pathogenesis of PPHN. Superoxide may scavenge NO and disrupt its signaling pathway. In the fetal lamb model of PPHN, increased superoxide levels have been demonstrated in the pulmonary arteries. [52, 53]

Antenatal and perinatal risk factors

Risk factors for PPHN include meconium stained amniotic fluid, perinatal acidosis and asphyxia, maternal risk factors such as prolonged rupture of membranes, maternal fever, or positive group B Streptococcal carrier status. PPHN should be considered in the etiology of hypoxic respiratory failure in term or near-term infants. In addition to these known risk factors, it has recently been postulated that the perinatal environment, including exposure to nicotine and certain medications, maternal obesity and diabetes, epigenetics, painful stimuli and birth by cesarean section may also affect the maladaptation of the lung circulation at birth[54].

Management in the delivery room

Early recognition of PPHN and correction of factors that prevent decrease in PVR are important to successful management of a late preterm or term infant with hypoxemic respiratory failure. One of the classic features of PPHN is labile hypoxemia. These infants exhibit frequent desaturation episodes and wide swings in SpO_2 and arterial PO_2 without changes in ventilator settings. A single, loud S2 and a systolic murmur of tricuspid regurgitation are often heard on auscultation.

Neonates with PPHN are often cyanotic secondary to significant right-to-left extrapulmonary shunting in the presence of high PVR. Significant resuscitative efforts may be required in the delivery room. Resuscitation measures in the delivery room are mainly based on the Neonatal Resuscitation Program and the American Academy of Pediatrics / American Heart Association guidelines[55-57]. Resuscitation in the delivery room should focus on optimal lung recruitment and ventilation. A preductal pulse oximeter is placed on the right upper extremity and saturations are maintained in the range recommended by the neonatal resuscitation program. Supplementation with excessive oxygen during resuscitation

results in rapid decrease in PVR but increases subsequent pulmonary arterial contractility and reduces response to inhaled NO in animal studies.[58, 59]

Postnatal Management: General measures

Diagnosis—In a term or near-term infant with respiratory distress, an initial evaluation would include a chest X-ray and an arterial blood gas. Hypoxemia disproportionate to the severity of parenchymal disease on chest radiography should suggest idiopathic PPHN. Evidence of the underlying parenchymal disease such as RDS, MAS, etc. may be seen on chest X-ray in secondary PPHN. This diagnosis can be confirmed by measuring preductal (right extremity) and postductal (either lower extremity) arterial oxygenation. A difference in arterial PO_2 ≥20 mmHg or oxygen saturation ≥5-10% should be considered suggestive of PPHN. Similar postductal desaturation may be observed in ductal-dependent systemic blood flow lesions (such as hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch and coarctation of aorta) and anatomic pulmonary vascular disease (pulmonary venous stenosis, total anomalous pulmonary venous return and alveolocapillary dysplasia/ malalignment of pulmonary veins). Infants with a closed ductus arteriosus and shunting at the atrial level and PPHN may not show differential oxygen saturation. The unusual occurrence of “reverse differential” oxygen saturation (lower preductal saturation compared to postductal measurement) is often due to poor perfusion in the right hand secondary to an peripheral intravenous arm splint but can be due to transposition of great arteries associated with PPHN or coarctation of aorta.

Echocardiography remains the gold standard diagnostic tool in PPHN. Right-to-left or bidirectional shunting of blood at the foramen ovale and/or the ductus arteriosus is classically seen, as well as high pulmonary arterial/right ventricular systolic pressure estimated by Doppler velocity measurement of tricuspid regurgitation jet. The direction of the shunt at atrial and ductual level also provides clues to management (figure 5). Left-to-right shunting at the foramen ovale and ductus arteriosus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should focus on optimizing lung recruitment (increasing PEEP/mean airway pressure or intratracheal surfactant). The presence of right-to-left shunting at foramen ovale and/or ductus arteriosus is suggestive of extrapulmonary shunting and which may respond to pulmonary vasodilator therapy. Similarly, right-to-left shunting at the ductal level and left-to-right shunting at the atrial level suggest PPHN with left ventricular dysfunction with pulmonary venous hypertension as seen in CDH, asphyxia or sepsis. Ductal dependent systemic circulation syndromes listed in the previous paragraph may be associated with a similar shunt pattern. Vasodilator therapy with milrinone may be considered in this setting. Echocardiography prior to initiation of therapy is also necessary to rule out cyanotic congenital heart disease, which may present with fixed hypoxemia and may be clinically indistinguishable from PPHN.[60]

Recently, B-type natriuretic peptide (BNP) was proposed as a biomarker in PPHN, especially to assess efficacy of treatment and to predict rebound PPHN.[61, 62] However, its value in the practical management of PPHN is presently unclear. Some centers obtain serial (monthly) echocardiograms with BNP levels to diagnose pulmonary hypertension associated with BPD in preterm infants.

Supportive measures—Once PPHN is diagnosed, supportive measures are vital in successful management efforts. Care should be taken to maintain normothermia and correct metabolic abnormalities such as hypoglycemia, hypocalcemia, acidosis and polycythemia. Intravenous nutrition with adequate glucose infusion rate, appropriate calcium and amino acid supplementation with an optimal chloride: acetate ratio should be administered preferably through a central line.

Covering eyes and ears and maintaining a low-noise environment is a common practice. Minimal stimulation, along with judicious use of sedation and analgesia with narcotic analgesics like morphine and fentanyl or benzodiazepines such as midazolam is recommended. Paralysis should be avoided as it has been associated with increased mortality.[63] Due to underlying shunts, any stimulus can result in a precipitous drop in oxygen saturations.

Systemic blood pressure should be maintained at normal values for gestational age. If there is hypotension and/or poor perfusion indicating hypovolemia, volume replacement in the form of 1-2 fluid boluses should be administered. If hypotension persists despite volume replacement, inotropic agents such as dopamine, dobutamine, and epinephrine are indicated. These agents are not selective to systemic circulation and may be associated with pulmonary vasoconstriction and elevation of PVR at high doses.

Hyperventilation and alkali infusions to maintain an alkaline pH were strategies previously in use but are now considered outdated. There were concerns of impaired cerebral perfusion and sensorineural deafness with respiratory alkalosis.[64, 65] Similar or better outcomes with less chronic lung disease were also observed in infants with PPHN maintaining normal PCO_2 (45–60 mmHg).[66, 67] Alkali infusion was associated with increased use of ECMO and need for oxygen at 28 days.[63] Thus, a lack of convincing data to support hyperventilation/ alkali infusion therapy and better therapeutic options such as inhaled vasodilators have led to decreased use of alkalosis. Most centers avoid acidosis based on animal studies demonstrating exaggerated hypoxic pulmonary vasoconstriction with pH < 7.25.[68]

Inhaled therapies

Oxygen and optimal oxygen saturations—Providing adequate oxygenation forms the mainstay of PPHN therapy. However, there are currently no randomized studies comparing different PaO_2 levels in the management of PPHN in a term infant. Hypoxia increases PVR [58, 68] and contributes to the pathophysiology of PPHN, although hyperoxia does not further decrease PVR and instead results in free radical injury. It has been shown that brief exposure to 100% oxygen in newborn lambs results in increased contractility of pulmonary arteries [59] and reduces response to iNO.[58, 69] In addition to direct inactivation of NO, reactive oxygen species can decrease eNOS activity, sGC activity and increase PDE5 activity, resulting in decreased cGMP levels and potentiating pulmonary vasoconstriction. In the ovine ductal ligation model of PPHN, maintaining oxygen saturations in the 90-97% range results in low PVR.[58] We recommend maintaining preductal oxygen saturations in low to mid-90s during management of infants with PPHN with PaO_2 levels between 55 and 80 mmHg.

Ventilation—Optimal lung expansion is essential for adequate oxygenation as well as the effective delivery of iNO.[70] Conventional and high frequency ventilation (HFV)[71] may be used to reduce the V/Q mismatch. In studies comparing the effectiveness of HFV with conventional ventilation in infants with PPHN and respiratory failure, neither mode of ventilation was more effective in preventing extracorporeal membrane oxygenation (ECMO).[72, 73] HFV in combination with iNO resulted in the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation.[74] Infants with RDS and MAS benefit most from a combination of HFV and iNO therapy.[75, 76] “Gentle” ventilation strategies with optimal PEEP, relatively low PIP and some permissive hypercapnia are now being recommended to ensure adequate lung expansion without causing barotrauma. In the presence of an indwelling arterial line, severity of PPHN is assessed by calculation of oxygenation index (OI).

OI = Mean airway pressure in cm H_2O × FiO_2 × 100 ÷ PaO_2 in mmHg

Surfactant—Exogenous surfactant therapy improved oxygenation and reduced the need for ECMO when PPHN was secondary to parenchymal lung disease such as RDS, pneumonia/sepsis or MAS.[77] A multicenter trial demonstrated that this benefit was greatest for infants with relatively mild disease, and with an oxygenation index (OI) of 15-25.[78] Over the past decade, the use of surfactant in treating secondary PPHN and respiratory failure has increased and might have contributed to improved effectiveness of iNO with reduced need for ECMO.

Nitric Oxide—In 1999, inhaled nitric oxide (iNO) was approved by the FDA for use in near-term and term infants with PPHN. It has been the mainstay of PPHN treatment. It achieves potent and selective pulmonary vasodilation without decreasing systemic vascular tone. In the intravascular space, it combines with hemoglobin to form methemoglobin, which prevents systemic vasodilation (selective effect). iNO reduces V/Q mismatch by entering only ventilated alveoli and redirecting pulmonary blood by dilating adjacent pulmonary arterioles (figure 6).

Large multi-center trials[79-81] have demonstrated that iNO reduces the need for ECMO. A meta-analysis of seven randomized trials of iNO use in newborns with PPHN also revealed that 58% of hypoxic near-term and term infants responded to iNO within 30 to 60 minutes.[82] While use of iNO did not reduce mortality in any study analyzed, but the need for rescue ECMO therapy was significantly decreased.

There has been significant debate concerning the optimal starting dose as well as time of initiation of iNO therapy. Inhaled NO has several potential side effects including platelet dysfunction, pulmonary edema, methemoglobinemia and production of toxic byproducts such as nitrates. In combination with superoxide, it further potentiates oxidative injury by forming peroxynitrites. Doses from 5-80 ppm have been studied; however, most randomized clinical trials support a starting dose of 20 ppm. This was also the dose at which peak improvement in the pulmonary-to-systemic arterial pressure ratio was noted in a study involving direct PAP measurements during cardiac catheterization.[83] Doses higher than 20 ppm have been associated with more adverse effects like methemoglobinemia with only a minimal increase in response rate. [79, 84]

Controversy exists over the appropriate timing of initiation of iNO in hypoxic respiratory failure. An OI of 25 is associated with a 50% risk of requiring ECMO or mortality [85], while an OI of 40 is generally accepted as an indication for ECMO. Konduri et al demonstrated that earlier initiation of iNO with an OI of 15-25 did not reduce the need for ECMO but may have a tendency to reduce the risk of progression to severe hypoxemic respiratory failure.[86] Based on current available evidence, an acceptable indication for treatment with iNO would be an OI >15-25 with echocardiographic evidence of PPHN or a higher OI with or without evidence of right-to-left shunt.

Due to rebound vasoconstriction and resultant pulmonary hypertension on abrupt withdrawal, iNO needs to be weaned gradually.[87] Weaning in steps from 20 ppm gradually over a period of time before its discontinuation has been shown to prevent the rebound effect.[88] If there is oxygenation response, inspired oxygen concentration is first weaned below 60% and then iNO is weaned at the rate of 5 ppm every 4 hours. Once iNO dose is 5 ppm, gradual weaning @ 1 ppm q 4 hours is performed at our institution.

Almost 40% of infants with PPHN do not respond or sustain a response to iNO. Adequate lung expansion should be established by increasing PEEP, surfactant therapy and use of

HFV prior to administration of iNO. If oxygenation remains low in spite of ventilator and hemodynamic optimization on iNO, ECMO is considered as a therapeutic option. The Committee on the Fetus and Newborn, American Academy of Pediatrics, has suggested that iNO use be limited to tertiary care centers where ECMO is available.[89] However, many centers without ECMO capability have access to iNO. Care should be taken to continue iNO therapy during transport from non-ECMO to ECMO centers.

Inhaled NO is contraindicated in infants with congenital heart disease known to be dependent on right-to-left shunting of blood (such as hypoplastic left heart syndrome, interrupted aortic arch, etc.). There is also a high risk of pulmonary edema in patients with pre-existing left ventricular dysfunction who are placed on iNO (figure 5 – right lower quadrant). This underlines the importance of obtaining an echocardiogram prior to iNO therapy, not only to document PPHN and shunting, but also to rule out congenital heart disease.

Prostacyclin (PGI_2) acts as a vasodilator in the intravenous as well as inhaled form by activating adenylate cyclase and increasing cAMP in pulmonary arterial smooth muscle cell (figure 1). Unlike inhaled vasodilators, intravenous vasodilators often cause systemic hypotension. *Inhaled PGI_2 (Epoprostenol)* use has been described in case reports.[90, 91] It may act synergistically with iNO to cause effective pulmonary vasodilation and also prevent the rebound hypertension seen while weaning iNO. Use of the oral PGI_2 analog Beraprost sodium as reported from Thailand, has caused significant improvement in the oxygenation index in five neonates with PPHN who did not respond to alkali therapy and HFOV.[92] Another analog, Iloprost, has also been used endotracheally and in the inhaled form along with iNO in intractable PPHN.[93] As yet there are no randomized controlled trials evaluating the effect of these vasodilators and consequently their use remains limited.

Inhaled PGE1—Aerosolized prostaglandin E1 (Alprostadil) has been used to treat pulmonary hypertension in adults as well as in experimental animal models. In a small pilot phase I-II study, Sood et al suggested that inhaled PGE1 was a safe selective pulmonary vasodilator in hypoxemic respiratory failure.[94] A pilot trial evaluating the use of inhaled PGE1 (IPGE trial) in iNO-resistant PPHN was stopped due to poor enrollment.

Systemic vasodilators: phosphodiesterase inhibitors

The high rate of failure to obtain a sustained oxygenation response to iNO therapy has led to the search for other targets to enhance pulmonary vasodilation (Figure 1). Inhibition of the cGMP degrading phosphodiesterase (PDE5) by sildenafil and inhibition of the cAMP degrading phosphodiesterase (PDE3) by milrinone are two of the most promising therapies.

Sildenafil—This drug is presently available both in oral and intravenous form in the United States and is FDA approved only for adults with pulmonary hypertension. Studies have shown that oral sildenafil (dose range 1-3 mg/kg every 6 h) improves oxygenation and reduces mortality, in centers limited by non-availability of iNO.[95, 96] Intravenous sildenafil was shown to be effective in improving oxygenation in patients with PPHN with and without prior exposure to iNO.[97] Being systemically administered, the risk of side effects like hypotension due to systemic vasodilation is high. This risk may be diminished by slowly administering a loading dose (0.4 mg load over 3 hours), followed by a maintenance dose (0.07 mg/kg/h). Sildenafil may reduce the rebound pulmonary hypertension noted during iNO weaning. A randomized control pilot trial of IV sildenafil prior to the use of iNO was stopped due to poor enrollment.

Milrinone—This inotropic vasodilator is commonly used in the pediatric and adult intensive care units but is not currently licensed for use in treating PPHN. It inhibits PDE3 and relaxes pulmonary arteries in the fetal lamb model of PPHN.[98] Infants with PPHN refractory to iNO therapy have responded to IV milrinone in 3 case series. [99100, 101] A loading dose (50 mcg/kg) followed by a maintenance dose (0.33 to 1 mcg/kg/h) is commonly used. As with any systemic vasodilator, hypotension is a clinical concern and blood pressure needs to be closely monitored. Milrinone may be the pulmonary vasodilator of choice in the presence of PPHN with left ventricular dysfunction [102].

Bosentan—This non-specific endothelin-1 receptor blocker has been used in the treatment of PPHN, mainly in adults. In the fetal lamb model of pulmonary hypertension, Ivy et al showed that chronic intrauterine ET receptor blockade decreased PAP *in- utero*, decreased RVH and distal muscularization of small pulmonary arteries, and increased the fall in PVR at delivery.[50] Use of bosentan in neonates was described by Goissen et al in two infants with transposition of the great vessels associated with pulmonary hypertension [103] and has been shown to be effective in PPHN [104].

Steroids in PPHN

Postnatal systemic steroids have been shown to decrease the duration of hospital length of stay and oxygen dependence in MAS.[105] In the fetal lamb model of PPHN, hydrocortisone treatment postnatally has been shown to improve oxygenation, increase cGMP levels and reduce ROS levels.[106] These data suggest a potential role for hydrocortisone in PPHN. Care should be taken to avoid using steroids in the presence of bacterial or viral infection. Recent evidence that genetic abnormalities in the cortisol pathway are associated with PPHN provide further basis for exploring the role of steroids in PPHN [30].

Extracorporeal membrane oxygenation

ECMO is a supportive measure that essentially gives time for the neonatal heart and lung to recover from the underlying pathology. With improved ventilation techniques and limitation of oxygen toxicity and the use of therapies like HFOV, surfactant, iNO and other vasodilators, ECMO use for neonatal respiratory disorders has decreased. The technical details as well as types of ECMO are discussed at length in other chapters.

Newer therapies

Several newer therapies for PPHN are under investigation. These include free radical scavengers like recombinant human superoxide dismutase (SOD) which has improved oxygenation in lambs with PPHN.[107],[108] Apocynin, an NADPH oxidase inhibitor, has also been shown to attenuate ROS-mediated vasoconstriction and increase NOS activity in PPHN lambs.[109] Use of antenatal betamethasone in animal studies has been shown to improve pulmonary arterial relaxation to ATP and NO donor in PPHN lambs.[110] Increased endothelial NOS and reduced markers of oxidative stress were also revealed in the steroid-exposed group. Activators of sGC [111, 112] may to be more effective than iNO in inducing pulmonary vasodilation especially in the presence of oxidative stress.

Neurodevelopmental outcomes

PPHN is a disease with significant long-term morbidity, irrespective of the treatment modality. These infants suffer from long-term sequelae such as neurodevelopmental, cognitive and hearing abnormalities.[113-115] Thus, it is essential to provide long-term multidisciplinary follow-up after discharge. Konduri et al in their long-term follow-up of infants randomized to early iNO in PPHN, noted neurodevelopmental impairment in about

25% of infants (early iNO, 27%; control, 25%).[113] The incidence of hearing impairment (early iNO, 23%; control, 24%) was also similar in their study.

Summary

PPHN is associated with high morbidity and mortality. Inhaled nitric oxide along with HFV, surfactant and supportive measures including sedation and blood pressure support remain the mainstays in PPHN management. ECMO is an option when these measures fail. Oral/IV sildenafil, IV milrinone and inhaled PGI_2 may have a synergistic effect with iNO and are being used more frequently. However, larger clinical trials are necessary to establish their treatment effect. Free radical scavengers like SOD, sGC activators and antenatal steroids are potential future therapies currently under investigation. Clinical trials to evaluate these newer therapies are difficult to perform because of a narrow window between failure to respond to iNO and need for cannulation for ECMO. Long-term follow-up is essential for these infants due to the high risk of neurodevelopmental and hearing abnormalities.

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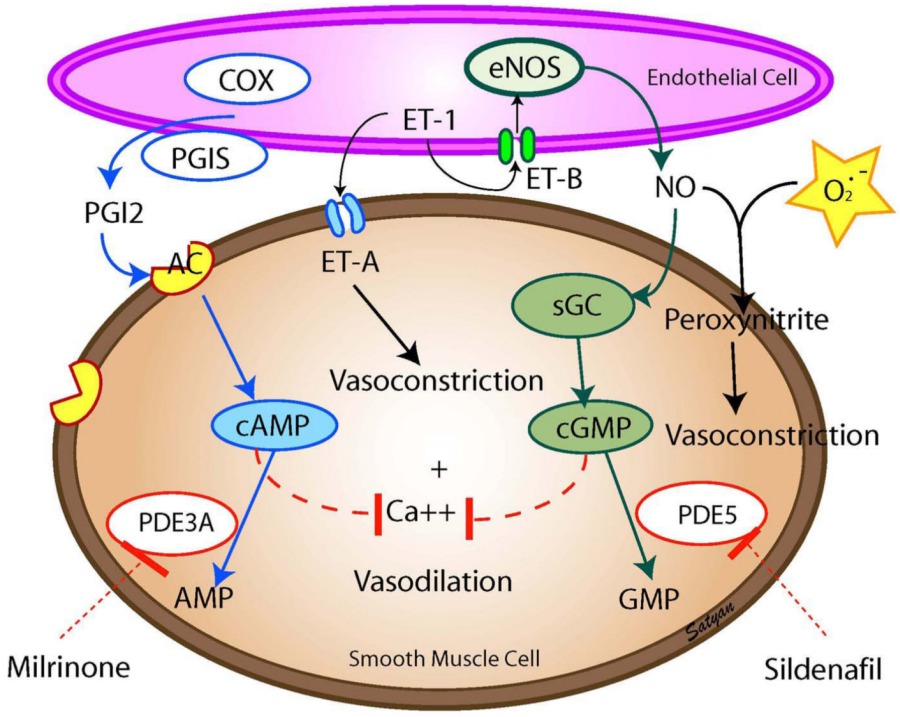

Figure 1.

Endothelium derived vasodilators – prostacyclin (PGI_2) and nitric oxide (NO) and vasoconstrictor (endothelin, ET-1). The enzymes, cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). 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. 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. Nitric oxide is a free radical and can avidly combine with superoxide anions to form a toxic vasoconstrictor, peroxynitrite. Hence, the bioavailability of NO in a tissue is determined by the local concentration of superoxide anions. Hyperoxic ventilation with 100% oxygen 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)*.

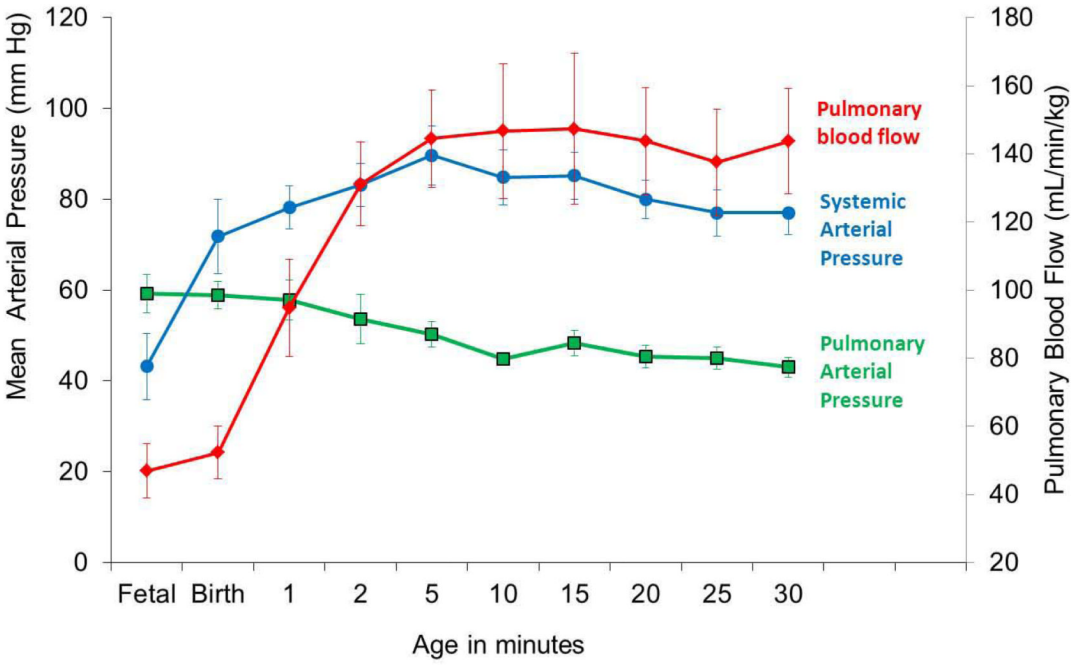

Figure 2.

Changes in pulmonary blood flow (secondary Y-axis on the right), mean systemic arterial pressure and mean pulmonary arterial pressure (primary Y-axis on the left) in normal term lambs ventilated with 21% oxygen over the first 30 min of life. The pulmonary arterial pressure is higher than the systemic arterial pressure during fetal period. Clamping the umbilical cord at birth increases systemic blood pressure and ventilation reduces pulmonary arterial pressure and increases pulmonary blood flow. Data derived from 8 lambs from the author's laboratory.

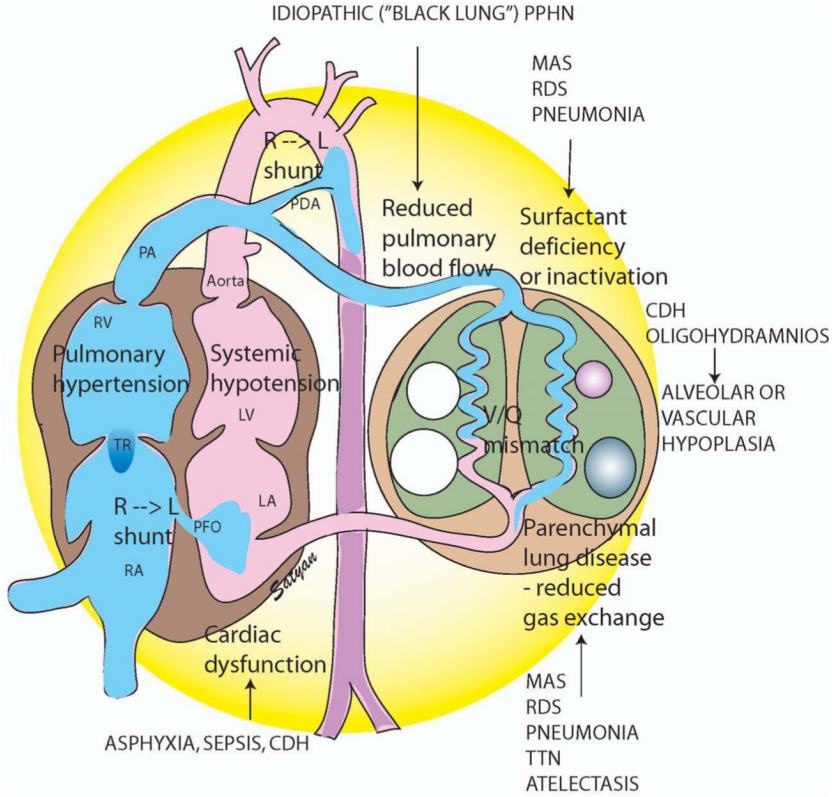

Figure 3.

Various etiological factors causing PPHN and hemodynamic changes in PPHN/HRF – PA – pulmonary artery; RV – right ventricle; LV – left ventricle; TR – tricuspid regurgitation; RA – right atrium; LA – left atrium; PDA – patent ductus arteriosus; PFO – patent foramen ovale. Surfactant deficiency (RDS) or inactivation (MAS or pneumonia) result in parenchymal lung disease and ventilation-perfusion (V/Q) mismatch. Increased pulmonary vascular resistance results in reduced pulmonary blood flow and right to left shunt through PDA and/or PFO. Pulmonary hypertension is often associated with systemic hypotension with septal deviation to the left. Cardiac dysfunction secondary to asphyxia, sepsis or congenital diaphragmatic hernia (CDH) may complicate HRF. Parenchymal lung disease secondary to RDS, pneumonia, transient tachypnea of newborn (TTN), pneumonia, and atelectasis can result in V/Q mismatch and hypoxemia and PPHN. Idiopathic or "black-lung" PPHN is not associated with parenchymal lung disease and results in reduced pulmonary blood flow with pulmonary vascular remodeling. Pulmonary hypoplasia secondary to CDH or due to oligohydramnios (prolonged leakage of fluid or reduced production due to renal compromise) causes alveolar and vascular hypoplasia and PPHN. The right subclavian artery (and blood flowing to the right upper extremity) is always preductal. The left subclavian artery may be preductal, juxtaductal or postductal. Hence, preductal oxygen saturations should be obtained from the right upper extremity *(copyright Satyan Lakshminrusimha).*

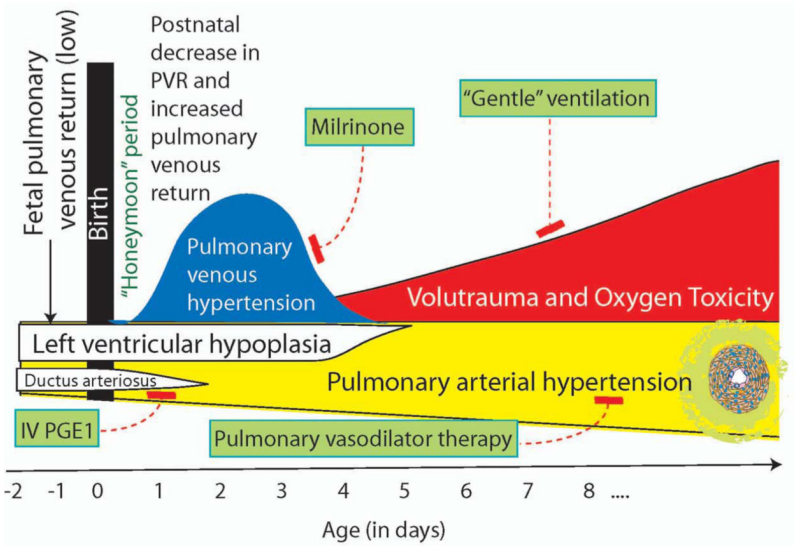

Figure 4.

Pathophysiology of hemodynamic abnormalities in congenital diaphragmatic hernia. During fetal life, reduced pulmonary venous return contributes to left sided cardiac hypoplasia. In the immediate postnatal period, a short period of better oxygenation is referred to as "honeymoon" period. Subsequently, a period of left ventricular dysfunction results in pulmonary venous hypertension. Progressive volutrauma and oxygen toxicity leads to chronic lung disease and contributes to pulmonary hypertension. Maintenance of ductal patency with intravenous PGE1 and enhanced left ventricular function with milrinone may improve oxygenation in CDH *(Copyright Satyan Lakshminrusimha)*

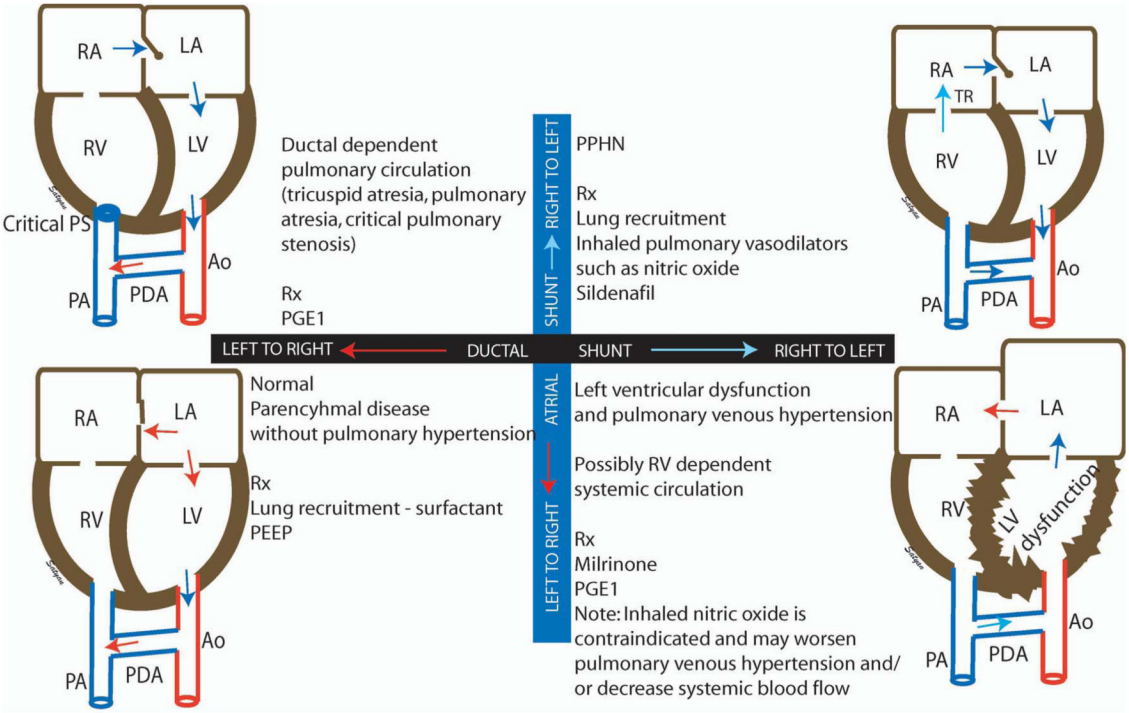

Figure 5.

Echocardiographic evaluation of neonatal hypoxemia based on ductal (black bar) and atrial (blue bar) shunts. Left to right shunt at the ductal and atrial level is considered normal but can also be seen in the presence of parenchymal lung disease resulting in hypoxemia in the absence of PPHN (lower left quadrant). The presence of right to left shunt at the atrial and ductal level is associated with PPHN (upper right quadrant). Right to left shunt at the ductal level but a left to right shunt at the atrial level is associated with left ventricular dysfunction, pulmonary venous hypertension and ductal-dependent systemic circulation (lower right quadrant) and is a contraindication for inhaled pulmonary vasodilators such as iNO. In patients with right sided obstruction (such as critical pulmonary stenosis – PS), right atrial blood flows to the left atrium through the PFO. Pulmonary circulation is dependent on a left to right shunt at the PDA (upper left quadrant). PA – pulmonary artery; RV – right ventricle; LV – left ventricle; TR – tricuspid regurgitation; RA – right atrium; LA – left atrium; PDA – patent ductus arteriosus; Ao – aorta; PGE1 (prostaglandin E1) *(Copyright Satyan Lakshminrusimha)*

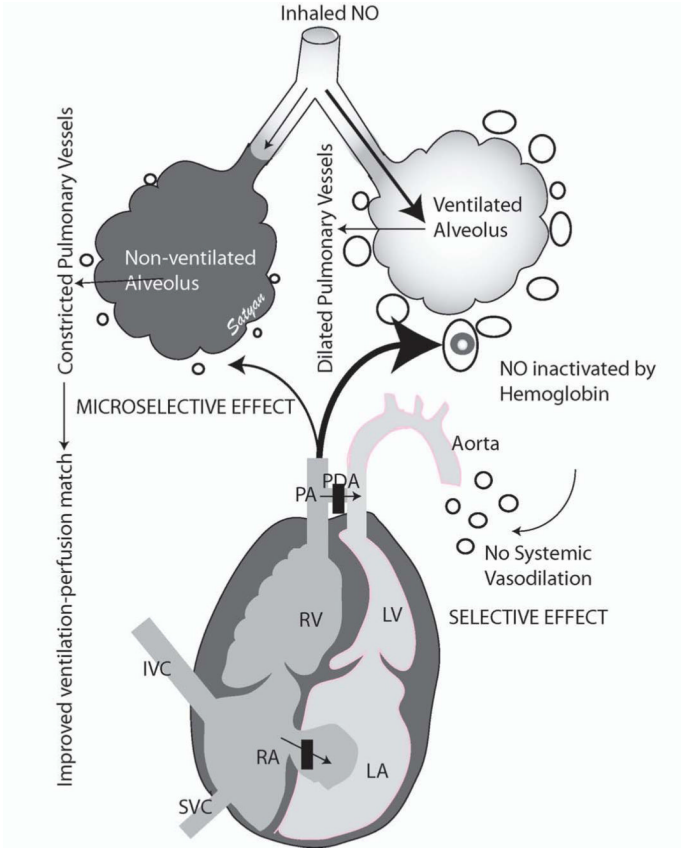

Figure 6.

Selective and micro-selective action of inhaled nitric oxide (NO); Inhaled NO is a selective dilator of the pulmonary circulation without any significant systemic vasodilation as it combines with hemoglobin to form methemoglobin. As it is an inhaled vasodilator, it selectively enters the well ventilated alveoli and improves blood flow to these alveoli and reduces V/Q mismatch (micro-selective effect) *(Copyright Satyan Lakshminrusimha)*

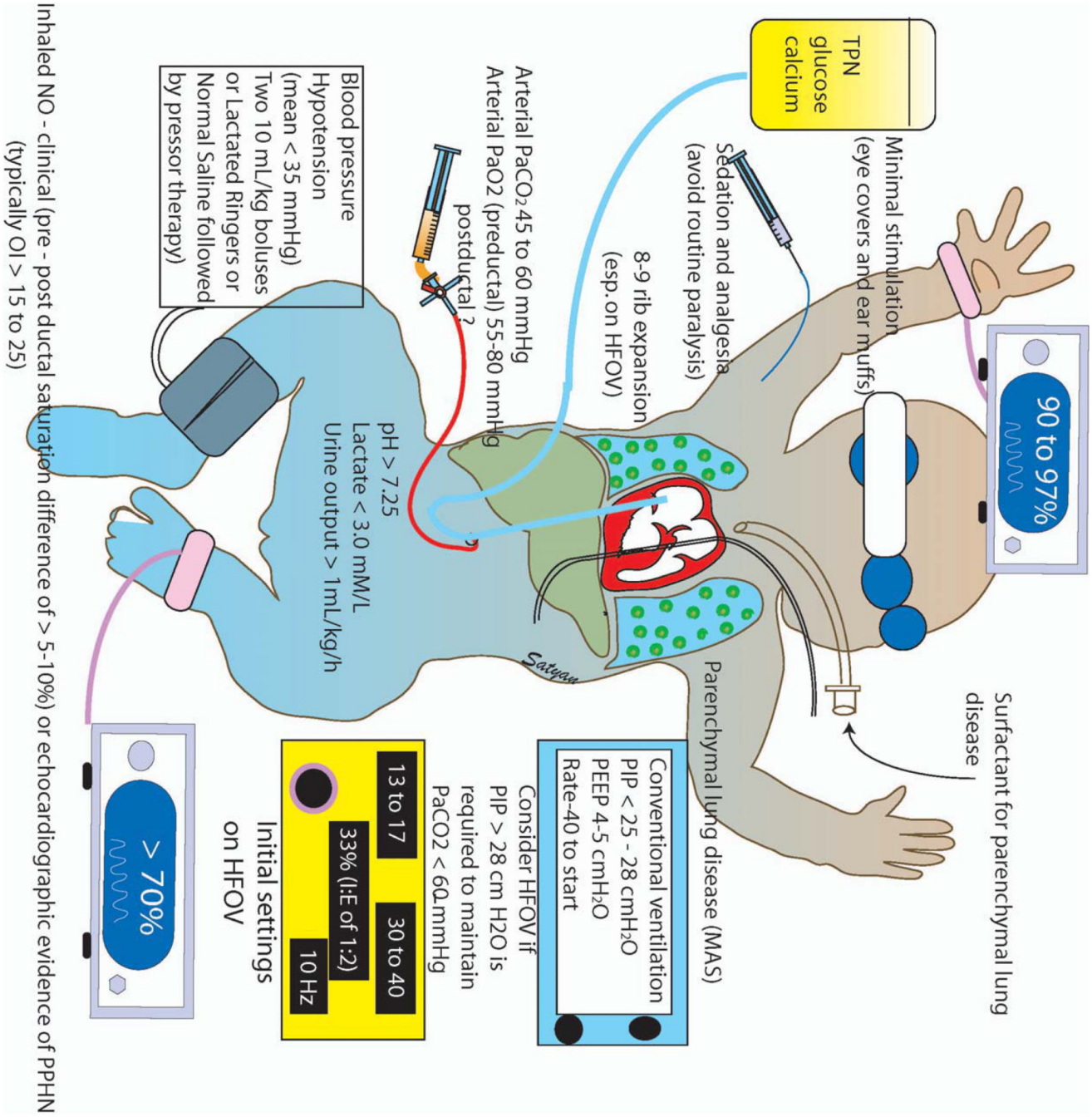

Figure 7.
Management of PPHN by "gentle ventilation" – see text for details *(Copyright Satyan Lakshminrusimha)*