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Persistent Pulmonary Hypertension of the Newborn

Pathogenesis, Etiology, and Management

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is characterized by severe hypoxemia shortly after birth, absence of cyanotic congenital heart disease, marked pulmonary hypertension, and vasoreactivity with extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale. *In utero*, a number of factors determine the normally high vascular resistance in the fetal pulmonary circulation, which results in a higher pulmonary compared with systemic vascular pressure. However, abnormal conditions may arise antenatally, during, or soon after birth resulting in the failure of the pulmonary vascular resistance to normally decrease as the circulation evolves from a fetal to a postnatal state. This results in cyanosis due to right-to-left shunting of blood across normally existing cardiovascular channels (foramen ovale or ductus arteriosus) secondary to high pulmonary versus systemic pressure.

The diagnosis is made by characteristic lability in oxygenation of the infant, echocardiographic evidence of increased pulmonary pressure, with demonstrable shunts across the ductus arteriosus or foramen ovale, and the absence of cyanotic heart disease lesions.

Management of the disease includes treatment of underlying causes, sedation and analgesia, maintenance of adequate systemic blood pressure, and ventilator and pharmacologic measures to increase pulmonary vasodilatation, decrease pulmonary vascular resistance, increase blood and tissue oxygenation, and normalize blood pH. Inhaled nitric oxide has been one of the latest measures to successfully treat PPHN and significantly reduce the need for extracorporeal membrane oxygenation.

Persistent pulmonary hypertension of the newborn (PPHN) is a complex disease of the neonate characterized by: severe hypoxemia shortly after birth; an absence of cyanotic congenital heart disease; marked pulmonary hypertension; and vasoreactivity with extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale.[1] It is a common problem in the neonate, with an incidence of about 1 : 1000 live births, and is associated with significant morbidity and mortality.[1,2]

This article discusses the pathogenesis, etiology, diagnosis, and current modalities of treatment of PPHN.

1. Pathogenesis

The fetal circulation has some important distinguishing characteristics, including a high pulmonary vascular resistance, low systemic resistance in the placenta, and the presence of transient circulatory channels such as the ductus venosus, ductus arteriosus, and the foramen ovale. Because of the high pulmonary vascular resistance and pressure, right-to-left shunting of blood across the transient circulatory channels occurs and the circulation to the lungs is <10% of the combined ventricular output.[3,4] The high pulmonary resistance is secondary to a number of factors, including: low arteriolar and alveolar oxygen levels; hypercarbia; acidosis; alveolar fluid pressure; lack of mechanical, rhythmic distention of the lung; and the net vasoconstricting action of a number of humoral agents.[3] Catecholamines, histamine, bradykinin, angiotensin, adenosine, serotonin, prostaglandins, thromboxane, atrial natriuretic peptide, endothelin, and nitric oxide (NO) are involved in the regulation of pulmonary vascular tone in the fetus.[4]

Several events occur immediately after birth that drastically alter the state of the fetal circulation. The umbilical cord is clamped and, with the removal of the low-resistance placental circuit, systemic vascular resistance increases. The lungs are inflated with air, effecting a marked decrease in pulmonary vascular resistance and a 10-fold increase in pulmonary blood flow.[3,5,6] Respiration also increases the oxygen tension of the pulmonary vascular bed and improves the pH, further decreasing pulmonary vascular resistance.[6] This transitional circulation occurs within the first 24 hours after birth, during which time pulmonary pressures also decrease to less than half that of systemic levels.[3,6] Vasodilator mediators such as NO and prostacyclin (epoprostenol) are thought to be crucial in this process.[2,3] Certain structural changes in the pulmonary vascular musculature also occur as part of the final phase of transition. These include a decrease in the medial wall thickness of preacinar vessels.[6]

PPHN is a state of persistent hypoxemia and cyanosis in the neonate resulting from failure of the postnatal decline of pulmonary artery resistance and pressure and a persistence of right-to-left shunting across the ductus arteriosus and foramen ovale. Several mediators may have a pathophysiologic role in PPHN:

- NO is produced in pulmonary vascular endothelial cells by the conversion of L-arginine to citrulline, which is catalyzed by the enzyme NO synthase. NO acts on vascular smooth muscle cells, stimulates guanylate cyclase, and increases cyclic guanosine monophosphate (cGMP) levels, which cause vasodilatation through calcium-activated potassium channels.[2,3] In animal models of experimental PPHN and in clinical studies, there appears to be limited endogenous synthesis of NO, decreased endothelial NO synthase expression, and inhibition of the release of NO and cGMP production.[2,3,7-9]
- Endothelin-1 (ET-1) is present in high levels in the fetus and acts as a potent and sustained pulmonary vasoconstrictor via calcium release within vascular smooth muscle cells. Postnatally, the effects of ET-1 on pulmonary vascular resistance are mediated through two receptor subtypes: ET_A and ET_B. ET_A is present in the vascular smooth muscle cell and contributes to vasoconstriction while ET_B is present in the vascular endothelial cell and mediates vasodilatation via the release of NO.[2,3,8] There are data to suggest that infants with PPHN have increased production of ET-1 in the pulmonary circulation.[8] Other studies have reported elevated immunoreactive ET-1 levels in the pulmonary blood of neonates with PPHN, with some reports of a decline in levels associated with an improvement in the disease.[10,11]
- Prostacyclin is produced by pulmonary vessels and is stimulated by the onset of breathing at birth. It may play a role in the normal postnatal decrease of pulmonary vascular resistance, particularly as a result of rhythmic distention of the lungs, but may not be essential to the transition.[3,6]

PPHN can be associated with maldevelopment, decreased area, and altered mechanical properties of pulmonary vascular smooth muscle cells resulting in significant vasoconstriction.[6] The maldevelopment is an abnormal muscularization of the pulmonary vessels from the preacinar to the intra-acinar or even alveolar levels, probably secondary to acute or chronic intrauterine hypoxia.[6,12] Apart from the pulmonary vascular pathology, left ventricular dysfunction also significantly contributes to the disease process and worsens the right-to-left shunting of blood.[4] Conversely, the elevated pulmonary vascular resistance in PPHN increases right ventricular afterload, impairs oxygen delivery, and causes right ventricular dysfunction.[12] When PPHN occurs in association with parenchymal lung disease, intrapulmonary shunting of deoxygenated blood contributes to the severe hypoxemia.[4]

2. Etiology

Several conditions are associated with PPHN (table I).[6,12] In the absence of cardiac or pulmonary disease, PPHN is referred to as idiopathic PPHN.

Conditions that lead to chronic hypoxia *in utero* or abnormal muscularization of the pulmonary vessels can lead to persistent

Table I. Causes of persistent pulmonary hypertension of the newborn

Persistent pulmonary vasoconstriction
Asphyxia[13]
Meconium aspiration syndrome[13]
Neonatal respiratory distress syndrome[14]
Sepsis/pneumonia (e.g. group B streptococcal disease)[15,16]
Antenatal indometacin/salicylate therapy[17]
Other (e.g. pulmonary alveolar dysplasia)[18]
Functional obstruction of pulmonary vascular bed
Hyperviscosity secondary to polycythemia[19]
Decreased pulmonary vascular bed
Congenital diaphragmatic hernia[20]
Pulmonary hypoplasia – oligohydramnios, pleural effusion, vascular anomalies, asphyxiating thoracic dystrophy, phrenic nerve agenesis, etc.[21]
Pulmonary venous hypertension
Total anomalous pulmonary venous return[22]
Left atrial or mitral obstruction[23]
Hypoplastic left heart syndrome[24]
Myopathic left ventricular disease (e.g. endocardial fibroelastosis and Pompe disease)[25,26]
Obstruction to left ventricular outflow (e.g. aortic stenosis, interrupted arch, and coarctation)[25,26]

pulmonary vasoconstriction and persistent pulmonary hypertension after birth. These conditions include asphyxia, aspiration syndromes (e.g. meconium aspiration), neonatal respiratory distress syndrome, and antenatal indometacin/salicylate therapy. Persistent pulmonary hypertension secondary to group B streptococcal sepsis or pneumonia may be thromboxane or streptococcal toxin mediated.[27,28]

In alveolar capillary dysplasia, there is failed formation and ingrowth of alveolar capillaries and medial musculature hypertrophy leading to persistent pulmonary hypertension.

Conditions that cause a decrease in the pulmonary vascular bed include congenital diaphragmatic hernia (CDH) and pulmonary hypoplasia secondary to oligohydramnios, pleural effusion, vascular anomalies, asphyxiating thoracic dystrophy, and phrenic nerve agenesis.

Conditions that increase pulmonary venous pressure include total anomalous pulmonary venous return, left atrial or mitral obstruction, obstruction to left ventricular outflow (e.g. aortic stenosis, coarctation of the aorta, and hypoplastic left heart syndrome), and myopathic left ventricular disease (e.g. endocardial fibroelastosis, Pompe disease, and pulmonary vein stenosis).

Conditions that cause a chronic increase in pulmonary flow include systemic right ventricle or single ventricle without pulmonary stenosis and peripheral arteriovenous fistula.

Conditions that cause a functional obstruction of the pulmonary vascular bed include hyperviscosity secondary to polycythemia.

3. Diagnosis

PPHN is suspected in a newborn infant who exhibits lability in oxygenation state or progressive cyanosis within the first 12–24 hours of life, sometimes after an initial period of good oxygenation. The diagnosis is established from the history, physical examination, laboratory tests, chest x-ray, preductal and postductal blood gases, hyperoxia test, and echocardiogram.

The history usually reveals a term or post-term infant with a history of perinatal asphyxia, meconium-stained fluid, or predisposing factors such as prolonged rupture of membranes, oligohydramnios, maternal group B streptococcal colonization, maternal smoking, and antenatal use of NSAIDs.[16,17,29]

Physical examination reveals progressive or intermittent cyanosis, variable degrees of respiratory distress, prominent right ventricular impulse, and a loud single or closely split second heart sound.[6] A murmur in the pulmonary or tricuspid area or rarely in the mitral area (mitral regurgitation) may be audible.[30] The systemic blood pressure (BP) may be normal or there may be signs of congestive heart failure and low BP.[30] In addition, there may be differential oxygen saturations in the upper and lower extremities due to shunting of deoxygenated blood through the ductus arteriosus.[6]

The chest x-ray is non-specific. It may be normal or there may be mild-to-moderate parenchymal lung disease. Other findings may include cardiomegaly with a cardiothoracic ratio >0.6, decreased pulmonary vascular markings in idiopathic PPHN, and pulmonary congestion.[12,30] The main pulmonary artery segment is typically prominent.[30] A chest x-ray is most useful to diagnose the cause of any acute deterioration in an infant with PPHN such as pneumothorax, pneumomediastinum, pulmonary hemorrhage, or the progression of parenchymal lung disease.[30]

Echocardiographic diagnosis of PPHN is based on the demonstration of high pulmonary artery pressures, often greater than systemic pressures, and a right-to-left shunt through the ductus arteriosus and/or foramen ovale. The indicators suggestive of increased pulmonary artery pressure are prolonged right ventricular systolic time interval (defined as a ratio of pre-ejection period to ejection period >0.5) and a shortened pulmonary flow velocity ratio (defined as a ratio of time to peak velocity at pulmonary valve to right ventricular ejection time <0.34).[6,30,31] A prolonged left ventricular systolic time interval is indicative of ventricular dysfunction.[30-33] A failure of acceleration of systolic blood flow between the large main pulmonary artery and the small peripheral pulmonary artery on Doppler is also suggestive of right-to-left intracardiac or ductal shunt.[6] On the other hand, the echocardiogram may be normal and the right-to-left shunt across the ductus arteriosus or foramen ovale may not be seen depending on the

level of the pulmonary artery pressure at the time of examination. Doppler measurement of pulmonary artery pressure by the peak velocity of tricuspid regurgitation is possible only in about 70% of patients who have tricuspid regurgitation.[31,32] Doppler indices of left ventricular dysfunction such as impaired ejection fraction and stroke volume may occur in 10% of patients and is associated with ischemic myocardial damage, which carries a poor prognosis.[31-33] In this subset of patients, pulmonary vasodilator therapy may be contraindicated because the systemic perfusion may be adversely affected.[34] Low left ventricular output and stroke volume have been reported to predict subsequent death in infants with PPHN.[32] Finally, the echocardiogram is important in ruling out the presence of cyanotic congenital heart disease.[31]

Analysis of arterial blood gases reveal hypoxemia with relatively normal carbon dioxide partial pressure ($PaCO_2$). The oxygen partial pressure (PaO_2) is labile and may show an intermittent and transient increase (>100 torr) with high inspired oxygen fraction and mechanical ventilation (hyperoxia test).[6] A simultaneous preductal and postductal arterial oxygen pressure gradient of >15mm Hg suggests a right-to-left shunt at the level of the ductus arteriosus.[6]

The changes in the ECG are non-specific but may include right or biventricular hypertrophy and ST and T wave changes suggestive of myocardial ischemia.[30] Other laboratory tests include a complete blood count and differential white cell count to detect polycythemia or sepsis, and serum glucose and calcium level tests to identify hypoglycemia and hypocalcemia.

4. Treatment

The modalities of treatment of PPHN are shown in table II. The objectives of therapy are to correct the underlying cause of PPHN, if known, to maintain adequate systemic BP, to decrease pulmonary vascular resistance, to maintain optimal oxygen delivery to the tissues, and to minimize ventilator-induced lung injury.

Table II. Treatment of persistent pulmonary hypertension of the newborn

Treat associated problems (e.g. antibiotics and partial exchange transfusion, etc.)
Ventilation support (e.g. oxygen, continuous positive airway pressure, and ventilator)
Correct acidosis (metabolic or respiratory)
Support blood pressure (e.g. plasma expander and sympathomimetics)
Sedation/paralysis (e.g. morphine, midazolam, and pancuronium)
Surfactant
Nitric oxide
Extracorporeal membrane oxygenator
Experimental vasodilating agents
Inhaled or intravenous prostacyclin (epoprostenol) and magnesium sulfate

Antibiotics are used to treat sepsis and pneumonia, partial exchange transfusion for polycythemia, and surgery for CDH. Blood pressure is maintained by volume support using colloids (plasmanate) or crystalloids (normal saline) and by inotropic agents such as dopamine, dobutamine, and milrinone. The goal is to correct systemic arterial hypotension and maintain an adequate systolic BP to minimize right-to-left shunting.[35] Dopamine is given at a dose of 2–10 μg/kg/minute to avoid the α-adrenergic effects of pulmonary vasoconstriction and an increase in afterload. Dobutamine, at a dose of 2.5–25 μg/kg/minute, is predominantly a β1 agonist and is indicated in cases of poor cardiac function.[35] The infant is maintained in a thermoneutral environment and sedated with morphine, fentanyl, or midazolam. There should be minimal handling of the infant and the infant's oxygenation and blood gas status should be monitored by the transcutaneous method and blood sampling through indwelling catheters. Neuromuscular paralytic agents, such as pancuronium, are only used as a last resort if synchronization of the infant with the ventilator is needed, particularly if high peak inspiratory pressures are used; this is because of reports of an increased risk of death associated with the use of these drugs.[36]

4.1 Surfactant Therapy

Exogenous surfactant acts by stabilizing alveolar volumes, improving gas exchange, and minimizing ventilation perfusion inequality. Certain causes of PPHN, such as meconium aspiration syndrome and CDH, are associated with deficiency of surfactant proteins and phospholipids or diminished surface activity.[37] However, clinical trials of surfactant therapy in neonates with PPHN have had variable results. Surfactant was found to improve oxygenation and decrease the need for an extracorporeal membrane oxygenator (ECMO), particularly when given early in the disease in infants with severe respiratory failure.[38] In addition to these benefits, in infants with meconium aspiration there was a reported decrease in the severity of pulmonary morbidity, air leaks, and length of hospital stay.[39] In animal models of meconium aspiration, the response to inhaled NO was augmented following early surfactant administration.[40] In contrast, surfactant did not improve lung compliance or decrease the time to extubation when given to infants with CDH treated with an ECMO.[41]

In summary, exogenous surfactant may be given to patients with meconium aspiration and pneumonia associated with PPHN though the optimal dose regimen is not well established.[42]

4.2 Mechanical Ventilation

The maintenance of adequate oxygenation is the primary goal in the management of PPHN and mechanical ventilation is one of the treatment modalities to achieve this goal. One of the early strategies in conventional ventilator therapy was hyperventilation

to increase blood pH, reverse ductal shunting,[36,43] and induce pulmonary vasodilatation. Hyperventilation, compared with alkali infusion, also reduced the risk of extracorporeal membrane oxygenation.[36] However, studies have shown that hyperventilation and the induction of metabolic and respiratory alkalosis in the treatment of PPHN have not significantly improved the clinical outcome and have been associated with adverse neurologic sequelae.[44] Multiple retrospective studies report a strong association between $PaCO_2$ levels <25–30mm Hg and an increased incidence of cystic periventricular leukomalacia and cerebral palsy in preterm infants and hearing loss in term and near-term infants.[44] Significant reduction of cerebral blood flow was observed in infants in whom the hyperventilation alkalosis strategy was employed.[45] Oxygen delivery to tissues may also be compromised by alkalosis due to impaired unloading of oxygen from hemoglobin. Hyperventilation can also induce lung injury due to barotrauma, volutrauma, air leaks, and chronic lung disease from high inflation pressure.[42,43] A review of autopsies of infants with PPHN secondary to CDH revealed diffuse lung injury secondary to mechanical ventilation, which may have contributed to the high mortality rate in CDH.[42,43] The critical determinants of lung injury are tidal volume and end inspiratory lung volume.

Recent management strategies have therefore been modified to accept pH levels of 7.4–7.5, $PaCO_2$ levels of 40–60mm Hg, and normal PaO_2 of 60–90mm Hg, in the hope of avoiding high peak inflating pressures and ventilator rates.[43,44,46,47] Permissive hypercapnia promises to maintain gas exchange with lower tidal volume and thus decrease injury.[48] Although the studies are still few, permissive hypercapnia ($PaCO_2$ as high as 65mm Hg) has been shown to increase survival rates in neonates with CDH.[49-52] It is well tolerated and the side effect of neurologic depression is reversible within 24 hours of restoring adequate ventilation.[53] On the other hand, a meta-analysis of two randomized clinical trials of mechanically ventilated neonates managed with permissive hypercapnia/minimal ventilation did not demonstrate any significant reduction in the incidence of death and chronic lung disease at 36 weeks, intraventricular hemorrhage, or perinatal leukomalacia.[54] Thus, ventilator strategies that target high levels of $PaCO_2$ (>55mm Hg) should only be undertaken in the context of well designed, controlled clinical trials to establish the safe, or ideal, range for $PaCO_2$ in ventilated newborns.

Time constant, the product of resistance and compliance, is variable in PPHN, since it is affected by the underlying pathology. Time constant in meconium aspiration syndrome is often increased due to increased resistance from air trapping.[55] In other underlying diseases such as pneumonia, hyaline membrane disease, or even in meconium aspiration, time constant is reduced due to decreased lung compliance.[55] Expiratory time constants in PPHN are also normal to increased. Thus, the ventilator expiratory time can be increased and the inspiratory time shortened.[56,57] As an adjunct to ventilator therapy, sedatives such as benzodiazepines and analgesics such as fentanyl may be used.

High-frequency ventilation (HFV) is an alternative mode of ventilatory support in infants who are non-responsive to conventional ventilator therapy.[42] It has been advocated to improve lung inflation while decreasing lung injury due to volutrauma and barotrauma.[58-60] In HFV, the tidal volume approaches or is less than the dead space and involves frequencies far in excess of physiologic respiratory rates.[57] Care must be taken since tidal volumes higher than the dead space may ensue with increases in frequency and percent inspiratory time settings.[61,62]

There are three types of HFV. High-frequency jet ventilation utilizes a flow interrupter that can deliver 60–600 insufflations/minute. Inspiratory gases are accelerated as they pass through the jet cannula and entrainment of gases occurs by the Bernoulli effect.[57] Compared with conventional ventilation, high-frequency jet ventilation is associated with significant improvement in oxygenation, ventilation, and oxygen indices while maintaining lower peak and mean airway pressures.[59] Another type of HFV is high-frequency flow interruption ventilation, which can attain sustained hyperoxygenation without hypocarbia and alkalosis.[63] There is a shorter time to wean from oxygen and extubation, a smaller incidence of chronic lung disease, and a shorter hospital stay compared with conventional ventilation.[46] High-frequency oscillatory ventilation, a third type of HFV, is unique in that both inspiration and expiration are active.[64] It utilizes tidal volumes that are frequently less than the dead space,[65] although tidal volumes higher than the dead space may ensue with increases in frequency and percent inspiratory time settings.[61,62] High-frequency oscillatory ventilation has also been shown to augment an inhaled NO response to PPHN by improving lung inflation and allowing better alveolar recruitment.[66-68] It is the preferred mode when there is coexisting parenchymal lung disease with PPHN.

4.3 Pulmonary Vasodilators

Pulmonary vasodilatation with multiple drugs has been evaluated for the treatment of PPHN, but none has been recommended for clinical use except for NO. Isolated case reports of adenosine infusion have shown improved oxygenation but with adverse effects of bradycardia, hypotension, and prolonged bleeding time, which have precluded its clinical use.[69] Tolazoline was formerly used as a vasodilating, α-adrenergic blocking agent. However, it induces histamine release, and adverse effects such as increased gastric secretions and bleeding as well as systemic hypotension and oliguria frequently occur.[42] Prostacyclin and magnesium infusions are effective in reducing pulmonary arterial pressures but also cause systemic hypotension.[35,70] Inhaled prostacyclin at a dose of 20–100 ng/kg/minute has been shown to improve oxygenation and reduce pulmonary artery pressures in PPHN, without affecting systemic BP.[71,72] In a case series report of four infants

with PPHN and hypoxemia refractory to inhaled NO, inhaled prostacyclin rapidly improved oxygenation, probably through an alternative cyclic adenosine monophosphate-mediated vasodilatation.[73]

4.4 Phosphodiesterase Inhibitors

Cyclic GMP is a critical second messenger system that causes pulmonary vasodilatation by interacting with the protein kinase class of enzymes. NO-induced pulmonary vasodilatation is mediated mainly by this pathway.[74] Phosphodiesterases (PDEs) are enzymes that cleave the cyclic nucleotides, control their intracellular levels and diffusion, maintain signaling homeostasis, and degrade NO.[75] Several recent studies have explored the role of PDE inhibitors in PPHN, with the rationale that they should increase cGMP levels, cause pulmonary vasodilatation by themselves, and enhance the effect of NO. Of the PDEs, PDE5 is found in high levels in the smooth muscle cells of the pulmonary vasculature.[76]

In animal models of pulmonary hypertension, lung PDE5 activity is reported to be elevated.[77] Dipyridamole, a PDE inhibitor, lowered pulmonary vascular resistance, increased the response to NO in animal studies and clinical case series, and was efficacious in preventing rebound pulmonary hypertension after weaning of NO.[78,79] However, significant adverse effects have been seen. Zaprinast and sildenafil are specific PDE5 inhibitors that act as selective pulmonary vasodilators and augment the magnitude of response to inhaled NO in animal models of PPHN.[80]

In animal models of meconium aspiration syndrome and PPHN, oral or intravenous sildenafil was as effective as NO at 20 parts per million (ppm) in causing pulmonary vasodilatation, enhanced its effect, and also increased cardiac output by 30%.[81,82] In the few available clinical trials, it attenuated the rebound pulmonary hypertension associated with weaning of NO and reduced pulmonary arterial pressures.[83] While this agent has immense promise as a therapeutic option in PPHN, there may be significant adverse effects in certain conditions. Recent data in animal models show that when combined with NO sildenafil may lower systemic vascular resistance and worsen hypoxemia and the ventilation perfusion mismatch in conditions where pulmonary hypertension coexists with parenchymal lung disease.[84] There is a need for more data on long-term outcomes, safety, and optimal administration in neonates. It is also not likely to be effective when NO treatment has failed, considering its mechanism of action.[75]

4.5 Nitric Oxide

Currently, the mainstay of treatment and the recommended pulmonary vasodilating agent for PPHN is inhaled NO. NO acts by relaxing the vascular smooth muscle cells by increasing cGMP levels through the guanylate cyclase pathway.[2,3] The action of inhaled NO is confined to the lungs (no systemic hypotension observed) since NO, which has a high affinity for hemoglobin, is inactivated in the lungs. Besides its vasodilating effect, NO also causes a better ventilation perfusion match with redistribution of pulmonary blood flow to better ventilated alveoli.[34] Inhaled NO may have other, as yet undetermined effects on lung inflammation, vascular thrombosis, and permeability.[34,85]

Since 1997, several randomized controlled trials have demonstrated that inhaled NO significantly improves oxygenation (in about 50% of treated patients) and reduces the need for ECMO in term (>34 weeks) neonates with hypoxemic respiratory failure.[85-87] A meta-analysis from the Cochrane Library concluded that the oxygenation index decreases by a weighted mean of 15.1 and the arterial PaO_2 increases by a mean of 53mm Hg.[88] Recent studies have shown that inhaled NO, when used in moderate PPHN (defined as arterial alveolar gradient [A-a DO2] of 500–599), results in sustained improvement in oxygenation, a decrease in ventilatory support in the first 36 hours, and prevents the progression of the disease to a severe form (A-a DO2 >600).[87] Inhaled NO is also useful in stabilizing patients during transport or prior to ECMO. The indication for the use of inhaled NO in PPHN is currently an oxygenation index of >25 with evidence of extrapulmonary shunting based on the criteria used in large clinical trials.[85,86] Despite its widespread use and enormous benefit, NO therapy has not affected mortality rates, the outcomes in patients with CDH have not improved, and there are risks of rebound hypertension on weaning and adverse effects at higher doses.[34,86] Likewise, its role in early and milder disease forms is unclear.

Clinical trials have evaluated doses of inhaled NO from 5 to 80 ppm. The acute improvement in oxygenation does not significantly differ beyond 20 ppm and the decrease in pulmonary pressures is greatest at 20 ppm.[89,90] At the high inhaled NO dose of 80 ppm, methemoglobin levels >7% occur more often (35%) with only minimal (6%) improvement in response.[89] A randomized controlled trial using low-dose inhaled NO at 2 ppm found that at that dose, inhaled NO did not acutely improve oxygenation or prevent clinical deterioration.[91] Furthermore, initial treatment with a subtherapeutic dose diminished the clinical response to subsequent inhaled NO at 20 ppm.[90] Therefore, at present, the recommended initial dose of NO is 20 ppm, which is weaned to 5 ppm in steps if the patient maintains stable good oxygenation for about 12 hours.[34] NO is discontinued if the oxygen requirement can be weaned to <50–60% while maintaining arterial PaO_2 at the desired level, usually within 5 days. In some instances, a rebound desaturation and hypoxemia may occur after inhaled NO is discontinued. This phenomenon seems to occur more in infants with higher pulmonary artery pressures at the time of NO withdrawal.[34] It is speculated that the rebound is secondary to the suppression of endogenous NO production by inhaled NO or an altered cGMP pathway.[34,72] If this occurs, inhaled NO is steadily weaned to as low as 1 ppm and then discontinued. Arterial oxygen should

be carefully monitored and an increase in oxygen support and reinstitution of NO may be needed in some cases. Newer adjuvant therapies such as PDE5 inhibitors may have a role in this situation.

Inhaled NO is safe at its recommended dose. Methemoglobin is formed as a metabolite of NO, but its blood concentration is normally <5%, which does not significantly affect the oxygen-carrying capacity of the blood. At higher doses, NO can increase cGMP in platelets and inhibit their aggregation and adhesion. However, in clinical trials there has been no increase in the occurrence of intracranial, pulmonary, or gastrointestinal hemorrhage in infants treated with inhaled NO.[34] Another potential concern is that peroxynitrites and nitrogen dioxide can be formed by NO and may cause oxidation injury to the lungs and inhibit surfactant function. Long-term outcomes in children with moderately severe PPHN are not different to those receiving NO from control individuals.[92]

4.6 Extracorporeal Membrane Oxygenation

ECMO is a final rescue mode of therapy in infants with reversible respiratory or cardiac failure when all other non-invasive measures have failed.[93] It is a modified cardiopulmonary bypass that ensures adequate oxygen delivery and gas exchange in patients with PPHN with or without cardiac support.[94] As such, the patient's innate organs are rested (lung rest) to facilitate repair and also avoid the barotrauma and volutrauma of mechanical ventilation management.[95] Aside from PPHN, ECMO has also been used in meconium aspiration syndrome, CDH, and cardiac anomalies.[96] Since ECMO is an invasive procedure, it is reserved for infants receiving maximum ventilatory support and those who meet the Bartlett criteria (oxygenation index >40), which is indicative of ≥80% risk of dying.[96-98] Over the last decade, the incidence in the use of ECMO in non-CDH, non-cardiac neonates has declined as a result of the emergence of alternative technologies such as inhaled NO, surfactant, HFV, etc.[99-101]

The principle behind ECMO involves obtaining access to drain blood from the venous circulation (internal jugular vein) into an extracorporeal circuit, where it is oxygenated, cleansed of carbon dioxide, and warmed before being returned to the patient.[93] Blood from the extracorporeal circuit can be returned to the patient either via the common carotid artery (venoarterial ECMO)[102] or the internal jugular vein (venovenous ECMO). Concern about the ligation of the carotid artery has prompted the development of a double lumen internal jugular catheter for venovenous oxygenation in infants in respiratory failure but with good cardiac function.[102,103] Venovenous and venoarterial cannulation have comparable survival rates for ECMO,[104,105] although venoarterial cannulation has been reported to have more neurologic complications such as seizure and cerebral infarction.[106] Since venoarterial cannulation is usually indicated in infants with PPHN who have poor-to-fair cardiac contractility, the decreased cerebral blood flow velocities in these infants compared with venovenous cannulation, may be explained by the poor cardiac function rather than the cannulation itself.[107] Newer techniques, such as percutaneous insertion of the catheters, minimize invasiveness and subsequent morbidity in these infants.[108,109]

As of July 2000, the Extracorporeal Life Support Organization Registry showed an overall survival rate of 78% in infants with a predicted mortality rate of 80%.[109] However, lower survival rates are still noted in infants with CDH.[110] From the 2002 Cochrane database review, ECMO has also been shown to significantly decrease mortality (odds ratio = 0.44; CI 0.31, 0.61) in non-CDH survivors as well as in CDH infants (odds ratio = 0.33; CI 0.21, 0.53).[111] A higher birth weight, higher 5-minute Apgar score, the absence of CDH, and postnatal diagnosis of CDH in ECMO patients are predictors of improved survival.[112,113] Survival rate is significantly lower among outborn infants, compared with inborn infants, probably due to the delay in the institution of ECMO. Thus, early transfer of infants to ECMO centers is recommended once the oxygenation index is >25,[114,115] plus the use of transport ECMO.[116]

Reported complications during ECMO have included hypercalcemia,[117] cannula thrombosis,[118] increased nosocomial infection,[119] asymmetric vasculopathy, and intraventricular hemorrhage.[120-122] Pulmonary function at 1 year of age was not impaired in infants who were treated with ECMO.[123] However, infants with CDH are at higher risk for pulmonary problems compared with non-CDH survivors.[124,125] At 10–15 years of age, ECMO survivors have similar weight and height as age-matched healthy control individuals. Although the ECMO group exhibited baseline and post-exercise lung function abnormalities, there were no significant differences in maximal oxygen consumption between the two groups.[126] There is a 15–20% incidence of neurodevelopmental disabilities among ECMO survivors,[126-128] although there is no difference in the neurologic outcome between ECMO and near-miss ECMO patients.[129] Adverse outcomes have been related to the severity of illness and presence of complications during ECMO.[112,128-130] Unusual findings of higher performance IQ at school age in infants placed on ECMO for a longer period have also been noted.[131]

5. Conclusion

PPHN is a state of persistent hypoxemia and cyanosis in the neonate due to failure of the postnatal decline of pulmonary artery resistance and pressure and a persistence of the right-to-left shunt across the ductus arteriosus and foramen ovale. Many factors or disease states may contribute to the development of the disease. At present, new modalities of treatment, particularly the use of inhaled NO, new types of ventilators, and ECMO have contributed to a significant decrease in mortality and short- and long-term morbidity among infants with the disease.

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