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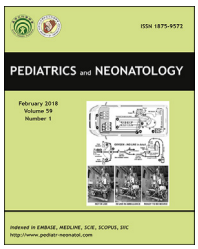

Review Article

Beyond the inhaled nitric oxide in persistent pulmonary hypertension of the newborn

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Persistent pulmonary hypertension (PPHN) is a consequence of failed pulmonary vascular transition at birth and leads to pulmonary hypertension with shunting of deoxygenated blood across the ductus arteriosus (DA) and foramen ovale (FO) resulting in severe hypoxemia, and it may eventually lead to life-threatening circulatory failure. PPHN is a serious event affecting both term and preterm infants in the neonatal intensive care unit. It is often associated with diseases such as congenital diaphragmatic hernia, meconium aspiration, sepsis, congenital pneumonia, birth asphyxia and respiratory distress syndrome. The diagnosis of PPHN should include echocardiographic evidence of increased pulmonary pressure, with demonstrable right-to-left shunt across the DA or FO, and the absence of cyanotic heart diseases. The mainstay therapy of PPHN includes treatment of underlying causes, maintenance of adequate systemic blood pressure, optimized ventilator support for lung recruitment and alveolar ventilation, and pharmacologic measures to increase pulmonary vasodilation and decrease pulmonary vascular resistance. Inhaled nitric oxide has been proved to treat PPHN successfully with improved oxygenation in 60—70% of patients and to significantly reduce the need for extracorporeal membrane oxygenation (ECMO). About 14%—46% of the survivors develop long-term impairments such as hearing deficits, chronic lung disease, cerebral palsy and other neurodevelopmental disabilities.

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1. Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is defined as failure to achieve or sustain the normal decrease in pulmonary vascular resistance (PVR) at birth. PPHN affects both term and preterm infants and commonly complicates the diseases of congenital diaphragmatic hernia, meconium aspiration, sepsis, congenital pneumonia, birth asphyxia and respiratory distress syndrome. Inhaled nitric oxide (NO) has been demonstrated as an effective treatment to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) therapy in infants with diverse causes of PPHN.[1] However, survivors of the infants with PPHN may develop long-term impairments, particularly neurodevelopmental disabilities.[2]

2. Normal fetal pulmonary vascular development and transition

At birth, a rapid decrease in PVR leads to an increase in pulmonary blood flow and enhances pulmonary venous return and left atrial pressure, promoting functional closure of the foramen ovale (FO). As PVR falls below systemic level, blood flow through the patent ductus arteriosus (DA) reverses to a left-to-right shunting. These physiologic changes effectively separate the pulmonary and systemic circulation and establish normal postnatal circulatory pattern. The normal transition is mediated partly by nitric oxide (NO)-cyclic guanosine monophosphate (c-GMP) pathway and prostacyclin-cyclic adenosine monophosphate (c-AMP) pathway. Both pathways lead to pulmonary vasodilation through a decrease in intracellular calcium concentrations (Fig. 1).

3. Pathophysiology

The common pathophysiologic features of PPHN include sustained elevation of PVR and hypoxemia secondary to right-to-left extrapulmonary blood flow shunting across DA or FO. Pulmonary hypertension may be associated with a wide range of cardiopulmonary disorders (Fig. 2). There are three main types of PPHN as follows:[3]

(1) Maladaptation: The structurally normal but abnormally constricted pulmonary vasculature due to lung parenchymal diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia, hypothermia, acidosis or hypoxia.
(2) Maldevelopment (excessive muscularization): Normal lung parenchyma but remodeled pulmonary vasculature characterized by increased smooth muscle cell thickness and distal extension of muscle to vessels that are usually nonmuscular.
(3) Underdevelopment: Hypoplastic pulmonary vasculature, as seen in congenital diaphragmatic hernia.

4. Other causes of neonatal pulmonary hypertension

Studies have demonstrated strong associations between PPHN and maternal smoking and ingestion of aspirin or other non-steroid anti-inflammatory drugs (NSAID).[4] Moreover, exposure to selective serotonin reuptake inhibitors during late gestation may increase the likelihood of PPHN.[5] A recent report showed that pulmonary hypertension was a rare but potentially fatal complication of ibuprofen administration in preterm infants.[6] Several case reports have described the correlation between pulmonary hypertension with congenital CMV infection,[7] severe neonatal anemia,[8] and increased blood viscosity such as polycythemia.

5. Evaluation of infants with PPHN

PPHN is typically characterized by labile SpO_2 which is poorly responsive to supplemental oxygen. Pulse oximetry may demonstrate the shunting of blood through the DA with a difference of greater than 10 percent (right upper extremity and either lower extremity) oxygen saturation. However, it is important to recognize that the absence of a preductal and postductal oxygenation gradient does not exclude the diagnosis of PPHN. A similar pattern of postductal desaturation with fixed hypoxemia may also be observed in ductus-dependent cardiac diseases, such as hypoplastic left heart syndrome, total anomalous pulmonary venous return and interrupted aortic arch.

Radiographic findings depend on the primary disease associated with PPHN and also are not diagnostic. Laboratory findings may include hypoglycemia, hypocalcemia, polycythemia, or thrombocytopenia. A prospective cohort study demonstrated that an initial brain natriuretic peptide (BNP) level of 550 pg/ml or greater was predictive of PPHN with a sensitivity of 85% and a specificity of 100%.[9]

The echocardiogram is crucial to exclude structural heart disease, determine the predominant direction of extrapulmonary shunting and assess bi-ventricular function. High pulmonary venous pressure secondary to left ventricular dysfunction will cause right-to-left shunting at the ductal level but left-to-right shunting at the FO level secondary to high left atrial pressure. Finally, the velocity of tricuspid regurgitation jet, acceleration of pulmonary arterial flow, position of the interventricular septum and direction of shunting flow at DA/FO are common parameters used to assess severity of PPHN.

6. Assessment of PPHN severity

Both alveolar-arterial oxygen differences ($AaDO_2$) and oxygenation index (OI) are used frequently in evaluating the severity of PPHN and disease progression. $AaDO_2$ represents the difference between alveolar and arterial oxygen content and is calculated by following formula:

$$AaDO_2 = \left(P_{ATM} - P_{H_2O}\right) \times FiO_2 - PaO_2 - PaCO_2/RQ$$

P_{ATM} represents atmospheric pressure, which is usually equal to 760 mmHg at sea level. P_{H_2O} refers to the pressure of vapored water in 1 atmospheric pressure and is considered to be 47 mmHg. FiO_2 is the fraction of inspired oxygen. Respiratory quotient (RQ) is used for $PaCO_2$ correction and the RQ value depends on energy sources of CO_2 production. Usually, the value of RQ equals 0.8 or 1 when the energy source is a combination of carbohydrate, protein and lipid

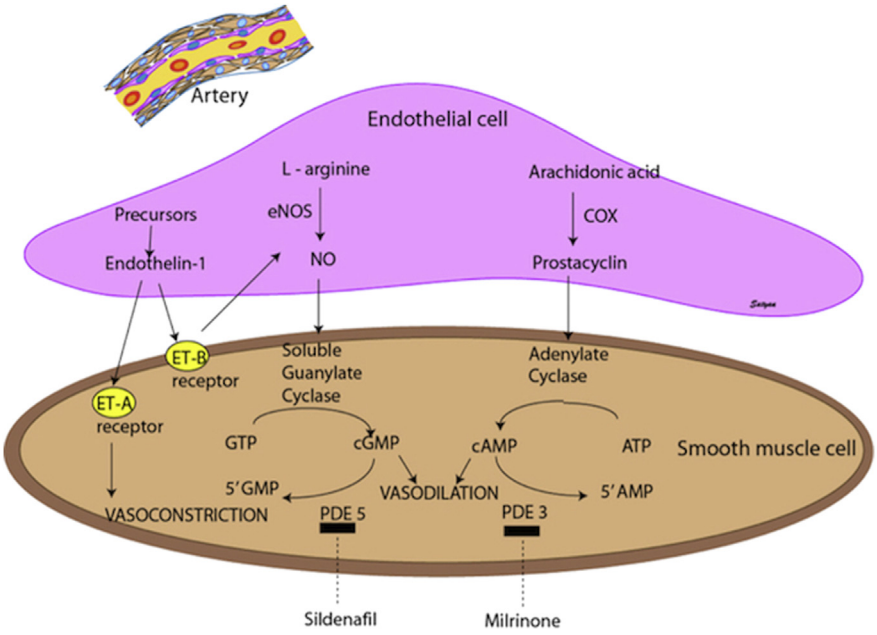

Figure 1 Endothelin-1, nitric oxide (NO) and prostacyclin (i.e., prostaglandin I_2) signaling pathways that regulate pulmonary vascular tone in the developing lung [Copyright Satyan Lakshminrusimha (SL)].

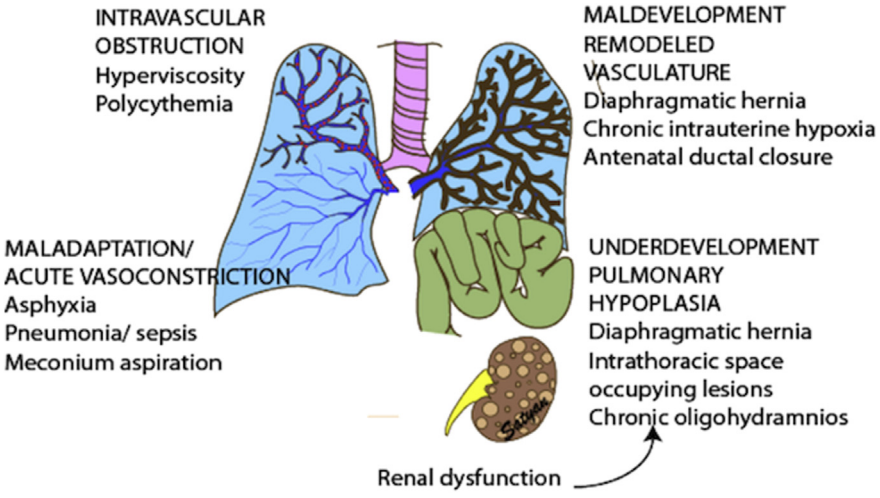

Figure 2 Pathophysiologic classification of PPHN [Copyright SL].

or purely glucose, respectively. The use of ECMO should be considered when $AaDO_2$ is above 600 with maximal support.

$$Oxygen\ index\ (OI) = [Mean\ airway\ pressure \times FiO_2 / PaO_2] \times 100$$

A term or late preterm infant with an OI $\geq$ 25 should receive care in a center where high-frequency oscillatory ventilation (HFOV), inhaled NO (iNO),[10] and ECMO are readily available.[1]

7. General support for PPHN

General management principles for PPHN include maintenance of normal temperature, electrolytes (particularly calcium), glucose, hemoglobin, and intravascular volume. A hemoglobin concentration between 15 and 16 g/dL is reasonable to preserve adequate tissue oxygenation. On the contrary, polycythemia should also be corrected with partial exchange transfusions. Oxygen concentration should be adjusted to maintain a targeted preductal PaO_2 goal of between 50 and 80 mmHg (oxygen saturation 90—97 percent), but caution is advisable in preterm very low birth weight (VLBW) infants. All of these modalities for general support are meant to optimize lung and cardiac function as well as to support sufficient oxygen delivery.

7.1. Assisted ventilation

Optimal lung expansion is essential for adequate oxygenation as well as the effective delivery of iNO.[1] "Gentle"

ventilation strategies with permissive hypercapnia are recommended to ensure adequate lung expansion with limited barotrauma. PaO_2 in the range of 50—70 mmHg and $PaCO_2$ between 40 and 60 mmHg as reported by Wung et al.[11] may be the optimal strategy to minimize lung injury associated with high tidal volume in acute phase of the disease although this has not been strictly tested. Moreover, $PaCO_2$ levels should not be lower than 35 mmHg, since aggressive hyperventilation with hypocapnia may cause cerebral vasoconstriction and reduce cerebral blood flow, which is identified to be a significant risk factor for hearing impairment in PPHN survivors.[2] Oxygen is a potent pulmonary vasodilator; however, no additional beneficial effects on pulmonary vasodilation have been found when the oxygen concentration is increased to greater than 50%.[12] Previous studies in neonatal lambs suggest that hyperoxia does not confer significant additional pulmonary vasodilation and may paradoxically impair the vasodilator responses to iNO through increasing lung injuries and oxidant stress.[13]

Although both conventional and high-frequency ventilation (HFV)[14] can reduce the V/Q mismatch, neither mode of ventilator is more effective in preventing ECMO.[15,16] HFV in combination with iNO results in the greatest improvement in oxygenation in some newborns who have severe PPHN complicated by diffuse parenchymal lung disease and underinflation.[17] Infants with RDS and MAS benefit most from a combination of HFV and iNO therapy.[14,15,18,19]

For infants without associated lung disease, hypoxemia is caused by right-to-left shunting rather than by ventilation-perfusion imbalance. Minimizing mean airway pressure and shortening inspiratory time are reasonable therapeutic approaches in this circumstance. When PPHN is associated with lung disease, atelectasis and the resulting maldistribution of ventilation may exacerbate high PVR. Assisted ventilation with optimal PEEP is used to recruit atelectatic segments, maintain adequate resting lung volume, and ensure appropriate oxygenation and ventilation. Some newborns with parenchymal lung disease associated with PPHN demonstrated marked improvements in oxygenation as well as decreased extrapulmonary shunting after lung recruitment during HFV.[10] Combined therapy with HFOV and iNO was reported to be more effective than HFOV or iNO alone, with a lower rate of death or need for ECMO.[1]

7.2. Sedation

Infants with PPHN may breathe out of synchrony with the ventilator and become agitated. Agitation may further increase right-to-left shunting, as well as catecholamine release, resulting in increased PVR. A patient-triggered-ventilator mode may improve synchrony. If asynchrony presents, application of sedatives is a common practice in management of PPHN, either by benzodiazepine or narcotic agents.

7.3. Surfactant therapy

Surfactant deficiency or inactivation is commonly attributed to PPHN, and administration of surfactant may be useful in management of PPHN when significant parenchymal lung disease exists. Previous evidence revealed beneficial effects in infants with parenchymal lung diseases such as MAS and sepsis, for which surfactant can improve oxygenation and decrease need for ECMO. A study of surfactant lung lavage showed an improvement in oxygenation, a decrease in mean airway pressure, and oxygen gradient between alveoli and arteries (A-a gradients); however, it did not improve the duration of mechanical ventilation, use of inhaled NO, length of hospitalization, or overall complications.[18] In infants with congenital diaphragmatic hernia, surfactant treatment increased risk of the need for ECMO, incidence of chronic lung disease and mortality rate among this population.[20,21]

7.4. Correction of acidosis

Alkalosis, induced either by hyperventilation or infusion of sodium bicarbonate, produces transient effect of pulmonary vasodilation. However, the use of sodium bicarbonate infusions to induce alkalosis provides no short-term or long-term benefit.[15] Furthermore, prolonged hypocapnic alkalosis may paradoxically potentiate ischemia-reperfusion-induced acute lung injury.[22] The effect on reducing cerebral blood flow through alkalosis-induced cerebral vasoconstriction has raised much concern because of the association with neurodevelopmental impairment, including sensorineural hearing loss.[15]

7.5. Glucocorticoids in PPHN

In the fetal lamb model of PPHN, postnatal hydrocortisone treatment has been shown to improve oxygenation, increase c-GMP levels, and reduce ROS levels.[23] Genetic abnormalities in the cortisol pathway and the association with PPHN provide further basis for exploring the role of glucocorticoids in PPHN.[24] However, routine glucocorticoids administration needs more evidence by clinical trials.

7.6. Optimized hemodynamics

Systemic hemodynamics should be optimized with volume and cardiotonic therapy to support both left and right ventricular function and to enhance systemic O_2 transport. PPHN is frequently associated with hypotension and low cardiac output, in part because increased right ventricular afterload with deviated interventricular septum toward left ventricle may restrict left ventricular filling and subsequently cause myocardial dysfunction. Attempt to reverse the ductal shunt by elevating systemic vascular resistance may temporarily improve pulmonary blood flow and oxygenation; however, this may further aggravate right ventricular dysfunction if PVR does not also fall. In infants with PPHN associated with left ventricular dysfunction, the hypoxemic respiratory failure may result from increased left atrial and pulmonary venous pressure, which gives rise to increased pulmonary arterial pressure and causes right-to-left shunting at ductal level but left-to-right shunting at atrial level with little pulmonary vasoconstriction. In such circumstances, pulmonary vasodilators should be used with caution and the treatment must be targeted to

improve left ventricular performance and also decrease left ventricular afterload.

Inotropic agents such as dopamine and milrinone are commonly administered to infants with PPHN. Dopamine can act on α_1-, α_2-, β_1- and dopaminergic receptors, contributing to increasing systemic blood pressure. More importantly, dopamine is not a selective vasoconstrictor of systemic circulation and may increase PVR in higher doses. The same concern should be considered while using epinephrine as an inotrope.[25] Milrinone, a phosphodiesterase type 3 (PDE3) inhibitor, which acts on cardiomyocytes as both inotrope and lusitrope (myocardial relaxation) and functions as a vasodilator on pulmonary arterial smooth muscle.[26] The term of "inodilator" has been used for its dual effects; and it is especially useful in the condition of left ventricular dysfunction with pulmonary hypertension.[27]

Some prospective studies have also reported the roles of norepinephrine and dobutamine in PPHN-induced cardiac dysfunction. Application of norepinephrine can increase systemic pressure and left ventricular output, which results in decreasing pulmonary-to-systemic artery pressure ratio, optimizing cardiac performance and improving post-ductal oxygen saturation.[28] However, in another study, the use of dobutamine seems superior to norepinephrine in restoring right ventricular contractility and cardiac output because of its more pronounced inotropic effect.[29]

7.7. Antibiotics

Nosocomial infection is another complication attributed to mortality of infants with PPHN. The clinician needs to be alert to the possibility of infection after three days of hospitalization when pulmonary condition should usually improve. Infection should also be suspected if the baby on the path of recovery shows signs of deterioration without other obvious explanation.

8. Pulmonary vasodilation agents

8.1. Inhaled nitric oxide

Inhaled NO improves oxygenation and reduces the need for ECMO therapy in patients with diverse causes of PPHN.[10,30–34] Several studies have suggested an effective dosage ranging from 5 to 20 ppm, and increasing the dose beyond 20 ppm in non-responders does not significantly improve outcomes. Approximately one third of infants with PPHN fail to respond to iNO, and higher NO concentration has some potential risks including methemoglobinemia and prolonged bleeding time. Although no iNO-associated serious adverse effects have been identified during long-term follow up, it is important to note that iNO does not reduce the mortality, length of hospitalization or risk of neurodevelopmental impairment associated with PPHN in centers with access to ECMO.[31,32,35]

The optimal threshold for introduction of iNO therapy remains unclear. The oxygen index (OI) is commonly used to assess the severity of PPHN. In previous randomized trials, hypoxic respiratory failure infants who were born after 34 weeks of gestation with OI greater than 25 under assisted ventilation were studied for iNO treatment. These studies have demonstrated that iNO therapy reduced the use of ECMO, but it had no significant benefits in mortality among this patient group.[30,33] One recent trial investigated earlier use of iNO in infants with moderate hypoxic respiratory failure, whose mean OI equaled 22, revealed improved oxygenation and a decreased the probability of developing severe hypoxemic respiratory failure compared to infants who received iNO therapy until OI was greater than 40. This study suggested that initiating iNO at early phase of disease was associated with decreased use of ECMO.[36]

The application of iNO therapy for newborns >34 weeks' gestation complicated with PPHN and hypoxemic respiratory failure is approved by the Food and Drug Administration. There is still lack of proper randomized placebo controlled trials to evaluate iNO use for preterm neonates of less than 34 weeks of gestation. However, some recent studies have reported beneficial effects for preterm infants with severe hypoxemic respiratory failure, particularly in association with prolonged oligohydramnios and pulmonary hypoplasia rather than parenchymal lung disease.[37]

8.2. Other pulmonary vasodilators

Several vasodilators have been proposed as alternative treatments for PPHN, such as magnesium sulfate, adenosine, phosphodiesterase inhibitors (sildenafil and milrinone), synthetic prostacyclin analogs (iloprost and treprostinil), and endothelin receptor antagonists (bosentan). Some specific pulmonary vasodilators commonly used to decrease pulmonary pressure are listed in Table 1.

8.3. Phosphodiesterase inhibitors

Sildenafil, a highly specific phosphodiesterase type 5 (PDE5) inhibitor, has the potential to independently decrease pulmonary vascular resistance through cGMP-mediated vasodilation pathway and improve oxygenation in infants with PPHN.[38] Sildenafil may serve as a useful adjunct for infants with poor iNO responsiveness. In some resource-limited countries, sildenafil can offer a less expensive but effective alternative.[39] In addition to acting as an adjuvant to iNO therapy, theoretically, sildenafil may be the ideal therapeutic choice in infants with PPHN following prolonged hyperoxic ventilation such as bronchopulmonary dysplasia.[40] As for safety profile, systemic reviews of 49 studies concerning the safety of sildenafil administration revealed no evidence of serious adverse events in infants.[41]

Milrinone has been shown to decrease pulmonary artery pressure and resistance in infants with PPHN. Recent studies indicate that the addition of intravenous milrinone to neonates with severe PPHN and poor iNO responsiveness was associated with improvement in oxygenation without compromising hemodynamic status.[42,43] The adjuvant use of milrinone to iNO promotes the effect of vasodilation and provides synergy. Furthermore, the properties of dual "inodilator" effects make it particularly effective in treatment of PPHN with associated left ventricular dysfunction.[27]

Table 1 Common pulmonary vasodilator agents.

Drugs	Dosage	Mechanism	Use in PPHN
Nitric oxide	Inhaled 5—20 ppm	Produced in the vascular endothelium, causing vasodilation through the increase in intracellular cGMP in the lung smooth muscle	Selective pulmonary vasodilator Monitor methemoglobin and NO_2 during use
Milrinone	Intravenous (IV) 0.3—0.8 mcg/kg/min	Inhibitor of the phosphodiesterase enzyme type III, responsible for degradation of cAMP	May potentiate the action of prostaglandins Improves right cardiac output by reduction of afterload
Prostaglandins	Prostacyclins: continuous IV or inhaled Iloprost: inhaled 0.5—2 mcg/kg/dose	Produced from arachidonic acid, causing vasodilatation by increasing cAMP in lung smooth muscle	Vasodilatation through alternative and complementary pathway to NO, may enhance its action Prostacyclin is a nonspecific pulmonary vasodilator and may have systemic effects
Sildenafil	IV or oral route 0.5—2 mg/kg/dose every 6 h	Inhibitor of the phosphodiesterase enzyme type V, responsible for degradation of cAMP	May potentiate NO action. Safe and easy to administer It may worsen oxygenation due to vasodilation of unventilated areas

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; NO_2, nitrogen dioxide; NO, nitric oxide.

8.4. Synthetic prostacyclin analogs

Prostacyclin (PGI_2) stimulates adenylate cyclase to increase intracellular cAMP level, which produces vasodilation through a decrease in intracellular calcium concentration. Recent studies showed that intravenous PGI_2 may be used as a rescue therapy for infants with severe PPHN. However, systemic hypotension may raise some concern.[44] The inhaled PGI_2 (e.g., iloprost or treprostinil) is possessed of vasodilator effects limited to pulmonary circulation, and its efficacy has been reported to be similar to that of iNO.[45] VLBW infants with RDS suffering from severe pulmonary hypertension may benefit from inhaled iloprost.[46,47] Inhaled iloprost may be a therapeutic option in newborns with PPHN when iNO and ECMO are not available. A recent study reported that inhaled iloprost appeared to be more effective than oral sildenafil as an alternative treatment of PPHN.[48] Further multicenter comparative randomized clinical trials are needed to confirm this suggestion.

8.5. Endothelin receptor antagonists

Endothelin-1 (ET-1), which is synthesized by vascular endothelial cell, acts on two kinds of endothelin receptor to cause vasoconstriction. Study in a newborn lamb model has demonstrated that the increased ET-A mediated vasoconstriction with loss of ET-B mediated vasodilation may be associated with the pathogenesis of PPHN.[49] Higher plasma level of ET-1 was also found in newborns with PPHN.[50] Bosentan is a non-selective ET-1 antagonist acting on both ET-A and ET-B receptors. In neonates, the evidence of bosentan use in PPHN is limited to two recent randomized controlled trials and some case reports.[51,52] A single-center randomized controlled trial showed that bosentan could improve oxygenation in PPHN newborns without iNO exposure.[51] Another multicenter trial revealed no additive effect of bosentan as adjuvant therapy to iNO in newborns with PPHN.[52]

9. Novel emerging targets and strategies

With greater understanding of the pathophysiology of pulmonary vascular disease in infants, investigation of novel therapies targeting intrinsic signaling pathways facilitating vascular regulation have been conducted to treat PPHN. Several approaches have been proposed such as antioxidants, L-citrulline, soluble guanylate cyclase (sGC) activators, Rho- kinase inhibitors and PPAR γ agonists. However, further evaluation and clinical trials are needed to elucidate the clinical effects.

9.1. Antioxidants

An increase in reactive oxygen species (ROS) such as superoxide and hydrogen peroxide in the smooth muscle and adventitia of pulmonary arteries has been demonstrated in the PPHN lamb model,[13] and it may promote vasoconstriction. The administration of recombinant human superoxide dismutase (rhSOD) diminished ROS production and improved endothelial nitric oxide synthase function in fetal lambs[53] and might be useful in the treatment of PPHN in newborns.

9.2. L-citrulline

To date, evidence reveals that an impaired L-citrulline—L-arginine—nitric oxide pathway is involved in the pathogenesis of chronic hypoxia-induced PPHN.[54] Hypoxia may reduce NO production through uncoupling nitric oxide synthase in pulmonary arterial endothelial cells, which results in decreasing NO formation from L-arginine. Application of L-arginine can improve NO signaling and assist vascular regulation. However, oral L-citrulline rather than L-arginine supplementation is even more effective in increasing serum L-arginine concentrations. Therefore, oral L-citrulline supplementation may be a novel strategy for treatment of PPHN associated with chronic hypoxia.

9.3. Soluble guanylate cyclase activators

Soluble guanylate cyclase (sGC) involved in NO-cGMP signaling pathway can enhance cGMP-mediated vasodilation effect. Decreased activity of sGC may reduce the cGMP production and contribute to PPHN.[55] When facing with hyperoxic exposure, the sGC becomes oxidized and it may reduce sGC function and impair its ability to produce cGMP-mediated vasodilation.[56] Cinaciguat, an sGC activator, has been shown to improve cGMP production after oxidative stress and ameliorate pulmonary vasodilation in fetal lambs with PPHN.[57] Additionally, better cinaciguat improvement of cGMP production is observed under hyperoxic condition, which makes it a promising treatment option for severe PPHN with hyperoxic exposure.

10. Extracorporeal membrane oxygenation (ECMO)

Infants who fail to respond to medical management with persistent OI >40 and metabolic acidosis require treatment with ECMO.[17] However, the use of ECMO may be associated with potential adverse effects, such as intracranial hemorrhage and ligation of common carotid artery. Recently, venovenous ECMO (VV-ECMO) has been used increasingly in the management of severe PPHN without the need for arterial cannulation and ligation.

11. Outcomes and prognosis

The long-term outcomes of infants with PPHN are mainly determined by their underlying diseases and the therapeutic interventions they receive at birth. The management for PPHN, including hyperoxic exposure, prolonged mechanical ventilation and ECMO, may also adversely affect outcomes. Feeding problems and short-term respiratory morbidities can be seen in 24% of PPHN survivors.[58] Furthermore, in long-term follow up, high risk of neurodevelopmental disabilities ranging from 14% to 46% has been reported, which includes sensorineural hearing loss, cerebral palsy and delays in either cognitive or motor performance. To date, four major clinical trials have been conducted to evaluate the long-term outcomes after treatment of iNO; nevertheless, no additional benefits have been found in reducing neurodevelopmental impairment or mortality.[32,35,59,60]

12. Summary

Persistent pulmonary hypertension is a serious event affecting both term and preterm infants in the neonatal intensive care unit. In the past 20 years, experimental work on basic mechanisms of vascular regulation of the developing pulmonary circulation has improved the therapeutic approaches to neonates with PPHN. In particular, inhaled NO has been proved to be a selective and effective pulmonary vasodilator, although successful clinical management requires meticulous care of all aspects of the associated lung and cardiac diseases. Current researches are focusing on developing a better understanding of cellular responses in the remodeled vasculature that will likely elucidate additional signaling pathways and lead to new therapeutic strategies.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

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