Persistent Pulmonary Hypertension of the Newborn: Therapeutical Approach

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Abstract: Persistent pulmonary hypertension of the newborn (PPHN), is defined as a failure of the pulmonary vasculature to relax at birth and consequently of the normal adaptation to extra uterine life of the fetal heart/lung system, resulting in hypoxemia. This condition, occurs in about 1-2 newborns per 1000 live births and despite significant improvements in treatment it is associated with substantial infant mortality and morbidity. Over the years wider application of inhaled nitric oxide (iNO) therapy and improved ventilation strategies including surfactant, high-frequency oscillatory ventilation has led to a decrease in the need for invasive life-sustaining therapies such as extracorporeal membrane oxygenation (ECMO). Mortality rate varies from 10 to 20 % of affected newborns in developed countries, but it is much higher when PPHN is refractory to the above reported therapies or when they are not available. As a consequence, development of new therapeutic strategies for severe PPHN is crucial. In particular, recent studies seem to show that sildenafil, a phosphodiesterase inhibitor type 5 that selectively reduces pulmonary vascular resistance may be a useful therapeutic adjunct to critically ill neonates with PPHN.

Key Words: Pulmonary hypertension of the newborn, Bronchopulmonary dysplasia, inhaled nitric oxide.

INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as mean pulmonary artery pressure (PAPm) >25 mmHg at rest or >30 mmHg with exercise, pulmonary wedge pressure ≤ 15 mmHg and pulmonary vascular resistance > 3 mmHg/l/min (Wood units is a heterogeneous condition brought on by a wide range of causes characterized by structural changes in small pulmonary arteries, that produce a progressive increase in pulmonary artery pressure and pulmonary vascular resistance, ultimately leading to right ventricle failure and death [1-3] (Table **1**).

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening condition, being among the most rapidly progressive and potentially fatal of vasculopathies. It was firstly described in 1969 by Gersony and co-workers as persistent foetal circulation [4,5]. In fact, it represents a disorder of vascular transition from fetal to neonatal circulation, resulting in cyanosis due to right-to-left shunting of blood through the ductus arteriosus and/or foramen ovale secondary to high pulmonary versus systemic pressure and manifesting as hypoxemic respiratory failure. This causes respiratory distress and cyanosis (sometimes differential). In particular, PPHN represents a common pathway of vascular injury activated by numerous perinatal stresses: hypoxia, hypoglycemia, cold stress, sepsis, and direct lung injury. Various mechanisms of vascular injury are involved in neonatal pulmonary hypertension:

endothelial dysfunction, inflammation, hypoxia, and mechanical strain.

As with other multifactorial diseases, a single inciting event may be augmented by multiple concurrent/subsequent phenomena that result in differing courses of disease progression [6].

The disease occurs in as many as 0.43-6.8 of 1000 live births, majority being term infants [7,8]. Patients with Down syndrome have an increased incidence of PPHN [9].

There is no race or gender related predisposition. Clinical examination reveals evidence of pulmonary arterial hypertension and right ventricular failure with systolic murmur of tricuspid and, at times, mitral regurgitation.

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 (Table **2**) [10-12]. Although inhaled nitric oxide (iNO) represents the gold-standard therapy for this pathology, high-frequency ventilation, surfactant and extracorporeal membrane oxygenation (ECMO) have been widely used in developed countries [13,14]. Mortality rate is approximately 10% to 20%, but is much higher when the above reported therapies are not available [7,15].

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Table 1. Clinical Classification of Pulmonary Hypertension – Venice 2003

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopatic (IPAH)
1.2. Familiar (FPAH)
1.3. Associated with (APAH):
1.3.1. Connective tissue disease
1.3.2. Congenital systemic to pulmonary shunts
1.3.3. Portal Hipertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Other (Thiroid disorders, glicogen storage disease, Gaucher's disease, hereditary hemorrhagic telangectasia, hemoglobinopathies,myeloproliferative disorders, splenectomy)
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary haemoangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left sides valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hipoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitude
3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Non thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneus
Sarcoidosis, histiocytosis X, lynphangiomatosis, compression of pulmonary vessels (adenophaty, tumor, fibrosing mediastinitis)

FETAL CIRCULATION

During the fetal period, blood is oxygenated through the placenta, and most of the cardiac output bypasses the lung through the ductus arteriosus. This increases the fetal pulmonary vascular resistance (FPVR) resulting in pulmonary pressures higher than systemic ones. Then FPVR drops with the initiation of ventilation and coincidentally, the ductus arteriosus constricts. To this regard, the increase in oxygen tension is an important trigger of ductus vasoconstriction.

A number of factors, including expansion of the lungs, increase in oxygenation, release of vasoactive mediators, growth factors and remodeling of the vascular wall, all contribute to the reduction in PVR [10,16,17]. The balance between the vasoconstrictor (endothelin) and vasodilator (nitric oxide and prostaglandin I2) mediators plays an important role in the regulation of the transition from fetal to postnatal circulation [18,19].

In particular, endothelin-1 (ET-1) appears to play an important role during that transition period and postnatally. ET-1 can dramatically increase resistance in the placental microcirculation and may be involved in blood flow redistribution with hypoxia [18].

On the other hand, nitric oxide (NO) which is a product of the conversion of L-arginine by the enzyme nitric oxide synthase (NOS), is critically involved in a variety of physiological situations including the cardiopulmonary transition from fetal to neonatal life [18-20]. NO synthases are widely distributed in the lung and are extensively involved in the control of airway and vascular homeostasis. NO stimulates soluble guanylyl cyclase, resulting in increased levels of guanosine 3',5'-cyclic monophosphate (cGMP) in lung smooth muscle cells. The gating of K+ and Ca2+ channels by cyclic GMP binding is thought to play a role in NO-mediated vasodilation. However, abnormal conditions may

Table 2. Non-Invasive Assessment of Pulmonary Pressure by Doppler Echocardiography

Pulmonary artery systolic pressure (PASP)
PASP = 4 x tricuspid regurgitation peak velocity^2 + right atrial pressure
Mean pulmonary artery pressure (MPAP)
MPAP = 79 - 0.45 (right ventricular outflow tract acceleration time)
MPAP = 4 x peak pulmonary regurgitation velocity^2
Pulmonary end-diastolic pressure (PEDP)
PEDP = 4 x (pulmonary regurgitation end-diastolic velocity)^2 + right atrial pressure

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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 through the ductus arteriosus and/or foramen ovale secondary to high pulmonary versus systemic pressure and consequently hypoxemia [10].

CLINICAL CONDITIONS PREDISPOSING TO PPHN

PPHN is seen in association with numerous diseases and conditions in the neonate. Infants with a wide variety of underlying clinical conditions develop PPHN. In fact, PPHN is a variety of disorders that have a common presentation [21-26] (Table **3**).

Table 3. Clinical Conditions Predisposing to PPHN

• Group B streptococcus infections
• Chorioamnionitis
• Meconium aspiration syndrome (MAS)
• Perinatal asphyxia
• Bronchopulmonary dysplasia (BPD)
• Congenital diaphragmatic hernia (CDH)
• Alveolar capillary dysplasia
• Congenital heart disease
• Congenital hepatic arteriovenous malformation
• Maternal use of selective serotonin reuptake inhibitors (SSRIs), nonsteroidal antiinflammatory drugs (NSAIDs) during pregnancy
• Idiopathic

Chorioamnionitis

Chorioamnionitis (CA) is the most frequent cause of fetal death in the second half of pregnancy and the leading cause of fetal and neonatal morbidity and mortality, including preterm labour/delivery, BPD, pulmonary haemorrhage and brain injury. CA is asymptomatic in a large amount of mothers (65%). Hence, a CA diagnosis is currently based on the histological examination of the placenta after delivery (histological CA) [27-32]. Histological CA is characterized and defined by the presence of acute inflammatory (i.e. neutrophilic) infiltrate in the placenta, membranes and umbilical cord [33]. It is detectable in about 50% of very low birth weight infants (VLBW) and up to 80% of the extremely low birth weight infants (ELBW), and likely to be mediated by a fetal systemic inflammatory response syndrome. The fetal systemic inflammatory response syndrome is defined by an elevated fetal plasma interleukin-6 levels. It has been recogized as the response of the fetus/placenta system to microbial exposure and a risk factor for the occurrence of severe fetal/neonatal morbidity and mortality [34].

The presence of CA and/or funisitis has been shown to be associated with more severe PPHN and consequently to require iNO therapy and more advanced respiratory support [35].

Perinatal Asphyxia

Persistent hypoxia sometimes results in persistence of constricted fetal pulmonary vascular bed causing PPHN. Cardiac abnormalities in asphyxiated neonates are often underdiagnosed and require a high index of suspicion. Electrocardiogram and echocardiography help in early recognition and hence better management of these cases [36,37].

Recently, it has been shown that in hypoxia-induced PPJN, vascular endothelial growth factor (VEGF), a potent mitogen with angiogenic and vasoactive properties, is increased, whereas vasodilation to VEGF is abolished. This reduced vasodilation may be due to decreased VEGFR2 expression [38]. As a consequence, impaired VEGF signaling may contribute to the pathogenesis of PPHN [39].

Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS) is a common severe respiratory disease in full term newborns and frequently results in inactivation of surfactant since meconium directly inhibits surfactant function [40]. Pneumothorax, change of fetal heart beat pattern and asphyxia are the most important risk factors associated with MAS which lead to the development of PPHN. As a consequence, avoidance of these events might be the key to reduce the incidence of PPHN and mortality rate of MAS [41,42]. Inflammation and inflammatory mediators play an important role in MAS [43].

In addition, meconium aspiration-induced hypertensive lung injury is frequently associated with neuronal damage. Recently, it has been shown in animal model that iNO treatment may inhibit DNA oxidation and neuronal injury in the hippocampus, associated with MAS [44].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a developmental abnormality resulting in a diaphragmatic defect which permits abdominal viscera to enter the chest. Most cases occur through the posterolateral foramen of Bochdalek. CDH is characterized by pulmonary hypoplasia and pulmonary hypertension and represents a major cause of severe,

refractory respiratory failure in the neonatal period and affects 1 in every 2,000 to 4,000 live births. Many infants with this condition are diagnosed antenatally through routine ultrasound screening. Nearly 90 percent present at delivery with severe respiratory distress requiring intubation. Many of these infants develop PPHN due to hypoplasia of the affected lung. Pulmonary hypoplasia and persistent pulmonary hypertension are the main causes of mortality and morbidity in CDH. The survival of infants with CDH is limited by the degree of pulmonary hypoplasia and requires sophisticated medical technology such as high-frequency ventilation and iNO. Some infants also require treatment with ECMO [45,46].

It seems that lung injury secondary to mechanical ventilation may play an important role in the mortality rate of patients with CDH, which may become increasingly significant when there is underlying pulmonary hypoplasia [47]. In addition, dysregulation of ET-1 receptors may contribute to PPHN associated with CDH [48,49].

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a typically multifactorial disease, which continues to be one of the most common prematurity-related long-term complications. It is defined as a persistent need for supplemental oxygen for at least 28 day with a persistence of respiratory features, such as retractions, tachypnea, and rales as a result of respiratory disease. Approximately 20% of VLBW infants show signs of BPD at 36 weeks of postmenstrual age [50]. Premature infants with BPD are at high risk for developing severe cardiovascular sequelae, such as PAH, systemic hypertension, left ventricular hypertrophy, congestive heart failure and prominent systemic-to-pulmonary collateral vessels (about 40% of cases) [22, 51-53].

Recently, we reported on a case of PAH in a VLBW infant with BPD where iNO therapy by nasal cannula and oral nifedipine treatment led to progressive improvement of clinical and echocardiographic signs of the disease [54].

THERAPEUTICAL MANAGEMENT

Therapeutical management of the disease is very complex, and 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. Ventilatory support is based on prolonged mechanical ventilation and particularly high-frequency ventilation, oxygentherapy, as well as surfactant replacement therapy, iNO and ECMO [10].

Extracorporeal Membrane Oxygenation

ECMO is a very beneficial, but invasive technique for providing life support to newborns with respiratory and cardiac failure refractory to maximal medical therapy, thus allowing the heart and lungs "to rest". The neonatal respiratory population has been a major benefactor of ECMO since 1982. ECMO has been used in treatment of neonates with a variety of cardio-respiratory problems, including MAS, PPHN, CDH, sepsis/pneumonia, respiratory distress syndrome, air leak syndrome, and cardiac anomalies.

For this group of high-risk neonates with an anticipated mortality rate of 80% to 85%, ECMO has an overall survival rate of 84%, with recent data showing nearly 100% survival in many diagnostic groups. Its use for neonatal respiratory disease increased dramatically until the past few years, when the number of neonatal respiratory ECMO cases began a downward trend. Fewer patients with PPHN are requiring ECMO support as frequently as in the past. Many attribute this decline to the newer respiratory therapies-mainly, high-frequency oscillatory ventilation, and iNO. Neonates who continue to require ECMO today are sicker than the historic norm [55-57].

However, it should be emphasized that neonatal ECMO survivors experienced lung injury correlated with the extent and duration of barotrauma and oxygen exposure lasting into later childhood and an increased risk of hearing loss [58,59].

Inhaled Nitric Oxide

NO is a major endogenous regulator of vascular tone. In addition, NO-cGMP signaling plays a relevant role in the regulation of the perinatal lung circulation and in mediating pulmonary vasodilatation during transition of the pulmonary circulation at birth. In fact, NO relaxes vascular smooth muscle by stimulating the intracellular cGMP production.

On the other hand, it is well known that PPHN is associated with a decreased NO release, impaired pulmonary vasodilation and it is partly due to impaired NO-cGMP signalling [13]. As a consequence, NO given as an inhalation (iNO) has been shown to be a novel selective pulmonary vasodilator without effects on the systemic circulation, a viable and efficient approach to restore pulmonary NO deficiency, that does not alter lung function [60].

Thus, the management of PPHN entered a new era with the development of iNO therapy for the relief of pulmonary hypertension.

Based on the evidence presently available, iNO reduces the need for ECMO in infants with PPHN without any major immediate side effects [8].

iNO should be used in an initial concentration of 20 ppm for term and near term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia [61, 62].

To this regard, a significant increase in plasma cGMP is already evident after 60 min of NO therapy [63].

iNO can be an interesting alternative in VLBW infants with severe BPD and PAH, although potential adverse effects in premature infants have to be studied more in depth [53, 64, 65]. In particular, INO therapy has been shown to decrease the risk of cerebral palsy in preterm infants with PPHN [66].

The favourable response to iNO is dependent on the degree of lung expansion and is more readily achieved by the use of high-frequency ventilation than conventional ventilation [67].

However, approximately half of infants fail to respond to iNO and its high cost limits its widespread use in Neonatal Intensive Care Units, especially in the developing world [10, 68,69]. In fact, iNO is cost-effective but not cost-saving in treating infants with PPHN from a societal perspective [70].

In a situation where the standard of practice with iNO and ECMO is not available or when infants are refractory to classic management with high-frequency oscillatory ventilation, oxygen therapy and iNO, development of new therapeutic pathways is crucial. Preliminary evidence suggests that other vasodilators given by the inhaled route may improve oxygenation and new vasodilators have become available [71].

Novel Therapeutic Strategies

Traditional vasodilators agents, such as epoprostenol and calcium channel blockers (CCB) are commonly used in PPHN but have not been shown to decrease significantly mortality risk [72, 73]. In addition, although experience with continuous adenosine infusion is still at an early stage, it might be worth considering its administration as a rescue therapy or even as an alternative to ECMO [74].

More recently, a number of recent studies have suggested a role for specific phosphodiesterase (PDE) inhibitors in the management of PPHN.

In particular, sildenafil, a cGMP-specific type V phosphodiesterase inhibitor appears the most promising of such agents, although its long term effects has to be furtherly investigated [75-77].

In particular, because cGMP is inactivated by phosphodiesterase (PDE) enzymes, it is likely that a cGMP-specific PDE5 inhibitor, such as sildenafil would promote angiogenesis and attenuate oxygen-induced lung injury. Thus, sildenafil may enhance NO-cGMP activity and may be effective in the treatment of PPHN [78, 79]. To this regard, it has been shown that sildenafil preserved alveolar growth and lung angiogenesis, and decreased pulmonary vascular resistance, right ventricular hypertrophy and medial wall thickness, thus suggesting a role for the NO/cGMP pathway during alveolar development. As a consequence, sildenafil may have therapeutic potential in diseases associated with impaired alveolar structures [80]. In particular, it can be considered for treatment of severe PAH secondary to BPD [81].

In addition, milrinone, a phosphodiesterase III inhibitor, routinely used in pediatric cardiac intensive care units to improve inotropy and reduce afterload, is a promising adjunctive therapy because of its pulmonary vasodilator properties and cardiotropic effects [82, 83].

CONCLUSION AND FUTURE DIRECTION

PPHN remains an important cause of mortality and morbidity in the term neonate. As a consequence, further well-controlled and multicenter studies with newer treatment modalities are crucial for the improvement of survival of PPHN. In fact, although inhaled NO therapy has improved the clinical course and outcomes of many infants, pulmonary hypertension can be refractory to iNO, suggesting the need for additional approaches to severe PPHN.

To develop novel therapeutic strategies for PPHN, ongoing studies has to explore basic mechanisms underlying the pathobiology of PPHN in experimental models, including strategies to enhance NO-cGMP signaling. In addition, further research is needed to understand the basis for the biologic susceptibility of some infants to environmental insults such as intra-uterine stress or exposure to NSAIDs in utero. The potential use of PDE5 inhibitors in a situation where the standard of practice with iNO and ECMO is not available or failed have to be considered. In particular, sildenafil appears the most promising of such agents. Randomized-controlled trials to determine the safety, efficacy, and long-term outcomes following treatment with sildenafil in PPHN are needed**.**

ABBREVIATIONS

ACD	=	Alveolar capillary dysplasia
BPD	=	Bronchopulmonary dysplasia
CA	=	Chorioamnionitis
CCB	=	Calcium channel blockers
CDH	=	Congenital diaphragmatic hernia
ELBW	=	Extremely low birth weight
ET-1	=	Endothelin-1
ECMO	=	Extracorporeal membrane oxygenation
cGMP	=	Guanosine 3',5'-cyclic monophosphate
iNO	=	Inhaled nitric oxide
MAS	=	Meconium aspiration syndrome
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
NSAIDs	=	Nonsteroidal antiinflammatory drugs
PAH	=	Pulmonary arterial hypertension
PAPs	=	Pulmonary arterial pressures
PCH	=	Pulmonary capillary hemangiomatosis
PDE	=	Phosphodiesterase
PVR	=	Pulmonary vascular resistance
PVOD	=	Pulmonary veno-occlusive disease
SSRIs	=	Selective serotonin reuptake inhibitors
VEGF	=	Vascular endothelial growth factor
VLBW	=	Very low birth weight

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