Persistent pulmonary hypertension of the newborn: a review

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ABSTRACT

Persistent pulmonary hypertension of the newborn (PPHN) is a serious medical emergency in the neonatal period which occurs because of failure of transition of the foetal circulation into the normal circulation. The condition is characterised by persistently elevated pulmonary vascular pressures and despite numerous modalities of treatment available, the condition carries with it a high rate of mortality and morbidity. Early awareness of predisposing conditions and early diagnosis leads to better outcomes in PPHN.

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INTRODUCTION

In intrauterine life, the foetus obtains oxygen through the low-resistance placental circulation and its pulmonary vascular resistance (PVR) is high as the lungs are fluid-filled. At birth, with air entering the lungs and the umbilical cord being clamped, the situation is reversed with the PVR falling due to vasodilatation of vessels with oxygenation and systemic vascular resistance (SVR) rising due to the elimination of the low-resistance placental circuit.

In persistent pulmonary hypertension of the newborn (PPHN) this transition is disturbed, resulting in sustained elevation of PVR. In PPHN, PVR exceeds SVR resulting in the right-to-left haemodynamic shunting through the patent foramen ovale and/or ductus arteriosus leading to the vicious cycle of hypoxaemia, further resulting in pulmonary vasoconstriction leading to diminishing pulmonary perfusion and systemic hypoxaemia.

A wide variety of predisposing factors can lead to PPHN which is reported to occur at a rate of 1–2 per 1,000 live births and is most common among full-term and post-term infants.^{1,2}

The infant with persistent pulmonary hypertension constitutes a medical emergency with a very high morbidity and mortality attached to it. It is therefore essential to understand the aetiopathogenesis, methods of diagnosis and monitoring, and the available treatment modalities to ensure better outcomes.

AETIOPATHOGENESIS

This condition was initially labelled “persistent foetal circulation (PFC)” syndrome by Gersony and coworkers in 1969; however, this term has now been abandoned as one of the characteristic features of the foetal circulation, the high-flow, low-resistance circuit through the placenta, is missing.^{3,4}

In PPHN, the foetal pulmonary vasculature is altered. This alteration can be due to intrauterine pulmonary vascular under-development (decreased vascular growth), mal-development (abnormal vascular structure) and/or mal-adaption (perinatal hypoxia-induced vascular spasm).⁴ Mal-development or remodelling of pulmonary vessels refers predominantly to abnormalities of vascular smooth muscle found in lungs of infants dying from PPHN wherein pulmonary artery smooth muscle hypertrophies and extends into the normally nonmuscular intracranial arteries.⁵

A number of predisposing factors have been implicated in the development of PPHN and the list of such factors keeps increasing with a better understanding of the condition.^{1–3} Some of the commonly implicated predisposing factors are shown in Table 1.

Of all the known predisposing factors, birth asphyxia (intrauterine as well as perinatal) and meconium aspiration are the most commonly encountered predisposing factors.⁴

DIAGNOSIS

A high index of clinical suspicion is warranted to diagnose PPHN in a baby without any known predisposing factor. The presence of any of the risk factors enumerated in Table 1 along with the following clinical features should prompt the diagnosis.^{1,2,9} Adjuncts to diagnosis include transcutaneous oxygen saturations, chest radiographs, electrocardiogram (ECG), and arterial blood gases (ABG). Echocardiography with real-time Doppler flow imaging continues to remain the gold standard for the diagnosis of PPHN. All details are explored in the following paragraphs.

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Table 1 Predisposing factors for persistent pulmonary hypertension of the newborn.

Predisposing factors	Remarks
1 Birth asphyxia	Both, intrauterine and perinatal hypoxia
2 Meconium aspiration	Other aspirations also predispose
3 Early-onset sepsis/pneumonia	Active constriction of pulmonary vessels possibly due to increased thromboxane ³
4 Pulmonary hypoplasia due to causes like congenital diaphragmatic hernia, amniotic fluid leak, oligohydramnios, pleural effusion	Reduction in the number of intralobar arteries; their increased muscularity ⁶
5 Maternal drug intake like NSAIDs (ibuprofen, aspirin, naproxen, indomethacin) and SSRI, especially fluoxetine	NSAIDs lead to in utero constriction of ductus arteriosus and pulmonary vasculature remodelling; use of SSRIs in late third trimester associated with PPHN ^{7,8}
6 Others factors like RDS, hypothermia, hypoglycaemia, polycythaemia	–
7 Familial occurrence	Familial occurrence uncommon, but genetic predisposition may influence PPHN risk
8 Idiopathic	Quite common but unrecognised hypoxia or ductal closure may account for a large proportion of “idiopathic” cases ³

PPHN: persistent pulmonary hypertension of the newborn, NSAIDs: non-steroidal anti-inflammatory drugs, SSRI: selective serotonin reuptake inhibitors, RDS: respiratory distress syndrome.

Clinical Manifestations

Affected infants are usually full-term or post-term and are frequently born through meconium-stained amniotic fluid. The infant is either ill in the delivery room itself or illness manifests within the first 12 hours of life.

Infants with PPHN related to polycythaemia, idiopathic causes, hypoglycaemia, or asphyxia may manifest with severe cyanosis and tachypnoea, although signs of respiratory distress may be minimal initially.

In neonates with PPHN related to meconium aspiration, pneumonia, diaphragmatic hernia or pulmonary hypoplasia cyanosis, grunting, nasal flaring, chest retractions, tachycardia, and shock predominate the clinical picture.

Cardiac exam may reveal prominent precordial impulse, single or narrowly split and accentuated second heart sound and/or a systolic murmur consistent with tricuspid valve regurgitation. Heart failure is usually not seen though hypotension is encountered.⁹

Oxygen Saturation (SPO₂)

Hypoxia is universal and is unresponsive to 100% oxygen given by hood, but may respond transiently to hyperoxic hyperventilation (by bag and mask or after intubation). Prolonged hyperventilation is not recommended due to the cerebral effects of prolonged hypocapnia.¹⁰

Difference in saturation between right upper and left upper limb (and lower limbs) of >10% in the absence of structural heart disease suggests PPHN.

Chest Radiograph

The chest radiograph usually appears normal in asphyxia-associated and idiopathic PPHN. In PPHN associated with pneumonia or congenital diaphragmatic hernia, it shows parenchymal opacification and bowel and/or liver in the chest, respectively. The cardiac silhouette usually is normal; pulmonary

blood flow is normal or decreased. Clinical picture and hypoxia is often out of proportion to findings on chest radiograph.

Electrocardiogram (ECG)

There is no feature on ECG specific to PPHN. The ECG may show right ventricular dominance pattern, which is within the range normal for age.

Arterial Blood Gas (ABG)

The gradient of oxygenation between simultaneous pre-ductal (upper extremity or head) and post-ductal (lower extremity or abdomen) ABGs can provide a clue—a difference in PaO₂ of >20 mmHg between the two ABGs is suggestive of PPHN. When hyperventilated for 10 minutes, infants with PPHN may show an increase in PaO₂ by >30 mmHg when pH is raised to 7.55.

Echocardiography

Echocardiography remains the gold standard for diagnosing PPHN. Real-time echocardiography combined with Doppler flow studies demonstrates right-to-left shunting across a patent foramen ovale and a ductus arteriosus. Deviation of the interatrial septum into the left atrium is seen in severe PPHN. Tricuspid or mitral insufficiency can be visualised. Pulmonary artery pressure can also be assessed. Echocardiography can also rule out other structural causes of heart disease.

Other Findings

Hypoglycaemia frequently complicates many of the associated conditions such as sepsis and meconium aspiration; hypocalcaemia also occurs frequently in these infants.³ Thrombocytopenia has been reported in severe cases. Persistent pulmonary hypertension of the newborn can be secondary to sepsis, so the baby may manifest with features of infection and appropriate investigations for sepsis need to be sent.

Table 2 Commonly used pharmacological agents for haemodynamic support in persistent pulmonary hypertension of the newborn.

	Drug with dose	Remarks
1	Dopamine (a) Moderate dose 3–5 µg/Kg/min (b) High dose 6–30 µg/Kg/min	Can improve cardiac output. But doses > 10 µg/Kg/min can increase PVR
2	Dobutamine Same dose as dopamine	Has inotropic effect more than chronotropic effect
3	Epinephrine 0.03–0.1 µg/Kg/min	Should be given cautiously as it can increase PVR
4	Milrinone (a) Loading dose 50 µg/Kg (b) Maintenance dose 0.25–0.5 µg/Kg/min	Add milrinone in place of dobutamine if BP is within the acceptable range, as milrinone is a pulmonary vasodilator ¹¹
5	Hydrocortisone 1 mg/Kg (can be repeated 12 hourly for 2–3 days)	In very sick neonates with hypotension refractory to catecholamine administration. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency ¹

PPHN: persistent pulmonary hypertension of the newborn, PVR: pulmonary vascular resistance.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis include cyanotic congenital heart disease (especially obstructed the total anomalous pulmonary venous connection) and entities that predispose to PPHN.¹

Signs favouring cyanotic congenital heart disease over PPHN include cardiomegaly, weak pulses, active precordium, pulmonary oedema, grade 3+ murmur, and persistent pre- and post-ductal PaO₂ at or < 40 mmHg.² However, differentiating PPHN from ductus-dependant pulmonary cardiac lesions can be very difficult. If uncertainty exists, Prostaglandin E₁ Infusion is generally the safest option during transport to a tertiary care centre.³

TREATMENT

Persistent pulmonary hypertension of the newborn is a medical emergency in which immediate management is essential and is directed towards reversing hypoxemia, improving pulmonary perfusion by reducing PVR, increasing systemic pressures to reverse the right-to-left intracardiac shunting and minimising hypoxic-ischaemic end-organ injury. Management efforts are multi-pronged and therefore include any or all of the following⁴:

- Preventing and anticipating PPHN.
- Ventilatory support to achieve optimal oxygenation.
- Haemodynamic support to maintain adequate cardiac output and optimal systemic blood pressure.
- Reducing the raised PVR.

Response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation as well as other associated metabolic and physiologic derangements that are known to occur in infants with PPHN. Some of the management options are discussed in detail below.

Supplemental Oxygen

This is the most important therapy to reduce abnormally elevated PVR. Oxygen should be given by nasal cannula or hood, in concentrations of upto 100% if necessary.

Intubation and Mechanical Ventilation

Indications for intubation and mechanical ventilation include²:

- persistent hypoxaemia despite maximal administration of supplemental oxygen;
- PaO₂ remains borderline despite supplementation with 100% oxygen and/or respiratory failure is demonstrated by marked hypercarbia and acidaemia.

Ventilatory strategies include conventional positive pressure ventilation with initial rates of 60–80/minute, an I:E ratio of 1:1.2, a PEEP of 3 cm H₂O, and sufficient peak pressure to achieve a PaCO₂ of not greater than 35–45 mmHg with the pH between 7.35 and 7.45. The PaO₂ should be maintained at 80–100 mmHg initially and 50–60 mmHg once stable (usually after 12–24 hours of ventilation). Weaning should be gradual; pressures are to be decreased before decreasing the FiO₂. Pneumothorax and PIE (pulmonary interstitial emphysema) are complications to watch out for. In addition, use of high pressures can impede venous return to the heart reducing cardiac output and increasing PVR. A recent strategy is to manage these patients without hyperventilation and/or alkalinisation. With experience, “gentle ventilation” with permissive hypercarbia has been reported to have excellent outcomes and a low incidence of bronchopulmonary dysplasia. If high frequency oscillatory ventilation (HFOV) is available it can be advantageously used in infants with pulmonary parenchymal disease and those awaiting inhaled nitric oxide therapy.^{1,3,9}

Sedation and Analgesia

Neonates with PPHN are extremely labile physiologically and any external stimulus can lead to worsening in their clinical

parameters. The stress response leads to catecholamine release which causes increase in PVR. This increase can be prevented by use of a narcotic analgesic like fentanyl which is given as an infusion (at 2–5 µg/Kg/minute). Neuromuscular blockade with pancuronium (0.1 mg/Kg/dose for every 1–4 hours) can be given to achieve muscle relaxation and full synchrony in infants being mechanically ventilated. Use of muscle relaxant is to be decided on a case-to-case basis.

Metabolic Alkalosis

The acidosis accompanying the hypoxia in infants with PPHN leads to increase in the PVR therefore alkalosis is the physiological stimulus that reduces PVR. One strategy applicable in ventilated infants is gentle hyperventilation. Use of intravenous NaHCO₃ with an aim to maintain pH between 7.35 and 7.45 is another strategy. With the use of intravenous NaHCO₃, there will be an increase in the sodium load which should be factored in.

Haemodynamic Support

It is necessary to maintain a cardiac good enough to ensure optimum tissue oxygenation and mixed venous oxygen content. The aim should be to maintain the systemic blood pressure above the pulmonary pressures so that the right-to-left intracardiac shunting is reversed. For this, usually a systolic blood pressure between 50 and 75 mmHg and diastolic pressures between 45 mmHg and 55 mmHg are adequate in the initial phase. This can be achieved by volume expansion and use of vasopressors as follows:

1. *Volume expansion.* Consider normal saline or packed RBCs for conditions associated with intravascular volume depletion like haemorrhage, capillary leak or hydrops as well as in clinical situations like septic shock where systemic pressures are decreased. The haemoglobin level should be kept >13 g/dL (PCV 40%) to optimise oxygen delivery to the tissues.³
2. *Vasopressor treatment.* In PPHN, vasopressors such as dopamine, dobutamine, and epinephrine, alone or in combination, are used to maintain the required systemic blood pressures and adequate cardiac output. In situations where cardiac function is very poor, milrinone may be used as it enhances cardiac output while simultaneously decreasing PVR.² The doses of various commonly used medications for haemodynamic support are shown in Table 2.

Correction of Metabolic Abnormalities

The correction of metabolic abnormalities is important in PPHN to provide adequate substrates for myocardial function and appropriate response to inotropic agents. Hypoglycaemia and hypocalcaemia are common and the infant needs to be monitored for these; any abnormality detected should be corrected promptly and adequately.

Correction of Polycythaemia

Partial exchange transfusion to reduce the haematocrit to 50–55% should be considered if central haematocrit is >65%.

This is essential to reduce the hyperviscosity that accompanies polycythaemia.

Surfactant

Meconium aspiration and bacterial pneumonia are both associated PPHN and in both these situations there is surfactant inactivation. Surfactant replacement therapy appears to improve gas exchange in these conditions and hence surfactant therapy may be used as an adjunct in these two conditions with PPHN.

Other Pharmacological Agents

Proposed medical therapies in PPHN include:

1. *Sildenafil.* A phosphodiesterase inhibitor type 5 that selectively reduces PVR. It is a class IIa recommendation in PPHN, i.e. weight of evidence is in favour of usefulness.¹¹ The dose ranges from 0.5 mg/Kg/dose to 2 mg/Kg/dose given 6 hourly by orogastric tube with dose titration based on response.⁴ A recent Columbian pilot study on neonates with PPHN showed 6/7 survival in sildenafil group vs 1/6 survival in placebo group.¹² Interestingly, in a report from Maharashtra, in an neonatal ICU setting where there was no ventilator, a favourable response was reported in 5/6 neonates with PPHN and the report concluded that oral sildenafil is useful in the treatment of PPHN in pre-term neonates when nonventilatory treatment is the only available option.¹³ Sildenafil should not be combined with nitric oxide or nitrates due to risk of severe hypotension.¹¹
2. *Magnesium sulphate.* The loading dose is 200 mg/Kg. If response is adequate, then an infusion at 20–100 mg/Kg/hour can be started.¹⁴ A recent Italian study concluded that where nitric oxide facilities are not available, magnesium sulphate is a cheap alternative for first line treatment of moderate PPHN.¹⁵ However, pre-term neonates are at high risk for respiratory depression due to magnesium sulphate. Oral sildenafil use may therefore be preferable in pre-term neonates.¹³
3. *Tolazoline.* A non-selective alpha adrenergic antagonist which is sometimes used as an adjunct to selectively vasodilate the pulmonary arterial system. The usual dose includes a loading dose of 1 mg/Kg followed with an infusion at 0.16 mg/Kg/hour. However, tolazoline use can result in systemic hypotension, renal failure, and gastrointestinal haemorrhage.^{9,10}
4. *Prostacycline (PGI₂).* Therapy with continuous inhaled or intravenous prostacycline has been shown to improve oxygenation and outcome in infants with PPHN.¹ At dose of 5–40 ng/Kg/minute, it is an effective pulmonary vasodilator but has many side effects that restrict its widespread use.⁹
5. *Adenosine.* A purine nucleoside, which is an effective pulmonary vasodilator. The vasodilatory effects are due to release of endogenous nitric oxide, stimulation of K⁺ ATP channels, and decreased entry of calcium into the vascular smooth muscle.¹⁶ An American pilot study showed that adenosine infusion at a dose of 50 µg/Kg/minute improves PaO₂ in infants with PPHN without causing hypotension or

tachycardia.¹⁷ An Australian study demonstrated a rise of arterial PaO₂ >20 mmHg in 5/6 neonates with PPHN within 30 minutes of adenosine infusion as measured via a right arterial catheter at 30, 60 or a maximum of 90 µg/Kg/minute and concluded that adenosine may be a therapeutic option in pre-term neonates with PPHN. Availability, simplicity of use, rapid onset of action, and an extremely short half-life are advantages over the other vasodilators, but it is expensive.¹⁴

6. *Diltiazem*. A calcium channel antagonist was shown to reduce right ventricular pressure in neonates with PPHN without overt side effects.¹⁸
7. *Other agent*. The other agents that have been tried in neonates with PPHN include nitroglycerine (infusion of 0.5–12 µg/Kg/minute), inhaled ethyl nitrate, etc.

Other Treatment Modalities

These other treatment modalities are not widely available in our setting either because of cost or for lack of adequate trained manpower and are therefore discussed in brief below:

1. *High frequency ventilation*. For those infants with parenchymal lung disease underlying their PPHN, both high frequency jet-ventilation (HFJV) and HFOV are highly effective in controlling the PaO₂. Hemojuvelin (HJV) results in reductions in both PaCO₂ and ventilator pressures in infants with PPHN but has no effect on ultimate outcome. High frequency oscillatory ventilation may be useful in the management of infants who are being considered for treatment with extracorporeal membrane oxygenation (ECMO).³ The combined use of inhaled nitric oxide (iNO) and high occupancy vehicle (HOV) has been demonstrated to be more successful than use of iNO or HFOV alone in rescuing infants at or near term with severe respiratory failure.⁹
2. *iNO*. Normally, NO is produced in the endothelial cells and diffuses to the smooth muscle cells producing smooth muscle relaxation. Infants with PPHN have been proved to have lower urinary nitrite and nitrate concentrations than infants without pulmonary disease thereby indicating their inability to produce enough NO endogenously. Inhaled nitric oxide is a potent pulmonary vasodilator with no effect on systemic vasculature as NO is rapidly inactivated by combination with haemoglobin. However, iNO may not be effective if the lungs are not adequately recruited, if myocardial function is severely impaired, or if systemic circulatory insufficiency is present. It is administered by conventional or high frequency ventilation in doses of 5–20 ppm. The patient should be weaned from iNO over a period of 12–48 hours as tolerated. NO has a very short duration of action, thus rebound vasoconstriction and hypoxaemia can result if NO is suddenly withdrawn. iNO is currently regarded as the gold standard therapy but 30% cases fail to respond. Nitric oxide should not be used for long term as it results in methemoglobinemia.^{3,4,9,11}
3. *ECMO*. A lifesaving therapy for infants with PPHN who fail conventional management and/or iNO treatment. Criteria for taking up an infant for ECMO are either an alveolar-arterial

oxygen difference (AaDO₂) >600 or oxygenation index (OI) >30 on 2 ABGs ≥30 minutes apart.

General Measures

1. *Decrease stimulation, minimise handling, light, and sound*. While slight disturbances like turning the baby or measuring temperature may precipitate severe hypoxaemia, major interventions such as endotracheal suctioning or physiotherapy may have devastating effects. Endotracheal suctioning should be carried out only when essential. Chest physiotherapy is contraindicated.⁹
2. *Avoid hypothermia*. All infants with PPHN should be nursed in a thermo-neutral environment. Cold stress raises the metabolic rate, increases oxygen consumption, and causes the infant to release norepinephrine which is a pulmonary vasoconstrictor.³
3. *Broad spectrum antibiotics*. These must be given to all these suffering infants.⁹
4. *Nutrition*. Enteral feeds should be avoided in the acute phase. Parenteral nutrition should be commenced in all infants who are still being ventilated on day 3 or 4.
5. *Venous and arterial access*. This should be reliable and well maintained as these infants are frequently sampled for various investigations and repeated estimation of blood gases. To avoid the repeated painful stimulus of sampling, an indwelling line is a must.

PROGNOSIS

With availability of both iNO and ECMO, mortality in PPHN has reduced from 25–50% to 10–15%.² In our setting, iNO as well as ECMO are not available hence mortality will be on the higher side. However, a high index of suspicion and early intervention with available treatment measures are the only options left with us. Survivors are at an increased risk of adverse sequelae including chronic pulmonary disease and long-term development of neuro-developmental disabilities, hearing impairment, and brain injury and therefore need to be on long-term follow-up.

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