

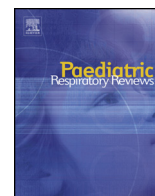
## **Diagnostico y manejo de Hipertensión Pulmonar Persistente en recién nacidos.**

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### **Resumen.**

La hipertensión pulmonar persistente del recién nacido (PPHN) se asocia a mortalidad y morbilidad; puede ser idiopática o secundaria a una serie de condiciones. La base del diagnóstico para excluir anomalías estructurales es la ecocardiografía. Niveles de Péptido natriurético tipo cerebral (BNP) están elevados en PPHN y son lo suficientemente sensibles para contribuir al diagnóstico de rutina. El manejo incluye mejorar la oxigenación mediante la optimización del volumen pulmonar con técnicas ventilatorias y / o surfactante y la administración de agentes vasodilatadores pulmonares. El óxido nítrico inhalado (ONi), un vasodilatador pulmonar selectivo, reduce la necesidad de oxigenación por membrana extracorpórea en recién nacidos a término; sin embargo no mejora la mortalidad ni tiene efectos positivos a largo plazo en los bebés prematuros o con hernia diafrágica congénita. Otros vasodilatadores pulmonares han sido reportados en algunas series con cierta eficacia ya sea solos o en combinación con iNO. Estudios clínicos aleatorizados con seguimiento a largo plazo son necesarios para identificar las estrategias terapéuticas óptimas en PPHN.



Mini-symposium: Alveolar and Vascular Transition at Birth

## Diagnosis and management of persistent pulmonary hypertension of the newborn



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### EDUCATIONAL AIMS THE READER WILL BE COME TO APPRECIATE:

- Pulmonary hypertension in the newborn can result from a number of underlying conditions.
- The prognosis of pulmonary hypertension is dependent on the underlying condition.
- Echocardiography is the gold standard of investigation which may identify both low right and left ventricular performance.
- That the key to treating infants with pulmonary hypertension is to improve their oxygenation, which can be achieved by optimising lung function, ECMO or pulmonary vasodilation.

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### SUMMARY

Persistent pulmonary hypertension of new born (PPHN) is associated with mortality and morbidity; it may be idiopathic or secondary to a number of conditions. The mainstay of diagnosis and to exclude structural abnormalities is echocardiography. Brain type natriuretic peptide (BNP) levels are elevated in PPHN, but are insufficiently sensitive to contribute to routine diagnosis. Management includes improving oxygenation by optimising lung volume by ventilatory techniques and/or surfactant and administering pulmonary vasodilator agents. Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, reduces the need for extracorporeal membrane oxygenation in term infants; it does not, however, improve mortality or have any long term positive effects in prematurely born infants or infants with congenital diaphragmatic hernia. Other pulmonary vasodilators have been reported in case series to be efficacious alone or in combination with iNO. Randomised trials with long term follow up are required to identify the optimum therapeutic strategies in PPHN.

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### INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) occurs when there is failure of the pulmonary vascular resistance to decrease appropriately during transition to extrauterine life [1]. Affected infants have structurally normal hearts, but large right to left shunts at atrial and ductal levels secondary to the pulmonary hypertension. The incidence of PPHN was reported to be 1.9 per

1000 live births in term neonates in a study involving 10 tertiary centres in the USA [2] and 0.43–6 per 1000 live births in the UK [3].

Pulmonary hypertension in the immediate newborn period can result from a number of underlying causes. Infants of mothers with diabetes, asthma and obesity have been reported to be at increased risk [4,5]. Other maternal factors include antenatal use of certain drugs; for example salicylates [6]. Exposure to in utero fluoxetine, a selective serotonin reuptake inhibitor (SSRI) induced pulmonary hypertension in fetal rats as a result of a developmentally regulated increased pulmonary vascular smooth muscle proliferation [7]. Use of SSRI in the third trimester in humans has been implicated in increasing the risk of PPHN, one study suggesting there may be four to five times increased risk [8], but the results of other studies are conflicting [7–12]. Use of SSRI before the

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twentieth week of pregnancy has not been associated with an increased risk of PPHN [10]. Maternal use of non-steroidal anti-inflammatory drugs (NSAIDs) has been suggested as a risk factor for pulmonary hypertension by inducing early closure of the ductus arteriosus. Fetal echocardiographic studies have demonstrated cyclooxygenase inhibitors to be associated with constriction of the ductus arteriosus, particularly in mothers who have received antenatal steroids [13,14]. The effect, however, was transient [15]. In a recently reported, large epidemiological study, no association of maternal non-salicylate NSAIDs use in the third trimester and an increased PPHN risk in the infants was found [16].

Infants who develop pulmonary hypertension have abnormal pulmonary vascular reactivity structure and/or growth. Intrapartum asphyxia and meconium aspiration syndrome (MAS) are associated with increased pulmonary vascular reactivity. Infection, particularly Group B Streptococcus, increases the risk of pulmonary hypertension due to the release of vasoactive substances. Congenital heart disease increases the risk due to myocardial failure. Abnormal vascular structure and growth occurs in infants with alveolar capillary dysplasia and congenital diaphragmatic hernia (CDH).

The mortality rate of infants with PPHN is approximately 10%, but is higher in infants with underlying conditions such as congenital diaphragmatic hernia (CDH). Up to 25% of infants with PPHN will have significant neurodevelopmental impairment at two years of age [17–19]. It is, therefore, important that both the diagnosis and management of the condition is optimised. The aim of this review is to examine the evidence base for the investigations and therapeutic strategies used in pulmonary hypertension of the newborn.

### Diagnosis

Infants with PPHN usually present within the first 12 hours after birth with cyanosis. In infants in whom the pulmonary hypertension is secondary to other conditions, the presentation is complicated by the features of that condition. Due to hypoxia, the infant may be acidotic and hypotensive and will remain cyanotic even when exposed to a high oxygen concentration. Respiratory distress is mild unless the pulmonary hypertension is secondary to lung disease such as meconium aspiration syndrome (MAS).

An oxygen saturation level pre ductal which is 5% higher (right arm) than post ductal (lower limbs) is found in PPHN and there is at least a 1–2 kPa difference in the pre and post ductal arterial oxygen level (PaO<sub>2</sub>). The appearance of the chest radiograph may be normal, unless there is underlying lung disease. The lung fields may be oligoemic due to poor pulmonary blood flow.

Echocardiography is the gold standard investigation in establishing the diagnosis of PPHN and to rule out structural abnormalities. From the tricuspid regurgitation (TR) jet, the right ventricular pressures can be calculated using the modified Bernoulli equation. In 30% of cases, a TR jet may not be seen due to poor right ventricular contractility; in such situations, evaluation of atrial and ductal shunting can be informative. There may also be bowing of the intra-atrial septum to the left. The alignment of the inter ventricular septum at the end of systole gives a rough estimate of the pulmonary blood pressures [20]: if the interventricular septum appears rounded the pulmonary pressure is less than 50% of the systemic systolic pressure, if the inter ventricular septum is flattened it is 50–100% of the systemic systolic pressure and if the interventricular septum bows into the left ventricle the pressure is 100% of systemic systolic pressure.

The right ventricle functions poorly in severe pulmonary hypertension and refractory low right and left ventricular output are associated with poor outcome. In severe PPHN, the left ventricular output may drop to below 100 ml/kg/min (normal

150–300 ml/kg/min). Left ventricular size and output has been suggested to correlate with the need for advanced therapies (mechanical ventilation, high frequency oscillation (HFO) and extracorporeal membrane oxygenation (ECMO)) for pulmonary hypertension [21].

Brain type natriuretic peptide (BNP) is secreted by the cardiac ventricles in response to increased wall stress and related ventricular filling pressures. BNP levels have been found to be elevated in at or near term neonates with PPHN and correlate with the tricuspid regurgitant jet [22]. In one series, however, BNP levels were not affected by inotrope administration and only weakly correlated with the oxygenation index [22]. BNP levels, therefore, do not seem likely to become part of routine investigation of an infant with PPHN.

### Management

The management of PPHN consists of treating the hypoxaemia and any underlying condition. Prior to the introduction of inhaled nitric oxide (iNO), the main stay of therapy as evidenced by review of the practices of 12 level three NICUs between 1993–1994 were hyperventilation (32–92%), alkali infusion (27–93%), sedation (77–100%), paralysis (33–98%), inotropes (48–100%) and tolazoline (31–81%) [2] (The figures in the brackets are the percentage of infants in each unit who would receive that therapy). The wide variation in the use of different agents likely reflects the limited evidence base. It was noted that hyperventilation reduced, but alkali therapy increased, the risk of ECMO and bronchopulmonary dysplasia (BPD) [2]. Hyperventilation was used to lower arterial carbon dioxide (PaCO<sub>2</sub>) levels and hence elevate pH with the aim of causing pulmonary vasodilation. Arterial carbon dioxide (PaCO<sub>2</sub>) levels of 2.5–3.5 kPa, however, resulted in a 50% reduction in cerebral blood flow velocity, which was associated with EEG abnormalities. Although no long term sequelae of hypocarbia in term born infants have been reported, periventricular leukomalacia is increased in prematurely born infants. Hyperventilation was also associated with a reduction in cardiac output due to the high inflating pressures and there was a 50% incidence in both air leaks and BPD. An elevated pH can also be achieved by an infusion of alkali, but chronic hypocapnic alkalosis markedly increases the hypoxic reactivity of the pulmonary vasculature.

There remains variation in the management of infants with PPHN. A survey of 217 neonatologists in Canada, Australia and New Zealand demonstrated that, although echocardiography and blood gases were the most common tests to assess the severity of the pulmonary hypertension, more neonatologists in Australia/New Zealand versus Canada were trained to perform echocardiography ( $p < 0.001$ ). In addition, a lower proportion of neonatologists in Australia/New Zealand compared to in Canada used milrinone ( $p < 0.001$ ), vasopressin ( $p = 0.02$ ) and inhaled prostacyclin ( $p = 0.02$ ), but more used sildenafil ( $p = 0.01$ ) [23].

The general management of infants with PPHN is to improve their systemic blood pressure (BP), as the size of the right to left shunt depends in part on the systemic BP. The most appropriate BP to achieve, however, has not been assessed in randomised controlled trials (RCTs) with long term outcomes. Infants with PPHN should be minimally handled, as a slight disturbance can precipitate severe hypoxaemia. As a consequence, suctioning should only be used when absolutely necessary and chest physiotherapy is contraindicated.

The key to treating infants with PPHN is improving their oxygenation, which can be achieved by optimising their lung volume. Increasing positive end expiratory pressure (PEEP) increases lung volume, but can result in lung over distension, especially in the absence of underlying lung disease and this would

result in undesirable elevation of PaCO<sub>2</sub> levels. Other strategies to optimise lung function are surfactant and high volume strategy HFO. Oxygenation can also be improved by use of ECMO or pulmonary vasodilators.

#### Surfactant

In a multicentre study of 328 infants with MAS, sepsis or PPHN, up to four doses of surfactant was associated with a reduction in the need for ECMO ( $p=0.038$ ) especially seen in the lowest oxygenation index (OI) stratum ( $p=0.013$ ) [24]. Meta-analysis of the results of four RCTs of surfactant administration in MAS demonstrated a significant reduction in the need for ECMO (odds ratio (OR) 0.64) [25].

#### High frequency Oscillation (HFO)

Although high volume strategy HFO can improve oxygenation and CO<sub>2</sub> elimination, there is very little evidence to support its use in infants with PPHN. A cross over trial of HFO and conventional ventilation in infants greater than 34 weeks of gestation and a birth weight of more than 2 kg demonstrated that, although significantly more of the infants randomised to HFO met ECMO criteria (67% versus 42%), once infants failed on their initial mode and were crossed over, more were rescued by HFO (63% versus 23%). Nevertheless, there were no significant differences between the two groups with regards to death, need for ECMO, bronchopulmonary dysplasia (BPD), intracerebral haemorrhage (ICH) and days in hospital [26]. Hence, a Cochrane review [27] concluded that HFOV could not be routinely recommended for infants born at term or near term with PPHN.

In a randomised trial of infants with severe pulmonary hypertension [28], HFOV was compared to inhaled nitric oxide (iNO) and conventional mechanical ventilation in infants with gestational ages of 34 weeks or greater with respiratory distress syndrome (RDS), MAS, idiopathic PPHN or pulmonary hypoplasia; infants with congenital diaphragmatic hernia (CDH) were excluded. Infants who failed either therapy were then crossed over, if they still failed to have an improvement in oxygenation (PaO<sub>2</sub> < 60 mm Hg) they received both therapies. The combination of HFOV and iNO was found to be the most effective therapy for the infants with respiratory distress syndrome (RDS) or MAS than treatment with HFOV or iNO alone. Whether HFOV is effective in infants with pulmonary hypertension associated with CDH remains unknown, hence a multicentre RCT (VICI trial) is being undertaken [29].

#### ECMO

A meta-analysis [30] of four trials of ECMO in infants with severe respiratory failure highlighted use of ECMO was associated with significantly improved survival with a relative risk (RR) of 0.44 (95% CI 0.31 to 0.61) for mortality. If infants with congenital diaphragmatic hernia (CDH) were excluded the relative risk was even lower (0.33 (95% CI 0.21, 0.53)). The ECMO study group reported follow up at one and seven years and highlighted that ECMO support reduced the risk of death without an associated increase in severe disability [31]. Overall, however, nearly half of the children recruited into the UK trial had died or were severely disabled by seven years of age, reflecting the severity of their condition [30].

The results of ECMO depend on the underlying condition, with more than 90% survival for infants with MAS, 78% survival for infants who had BPD, but they suffer prolonged ventilator dependence and neurodevelopmental sequelae and 70% for infants with Down's syndrome, but they suffer post ECMO mortality. The benefit of ECMO for babies with CDH is unclear; follow up of

73 CDH infants supported by ECMO during 1991 to 2000 and followed until 2003 demonstrated only 37% survival to one year [32]. At follow up, 48% had respiratory symptoms, 59% gastrointestinal symptoms and 19% severe neurodevelopmental deficit; only 12% of survivors had no significant neurodevelopmental deficit and required no further medical/surgical intervention [32].

#### Pulmonary vasodilators

##### Inhaled Nitric Oxide

Nitric Oxide is produced in the vascular endothelial cells by the action of nitric oxide synthetase enzyme (NOS) on the terminal nitrogen of L- Arginine. There are three iso-forms of NOS in the lung, but the endothelial iso-form is the most important regulator of nitric oxide production. Nitric Oxide thus produced diffuses through the endothelium to its site of action on the vascular smooth muscle. The mRNA for lung endothelial NOS and protein are present in early fetal life and increase with increasing gestational age in preparation for postnatal adaptation to take place. There is a higher response to endothelial acting vasodilators such as iNO, oxygen and acetylcholine in infants at/or near term compared to those born prematurely [33,34]. Nitric oxide activates guanyl cyclase leading to the conversion of cyclic guanyl triphosphate (cGTP) to cyclic guanyl monophosphate (cGMP). cGMP activates cGMP gated ion channels and the cGMP dependent protein kinase. Those channels inhibit the influx of intracellular calcium by opening the calcium sensitive potassium channels leading to the polarisation of the membrane resulting in reduction of vascular smooth muscle tone. Inhaled NO (iNO) acts locally without systemic side effects, as on entry into the blood stream iNO binds strongly to haemoglobin to form nitrosylhaemoglobin, which in turn is rapidly converted to methaemoglobin.

iNO has been shown to acutely improve oxygen requirement [35] and reduce the need for ECMO [36,37] in infants born at term. A meta-analysis [38] highlighted iNO in term infants' results on average in a decrease in the OI of 15.1 within 30 and 60 minutes of administration and increased the PaO<sub>2</sub> by 53 mmHg. iNO use was also associated with a reduction in the need for ECMO (RR 0.63, 95% confidence intervals 0.54, 0.75). The number needed to treat to prevent one infant requiring ECMO was 5.3 [38]. There was, however, no significant reduction in the mortality rate or duration of hospitalisation or improvement in lung function at follow up [39]. Neurodevelopmental outcome also did not differ significantly between infants treated with iNO and those not so treated [18,19]. It should be started at 20 parts per million (ppm) [40] with careful monitoring of methaemoglobin and nitrogen dioxide levels. Starting iNO at an OI between 15 and 25 compared with initiation at an OI of greater than 25 in term and near term infants resulted in better oxygenation, but did not reduce the incidence of ECMO/mortality [41]. In infants with CDH, iNO has been shown to have only a short term effect on oxygenation, hence it may have a place for stabilising infants prior to ECMO [42]. In a RCT, iNO was not found to reduce the need for ECMO or death in infants with CDH [43]. Late pulmonary hypertension can occur in a subset of CDH infants, a retrospective analysis suggested such infants may benefit from inhaled NO delivered via nasal cannula [44].

A Cochrane review of the use of iNO for respiratory failure in prematurely born infants identified 14 RCTs [40]. The RCTs were grouped into three categories: (i) early (<3 days) rescue use based on oxygenation criteria (ii) early (<3 days) routine use in intubated prematurely born infants and (iii) later (>3 days) rescue use based on risk of BPD. The nine trials of early rescue treatment of prematurely born infants with iNO based on oxygenation criteria failed to demonstrate any significant effect on mortality or BPD (RR 0.94, 95% CI, 0.87, 1.07). Two studies of the later rescue use of iNO in prematurely born infants depending on their risk of BPD also did

not reveal a significant effect on mortality of BPD (RR 0.90, 95% CI 0.80, 1.02). The three trials of early routine use of iNO in prematurely born infants with pulmonary disease highlighted a reduction in death or BPD (RR 0.93, 95% CI, 0.86, 1.01), but this did not reach statistical significance. In the early rescue group, there was a non significant increase in severe intraventricular haemorrhage (IVH) but no excess of neurodevelopmental impairment was reported. Despite those results, a retrospective review of 155,872 infants born before 34 weeks cared for between 2000 and 2008 demonstrated that overall iNO use had increased from 0.3 to 1.8% and in infants born between 23 and 26 weeks of gestation from 0.8 to 6.6% [17].

#### Phosphodiesterase 5 inhibitors

Sildenafil is a selective cGMP phosphodiesterase 5 inhibitor and hence enhances NO mediated vasodilatation. It has been used as a weaning adjunct in infants in the post operative period for congenital heart disease surgery [45,46]. Its limitation is that it is administered orally and in unwell infants absorption is inconsistent and unpredictable. A further limitation is that many of the results of the efficacy of Sildenafil outlined above are from case series or small RCTs. In a proof of concept, randomised, masked study [47] in infants with severe PPHN and an OI greater than 25, Sildenafil administered enterally to six infants, compared to the seven who received placebo was associated with an improvement in oxygenation. In a small RCT (n=29) which included infants and children, a single dose of sildenafil prevented rebound after withdrawal of iNO and was associated with a reduction in the duration of ventilation [48]. A meta-analysis of three RCTs which included a total of 77 infants with PPHN in resource limited settings concluded that sildenafil reduced mortality (RR 0.20, 95% CI 0.07-0.57) and the number required to treat to prevent one infant dying was three (95% CI 2 to 6) [49]. The Cochrane review concluded that sildenafil has significant potential in the treatment of PPHN especially in resource limited settings. A large scale randomised trial comparing sildenafil with the currently used vasodilator, inhaled nitric oxide, however, is needed to assess efficacy and safety [49].

#### Phosphodiesterase 3 inhibitors

Phosphodiesterase 3 inhibitors increase cAMP levels increasing myocardial contractility and cardiac output. Phosphodiesterase 3 inhibitors can potentiate the effects of NO by improving diastolic function. Milrinone is a phosphodiesterase 3 inhibitor, but there are only case reports of its efficacy in neonates. One such report highlighted milrinone improved pulmonary vasodilatation and reduced oxygen requirement in nine infants with PPHN who were unresponsive to iNO [50] and in another report of four neonates, similar positive effects on oxygenation were noted, but all four subsequently developed IVHs [51]. In a case series of 11 neonates with a suboptimal response to iNO, milrinone (50 mcg/kg) loading dose over sixty minutes followed by a maintenance infusion of 0.33-0.99 mcg/kg/min for 24-72 hours was associated with improvements in oxygenation and a reduction in iNO dose [52]. There were also improvements in right and left ventricular output and lower pulmonary artery pressures [52]. A Cochrane review [53] found there were no studies that met the criteria for inclusion in the meta-analysis.

#### Adenosine

Adenosine is a purine nucleoside with a half life of ten seconds and acts via adenosine receptors on vascular smooth muscle endothelium to increase cAMP resulting in smooth muscle relaxation and vasodilatation. Adenosine may also stimulate potassium (K<sup>+</sup>) ATP channels resulting in hyperpolarisation of smooth muscle [54]. Patients with pulmonary hypertension have

low plasma adenosine levels. In a case series of nine infants with pulmonary hypertension already requiring mechanical ventilation and iNO, a continuous infusion of adenosine at 50 mcg/kg/min resulted in an improvement in oxygenation in six of the infants [54]. The three infants who did not respond had CDH, capillary alveolar dysplasia or MAS.

#### Magnesium sulphate

Magnesium sulphate is a calcium antagonist and a modulator of vascular tone. It can result in improvements in oxygenation in infants with PPHN, but levels need to be monitored as side-effects can occur including sedation, muscle relaxation, disturbance of levels of calcium and potassium and hypotension. A Cochrane review [55] concluded that there were no eligible trials of magnesium sulphate to be included in a meta-analysis.

#### Thromboxane synthase inhibitors

The increased production of the arachidonic acid metabolite, thromboxane A<sub>2</sub> may result in pulmonary hypertension. In a study of three day old piglets, the effects of furegrelate sodium, a thromboxane synthase inhibitor on the development of pulmonary hypertension were evaluated [56]. The piglets were exposed to 21 days of normoxia (inspired oxygen fraction (FiO<sub>2</sub>) 0.21) or hypoxia (FiO<sub>2</sub> 0.10). In the piglets who received furegrelate three times a day at the start of hypoxic challenge, the pulmonary vascular resistance index was reduced by 34% [56].

#### Endothelin receptor blockers

Endothelins (ET) are endothelial cells derived vasoconstrictor peptides. The isopeptide ET-1 binds primarily to the ET<sub>A</sub> receptor, which is present on smooth muscle cells in the fetal lung. ET-1 is a potent vasoconstrictor and circulating ET-1 levels are high in fetal and transitional circulations. Bosentan is a dual endothelin (ET<sub>A</sub> and ET<sub>B</sub>) receptor blocker. It has been reported to be successful as an adjunct to iNO and oral sildenafil in case reports [57].

### FUTURE DIRECTIONS FOR RESEARCH

- Identification of accurate biomarkers for infants at highest risk of PPHN and to monitor their progress and response to therapy.
- A randomised trial with long term outcomes to compare the efficacy and safety of sildenafil and inhaled nitric oxide.
- Appropriately designed studies to assess the potential of other pulmonary vasodilators.

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