Persistent pulmonary hypertension of the newborn

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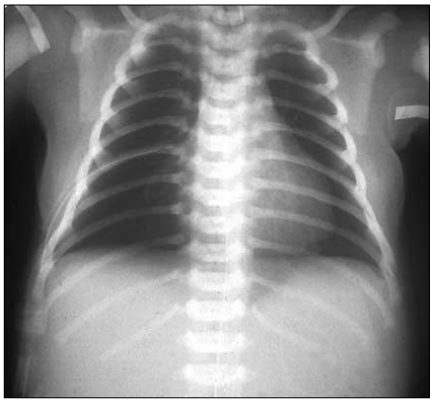
Pulmonary hypertension refers to the elevation of the pulmonary artery pressure above normal. In utero a raised pulmonary arterial pressure in the baby is normal; at birth there is a marked decrease in pulmonary vascular resistance allowing the lung to establish gas exchange. Persistent pulmonary hypertension of the newborn (PPHN; *Figure 1*) occurs when this decrease fails to occur.

INTRODUCTION

PPHN occurs in 1–6/1000 live births and is a major cause of morbidity (15–25% neurological handicap) and mortality (20–25%) in the term and near-term infant. It is a syndrome characterized by systemic arterial hypoxaemia resulting from right to left shunting of blood secondary to increased pulmonary vascular resistance. This syndrome has previously been described as persistent fetal circulation. Several authors have tried to elucidate the aetiology of this failed transition from fetal to early postnatal pulmonary circulation. PPHN can be precipitated by meconium aspiration syndrome (*Figure 2*), respiratory distress syndrome, pneumonia, sepsis or severe hypoxia.

Figure 1. Persistent pulmonary hypertension of the newborn showing clear lung fields.



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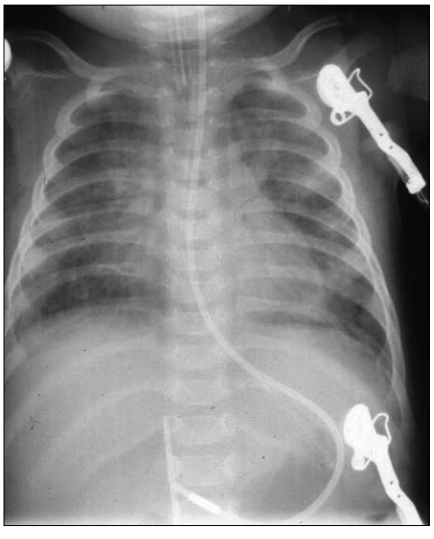
CHANGES IN THE PULMONARY CIRCULATION AT BIRTH

Very little blood flows into the fetal lungs before birth because the fetal pulmonary vascular resistance is very high compared to the systemic vascular resistance. The high pulmonary vascular resistance diverts the blood away from the lungs through the foramen ovale and the patent ductus arteriosus into the low resistance systemic and placental circuits.

With birth the placental circulation is removed and systemic vascular resistance increases. This increases pressure in the left ventricle and atrium, which helps the closure of the foramen ovale. With the onset of ventilation, the oxygen tension in the alveolus and in arterial blood increases; there is a subsequent reduction in pulmonary vasoconstriction resulting in a reduction in pulmonary vascular resistance below that of the systemic circulation. The increased arterial oxygenation also results in constriction of the ductus arteriosus. The end result of these changes is a closure of the fetal conduits with the redirection of blood into the lungs and transition of the lung into an air-filled structure directly involved in oxygenation of the blood. Neonatal cardiopulmonary adaptation is then complete.

Figure 2. Chest X-ray from infant with persistent pulmonary hypertension of the newborn showing meconium aspiration.

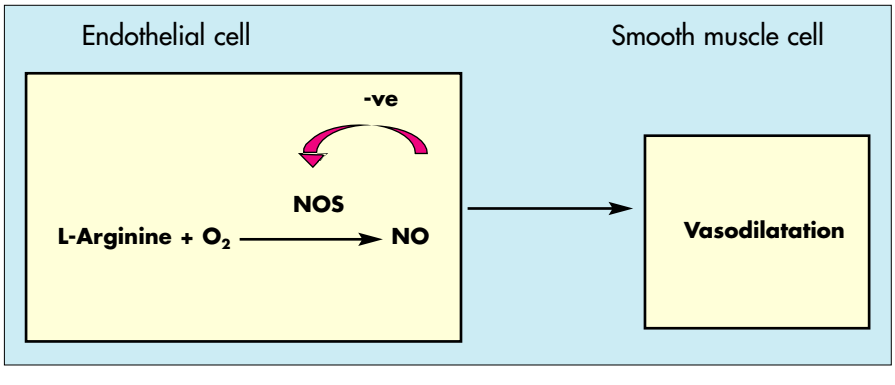


CONTROL OF VASCULAR TONE

The pulmonary endothelium plays a crucial role in the adaptation and regulation of vascular tone in the normal and hypertensive circulations. Nitric oxide (NO) is synthesized in the vascular endothelium (*Figure 3*) by nitric oxide synthase (NOS) from l-arginine (LA) (Palmer et al, 1988) via the oxidation of the terminal guanidino nitrogen atom of the amino acid. This reaction is competitively inhibited by asymmetric di-methyl arginine (ADMA), in a dose-dependent fashion.

NO is a smooth muscle relaxant that reduces pulmonary arterial pressures by reducing the resting pulmonary vas-

Figure 3. Nitric oxide production within the endothelial cell. NO = nitric oxide; NOS = nitric oxide synthase.



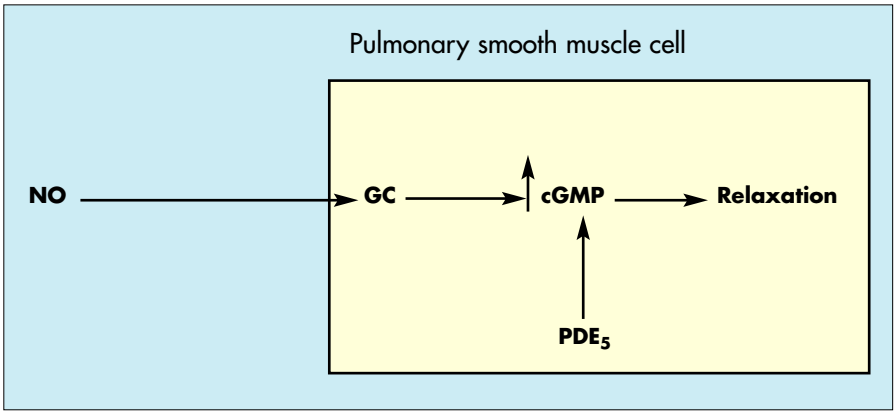


Figure 4. Vasodilatation within the pulmonary smooth muscle cell. cGMP = guanosine 3′,5′ monophosphate; GC = guanylate cyclase; NO = nitric oxide; PDE_5 = phosphodiesterase type 5.

cular tone (Furchgott, 1983), thus it is a potent endogenous pulmonary vasodilator. NO is chemically unstable, with a half-life of 3–5 seconds in aqueous solution under physiological conditions which may be shorter in vivo. NO reacts with oxyhaemoglobin and undergoes spontaneous oxygenation to nitrite (NO_2^-) and nitrate (NO_3^-) ions (Ingarro, 1990).

NO relaxes smooth muscle cells (Bhagat and Vallance, 1996) by activating the soluble enzyme guanylate cyclase, which increases the intracellular cyclic guanosine 3',5' monophosphate (cGMP) concentrations (*Figure 4*). This initiates a cascade (Moncada et al, 1991) that results in the relaxation of the arterial smooth muscle (Frostell et al, 1991). The duration and intensity of the cGMP signal transduction is controlled by the phosphodiesterases, a superfamily of phosphohydrolases that degrade 3',5' cyclic nucleotides. In the pulmonary circulation, cGMP is inactivated by a specific phosphodiesterase, phosphodiesterase type 5 (PDE_5), controlling the degree of pulmonary tone.

PATHOPHYSIOLOGY

PPHN is a syndrome that results when the pulmonary vascular resistance fails to decrease after birth and remains equal to or greater than systemic vascular resistance. Thus the blood continues to flow through the foramen ovale and the ductus arteriosus, bypassing the lungs and failing to oxygenate appropriately. Arterial oxygen tension falls to very low levels. Pulmonary and systemic resistances remain high, placing a mechanical load on the heart which, when combined with the hypoxaemia, compromises myocardial performance resulting in right heart dilatation, tricuspid insufficiency and right heart failure.

PATHOGENESIS

The exact pathogenesis of PPHN continues to be undefined, although there is a suggestion that this syndrome may be the result of an imbalance between vasoconstricting and vasorelaxing factors. Possible mechanisms include an abnormal responsiveness of the pulmonary vasculature to hypoxia with an inability to relax. In support of this is pathological evidence from babies that died from PPHN showing a greater thickness of the medial smooth muscle compared to normal babies (Haworth and Reid, 1976).

Another possible mechanism is a disruption in the transition from fetal to normal circulation as a result of alterations in vasoactive mediator levels. Decreased or absent endothelial NOS mRNA has been reported in infants with PPHN (Villanueva et al, 1998). Elevated levels of endothelin-1, a recognized vasoconstrictor, and reduced cGMP plasma concentrations in infants with PPHN have also been described (Christou et al, 1997; Kuo and Chen, 1999). Infants with PPHN have also been reported to be deficient in arginine (Vosatka et al, 1994) and several studies have shown reduced pulmonary adenosine concentrations in fetal as compared to newborn lambs (Konduri et al, 1992) and in patients with pulmonary hypertension (Saadjian et al, 2000).

DIAGNOSIS

The syndrome is usually noted in term or post-term infants within the first few days of life. The baby presents in respiratory distress and is cyanosed, with a chest radiograph that can be normal or demonstrate various abnormalities compatible with aspiration, pneumonia, congenital diaphragmatic hernia or hyaline membrane disease. Supplemental oxygen is needed to correct hypoxaemia. An oxygen tension gradient may occur between preductal and postductal arterial circulations. When PPHN is suspected echocardiographic examination is requested to rule out cardiac anatomical defects and confirm the pulmonary hypertension. Systemic hypotension can occur.

TREATMENT

The aim of treatment is to improve alveolar oxygenation, minimize pulmonary vasoconstriction, and maintain systemic pressure and perfusion. Treatment initially involves good supportive intensive care.

Ventilatory support

The aim is to achieve adequate ventilation and oxygenation with mild hypocapnoeic alkalosis to attenuate hypoxic pulmonary vasoconstriction. The use of high frequency oscillation may be considered if conventional ventilator support fails to achieve appropriate ventilation. Once pulmonary pressures have stabilized normalization of arterial gases can occur.

Sedation and paralysis

These infants are often quite agitated and 'fight the ventilator'. In order to gain control these infants may need paralysis and sedation in the initial stages. Once pulmonary pressures have been controlled paralysis can be stopped.

Alkalosis

Pulmonary vasoconstriction is related to intracellular pH rather than partial pressure of carbon dioxide (pCO_2)

levels (Schreiber et al, 1986). Thus in the initial acute stage systemic alkalosis may help control pulmonary hypertension. Alkalosis can be achieved with parenteral agents such as sodium bicarbonate.

Circulatory support

When circulatory collapse has occurred the use of inotropic agents can increase systemic resistance and improve perfusion. Maintenance of systemic arterial pressure may result in decreased right–left shunt, encouraging pulmonary blood flow and result in improved oxygenation.

Pulmonary vasodilators

Over the last few years there have been significant advances in the treatment of infants with PPHN with the use of intravenous and inhaled vasodilators like prostacyclin, dipyridamole and inhaled NO (iNO). The relative lack of specificity for the pulmonary circulation and significant systemic vasodilatory effects limit the use of agents like dipyridamole and prostacyclin to treat PPHN, although they continue to have some role (Max and Rossaint, 1999). iNO is a novel selective pulmonary vasodilator without significant systemic effects and is used as a pulmonary vasodilator in neonates with PPHN.

Several randomized controlled trials have shown improved oxygenation (Wessel et al, 1997) and a reduction in the need for extracorporeal membrane oxygenation (ECMO) with the use of iNO in infants with PPHN and hypoxic respiratory failure but no apparent reduction in mortality (Neonatal Inhaled Nitric Oxide Group, 1997; Roberts et al, 1997).

However, many questions remain as to the exact dosage and application of iNO (Wood et al, 1999), as well as its toxicity and long-term effects (Weinberger et al, 1999). Early studies suggest that iNO is not associated with significant toxicity or adverse effects, however, the long-term pulmonary and neurodevelopmental consequences of iNO therapy have not been established, with several authors reporting increased nitrotyrosine levels in infants after prolonged iNO use (Hallman et al, 1998). More recently changes in the licensure of NO may make the cost of its use prohibitive to smaller units (Pierce et al, 2002).

Other therapies

Pulmonary surfactants have been used just after delivery or on intubation to improve alveolar oxygenation. Tolazoline has been used in the past, however, its non-specific vasodilatation of both pulmonary and systemic circulations can limit its use. The exact mechanism of action of tolazoline is not clear – it appears to act as an alpha-sympathetic blocker, although several authors suggest a histamine-mediated vasodilatation (Stevenson et al, 1979).

Adenosine has been shown to improve oxygenation in infants with PPHN (Konduri et al, 1996; Patole et al, 1998), and adenosine has been shown to enhance the sensitivity of hypoxic rat muscle to NO (Marshall, 2001). There has been some evidence to support a possible role for this agent (Ng et al, 2003).

Amplification of the NO signalling cascade by means of selective phosphodiesterase inhibition has renewed interest in the phosphodiesterases and cGMP. The primary mechanism of pulmonary vasodilation is via the NO–cGMP signal transduction pathway making agents like sildenafil, a selective PDE_5 inhibitor, that amplify this pathway of possible therapeutic benefit. Oral sildenafil has been shown to selectively block the degradation of cGMP in the corpus cavernosa, enhancing erectile function in men with no significant systemic effects (Jackson et al, 1999).

Several animal studies have looked at the vasodilatory effects of the phosphodiesterase inhibitors: in newborn lambs with PPHN and in awake lambs with thromboxane-induced pulmonary hypertension a specific decrease in pulmonary artery pressures was seen (Dukarm et al, 1999; Weimann et al, 2000). Sildenafil has also been shown to enhance the relaxation induced by NO in vitro in isolated rabbit aortic rings (Wallis et al, 1999) and in porcine internal mammary artery (Wallace and Tom, 2000). Sildenafil has been used safely in infants to ameliorate the rebound pulmonary hypertension seen on withdrawal of iNO (Atz and Wessel, 1999) and as a long-term treatment in a child with primary pulmonary hypertension (Abrams et al, 2000). Other therapies proposed as beneficial in PPHN include magnesium sulphate as a vasodilator (Tolsa et al, 1995).

Extracorporeal membrane oxygenation

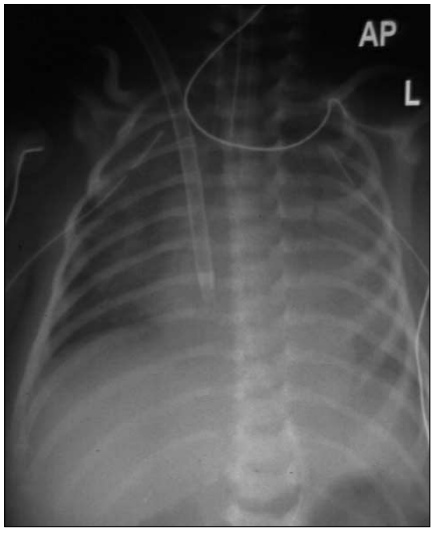
When other therapies have failed to result in improvement ECMO has been used to good effect (UK Collaborative ECMO Trial Group, 1996) (*Figures 5* and *6*).

Spontaneous resolution of this syndrome may occur 36 hours to several days after birth. Follow up of survivors has revealed few abnormalities of pulmonary and circulatory systems with excellent neurodevelopmental outcomes (Bernbaum et al, 1984).

CONCLUSION

A better understanding of the regulation of pulmonary vascular tone and the mechanisms and substances within this system will continue to lead to the use of new drugs to treat hypoxic respiratory disease in infants. Recent efforts have been devoted to under-

Figure 5. Baby with persistent pulmonary hypertension of the newborn on venovenous extracorporeal membrane oxygenation.



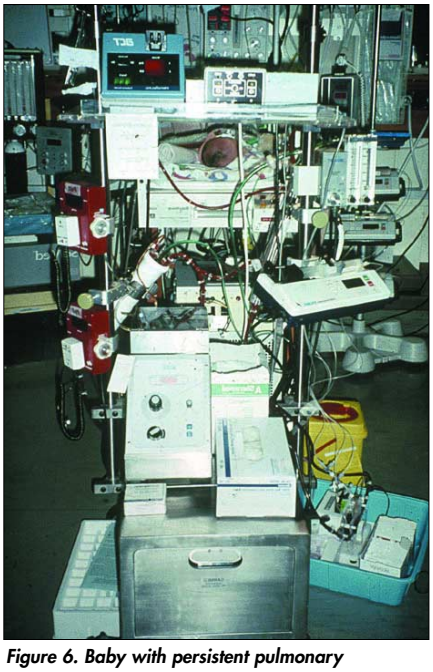


Figure 6. Baby with persistent pulmonary hypertension of the newborn on extracorporeal membrane oxygenation.

standing the cellular mechanisms underlying the pathophysiology of pulmonary hypertension, concentrating on endothelial cell dysfunction and defects in vasodilatation. HM

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KEY POINTS

- Persistent pulmonary hypertension of the newborn (PPHN) is a relatively common syndrome with a high morbidity and mortality.
- PPHN occurs when there is a failure in the normal postpartum drop in pulmonary pressures.
- The exact pathogenesis of PPHN is undefined although it may be caused by an imbalance of pulmonary vasoconstricting and vasorelaxing factors.
- Treatment for PPHN initially involves good supportive intensive care.
- Recently the use of selective pulmonary vasodilators has advanced the treatment of PPHN.