REVIEW

Pathophysiology of persistent pulmonary hypertension of the newborn: Impact of the perinatal environment

Physiopathologie de l’hypertension artérielle pulmonaire persistante du nouveau-né : rôle de l’environnement périnatal

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Summary The main cause of pulmonary hypertension in newborn babies results from the failure of the pulmonary circulation to dilate at birth, termed “persistent pulmonary hypertension of the newborn” (PPHN). This syndrome is characterized by sustained elevation of pulmonary vascular resistance, causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia. It can also lead to life-threatening circulatory failure. There are many controversial and unresolved issues regarding the pathophysiology of PPHN, and these are discussed. PPHN is generally associated with factors

Abbreviations: CDH, congenital diaphragmatic hernia; cGMP, cyclic guanosine monophosphate; ECMO, extracorporeal oxygenation; eNOS, endothelial nitric oxide synthase; iNO, inhaled nitric oxide; NO, nitric oxide; NOS, nitric oxide synthase; PaCO2, partial pressure of carbon dioxide in arterial blood; P02, oxygen pressure; PPHN, persistent pulmonary hypertension of the newborn; PUFA, polyunsaturated fatty acid; PVR, pulmonary vascular resistance; SpO2, saturation of peripheral oxygen; SSRI, selective serotonin reuptake inhibitor; VEGF, vascular endothelial growth factor.

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such as congenital diaphragmatic hernia, birth asphyxia, sepsis, meconium aspiration and respiratory distress syndrome. However, the perinatal environment—exposure to nicotine and certain medications, maternal obesity and diabetes, epigenetics, painful stimuli and birth by Caesarean section—may also affect the maladaptation of the lung circulation at birth. In infants with PPHN, it is important to optimize circulatory function. Suggested management strategies for PPHN include: avoidance of environmental factors that worsen PPHN (e.g. noxious stimuli, lung overdistension); adequate lung recruitment and alveolar ventilation; inhaled nitric oxide (or sildenafil, if inhaled nitric oxide is not available); haemodynamic assessment; appropriate fluid and cardiovascular resuscitation and inotropic and vasoactive agents.

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Résumé  La principale cause d’hypertension pulmonaire du nouveau-né résulte d’une vasodilatation pulmonaire insuffisante à la naissance, appelée « hypertension artérielle pulmonaire persistante du nouveau-né » (HTAPP). Ce syndrome est caractérisé par une élévation des résistances vasculaires pulmonaires, responsable d’un shunt droit-gauche par le foramen ovale et le canal artériel et d’une profonde hypoxémie. L’HTAPP est à risque vital lorsque qu’elle s’accompagne d’une défaillance circulatoire. La prise en charge nécessite un recrutement pulmonaire adéquat, l’inhalation de monoxyde d’azote et un support cardiovasculaire adapté. Néanmoins, la physiopathologie et la prise en charge sont toujours l’objet de recherches innovantes. Ainsi, de plus en plus d’arguments existent pour penser que l’environnement périnatal joue un rôle déterminant dans la genèse et l’aggravation de ce syndrome.

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Background

Pulmonary hypertension in newborns results from the failure of the pulmonary circulation to dilate at birth. Termed ‘persistent pulmonary hypertension of the newborn’ (PPHN), it occurs in an estimated 1–2 infants per 1000 live births [1]. This syndrome is characterized by sustained elevation of pulmonary vascular resistance (PVR), causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia [2,3] (Fig. 1). PPHN is frequently associated with low systemic pressure and low cardiac output because of increased right ventricular afterload and myocardial dysfunction [2,4]. PPHN-induced circulatory failure is a life-threatening condition. Cardiac failure further impairs oxygen delivery to the tissues and contributes to significant mortality and morbidity in newborn infants with PPHN [2–4].

Management requires adequate lung recruitment and alveolar ventilation, inhaled nitric oxide (iNO), and appropriate fluid and cardiovascular resuscitation [5]. Early initiation of inotropic and vasoactive agents is commonly used to increase cardiac output, maintain adequate blood pressure and enhance oxygen delivery to the tissue [4,6]. Nevertheless, there are many controversial and unresolved issues regarding the pathophysiology and the most effective management of PPHN. Growing evidence is emerging that indicates that the perinatal environment plays a key role in this syndrome.

Pathophysiology

Foetal circulation

The foetal pulmonary circulation is characterized by high PVR and low blood flow. Despite high pulmonary artery

Figure 1. Schematic representation of the circulation in PPHN. Sustained elevation of PVR contributes to low pulmonary blood flow and high pulmonary pressure, causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and foramen ovale and severe hypoxaemia. LA: left atrium; LV: left ventricle; PPHN: persistent pulmonary hypertension of the newborn; PV: pulmonary vein; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle.
pressure, the lungs are perfused with less than 10% of the combined ventricular output during late gestation [7]. Owing to high PVR in the foetus, most of the right ventricular output crosses the ductus arteriosus into the descending aorta, thereby increasing umbilical-placental flow and gas exchange.

Mechanisms that maintain high PVR in utero are incompletely understood, but include low foetal oxygen pressure (P02) [7], lack of a gas—liquid interface [8] and production of vasoconstrictor mediators such as endothelin-1 [9]. Nitric oxide (NO) production also modulates foetal pulmonary vascular tone in response to diverse stimuli, including acute changes in haemodynamic forces [8]. In foetal lambs, acute compression of the ductus arteriosus abruptly increases blood flow and pressure, and causes acute pulmonary vasodilation through the shear stress-induced release of NO [10–13]. However, despite maintenance of constant pressure, pulmonary blood flow progressively falls and PVR increases over time [14,15]. Therefore, the foetal pulmonary circulation is characterized by an ability to oppose vasodilation over time and to regulate its flow.

**Pulmonary adaptation at birth**

At birth, pulmonary blood flow increases dramatically, by 8–10-fold, and PVR drops immediately. Several stimuli, including drainage and absorption of foetal lung liquid, rhymic distension of the lung, increased P02 and altered production of several vasoactive products, including NO, are known to contribute to pulmonary vasodilation at birth [8]. The effects of several birth-related stimuli, including increased blood flow or shear stress, increased P02 and ventilation are partly dependent upon activation of nitric oxide synthase (NOS) [8,10–13].

The increase in NO production accounts for nearly 50% of the abrupt fall in PVR at birth in foetal lambs [8]. NO mediates vasodilatation by stimulating soluble guanulate cyclase-induced cyclic guanosine monophosphate (cGMP) production [16]. cGMP is downregulated by phosphodiesterase 5 activity. Phosphodiesterase 5, which is abundantly expressed in lung tissue, particularly during foetal life, is a key regulator of perinatal pulmonary circulation [17] (Fig. 2).

**Maladaptation of the pulmonary circulation at birth**

PPHN is a clinical syndrome that is associated with diverse neonatal cardiopulmonary diseases, including birth asphyxia, sepsis, meconium aspiration and respiratory distress syndrome, or it can be idiopathic [1–3].

The usual clinical expression of PPHN consists of an unstable refractory hypoxaemia with pre- and postductal saturation of peripheral oxygen (SpO2) gradient. Pulmonary hypertension can be associated with a systemic hypotension and symptoms of shock, termed ‘obstructive’ shock, the clinical and biological signs of which are non-specific: grey colour, tachycardia, refill capillary time more than 3 seconds, oliguria, systemic hypertension and lactic acidosi. Doppler echocardiography is required to determine the main component of the shock. Management priority is not to normalize postductal SpO2, but to optimize the circulatory function. A rigorous clinical and echocardiographic assessment is required for early diagnosis of circulatory failure. More relevant than changes in postductal SpO2, reflecting right-to-left ductus arteriosus shunting, the decrease in preductal SpO2 results from an increase in the right-to-left shunting through the foramen ovale. It occurs when the pulmonary venous return decreases (which reduces the left atrial pressure) or in case of right cardiac failure (leading to elevation of right atrial pressure). Both are markers for potential circulatory failure. In most cases, low postductal SpO2 alone (i.e. with normal preductal SpO2) does not cause tissue hypoxia. In contrast, a drop in preductal SpO2 is usually associated with symptoms of shock and an increased lactate concentration.

Experimental studies of chronic pulmonary hypertension in newborn animals have demonstrated impaired endothelial release of NO and increased production of vasoconstrictors (e.g. endothelin-1) [18]. In normal foetal lambs, acute compression of the ductus arteriosus causes progressive pulmonary vasodilation, which is blocked by NOS inhibition, suggesting that NO mediates shear stress-induced vasodilation. After NOS inhibition, acute ductus arteriosus compression causes a marked pulmonary vasoconstrictor response, suggesting that NOS blockade unmasks a potent myogenic response in the normal foetal lung [14]. In contrast, exposure to chronic pulmonary hypertension for 2 days impairs flow-induced vasodilation and enhances the myogenic response during acute ductus arteriosus compression in the absence of NOS inhibition [19,20]. Therefore, with prolonged pulmonary hypertension during the perinatal period, pulmonary blood flow is autoregulated and independent of pulmonary artery pressure. The most striking feature of perinatal pulmonary hypertension is the loss of the normal

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**Figure 2.** NO/cGMP pathway. NO, produced by endothelial NOS, diffuses towards the smooth muscle cell in which it stimulates soluble guanulate cyclase to produce cGMP. The mechanism whereby increased cGMP regulates pulmonary vascular tone includes activation of K+ channels, causing smooth muscle cell membrane hyperpolarization and inactivation of VOCC. Closure of VOCC causes a decrease in cytosolic Ca++ concentration and vasodilation. Intracellular concentration of cGMP is downregulated by PDE5 activities. Ca++: calcium; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; GMP: guanosine monophosphate; K+: potassium; NO: nitric oxide; NOS: nitric oxide synthase; PDE 5: phosphodiesterase 5; SMC: smooth muscle cell; VOCC: voltage-operated calcium channels.
vasodilator response to birth-related stimuli causing a para-
doxical vasoconstriction to acute haemodynamic stress.

Several investigators have suggested that an increase in PDE5 activity may contribute to this phenomenon. Lung PDE5 activity increased by 150% in foetal lambs with ductus arteriosus ligation for 8 days compared to control lambs [21]. Sildenafil attenuates the progressive elevation of basal pulmonary vascular tone observed during chronic pulmonary hypertension, and preserves, at least in part, the physiological pulmonary vascular response to vasodilators [22].

More recently, the role of vascular endothelial growth factor (VEGF) in foetal lung development and the patho-
genesis of PPHN have been reported. VEGF is a potent endothelial cell mitogen and regulator of angiogenesis. In vivo inhibition of VEGF receptors in normal foetal sheep results in impaired vascular growth and pul-
monary hypertension [23]. Impaired alveolarization and vessel growth in chronic intrauterine pulmonary hyper-
tension are associated with decreased VEGF protein expression [24].

Risk factors for PPHN: impact of the environment

PPHN is usually associated with pulmonary parenchymal dis-
ease, such as meconium aspiration, pneumonia or hyaline
membrane disease; or with disease-related lung hypoplasia
including congenital diaphragmatic hernia (CDH) or prema-
ture rupture of the membrane-mediated oligohydramnios
[1—3]. However, growing evidence indicates that the foetal
environment plays a critical role in the maladaptation of the
lung circulation at birth. Evidence of a role for epigenetics in
the development of pulmonary arterial hypertension is also
emerging. Epigenetic mechanisms are involved in the reg-
ulation of gene expression, which are controlled, at least in
part, by environment. In newborn rats with pulmonary hyper-
tension, the increased expression of endothelial NOS is
associated with changes in epigenetic regulation [25]. In the
same way, pulmonary hypertension has been associated with
abnormal epigenetic regulation of superoxide dismutase and
hypoxia inducible factor [26].

Antenatal smoke exposure

Cotinine concentrations in cord blood – a biological marker for nicotine exposure — have been found to be higher in infants with PPHN than in healthy control newborn infants [27]. Prenatal cigarette smoke has been found to increase the risk of PPHN among premature infants less than 30 weeks gestational age, suggesting a toxic effect on the pulmonary vascular development and maturation [28]. Studies of lungs exposed in utero to cigarette smoke have shown marked structural and functional changes, such as decreased alve-
olar attachments to the airway wall and increased airways
responsiveness. Endothelial dysfunction in intrapulmonary
arteries has been found during exposure to tobacco smoke
contributing, at least in part, to vasoconstriction and smooth
muscle cell proliferation [29]. In an experimental model of
foetal lambs, we found that prenatal exposure to cigarette
smoke causes a potent and sustained pulmonary vasocon-
striction in the foetus, and blunts the vasodilator response
to an increase in oxygen tension [30]. These effects are
associated with a marked decrease in foetal oxygination.
As the postnatal circulatory adaptation is highly dependent
on the decrease in PVR and the vasodilator response to
birth-related stimuli, such as oxygen, we speculate that pre-
natal exposure to tobacco smoke increases the risk of PPHN
through failure of the pulmonary circulation to dilate at
birth.

Role of stress or pain

Corticosteroids and catecholamine are the main stress hor-
mones. Their effects on lung parenchyma maturation, lung
fluid clearance and surfactant release at birth have been
widely investigated. Evidence has emerged that the stress
hormones promote normal circulatory adaptation at birth.
Several experimental and clinical studies have shown that
norepinephrine improves circulation in the perinatal lung.
In foetal lambs, norepinephrine has been shown to increase
lung blood flow and reduce PVR [31]. Norepinephrine induces
an NO-dependent pulmonary vasodilation in the ovine foetus
through activation of α1-adrenoceptors [32—35]. In a large
retrospective review of nearly 30,000 consecutive deliver-
ies over 7 years, the incidence of PPHN in newborn infants
delivered by elective Caesarean was almost five times higher
than among those delivered vaginally [36]. A likely hypo-
thesis for PPHN after Caesarean is that there might be an
advantage to labour and vaginal delivery for the pulmonary
vascular bed of the neonate. Mechanisms explaining the
increase in PPHN after Caesarean remain unclear. A surge of
catecholamines, especially norepinephrine, is observed
at birth. However, neonatal norepinephrine concentrations
are significantly lower after Caesarean section than after
vaginal delivery. Lower levels of circulating norepinephrine
after Caesarean section may explain, at least in part, the
high incidence of PPHN in newborn infants delivered by Cae-
sarean section [37].

In contrast, evidence exists that painful stimuli impair
normal adaptation at birth and promote PPHN. Hypox-
aemia is usually observed during stressful intensive care
procedures in newborn infants with respiratory failure,
the duration of which may be reduced by opioid anal-
gesia [38]. In foetal lambs, nociceptive stimuli increase
pulmonary artery pressure and PVR [39,40]. This vaso-
constrictive response is abolished by analgesia and by
α1-adrenoceptor blockade [41]. These results provide new
insights into the mechanisms by which stressful events may
worsen hypoxaemia in newborn infants with PPHN. Noci-
ceptive stimulation, through α1-adrenoceptor activation,
may elevate pulmonary vascular tone leading to increased
right-to-left shunting through the ductus arteriosus and the
foramen ovale and to severe hypoxaemia.

Drug exposure

Drug administration during pregnancy may increase the risk
of maladaptation at birth.

The likelihood of PPHN increases after antenatal expo-
sure to aspirin or other non-steroidal anti-inflammatory
drugs [42]. Mechanisms of antenatal non-steroidal
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anti-inflammatory-induced PPHN may include antenatal closure of the ductus arteriosus or decreased production of vasodilator prostaglandins. Similar risks after birth: ibuprofen administration has the potential to cause PPHN in preterm infants with patent ductus arteriosus [43].

Selective serotonin reuptake inhibitors (SSRIs), used to treat maternal depression, elevate the basal vascular tone in the foetal lung [44]. Pulmonary vascular remodelling and right ventricular hypertrophy have been observed in rat pups after maternal exposure to fluoxetine [45]. A case-control study to assess whether PPHN is associated with exposure to SSRIs has been conducted during late pregnancy [46]. A total of 377 women whose infants had PPHN and 836 matched control women were enrolled in the study. Fourteen infants with PPHN had been exposed to antenatal SSRIs, as compared with six control infants (adjusted odds ratio 6.1, 95% confidence interval 2.2–16.8) [46]. These data support an association between the maternal use of SSRIs in late pregnancy and PPHN in the offspring.

In case of severe respiratory failure, early initiation of inotropic and vasoactive agents is warranted to increase cardiac output, maintain adequate blood pressure and enhance oxygen delivery to the tissue [47]. Dopamine is the sympathomimetic amine most frequently used for septic shock in newborn infants. The ability of dopamine to raise systemic blood pressure has been clearly documented. However, dopamine has also been suggested to increase pulmonary artery pressure and pulmonary/systemic mean arterial pressure ratio in experimental models and in human [31,48]. Caution should therefore be advocated in the use of dopamine in newborn infants at risk of, or with, PPHN.

Perinatal nutrition

It has been well established that maternal obesity and diabetes are associated with increased risks of maladaptation at birth [49]. The exact mechanisms are unclear, but include perinatal asphyxia, parenchymal disease and polycythaemia. Studies have highlighted that infants with PPHN are deficient in the amino acid, L-arginine, which is required for NO synthesis [50]. Evidence exists that differential vascular effects can be expected according to lipid intake. Indeed, dietary fish oils have beneficial effects on cardiac and vascular function, including effects on platelet/vessel wall interactions, endothelial function and inhibition of smooth muscle cell proliferation. The n3 polyunsaturated fatty acids (PUFAs) are metabolized by several enzymes, including cyclooxygenase, to produce prostaglandins (PGE3, PGI3), which are known potential vasodilator mediators. In addition, n3 PUFA competes with arachidonic acid (n6 PUFA) for enzymatic conversion. This competition decreases formation of vasoactive arachidonic acid metabolites such as thromboxane A2, a potent pulmonary vasoconstrictor. Thus, some evidence suggests that n3 PUFA may be beneficial in conditions associated with pulmonary hypertension. Also, n3 PUFA induces a potent pulmonary vasodilatation in the perinatal lung [51]. This effect is abolished by cytochrome 450 epoxidegenase, but not by NOS inhibitors. Our data provide evidence for potential beneficial effects of n3 PUFA on the pulmonary circulation through production of epoxides. n3 PUFA supplementation may help to prevent maladaptation at birth, in particular in conditions with prolonged pulmonary hypertension such as CDH or pulmonary hypoplasia.

Oxygen and hyperoxia

While oxygen stimulates endothelial nitric oxide synthase (eNOS) and NO production and contributes to pulmonary adaptation at birth [8], high concentrations of oxygen, such as are used to treat PPHN, may produce reactive oxygen species. For instance, hydrogen peroxide (H2O2) could decrease eNOS promoter activity, associated with an endothelin-1-mediated downregulation of eNOS expression [52]. Uncoupled eNOS has been shown to increase superoxide radicals, which rapidly combine with NO to form peroxynitrite, a potent pulmonary vasoconstrictor and potential cellular toxin. Furthermore, hyperoxia may blunt NO-mediated pulmonary vasodilation through increasing phosphodiesterase 5 activity. In accordance with these studies, recombinant human superoxide dismutase enhances vasodilation after birth in experimental models of PPHN [53].

Principles of management

Basic principles

In PPHN with right-to-left shunt through the ductus arteriosus, the contribution of hypoxaemia to tissue oxygenation (low partial pressure of oxygen in arterial blood [PaO2]) is likely to be modest, provided SpO2 in the preductal area is greater than 80%, circulatory function is adequate and haemoglobin concentration is normal. Similarly, hypoxaemia during foetal life (SpO2 60–75%) or during cyanotic congenital heart diseases is not associated with tissue hypoxia, as long as cardiac function is normal. However, there is some evidence to suggest that cardiac dysfunction may play a major role in PPHN. Severe pulmonary hypertension increases right ventricular afterload that may result in right ventricular failure. The resulting elevation of right ventricular telediastolic pressure causes right-to-left shunting through the foramen ovale and worsens hypoxaemia. Because of a high degree of interdependence between the right and the left ventricles due to the presence of common structures (the interventricular septum and the inextensible pericardium), changes in the right ventricle size and geometry may alter the left ventricular function. This may explain why PPHN is usually associated with low systemic pressure and low cardiac output requiring the use of cardiac support [2–4]. Right ventricle failure occurs when the ductus arteriosus is closed or restricted. In severe PPHN with right-to-left shunting through the ductus arteriosus, both the left and right ventricle contribute to systemic blood flow (Fig. 3). Therefore, management of the newborn infant with PPHN requires both lowering of PVR and support of cardiovascular function (Table 1).

Environmental factors

First, exposure to environmental factors that worsen PPHN should be avoided. Noxious stimuli, including tactile stimuli, tracheal suction and heel pricks have to be limited as much
as possible. A specific pain scale for newborns should be used to titrate analgesia and optimize their environment (reduce noise and light, ‘cocooning’). Overdistension of the lungs contributes to a decrease in pulmonary blood flow and should be prevented, in particular in conditions associated with pulmonary hypoplasia (CDH and premature rupture of the membranes). Polycythaemia-mediating increased blood viscosity and increased pulmonary artery pressure should be corrected.

**Mechanical ventilation**

Management requires adequate lung recruitment and alveolar ventilation, appropriate fluid and cardiovascular resuscitation and use of pulmonary vasodilators [5]. In CDH, mask ventilation should be avoided during resuscitation in the delivery room to prevent gut distension located in the thoracic cavity. High airway pressures should also be avoided, to prevent pulmonary barotraumas while maintaining preductal oxygen saturation greater than 85% and partial pressure of carbon dioxide in arterial blood (PaCO₂) of 40–55 mmHg. Centres with better-than-expected CDH survival report the combination of establishing clinical care guidelines that set limits on ventilatory pressures to avoid lung overdistension and accepting adequate blood gas rather than optimal PaCO₂ and PaO₂, as long as there is evidence of adequate cardiac output and organ function [54].

Infants with significant right-to-left shunting require pulmonary vasodilator therapy. Currently, iNO is recommended for infants with PPHN [55]. This improves outcomes in hypoxaemic term and near-term infants by reducing the incidence of the combined endpoint of death or need for extracorporeal oxygenation (ECMO) [55]. Oxygenation improves in approximately 50% of infants receiving iNO [55]. Improvement in oxygenation has also been reported with the use of iNO in newborns with CDH and PPHN [56]. However, early use of iNO does not appear to improve the combined endpoint of

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**Figure 3.** Schematic representation of the circulation in PPHN. Because of elevated PVR, part of the right ventricular outflow is directed towards the systemic circulation through the ductus arteriosus, contributing to systemic blood flow. Despite a right-to-left ductus arteriosus shunting-mediating drop in postductal SpO₂, oxygen supply is usually adequate as long as the ductus arteriosus is widely patent. Both aortic and pulmonary artery pressures are closely related when the ductus arteriosus is patent (low ductal resistance). Thus, aortic pressure plays a critical role in pulmonary circulation. A drop in aortic pressure is associated with a decrease in pulmonary artery pressure, and since pulmonary artery pressure is the driving force for lung blood flow, a decrease in aortic pressure-induced drop in pulmonary artery pressure may worsen hypoxaemia and oxygen delivery. This electrical representation further highlights that a patent ductus arteriosus and normal right ventricle function are required for sustaining systemic blood flow and oxygen supply. F(PAP): proportional to pulmonary artery pressure; PA: pulmonary artery; PAP: pulmonary artery pressure; PPHN: persistent pulmonary hypertension of the newborn; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.
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Table 1 Steps in the management of PPHN.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
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<tbody>
<tr>
<td>1</td>
<td>Prevent exposure to environmental factors that may worsen PPHN (e.g. stress, painful stimuli, noise, excessive light, lung overdistension)</td>
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<tr>
<td>2</td>
<td>Provide adequate lung expansion and ventilation</td>
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<tr>
<td>3</td>
<td>Provide inhaled nitric oxide</td>
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<tr>
<td>4</td>
<td>Assess for haemodynamics (clinical examination, chest X-ray, cardiothoracic index, Doppler echocardiography)</td>
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<tr>
<td>5</td>
<td>Provide appropriate fluid expansion and vasoactive support according to the main component of the circulatory failure (obstructive, hypovolaemic, distributive or cardiogenic)</td>
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<tr>
<td>6</td>
<td>ECMO may be required in life-threatening obstructive shock</td>
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</tbody>
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ECMO: extracorporeal oxygenation; PPHN: persistent pulmonary hypertension of the newborn.

death/ECMO in infants with CDH alone [57]. Usual concentrations of INO for the treatment of PPHN are 5–20 ppm.

Supporting cardiovascular function

Early initiation of inotropic and vasoactive agents is warranted to increase cardiac output, maintain adequate blood pressure and enhance oxygen delivery to the tissues. Systemic hypotension is usually poorly tolerated, with worsening of hypoxia explained by:

• a decrease in left ventricle filling causing a decrease in oxygen delivery to the tissue;
• a decrease in coronary flow;
• a drop in pulmonary pressure resulting in a decrease in pulmonary blood flow.

Indeed, as the ductus arteriosus is usually patent in newborns with PPHN, pulmonary artery pressure and aortic pressure are closely related (Fig. 3). A decrease in systemic pressure-mediated drop in pulmonary artery pressure causes a decrease in pulmonary blood flow, as Flow = f(Pressure). Therefore, careful assessment of haemodynamics (clinical examination, chest X-ray, cardiothoracic index and echocardiography) is required in PPHN to provide optimal treatment.

Four types of shock, according to the main mechanism responsible for the cardiocirculatory failure, can be distinguished in the newborn:

• hypovolaemic;
• vasoplegic;
• cardiogenic;
• obstructive.

Fluid resuscitation should only be used if there is evidence for hypovolaemia. Cardiogenic shock—a rare event in PPHN as long as the ductus arteriosus is widely patent—may require inotropic drug infusion (dobutamine). The use of vasoactive drug is usually warranted in vasoplegic or obstructive shock.

ECMO

ECMO may be required to ensure effective oxygenation and decarboxylation, to limit the baro-volotrauma of the lungs and to improve right cardiac failure. ECMO is indicated when hypoxaemia persists despite optimal medical management. ECMO may be indicated based on the following criteria [1]:

• preductal SpO2 less than 80% despite peak inspiratory pressure greater than 28 cmH2O (or mean airway pressure greater than 15 cmH2O in high frequency oscillatory ventilation);
• PPHN and circulatory failure resistant to adequate management;
• gestational age greater than 34 weeks;
• birth weight greater than 2 kg.

Pulmonary vasodilator drugs

There is limited experience in PPHN with other pharmacological pulmonary vasodilators.

Phosphodiesterase inhibitors reduce the degradation of cGMP produced by endogenous or inhaled NO. Sildenafil has been found to improve cardiac output and respiratory function by reducing pulmonary hypertension refractory to inhaled NO in seven newborns with CDH [58]. In chronic pulmonary hypertension associated with CDH, sildenafil has been found to improve pulmonary vascular function and promoted lung growth [59]. Evidence exists that sildenafil is well tolerated in the newborn infant with PPHN [60]. A meta-analysis of three trials including 77 newborn infants with PPHN has indicated that sildenafil may improve oxygenation and reduce mortality [61]. The studies were performed in resource-limited settings where INO was not available. The results of the meta-analysis suggest that sildenafil in the treatment of PPHN has significant potential, especially in resource-limited settings.

The use of prostacyclin and analogues is an established therapy for children and adults with primary pulmonary hypertension. In a recent population-based study, the use of prostacyclin, along with various other measures, has been associated with a high survival rate [62]. Subcutaneous treprostinil has been found to improve functional symptoms in young children with refractory pulmonary arterial hypertension [63]. However, its use in PPHN has not been reported.

Similarly, there is evidence to suggest that endothelin receptor blockade may improve pulmonary blood flow in PPHN. In an experimental model of foetal pulmonary hypertension, intrauterine endothelin receptor blockade decreased pulmonary artery pressure, decreased right ventricular hypertrophy and distal muscularization of small pulmonary arteries and increased the fall in PVR at delivery [64]. Bosentan is a non-specific endothelin-1 receptor inhibitor that improves pulmonary hypertension in adult patients. Although recent reports suggest that bosentan may improve PPHN [65], there is still insufficient evidence to support the use of bosentan in the management of PPHN.

Conclusions

Growing evidence indicates that the perinatal environment plays a key role in the failure of cardiopulmonary transition...
to adequate pulmonary circulation at birth. Reduction of exposure to risk factors should be the first step in the prevention of PPHN. New insights showing that PPHN may be associated with epigenetic modifications suggest that novel pharmacological interventions targeting modulation of epigenetic regulation may be beneficial.

PPHN causes hypoxaemia through extrapulmonary right-to-left shunting. The management priority should be to optimize circulatory function rather than normalize post-duralct SpO2, because PPHN-induced circulatory failure is a life-threatening condition.

Management of PPHN requires adequate lung recruitment and alveolar ventilation, iNO and appropriate fluid and cardiovascular resuscitation. Early initiation of inotropic and vasoactive agents is commonly used to increase cardiac output, maintain adequate blood pressure and enhance oxygen delivery to the tissue. However, a rigorous clinical and echocardiographic assessment is required for optimal management of PPHN-associated circulatory failure.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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