Seminars in Fetal & Neonatal Medicine xxx (2017) 1–7

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Persistent pulmonary hypertension of the newborn

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Keywords:
Hypoxemia
Nitric oxide
Sildenafil
Milrinone
Prostacyclin
Bosentan

A B S T R A C T

Failure of the normal circulatory adaptation to extrauterine life results in persistent pulmonary hypertension of the newborn (PPHN). Although this condition is most often secondary to parenchymal lung disease or lung hypoplasia, it may also be idiopathic. PPHN is characterized by elevated pulmonary vascular resistance with resultant right-to-left shunting of blood and hypoxemia. Although the preliminary diagnosis of PPHN is often based on differential cyanosis and labile hypoxemia, the diagnosis is confirmed by echocardiography. Management strategies include optimal lung recruitment and use of surfactant in patients with parenchymal lung disease, maintaining optimal oxygenation and stable blood pressures, avoidance of respiratory and metabolic acidosis and alkalosis, and pulmonary vasodilator therapy. Extracorporeal membrane oxygenation is considered when medical management fails. Although mortality associated with PPHN has decreased significantly with improvements in medical care, there remains the potential risk for neurodevelopmental disability which warrants close follow-up of affected infants after discharge.

1. Introduction

Following birth, a rapid decrease in pulmonary vascular resistance (PVR) and an increase in pulmonary vascular blood flow is needed to establish the lungs as the organ of gas exchange. Failure of the normal pulmonary vascular adaptation at birth results in PPHN, a condition that is characterized by elevated PVR with right-to-left shunting of deoxygenated blood at the patent foramen ovale (PFO) and/or the patent ductus arteriosus (PDA), and resultant hypoxemia. The incidence of PPHN has been reported to range anywhere between 0.4 and 6.8 per 1000 live births in the USA and between 0.43 and 6 per 1000 live births in the UK [1,2]. Despite advances in the management of infants with PPHN, the early mortality in infants with moderate-to-severe disease is ~10%, and is considerably higher in infants with pulmonary hypoplasia and congenital diaphragmatic hernia. PPHN is associated with serious long-term morbidities; up to 25% of infants with PPHN will have significant neurodevelopmental impairment at 2 years of age [3–5].

2. Fetal and transitional circulation

During fetal life, the placenta functions as the site of gas exchange. There is reduced pulmonary blood flow because of elevated PVR and, therefore, most of the right ventricular output crosses the ductus arteriosus to the aorta, with only 13–21% of the combined ventricular output perfusing the fetal lungs [6,7]. Various factors play a role in the elevated fetal PVR including mechanical factors (fluid-filled lungs), hypoxic pulmonary vasoconstriction, and circulating vasoconstrictors (endothelin-1 and products of the prostaglandin pathway, i.e. thromboxane and leukotriene) [8].

At birth, a series of circulatory events takes place including removal of the low-resistance placental circulation with a subsequent increase in systemic arterial pressure. Simultaneously, the PVR decreases rapidly with an increase in pulmonary blood flow. Pulmonary vasodilation is facilitated by ventilation of the lungs and an increase in oxygen tension [8]. There is an 8–10-fold increase in pulmonary blood flow, which results in an increase in right atrial pressure and closure of the PFO. Since the PVR is now lower than the systemic vascular resistance (SVR), the flow reverses across the PDA and the increase in arterial oxygen saturation leads to closure of the ductus arteriosus and ductus venosus. Further decrease in PVR is accompanied by rapid structural remodeling of the pulmonary vascular bed [9].

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http://dx.doi.org/10.1016/j.siny.2017.03.004
1744-165X/

Vasoactive products released by the endothelium play an important role in the normal cardiopulmonary transition at birth. Endothelial nitric oxide (NO) production in the lungs increases at birth secondary to shear stress from increased pulmonary blood flow and increased oxygenation. NO mediates pulmonary vasodilation via soluble guanylate cyclase and cyclic guanosine monophosphate (cGMP). The arachidonic acid–prostacyclin pathway also plays an important role in pulmonary vasodilation via activation of adenylate cyclase and subsequent increase in cyclic adenosine monophosphate (cAMP) concentration in the vascular smooth muscle cells. Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have also been shown to increase cGMP levels, with resultant pulmonary vascular dilation [10].

3. Pathophysiology of PPHN

Persistent pulmonary hypertension of the newborn results from a failure of the normal circulatory transition at birth, and is characterized by hypoxemia secondary to elevated pulmonary vascular resistance and right-to-left extrapulmonary shunting of deoxygenated blood. It may be secondary to: (i) maladaptation of the pulmonary vasculature, where the vasculature is structurally normal but constricted, and is associated with lung parenchymal diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia, and sepsis; (ii) remodeled pulmonary vasculature with normal lung parenchyma (idiopathic PPHN; 10%); or (iii) hypoplastic pulmonary vasculature as occurs in patients with lung hypoplasia secondary to congenital diaphragmatic hernia (CDH) or oligohydramnios. Infants born to mothers with diabetes, asthma, and obesity have been reported to be at increased risk of developing PPHN. Neonatal risk factors include male gender, delivery by cesarean section, delivery before 37 weeks and after 41 weeks of gestational age, and small or large for gestational age [11]. Among preterm infants born before 33 weeks of gestation, prolonged premature rupture of membranes and oligohydramnios are known risk factors for early pulmonary hypertension [12,13]. Although the antenatal use of non-steroidal anti-inflammatory drugs has previously been implicated in the early closure of the PDA with subsequent development of PPHN [14], a more recent retrospective epidemiologic analysis revealed no evidence to support this hypothesis [15]. Exposure to selective serotonin reuptake inhibitors in animal models and in humans in the third trimester has also been implicated in increasing the risk of PPHN [16–21].

Few genetic risk factors have been identified in patients who develop PPHN. Trisomy 21 is associated with a risk of developing PPHN, partly secondary to structural heart defects; however, an increased incidence of PPHN is seen in these infants independent of the presence of cardiac lesions [22–24]. Genetic abnormalities of surfactant function, specifically surfactant protein B deficiency and mutations in the ATP-binding cassette transporter 3 gene, have been reported as causes of PPHN refractory to therapy [25–27]. A rigorous genotype analysis revealed that genetic variations in corticotropin-releasing hormone receptor-1 and corticotropin-releasing hormone binding protein are associated with an increased risk of PPHN [28]. More recently, a single nucleotide polymorphism in the EDN1 gene has been reported to be associated with an increased risk of PPHN in Chinese neonates with respiratory disease [29]. In term neonates with respiratory failure, with and without echocardiographic evidence of PPHN, a polymorphism in the rate-limiting enzyme of the urea cycle, carbamoyl-phosphate synthetase-1, was associated with pulmonary hypertension, low plasma arginine concentrations, and low plasma nitric oxide metabolites [30].

Alveolar capillary dysplasia (ACD), a condition characterized by misalignment of the pulmonary veins, is a rare cause of interstitial lung disease. It presents with severe hypoxemia and PPHN early in life, and is often fatal [31,32]. Approximately 10% of reported cases of ACD are familial, and deletions in the FOXF1 transcription factor gene or deletions upstream of FOXF1 have been reported in 40% of infants with ACD [33].

Congenital diaphragmatic hernia is a developmental defect where there is abnormal development of the diaphragm and herniation of the abdominal viscera into the thoracic cavity, with resultant variable degree of pulmonary hypoplasia. There is a developmental arrest in the normal pattern of airway branching and impaired alveolarization, as well as in pulmonary arterial branching with reduced cross-sectional area of the pulmonary vascular bed and thickening of the media and adventitia of arterioles. The mortality rate remains quite high (20–30%) and is dependent on the severity of pulmonary hypoplasia and PPHN.

PPHN has traditionally been considered a disease of term and late preterm infants; however, it is now increasingly being recognized in preterm infants. The presence of RDS, fetal growth restriction, and prolonged rupture of membranes with varying degrees of pulmonary hypoplasia have been described as risk factors associated with PPHN in preterm infants [12,13,34]. Pulmonary hypertension is now recognized as a frequent complication of bronchopulmonary dysplasia; however, this entity is distinct from PPHN, and is secondary to a reduced pulmonary vascular bed, vascular remodeling, and impaired distal lung growth [35].

4. Clinical diagnosis and management of PPHN

Newborns with PPHN present with labile and/or profound hypoxemia and differential cyanosis (higher pre-ductal SpO_2 and PaO_2 compared to post-ductal measurements). However, these findings are not specific to PPHN and it is important to differentiate cyanotic heart disease from PPHN. Echocardiography remains the gold standard to confirm the diagnosis of PPHN, and is useful in identifying sites of extrapulmonary shunting, and assessing right and left ventricular function (to guide appropriate vasodilator therapy).

4.1. Supportive care

The severity of PPHN ranges from mild hypoxemia with minimal respiratory signs to severe and labile hypoxemia with cardiopulmonary instability. General management principles include maintenance of normothermia, providing optimal nutritional support, avoidance of stress, maintaining a “low-noise” environment, gentle handling with sedation as needed, and maintenance of adequate intravascular volume and systemic blood pressure. Skeletal muscle relaxation has previously been shown to be associated with increased mortality and should be avoided [1]. The underlying disease process should be treated appropriately.

Acidosis induces pulmonary vasoconstriction and should be avoided. In the pre-NO era, alkalosis by infusing sodium bicarbonate solutions or by hyperventilation was frequently used to dilate the pulmonary vasculature [1]. Whereas transient improvement in oxygenation was frequently observed with these therapies, prolonged alkalosis was shown to induce an exaggerated pulmonary vascular constriction response to hypoxia in animal models [36]. Furthermore, alkalosis induces cerebral vasoconstriction with reduced cerebral blood flow and increases the risk of neurodevelopmental impairments [37,38]. Therefore, both acidosis and alkalosis should be avoided in neonates with PPHN.

Please cite this article in press as: Fuloria M, Aschner JL, Persistent pulmonary hypertension of the newborn, Seminars in Fetal & Neonatal Medicine (2017), http://dx.doi.org/10.1016/j.siny.2017.03.004