Diagnosis and management of pulmonary hypertension of the newborn

P Bendapudi

S Barr

Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical condition associated with significant mortality and morbidity unless managed quickly and expertly. PPHN occurs following failure of normal postnatal adaptation of the fetal circulation. If pulmonary pressures fail to reduce following birth the resulting pulmonary hypertension leads to right to left shunting of blood which will lead to hypoxaemia, cyanosis and poor perfusion. The thrust of treatment is early diagnosis, appropriate ventilator strategies to help lower pulmonary pressures, aggressive cardiovascular support to maintain systemic pressures and minimal handling.

Keywords echocardiography; inhaled nitric oxide; normal postnatal adaptation; persistent pulmonary hypertension; supra systemic pulmonary pressures

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is an acute neonatal emergency which requires prompt diagnosis and aggressive management. PPHN is defined as "a potentially life threatening condition characterised by a failure of pulmonary vascular resistance to decrease adequately during transition to extra uterine life".

PPHN is more likely to occur in term babies and is slightly commoner in boys. The incidence is 1.9/1000 births. PPHN usually presents within the first 24 hours of life and is associated with both significant mortality and morbidity. Mortality can be as high as 20% and up to 25% of all survivors have long term neuro-developmental sequelae.

It is a clinical syndrome that can occur in association with diverse neonatal cardiorespiratory disorders. Table 1 shows the most common underlying aetiologies associated with PPHN. Neonates with complicated labours such as meconium stained liquor, low Apgar scores and abnormal Cardiotocograms (CTGs) are also known to be at higher risk of PPHN.

P Bendapudi *MBBS MRCPCh is ST 5 Trainee in Neonatal Medicine at the University Hospital of Wales, Heath Park, Cardiff, UK. Conflict of interest: none declared.*

S Barr *MB Bch MSs FRCPCH is Consultant Neonatologist at the University Hospital of Wales, Heath Park, Cardiff, UK. Conflict of interest: none declared.*

PPHN is characterized by respiratory distress, cyanosis and hypoxaemia secondary to right to left shunting of blood. The right to left shunt occurs in up to three areas, the atria (foramen ovale), the ductus arteriosus and/or intra pulmonary vessels. Right to left shunting leads to poor tissue oxygenation and increasing acidosis and the inappropriately high pulmonary vascular resistance leads to worsening right heart failure. A rapid downward clinical spiral will ensue unless the elevated pulmonary vascular resistance and pulmonary pressure are resolved.

Management options are essentially twofold: one is to aim to lower the pulmonary vascular resistance which will lead to lowering of the pulmonary pressures; so the degree of right to left shunting will be mitigated. The second strategy is to increase the systemic blood pressure to supra-pulmonary levels to try to overcome the right to left shunt. In practice, pragmatically, both strategies are employed simultaneously.

Pathogenesis and physiology

The main organ responsible for fetal gas exchange is the placenta. In utero, the pulmonary vascular resistance is high, hence, pulmonary blood flow accounts for less than 10% of the combined ventricular output. However, soon after birth, following the first gasp, pulmonary artery pressure falls and pulmonary blood flow increases. Clamping of the umbilical cord results in, firstly, the loss of the low pressure placental circulation leading to a decreased venous return to the right atrium; and secondly an immediate rise in systemic blood pressure. Increased pulmonary venous return into the left atrium results in equalization of right and left atrial pressures leading to closure of foramen ovale. Closure of the ductus arteriosus is mediated by the rise in the oxygen content of blood flowing through the duct and a fall in prostaglandin I2 and E2 levels. Prostaglandin I2 and E2 are vasodilators and high concentrations maintain the patency of the ductus arteriosus in utero. The functional and morphological closure of these shunts typically occurs within the first 24–48 hours following birth.

Blood pH, oxygen and carbon dioxide content, all affect the reactivity of the pulmonary vasculature. Acidosis, hypoxia and hypercarbia all, cause vasoconstriction and increased pulmonary artery pressure, hence maintaining a fetal type of circulation and a right to left shunt.

PPHN may be classified according to the underlying anatomy and physiological status of the pulmonary vascular bed. The pulmonary vascular bed may be inappropriately small e.g. pulmonary hypoplasia. A structurally normal pulmonary vascular bed may have maladapted tone due to increased vascular musculature tone secondary to a chronic injury e.g. in intra uterine growth restriction (IUGR). However, the most common scenario seen in PPHN is a structurally and physiologically normal pulmonary vascular bed with transient maladaptation secondary to a perinatal insult that inhibits the usual postnatal fall in pulmonary vascular resistance (Table 2).

Examination

Primary respiratory disease and congenital cyanotic heart disease are the main differential diagnoses to be excluded. Careful examination is important, in particular, focussing on the respiratory and the cardiovascular systems, as positive findings may

Common underlying aetiologies for PPHN

Underlying condition	Frequency in percent
Meconium aspiration	41
Idiopathic	17
Pneumonia/RDS	14
RDS	13
Congenital diaphragmatic hernia	10
Hypoplastic lungs	4
Pneumonia	1

Table 1

suggest another diagnosis. In particular, signs of respiratory distress, cyanosis, presence of equal breath sounds, murmurs, and the quality of femoral pulses, are important to note.

Investigations

Pulse oximetry: this is a simple and valuable investigation. Simultaneous comparison of pre-ductal oxygen saturation readings from the right arm with post-ductal oxygen saturation readings from a foot is made. Differences of more than 10% suggest a significant shunt. If the pre-ductal saturations are higher than the post-ductal, this suggests a right to left shunt compatible with PPHN. Continuous pulse oximetry from both pre- and post-ductal sites during treatment helps in monitoring patient progress and response to treatment.

Echocardiography: this is the gold standard in confirming the diagnosis of PPHN and importantly excluding other cardiac pathology. Echocardiography assessments may be technically challenging, in the NICU environment especially if the patient is unwell and is receiving oscillation ventilation. Echocardiographic assessment of PPHN should ideally include the following information.

Tricuspid regurgitation (TR) – evaluation of the TR jet enables the right ventricular pressures to be calculated by using a modified Bernoulli equation. The right ventricular pressures will act as a proxy for pulmonary artery pressure. This will inform a target systemic blood pressure to aim for in order to increase systemic pressures higher than pulmonary pressures so that right to left shunting is decreased.

Atrial shunt – in PPHN the Patent Foramen Ovale (PFO) will show some degree of right to left shunting and bowing of the inter atrial septum to the left because of high pulmonary pressures.

Ductus arteriosus – if the duct is open and flow is purely right to left, this indicates higher pressures in the pulmonary artery than in the descending aorta throughout the cardiac cycle. A bi-directional flow in the PDA is seen when the aortic and pulmonary pressures are roughly equal, as flow is right to left during systole and left to right in diastole.

Intraventricular septum – the alignment of the intra ventricular septum at the end of systole is important. If the intraventricular septum is flat or bowing into the left ventricle it suggests pulmonary pressures are equal to or greater than systemic pressures.

Cardiac function and output – assessment of both left and right ventricular output is crucial. Refractory low right and left ventricular output is worrying and associated with poor outcome. In severe PPHN, the left ventricular output may drop to below 100 ml/kg/minute (normal – 150–300 ml/kg/minute). Repeated echocardiographic assessments are useful in monitoring responses to treatment options.

Other investigations to consider

Hyperoxia test: if echocardiography is unavailable the hyperoxia test may be useful to aid diagnosis and to differentiate between a pulmonary cause and cyanotic cardiac disease. Oxygenate in 100% oxygen for 15 minute and then assess an arterial blood gas from the lower limbs. The oxygen content should rise if lung disease is present, but there will be no improvement in oxygen content if cyanotic congenital heart disease is present, and in PPHN the oxygen content may raise only modestly.

CXR: oligaemic lung fields are frequently seen in PPHN due to poor pulmonary blood flow secondary to high pulmonary

Pathophysiological models resulting in PPHN

	Under development	Maldevelopment	Maladaptation
Pathology	Cross sectional area of the pulmonary vasculature is reduced PVR is elevated and fixed	Occurs in the setting of normal lung development Associated with abnormally thickened muscle walls of pulmonary arterioles Higher plasma concentrations of the vasoconstrictor endothelin-1 and lower concentrations of cyclic guanosine monophosphate	Normal pulmonary vasculature Failure of normal postnatal adaptation to take place in view of perinatal insults Appropriate support during this period with treatment of underlying trigger aids in improvement
Examples	Pulmonary hypoplasia Developmental anomalies of the lung such as congenital diaphragmatic hernia	Idiopathic PPHN	Perinatal asphyxia Meconium aspiration Group B streptococcal infection

Table 2