Paediatric Respiratory Reviews 16 (2015) 157–161

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-symposium: Alveolar and Vascular Transition at Birth

Diagnosis and management of persistent pulmonary hypertension of the newborn

Perraju Bendapudi, Gopinath Gangadhara Rao, Anne Greenough *

Division of Asthma, Allergy and Lung Biology, MRC Centre for Allergic Mechanisms in Asthma, King's College London

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.

ARTICLE INFO

Article history:
Received 4 February 2015
Accepted 4 February 2015

Keywords:
Pulmonary hypertension
Meconium aspiration syndrome
Congenital diaphragmatic hernia
Nitric oxide
Pulmonary vasodilator

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.

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

* Corresponding author. NICU, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom. Tel.: +44 02032993037; fax: +44 02032998284.
E-mail address: anne.greenough@kcl.ac.uk (A. Greenough).

http://dx.doi.org/10.1016/j.prrv.2015.02.001
1526-0542/

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_2). The appearance of the chest radiograph may be normal, unless there is underlying lung disease. The lung fields may be oligaemic 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 ($PaCO_2$) levels and hence elevate pH with the aim of causing pulmonary vasodilation. Arterial carbon dioxide ($PaCO_2$) 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 prostaclycin ($p=0.02$), but more used sidenafil ($p=0.01$) [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