EDITORIAL ARTICLE

Pulmonary hypertension of neonatal and infants

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ABSTRACT

PVR drops from high foetal values during the transition to ventilation of the lungs at birth, resulting in an 8 to 10-fold increase in pulmonary blood flow (Qp). This transition does not occur in all neonates, resulting in Pulmonary Hypertension (PH). In infants, PH can manifest as (a) primary PH in term neonates (idiopathic), (b) PH secondary to lung disease or hypoplasia in term infants, (c) acute PH in preterm infants with Respiratory Distress Syndrome (RDS), (d) chronic PH in preterm infants with Bronchopulmonary Dysplasia (BPD), and (e) Post-Neonatal PH. Due to elevated Qp, a hemodynamically significant Patent Ductus Arteriosus (PDA) might worsen PH in premature newborns. BPD with PH can be complicated by Pulmonary Vein Stenosis (PVS). Clinical characteristics, echocardiography, and, in some persistent cases, cardiac catheterization are used to diagnose PH. Oxygen, invasive or non-invasive ventilation, acidosis correction, surfactant, and selective and non-selective pulmonary vasodilators such inhaled nitric oxide and sildenafil are all used to treat PH. Early closure of a hemodynamically significant PDA has the potential to reduce BPD and PH-related Pulmonary Vascular Remodelling. With the recent increase in thiamine-responsive acute pulmonary hypertension in early infancy, the function of thiamine in the pathophysiology of PH is also explored. Right ventricular dysfunction, uncoupling, and failure can all be avoided with early detection and treatment of PH.

Key Words: *Oxygen; Nitric oxide; Sildenafil; Pulmonary vascular resistance*

INTRODUCTION

The placenta is the organ of gas exchange during the foetal period, with umbilical venous PO2 in the low 30s and umbilical arterial PO2 in the low to mid-20s (mmHg) [1]. Hypoxic Pulmonary Vasoconstriction (HPV) occurs as a result of the relative hypoxia, resulting in high Pulmonary Vascular Resistance (PVR) and low pulmonary blood flow (Qp) to the foetal lung. During birth, air ventilation raises alveolar and arterial PO2, leading in pulmonary vasodilation, a decrease in PVR, and an increase in Qp of 8 to 10-fold. PVR failure at birth can result in Pulmonary Hypertension (PH) in the newborn due to a variety of factors including birth hypoxia, parenchymal lung disease (e.g., Meconium Aspiration Syndrome (MAS), pneumonia, Respiratory Distress Syndrome (RDS), and others. The transition may occur in a normal fashion in some newborns, but an increase in PVR after birth can lead to post-neonatal PH [2]. Preterm newborns with Bronchopulmonary Dysplasia (BPD) show this increase. The pathophysiology and management of neonatal and postneonatal PH are covered in this special issue of Children.

Term Infants with pulmonary hypertension

In the first few weeks after birth, about 0.2 percent of term and late-preterm newborns develop labile hypoxia and a bidirectional or left-to-right shunt through the Patent Ductus Arteriosus (PDA) and Oval Foramen (PFO). Hypoxemic Respiratory Failure (HRF) is common in these neonates [3]. Many of these newborns have differential cyanosis with increased SpO2 in the preductal areas (right hand) compared to the postductal regions (left hand) due to shunting through the PDA (any foot).He show a relationship between the presence of a preductal to postductal SpO2 gradient of 3% and a larger proportion (89%) of samples associated with bidirectional shunting at PDA in a lamb model of hypoxia, MAS, and PH [4]. He found a link between a 3% preductal to postductal SpO2 gradient and a larger number of samples (89%) with bidirectional shunting at PDA. More notably, bidirectional shunting was still related with bidirectional shunting at PDA in 56 percent of samples despite having a low preductal to postductal SpO2 gradient (3%). The absence of a preductal–postductal SpO2 gradient in a term infant does not rule out PH, according to this report. Without this preductal to postductal SpO2 gradient, bidirectional shunt can still exist at the PFO level. This

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study's findings highlight the need of receiving an early echocardiography in newborns with hypoxemia and PH suspicion

The core of care for neonates with PH is ventilation with supplementary oxygen. The ideal SpO2 and PaO2 targets in neonatal PH, as well as the best site to check these targets (preductal vs. postductal), are unknown. The importance of alveolar PAO2 in hypoxic pulmonary vasoconstriction is discussed by Chandrasekaran et al. [5]. Because alveolar PAO2 more closely resembles preductal PaO2 than postductal PaO2, monitoring preductal saturation is thought to be more beneficial in the treatment of PH [6]. During the care of acute newborn PH, current guidelines prescribe preductal SpO2 in the low to mid-90s and to avoid preductal SpO2 below 98 percent [7].

Preterm infants with pulmonary hypertension

PH can appear early (typically the first week) in preterm newborns and be related with Respiratory Distress Syndrome (RDS) or later with bronchopulmonary dysplasia (BPD). Inhaled Nitric Oxide (INO) is contentious in preterm newborns. The NIH consensus statement concluded that there was no evidence to justify the use of iNO in preterm infants born before 34 weeks of pregnancy. Although this remark implied that certain infants with pulmonary hypertension and pulmonary hypoplasia might benefit, the data was limited. A key worry is the lack of clinical trials addressing PH in preterm newborns. It was discovered that nearly half of preterm children with PH can have an acute echocardiographic response, which is linked to survival [8]. However, trials examining therapy other than iNO in premature infants with BPD are scarce. In 1967, Dr. William Northway recognised and reported the first case of BPD. The existence of PH in combination with BPD is linked to a higher death rate in these individuals, which is proportional to the severity of the PH. PH in BPD is caused by increased pulmonary vascular tone and reactivity, vascular remodelling, aberrant vasculogenesis, and angiogenesis. Low birth weight, SGA status, severity of BPD, oligohydraminios, maternal smoking, and maternal preeclampsia are all risk factors for PH in preterm newborns. Early indications of PH (septal flatness by echo on day 7 of postnatal age) may be related with poor outcomes, including higher mortality, according to data from serial echocardiograms. Increased target SpO2 and the closure of atrial septal connections have been shown to minimise the incidence of PH in premature babies. Therapeutic goals to promote birth transition, avoid BPD, and minimise the risk of PH, as well as to improve long-term outcomes, are critical. offer findings on targeted therapy in 101 preterm children with BPD and PH in this issue of Children. Despite the high mortality rate (32.7%), few deaths occurred after hospital discharge, and 77.2 percent of patients were weaned off PH drugs by a median of two years (range 0–8 years) at follow-up.

Treatment

The kind of pulmonary hypertension, whether arterial, venous, hypoxic, thromboembolic, or miscellaneous, determines the treatment. If left heart disease is the reason, medicines to improve left ventricular function or repair/replacement of the mitral valve or aortic valve are utilised to treat it. Vasoactive agents such as prostanoids, phosphodiesterase inhibitors, and endothelin antagonists should not be used routinely in patients with left heart failure or hypoxemic lung diseases (groups II or III pulmonary hypertension), as these are approved for a different condition called primary pulmonary arterial hypertension. Doctors will perform cardiac catheterization of the right heart, echocardiography, chest CT, a six-minute walk test, and pulmonary function tests at the very least to make the distinction.

Only 5% of IPAH patients who are vasoreactive by Swan-Ganz catheter benefit from high-dose calcium channel blockers. Unfortunately, calcium channel blockers have been widely overused, with many patients with non-vasoreactive PAH being prescribed them, resulting in increased morbidity and mortality. The definition of vasoreactivity has shifted. When challenged with adenosine, epoprostenol, or nitric oxide, only those patients whose mean pulmonary artery pressure lowers by more than 10 mm Hg to less than 40 mm Hg with an unaltered or increased cardiac output are deemed vasoreactive. Only half of these individuals are long-term responders to calcium channel blockers.

Role of the pda

Very low birth weight neonates have an open ductus in the first few days after delivery. The bulk of these infants' ductus progressively closes as they get older. In less mature neonates, the ductus is more likely to remain open for extended periods of time (26 weeks gestation at delivery). A persistently open PDA and pulmonary over-circulation will result in increased left atrial pressure and left ventricular diastolic dysfunction. Extremely preterm children with a significant left-to-right shunt due to PDA (25 weeks, 750 grammes birth weight) may be at risk of pulmonary vascular remodelling. The presence of distal pulmonary vasculature during cardiac catheterization can be used to identify this remodelling. Right ventricular dysfunction can be caused by pulmonary vascular disease. Increased PVR has been linked to a delay in PDA closure. High PVR prior to closure and prolonged exposure to PDA (>8 weeks) appear to be two risk factors in extremely preterm children with persisting elevations in respiratory severity score following PDA closure.

Is transcatheter PDA closure in preterm infants associated with a lower incidence of pulmonary hypertension? Is transcutaneous closure just beneficial for newborns who require extensive respiratory support, such as invasive mechanical ventilation? The Preliminary Percutaneous Intervention vs. Observational Trial of Arterial Ductus in Low-Weight Infants (PIVOTAL) study is attempting to answer these problems (NCT03982342). When deciding whether or not to transcatheterally close a PDA, the risks of anaesthesia and catheterization must be considered. The left ventricle in normal neonates has a conical shape and contracts efficiently against high afterload (systemic pressure). Because the right ventricle is crescentic, it is usually subjected to low afterload (pulmonary arterial pressure). The mechanism known as RV:PA coupling causes right ventricular hypertrophy by increasing right ventricular afterload and initially increasing the efficiency of the right ventricle by enhancing function and producing right ventricular hypertrophy. The existence of an open ductus acts as a pop-off valve, limiting pulmonary arterial pressure rises to safe levels. Extreme elevations in afterload, which are frequently linked with the closure of the ductus, can uncouple the right ventricle, resulting in dysfunction.

Thiamine deficiency and postneonatal pulmonary hypertension

In the absence of BPD or other lung diseases, PH is uncommon after

the newborn era. Acute PH in early infancy has been reported multiple times recently. Without particular medication, these newborns rapidly deteriorate and have a high fatality rate. The use of thiamine has resulted in a significant improvement in PH. Preventing this illness requires public awareness and appropriate dietary thiamine supplementation among breastfeeding women. Pulmonary hypertension contributes to morbidity and mortality during the newborn and post-neonatal periods. Early detection and targeted treatment of PH can increase survival rates. Several pieces by notable experts are included in this issue of Children, and they address some of the difficulties surrounding the diagnosis and management of neonatal and postneonatal PH.

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