A Clinical Review of Persistent Pulmonary Hypertension in the Newborn

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Abstract

Persistent pulmonary hypertension in the newborn (PPHN) is an illness of the circulatory and respiratory systems which affects approximately 0.002% of newborns but carries a significant morbidity and mortality burden. Diagnostic measures are focused on determining etiology whereas treatment measures are intended to improve pulmonary function. It is crucial for neonatal providers to be aware of patients at risk for developing PPHN and be prepared to initiate treatment early. This article reviews pathophysiology, etiology, risk factors, diagnosis, and treatment of PPHN.

Introduction

Persistent pulmonary hypertension in the newborn (PPHN) is defined as failure to successfully transition from intrauterine to postnatal circulation resulting in high pulmonary vascular resistance and hypoxemia.[1,2] Onset is generally seen within hours of birth and manifests in severe respiratory distress.[3] PPHN presents in 2 out of every 1,000 live births and is associated with a variety of infections, congenital conditions, and peripartum complications. Mortality estimates of infants diagnosed with PPHN range from 5-15% and those who survive are at risk for hospital readmission in the first year of life as well as chronic neurodevelopmental problems.[1,2,4] The purpose of this article is to present the pathophysiology, risk factors, diagnosis, and treatment of PPHN so neonatal providers can more easily identify patients potentially at risk and be prepared to diagnose and treat PPHN.

Pathophysiology

The normal transition from intrauterine circulation to postnatal circulation is initiated by the clamping of the umbilical cord and ventilation of the lungs.[5,6] Clamping the umbilical cord terminates the low resistance placental circulation which was responsible for oxygenation of the

fetus in utero and increases systemic arterial pressure. Ventilation of the lungs during the infant's first breaths works to decrease pulmonary arterial pressure and increase pulmonary blood flow resulting in systemic and pulmonary circulation changes which influence the flow of blood through the foramen ovale and ductus arteriosus.[5] Part of this transition process is regulated by the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) and prostacyclin-cyclic adenosine monophosphate (cAMP) pathways which both ultimately cause pulmonary vasodilation by lowering intracellular calcium concentrations.[6] These and other various mechanisms all work to decrease pulmonary vascular resistance and increase pulmonary blood flow so the infant may successfully graduate to cardiopulmonary circulation. [1]

PPHN occurs when this process is interrupted and the transition is unsuccessful. Elevated pulmonary vascular resistance (PVR) decreases pulmonary blood flow which results in insufficient oxygenated blood flow to the body. This causes hypoxia, acidosis, and decreased end organ perfusion. The resulting hypoxemia and acidosis worsen PVR by further increasing vasoconstriction. Moreover, when PVR is greater than systemic vascular resistance, blood is shunted from the right side of the heart to the left through the ductus arteriosus and foramen ovale which causes more hypoxemia.[2] The myriad etiologies of increased PVR causing PPHN are sorted into four major causes: 1) idiopathic structural remodeling of pulmonary vasculature; 2) abnormal pulmonary vasculature due to conditions such as infection, meconium aspiration syndrome (MAS), or respiratory distress syndrome (RDS); 3) lung hypoplasia due to congenital disorders such as congenital diaphragmatic hernia (CDH); and 4) intravascular obstruction due to increased blood viscosity as seen in polycythemia vera.[1,2]

Etiology and Risk Factors

Various perinatal conditions and maternal factors are associated with PPHN. The most commonly found etiologies are infection (30%), MAS (24%), idiopathic (20%), RDS (7%), and CDH (6%).[2,7] Infants who are late preterm (34-36 weeks) and term (39-40 weeks) are more likely to present with PPHN. One study found PPHN in 5.4 per 1,000 live late preterm births and in 1.6 per 1,000 live term births.[7] Infants who are of Black or Asian race are at higher risk of developing PPHN as are infants who are born via cesarean section.[3,7,8] PPHN is more likely to present in infants who are either small for gestational age (SGA) or large for gestational age

(LGA).[1,7] Infants who are SGA may be at risk due to incomplete pulmonary development or dysfunction of pulmonary artery endothelial cells. A diagnosis of LGA is often associated with maternal obesity or diabetes which are both independent risk factors for PPHN. A hyperglycemic state in a fetus can inhibit sufficient production of nitric oxide which impairs vasodilation of the pulmonary vasculature, thereby setting the stage for PPHN. Furthermore, a population-based cohort study by Steurer et al[7] discovered a stronger association between PPHN and preexisting diabetes mellitus compared to gestational diabetes. The authors proposed this could be due to a greater effect of long-term systemic inflammation on fetal lung maturity than short-term inflammation.[7] Medications associated with a higher risk of PPHN include NSAIDs and SSRIs. Maternal use of NSAIDs can precipitate premature closure of the ductus arteriosus which is thought to encourage the development of PPHN. [2] Maternal use of SSRIs in the third trimester potentially augments the risk of PPHN which is possibly due to increased vasoconstriction and smooth muscle cell proliferation caused by high amounts of serotonin in the blood.[3]

Diagnosis

PPHN often presents with severe respiratory distress within hours of birth.[3] Auscultation of the heart may reveal a loud S2 or systolic murmur.[8] Clinical manifestations include labile oxygenation, different pre-ductal and post-ductal oxygen saturations, and profound hypoxia despite oxygen supplementation or mechanical ventilation.[9] A difference of 5-10% between pre-ductal (right upper extremity) and post-ductal (lower extremity) oxygen saturation is cause for concern and should instigate a thorough cardiopulmonary work-up. [2] However, lack of difference between pre and post-ductal saturation does not mean PPHN is not present. [6] Non-specific lab findings might include hypoglycemia, hypocalcemia, polycythemia, or thrombocytopenia.[6] A recent prospective cohort study reported a BNP level greater than 500 pg/mL was predictive of PPHN.[10] A radiograph of the chest is an important tool to determine etiology and guide treatment plans but cannot diagnose PPHN. [2,6] An echocardiogram, however, is the gold standard for definitively diagnosing PPHN.[2] Echocardiography is used to evaluate cardiac function, exclude structural heart disease as the cause of hypoxemia and pulmonary hypertension, and monitor response to treatment. It may also be used to evaluate severity by measuring the velocity of tricuspid regurgitation and pulmonary arterial flow, the position of the interventricular septum,

and the direction and extent of shunting occurring at the ductus arteriosus and foramen ovale. Another parameter to assess the severity of PPHN is oxygenation index (OI). A patient with an OI greater than 25 will likely need to be treated with high frequency ventilation, nitric oxide, or possibly extracorporeal membrane oxygenation.[6]

Treatment

Ultimately, the goal in managing patients with PPHN is to achieve pulmonary vasodilation and adequate oxygenation while maintaining hemodynamic stability. A significant first step in accomplishing this goal is to perform a thorough diagnostic work up to determine the major cause of PPHN as some etiologies are treated differently than others and some therapeutics may be harmful instead of beneficial. General supportive measures include maintaining normothermia, managing electrolyte and glucose levels, optimizing intravascular volume while preventing fluid overload, treating anemia, and providing adequate nutrition.[6,8] Nursing should be instructed to be efficient with their care and minimize handling of the patient to prevent episodes of respiratory distress due to emotional upset.[8] Infectious causes of PPHN should be treated with empiric antibiotics and narrowed with the results of culture and sensitivity.[6] Hemodynamic support may be achieved with adequate intravascular volume in addition to inotropes and vasopressors to improve cardiac output. Specific goals of pulmonary management include reducing pulmonary vascular resistance, improving ventilation while avoiding injury, and ensuring adequate oxygenation without causing oxygen toxicity.[8]

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) is the first line therapy used to lower PVR in infants with PPHN and is the only therapy approved by the FDA for patients greater than 34 weeks gestational age.[2,6] Contraindications to using iNO include the presence of left sided outflow obstruction and severe left ventricular dysfunction.[8] Administration of iNO encourages production of cGMP by pulmonary arterial smooth muscle cells which promotes pulmonary vasodilation. Oxygenation is improved in about 50% of those placed on iNO and reduces the need for ECMO in term infants with hypoxemic respiratory failure. Unfortunately, iNO is not proven to be effective in infants with CDH. [11] Inhaled NO should be initiated when a patient's OI

is 20 or sooner if there is echocardiographic evidence of PPHN.[2] The starting dose for iNO is 20 ppm which is where the greatest impact on oxygenation and pulmonary arterial pressure occurs without raising nitrogen dioxide, methemoglobin, or bleeding time to harmful levels.[2,6] Methemoglobin levels should be monitored at 2 hours and 8 hours post initiation, then daily during the course of iNO therapy. As the infant's clinical picture improves, iNO should be tapered off slowly and judiciously to prevent rebound vasoconstriction and subsequent deterioration.[2]

Mechanical ventilation

Mechanical ventilation, including high frequency ventilation, is often necessary to stabilize infants in respiratory distress. High frequency ventilation is used to maintain adequate lung volume while preventing barotraumatic injury to the lungs.[2,6] It can improve V/Q mismatch and prevent atelectasis which helps to optimize pulmonary function.[6] Extremes of lung volumes, whether high or low, should be avoided as they can both contribute to increased PVR.[8] Effective management of high frequency ventilation in combination with iNO increases oxygenation in patients who have PPHN caused by abnormal pulmonary vasculature such as in RDS, MAS, and pneumonia. Unfortunately, this combination does not improve idiopathic PPHN.[2] The highest oxygenation concentration found to have the most impact on pulmonary vasodilation is 50%; settings any higher make no clinically significant difference in improving PPHN and increase the patient's risk of the harmful effects of oxygen toxicity. Careful management of carbon dioxide levels is critical in patients with PPHN. Hypocapnia causes cerebral vasoconstriction and therefore decreases blood flow to the brain which augments a patient's risk for neurodevelopmental sequelae, particularly sensorineural hearing loss. This leads to a strategy of permissive hypercapnia where PaCO2 is allowed to remain above 35 mmHg. High frequency ventilation is not more effective at preventing need for extracorporeal membrane oxygenation (ECMO) than conventional mechanical ventilation.[6] Similarly, there is no current evidence to show which type of high frequency ventilation is most effective in the management of PPHN. When decreasing ventilatory support, settings should be lowered slowly and cautiously to avoid causing rebound pulmonary vasoconstriction.[8]

Surfactant

Surfactant deficiency is a common factor found in conditions associated with PPHN including MAS, RDS, and pnuemonia.[2] Providing exogenous surfactant is a potential therapy for patients with PPHN, however there is some debate over efficacy and methods of administration.[8] In a study by Gonzalez et al,[12] the use of surfactant in addition to iNO was compared to iNO therapy alone in neonates with moderate to severe hypoxemic respiratory failure. The results showed the combination of surfactant and iNO improved both oxygenation and recovery time and ultimately led to a decrease in deaths and need for ECMO. Gonzalez et al[12] propose that surfactant increases alveolar recruitment allowing for greater circulation of iNO which therefore improves pulmonary vasodilation.[12] Unfortunately, administration of surfactant to patients with PPHN caused by CDH increases the risk of requiring ECMO, the incidence of chronic lung disease, and mortality.[6]

Sildenafil

Sildenafil inhibits phosphodiesterase type 5 which prevents the breakdown of cGMP, therefore promoting smooth muscle relaxation and vasodilation.[13] It is initiated as an additional vasodilator when no response to iNO has occurred or when iNO is unavailable, such as in resource limited settings. Although many studies have found no adverse effects with administration of sildenafil, patients should be monitored closely for drops in systemic blood pressure.[2,6] Additionally, the FDA has warnings of increased mortality attached to high doses of sildenafil in neonates.[2]

Milrinone

Milrinone is a phosphodiesterase 3 inhibitor with inotrope and lusitrope properties which can be used in combination with other vasodilatory therapeutics for treatment of PPHN.[6] Milrinone causes pulmonary and systemic arterial vasodilation and can improve the diastolic function of the heart.[4] The use of milrinone with sildenafil may decrease pulmonary arterial pressure more than sildenafil or milrinone alone which is a critical result for resource limited settings without access to iNO.[5] Additionally, milrinone may reduce rebound pulmonary hypertension when patients are weaned off iNO.[8]

Prostaglandin

For patients with PPHN caused by CDH, prostaglandin is a vital aspect of treatment. The administration of prostaglandin maintains patency of the ductus arteriosus which decreases pulmonary arterial pressure and improves cardiopulmonary function. In patients with PPHN associated with conditions other than CDH who have not responded to iNO therapy, prostaglandin administration should be provided when diagnostics show restrictive ductus arteriosus in addition to suprasystemic pulmonary hypertension.[14]

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is the final treatment option for infants with PPHN who have not responded to initial therapies, including patients with persistent OI greater than 40 or metabolic acidosis. [6] A retrospective analysis of PPHN patients on ECMO over a 10-year period demonstrated a survival rate of 81%. Survival rates decreased the longer the patients remained on ECMO – those on ECMO for 7 days had a survival rate of 88% while those on ECMO for 21 days had a survival rate of 25%. The study reported risk factors for increased mortality which included gestational age less than 37 weeks, pre-ECMO pH less than 7.2, pre-ECMO SaO_2 less than 65%, and duration of ECMO lasting greater than 7 days.[15]

Typically, venovenous (VV) ECMO is the preferred option for patients with preserved cardiac function who are in respiratory failure whereas venoarterial (VA) ECMO is the preferred option for patients with heart failure.[16] Infants with PPHN are most often placed on VV-ECMO initially because it is the most appropriate choice for the pathology of the condition and because it is less invasive than VA-ECMO.[6] Sometimes it is necessary to switch VV to VA-ECMO if a patient is decompensating or a problem occurs with the circuit. Conversion from VV to VA-ECMO results in higher rates of morbidity and mortality than remaining on either VV or VA-ECMO.[17] General complications of ECMO include failure of the machinery, coagulation which causes blockage of the circuit, intracranial hemorrhage, renal failure, and infection.[16] EMCO is not a benign treatment as complications can be severe, therefore a discussion must take place between providers and parents about potential risks versus benefits.

Morbidity and mortality

The morbidity and mortality rates for infants with PPHN are significant, therefore conversation with parents regarding expectations for survival and potential sequelae is essential. A population-based study published by Steurer et al[1] in 2019 reports mortality rates of 7-15% in infants with PPHN. This study also describes a pre-discharge mortality rate of 6.5% and a 1-year post-discharge mortality rate of 0.7%.[1] These statistics are consistent with another study published by Steurer et al[7] in 2016 which found an overall mortality rate of 7.6% within the first year of life for all patients with PPHN. Steurer et al[7] also observed high post-discharge mortality in Hispanic infants with PPHN (8.2%) which is consistent with the study published by Steurer et al[1] in 2019. Other risk factors for post-discharge morbidity and mortality include severe PPHN, PPHN caused by CDH or other congential pulmonary anomalies, and infants who are SGA.[1] Steurer et al states[1] mortality rates were lowest for infants with idiopathic PPHN (2.9%) and PPHN associated with MAS (3.9%). Steurer et al[1] also report 28.6% of infants with PPHN were readmitted to the hospital within the first year of life compared to 9.8% of infants without PPHN. Of these patients, 10.4% were readmitted for a respiratory cause.[1] Morbidities of infants who survive PPHN include neurodevelopmental disabilities and respiratory issues, likely due to the persistent hypoxemia and aggressive treatment endured by patients during the course of the disease.[3] There are various estimates of rates of sequelae among survivors. Shu et al[9] reports cognitive or hearing deficits in 6.4% of survivors as well as feeding difficulties and short-term respiratory problems in 24%. A recent randomized open label pilot study showed one or more neurodevelopmental disability in 34.5% of survivors by 24 months of age.[4] Infants who survive PPHN are found to have chronic lung disease, cerebral palsy, and seizures.[3,6] Providers should stress to parents of infants who survive PPHN that their child must be followed closely by a pediatrician so as to recognize and treat these potential sequelae as early as possible.

Conclusion

Persistent pulmonary hypertension in the newborn is a condition caused by high pulmonary vascular resistance and hypoxemia which presents with respiratory failure. Diagnostic measures are focused on determining etiology while treatment measures are intended to improve oxygenation, facilitate pulmonary vasodilation, and optimize lung function. Although the rate of

PPHN in the general population is only 0.002%, the morbidity and mortality for patients with PPHN is significant. Patients at higher risk for PPHN include those with infection, MAS, or CDH, those who are SGA or LGA, or are of Black or Asian race. Patients whose mothers delivered via cesarean section, are obese or diabetic, or have used NSAIDs or SSRIs in the third trimester are also at increased risk. Patients who survive PPHN are at risk for chronic neurodevelopmental deficits and respiratory disorders. It is imperative for neonatal providers to recognize patients with potential risk factors and closely monitor these patients for signs of respiratory decompensation. Providers should also be prepared to educate parents on disease course, complications of treatment, and long-term sequelae.

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