Persistent Pulmonary Hypertension
of the Newborn

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Introduction:

Persistent pulmonary hypertension of the newborn (PPHN) was first described by Gersony et al[1] of persistence of the fetal circulation in 1969. It is a clinical syndrome characterized by respiratory distress, hypoxemia, elevated pulmonary vascular resistance and a right to left shunting of venous blood across the foramen ovale and/or ductus arteriosus. The etiology of PPHN is not completely understood. Basically, the pulmonary vascular resistance may remain elevated due to prenatal pathology or postnatal events which interfer with the normal circulatory transition from fetal to extrauterine life.

Nowadays, the clinician is still faced daily with the difficulty of caring for PPHN, and this syndrome continues to cause significant morbidity and mortality.

Pathophysiologic Classification:

A variety of disorders may lead to increased pulmonary vascular resistance, right to left prepulmonary vascular shunting, and decrease pulmonary perfusion. The most important feature of PPHN is increased pulmonary vascular resistance (PVR). From Poiseuille's law:

$$\text{Resistance} = \frac{8\ (\text{viscosity})\ (\text{vessel length})}{\pi\ (\text{no. of vessels})\ (\text{vessel radius})^4}$$

Thus, within the pulmonary circulation, resistance varies directly with blood viscosity and pulmonary vessel length and inversely with the number of vessels, the changes in vessel radius are amplified to the fourth power in their effect on resistance. Pulmonary vascular pressure is the product of pulmonary blood flow and pulmonary vascular resistance (P=FXR). So, the higher the pulmonary resistance, the higher the pulmonary vascular pressure.

Both physiological and structural factors contribute to the development of PPHN. Physiological abnormalities include acute pulmonary vasoconstriction as in meconium aspiration or iatrogenic stress; hypoxia and acidemia; alveolar over-inflation; release of vasoactive substances; polycythemia-hyperviscosity. Structural abnormalities include pulmonary arterial smooth muscle hypertrophy and reduced cross-sectional area of the pulmonary vascular bed. Flow obstruction secondary to hyperviscosity in polycythemia, congenital heart disease, mis-alignment of pulmonary vessels.

Thus, PPHN can simply classified as:
1. Primary: the pulmonary capillaries or arterioles are thickened.
2. Secondary to severe birth asphyxia; severe lung disease, e.g. RDS, meconium aspiration or Transient tachypnea of newborn; pneumonia, e.g.. group B streptococcus; congenital diaphragmatic hernia; pneumothorax; polycythemia; hypoglycemia; maternal ingestion of aspirin or indomethacin.
3. Iatrogenic: overventilation.

Clinical features

The incidence of PPHN has been estimated to be 1:1450 live birth in Europe and up to 2% of all NICU admissions required ECMO in North America. These neonates usually present with severe hypoxia, acidosis, tachypnea , tricuspid or mitral regurgitation, PDA, Chest x-ray reveal clear and hypovascular lung fields and no anatomical cardiac lesions. The disesase may present immediately after birth, such as, severe asphyxiated neonates or congenital diaghragmatic hernia with severe lung hypoplasia. It may present after 4-12 hours (subacute), for example, MAS, or present after 12-24 hrs (late), such as infant with sepsis and those with progressive airway obstruction.

Diagnosis and Investigation:

Newborn with PPHN are typically term or post-term. A diagnosis of PPHN should be considered in a infant with extreme hypoxemia despite adequate ventilatory support. There are a number of clinical tests which can be used as screening procedures.

Hyperoxia test. An increase of the FiO_2 to 0.8~1.0 allows diffusion of oxygen evenly into poorly ventilated areas of the lung and abolishes any ventilation – perfusion abnormalities. This results in an improvement in PaO_2 in most infants with parenchymal lung disease but no response in those with PPHN or cyanotic congenital heart disease.

Preductal and postductal PaO_2 or oxygen saturation differences. Right to left shunting of blood from the pulmonary artery to the thoracic aorta via the PDA results in a higher PaO_2 in preductal blood (obtained from a right radial or temporal artery) compared with postductal blood (obtained from the left radial, umbilical or tibial artery). A difference of PaO_2 more than 15~20 $mmHg^2$ indicates a significant right-to -left ductal shunt. However, PPHN can not be excluded if there is no preductal and postductal PaO_2 or oxygen saturation difference,

as the right to left shunting may be predominantly at the atrial level.

Hyperoxia-hyperventilation test. The infant is manually ventilated at a rate of 100-150 breaths per minute for 10 minutes. This should result in a decrease in $PaCO_2$ to about 25 mmHg and a concomitant increase in the arterial PH. In PPHN, an increase of PaO_2 by at least 30 mmHg is considered a positive response[3] and little or no response is seen in infants with cyanotic CHD.

Echocardiography. The systolic time interval ratio in both ventricles are elevated: by M mode echocardiography, the right ventricular pre-ejection period to right ventricular ejection time has been found to be over 0.40~0.50 and the left ventricular pre-ejection period to left ventricular ejection time to be over 0.38.[4-5] Two dimensional echocardiography shows a deviation of the interatrial septum toward the left and tricuspid regurgitation. The technique of contrast echocardiography involves the injection into a peripheral vein of 0.5 cc/kg of 5% dextrose after gentle agitation in a syringe. Passage of micro-bubbles into the left atrium or aorta can be detected with echocardiography. With the use of colored Doppler echocardiography, right to left shunting of blood through the foramen ovale and ductus arteriosus can be directly visualized.

The clinical severity can be assessed by Alveolar-arterial oxygen gradient $(AaDO_2)$ = 760-47- $PaCO_2/R — PaO_2$, when FiO_2 =1.00 where 760 = barometric pressure, 47 = water vapor pressure, R= respiratory quotient, (normal $AaDO_2$ < 20 mmHg). Oxygen Index (O.I.) = MAP x FiO_2 (%) /PaO_2 where MAP = mean airway pressure. The higher the $AaDO_2$ and O.I., the more severe of the respiratory distress.

Other investigations should include hematological and biochemical examinations. Arterial blood gases, chest X-ray and bacteriology study.

Management

Efforts to lower pulmonary vascular resistance and reverse right to left shunt, maintain blood pressure, tissue perfusion and avoid lung damage are the principles of treatment.

General stabilization should include correction of low PaO_2, acidosis, hyperinflation and hypoinflation of the lung, hypothermia, polycythemia- hyperviscosity, hypotersion and metabolic abnormalities, such as hypoglycemia, hypocalcemia and hypomagnesemia. Minimal handling is very important in caring of these babies since they are extremely labile and withstand any stress or handling very poorly.

Ventilator Therapy. Similar to the principle used in the hyperoxia- hyperventilation test, hyperventilation therapy[6-7] has been advocated to maintain a critical level of PaO_2 for reducing pulmonary vascular resistance. Actually, a very low PaO_2 has a potentially deleterious effect on cerebral and renal blood flow, complications include chronic lung disease (31%), pneumothorax (45%)[8], sensorineural deafness and adverse neurological outcomes.[8]

Successful management of infants with severe respiratory failure and PPHN without hyperventilation had been reported.[9] This treatment regimen focuses on minimizing barotrauma with the use of IMV without muscle paralysis, rate match to patient's rate. PIP minimal for chest rise and the maintenance of the PH $\geq$ 7.25, $PaCO_2$ at 40-60 mmHg (permissive hypercarbia), PaO_2 at 50-70 mmHg. Using this methods of mechanical ventilation have not required a prolonged hospitalization and have a good neurological outcome.[10]

Weaning process should be carried out very carefully and slowly with stepwise FiO_2 reductions and PIP reductions to avoid hypoxic flip-flop.

High frequency ventilation. Both high frequency jet ventilation and high-frequency oscillator ventilation are very effective in controlling $PaCO_2$. So, it was postulated that these ventilatory modalities may be effective in improving oxygenation in PPHN patients. However, most studies showed no effect on ultimate outcome[11] and even had increased incidence of severe IVH. In a single randomized trial, high frequency oscillator ventilation was more successful than conventional ventilation in reducing the need for ECMO[12].

Drug Therapy

Fluid and Electrolyte. Correction of hypocalcemia, hypoglycemia, hypo-magnesemia, polycythemia and acidosis are very important for general stabilization of infants with PPHN, but any attempt to induce alkalosis by hyperventilation or continuous infusing alkali is not recommended since alkalosis will shift the oxygen hemoglobin dissociation curve to the left which may impair tissue oxygenation. In fact, there was no evidence that alkalosis alone would lower PVR nor that alkalosis and hypocarbia could prevent an increase in PVR in the presence of hypoxia[13,14].

Vasodilators. For the infants with PPHN who remains hypoxic despite adequate mechanical ventilation, tolazoline[9], nitroprusside[15], prostacyclin[16], prostaglandin E_1[17], nitroglycerin[18] and magnesium sulfate[19] have been used to reduce the pulmonary vascular resistance with variable success. All these drugs are not specifically dilate the pulmonary vasculature and have some adverse effects.

Nitric oxide (NO) was considered to be a selective pulmonary vasodilator, which can diffuse to vascular smooth muscle, stimulating production of cGMP and causing selective pulmonary vasodilatation, thus improving oxygenation. In 1992 Kinsella [20] and Roberts[21] both described the positive effect of iNo on neonate with severe PPHN. Later on, other studies[22] showed that iNO did cause selective and sustained pulmonary vasodilation in neonates with PPHN. Multicenter randomized clinical trial[23] have demonstrated that iNO

therapy reduces the need for ECMO. Since 1994, Wung at Columbia[10], documented that iNO appeared to be effective for non-hyperventilated patients with PPHN. Infants treated with iNO are more stable, both in oxygenation and hemodynamic status, than those treated with priscolin.

Steinhorn et al have suggested that, when parenchymal disease co-exist with PPHN, iNO seems less effective. In practice, possible strategies, which might improve lung recruitment and subsequent responsiveness to iNO, include: exogenous surfactant, HFV, and phosphodiesterase inhibition.

Of course, during iNO therapy, monitor NO_2, methemoglobin concentration is mandatory to prevent its potential toxic effect. A randomized, multicenter trial[24] showed that treatment with HFOV + iNO was often successful in patients who failed to response to HFOV or iNO alone in severe PPHN, because this combined treatment might improve intrapulmonary shunting in patients with severe lung disease and PPHN.

Muscle relaxant should be avoided, especially in those prolonged overventilated neonates, since it will increase pulmonary vascular resistance from overinflation, damage to lung parenchyma, impairment of venous return and eventually respiratory failure[9,10]. Sedatives, such as Phenobarbital can be used p.r.n. for agitation of infants on Tolazolin[10]. Volume expanders, (colloid solution) such as plasmate, FFP or whole blood, may be used to keep the systolic pressure at 60-80 mmHg or mean pressure at 50-60 mmHg, but albumin is not recommended unless the infant has low albumin, since the patient with respiratory failure usually has increased capillary leakage and infused albumin will leak into alveolar space and inhibits surfactant function[10]. If there is no sustained response to volume expansion, dopamine should be given, but over 10μ g/kg/min is not recommended, because of the danger of

alpha- adrenergic effect which can lead to further pulmonary vasoconstriction[10].

Surfactant. It has been documented that alveolar surfactant can be inactivated by meconium[25]. Several studies have suggested that surfactant replacement in infants with severe MAS may attenuate the clinical sequelae of meconium aspiration[26]. Furthermore, meconium may persist in the trachea for a period of time despite spontaneous respiration, thus bronchial lavage and surfactant supplement has been suggested.[27] However, randomized control trials should be done before widespread clinical use of this treatment which is potentially traumatic to the lung.

ECMO

ECMO is used to be the last resort to rescue the PPHN Neonates. Although marked changes have occurred in the practice of neonatal ECMO since the first survivor in 1957. The appropriate place for ECMO in the therapy of respiratory failure remains to be determined by comparison with optimal ventilatory therapy in terms of morbidity, mortality and cost of care as the outcome variables.

Nautral history, complications and prognosis

This varies with the underlying etiologies, PPHN may expected to have a short natural history (3-5 days), However, severe cases do not response within 3-4 days to conventional mechanical ventilation, high frequency ventilation, vasodilators (include iNO) and eventually have to put on ECMO. Complications include pulmonary interstitial emphysema, pneumothorax, chronic lung disease; cerebral infarction in severe asphyxiated babies; cerebral hemorrhage in those attached to ECMO. Sequelae depend upon the intensity of respiratory support caused CLD and the neurological damage resulted from either severe hypoxia or

4

techniques, such as ECMO. An overall mortality of 30-40% is reported in North America.

Conclusion

Significant progress has been made in the understanding of pathophysiology of PPHN, and its new therapies, such as high frequency ventilation, iNO, ECMO. However, management of these infants remains very difficult and present one of the major challenges in NICU.

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