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Persistent Pulmonary Hypertension of the Newborn: Epidemiology, Pathophysiology and Diagnosis

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Abstract:

Persistent pulmonary hypertension of the newborn (PPHN) is often secondary to parenchymal lung disease (such as meconium aspiration syndrome) or lung hypoplasia (with congenital diaphragmatic hernia) but can also be idiopathic. PPHN is characterized by elevated pulmonary vascular resistance, resulting in right-to-left shunting of blood and hypoxemia. The diagnosis of PPHN is based on clinical evidence of labile hypoxemia often associated with differential cyanosis and confirmed by echocardiography.

Keywords: Persistent Pulmonary Hypertension, Newborn, Lung.

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. Affected infants have structurally normal hearts, but large right to left shunts at atrial and ductal levels secondary to the pulmonary hypertension **(1).**

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by sustained elevation of pulmonary vascular resistance (PVR) and is often associated with normal or low systemic vascular resistance (SVR). This leads to extrapulmonary shunting from right to left across persistent fetal channels - patent ductus arteriosus (PDA) and patent foramen ovale (PFO) leading to labile hypoxemia. This disorder was previously referred to as persistent fetal circulation (PFC) and is often secondary to an unsuccessful pulmonary transition at birth **(2).**

Persistent pulmonary hypertension of the newborn (PPHN) is a serious condition where a newborn's circulation system doesn't adapt to breathing outside the womb. To diagnose PPHN, clinicians often use echocardiography, cardiac catheterization, and other diagnostic tools to assess pulmonary pressures and vascular resistance. Pulmonary artery pressure is the most common method used. It estimates pulmonary artery pressure by measuring the pressure gradient across the tricuspid valve (tricuspid regurgitation jet). Elevated pulmonary artery pressure is indicative of PPHN **(3).**

Pulmonary wedge pressure measured using cardiac catheterization, pulmonary wedge pressure in neonates should typically be low (around 6-12 mmHg). Elevated wedge pressure suggests left heart disease rather than PPHN. Pulmonary vascular resistance (PVR) can be calculated using the formula: PVR = (mean pulmonary artery pressure − pulmonary wedge pressure) / cardiac output. Normal PVR in neonates ranges from 0.5 to 2 Wood units. Increased PVR indicates elevated resistance in the pulmonary vasculature, which is consistent with PPHN **(4).**

Typical diagnostic values for PPHN include mean pulmonary artery pressure greater than 25 mmHg, pulmonary wedge pressure: normal (6-12 mmHg), and pulmonary vascular resistance elevated, typically greater than 2 Wood units **(5).**

Persistent pulmonary hypertension of the newborn (PPHN) is secondary to failure of normal circulatory transition at birth. It is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood **(1).**

Recent classifications of Persistent Pulmonary Hypertension of the Newborn (PPHN) incorporate a more nuanced understanding of its pathophysiology and underlying causes. The classification system has evolved to reflect the advances in diagnostic techniques and our growing knowledge of neonatal physiology and pathology. Recent classification is: **(6)** Maladaptation: abnormal pulmonary vascular response in lung parenchymal disorders such as meconium aspiration syndrome, Underdeveloped vasculature: decreased pulmonary vasculature as seen in small for gestational age or oligohydramnios and Idiopathic persistent pulmonary hypertension in the newborn: likely due to excessive pulmonary vascular smooth muscle thickness **(7).**

Symptoms range from mild respiratory distress to severe hypoxic respiratory failure requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Persistent pulmonary hypertension in the newborn is a potentially life-threatening condition in the early neonatal phase. It is essential for the healthcare provider to promptly identify and provide appropriate care to neonates **(8).**

Epidemiology:

The overall incidence of persistent pulmonary hypertension in newborns is 1.8 per 1000 live births. However, contrary to popular belief, the incidence of persistent pulmonary hypertension in newborns is higher in late preterm infants at 5.4 per 1000 live births. In term infants, the incidence is 1.6 per 1000 live births. Mortality ranges from 7.6 to 10.7%, depending on the severity of the condition. Boys had a higher risk than girls with an adjusted risk ratio of 0.8, 95% CI 0.7-0.8. African American babies had the highest risk, followed closely by Hispanic and Asian infants **(7).**

The classification of persistent pulmonary hypertension of the newborn (PPHN) has evolved over time as our understanding of the condition has improved. In 1960s-1970s, initial reports of PPHN were primarily clinical, focusing on symptoms like cyanosis and respiratory distress in otherwise structurally normal hearts. The term "persistent fetal circulation" was often used. Then in 1980s, with advancements in neonatal care, more attention was given to the underlying pathophysiology, including the role of high pulmonary vascular resistance and right-to-left shunting. The term PPHN began to be widely used. In 1990s, The understanding of different causes of PPHN led to classifications based on etiology into idiopathic and secondary until recent classification in 2010s **(9).**

Etiology:

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a condition characterized by high pulmonary vascular resistance (PVR) after birth, leading to significant hypoxemia. The etiology of PPHN is multifactorial, encompassing a variety of underlying conditions and mechanisms. Understanding the etiological factors is crucial for effective diagnosis, management, and improving neonatal outcomes **(10).**

- **Meconium Aspiration Syndrome (MAS)**: MAS occurs when a newborn inhales a mixture of meconium and amniotic fluid into the lungs, leading to airway obstruction, inflammation, and chemical pneumonitis. This condition can cause significant hypoxemia and increase PVR due to the mechanical obstruction of airways, release of inflammatory mediators, and potential development of surfactant dysfunction. The combination of these factors can lead to PPHN.
- **Respiratory Distress Syndrome (RDS)**: RDS is common in premature infants due to surfactant deficiency, which results in alveolar collapse and poor gas exchange. The lack of adequate surfactant leads to widespread

atelectasis, hypoxemia, and increased work of breathing. The resulting hypoxemia and acidosis can cause pulmonary vasoconstriction and contribute to the development of PPHN.

- **Pneumonia and Sepsis**: Neonatal pneumonia and sepsis can cause systemic and pulmonary inflammation, leading to increased PVR and PPHN. Bacterial or viral infections trigger the release of inflammatory cytokines, which can result in endothelial dysfunction, increased vascular permeability, and pulmonary edema. These pathological changes elevate PVR and exacerbate hypoxemia, promoting PPHN.
- **Congenital Diaphragmatic Hernia (CDH)**: CDH is a birth defect where abdominal organs herniate into the thoracic cavity through a defect in the diaphragm, impairing lung development. The resultant pulmonary hypoplasia and abnormal vascular development increase PVR, leading to PPHN. The severity of PPHN in CDH correlates with the degree of pulmonary hypoplasia and the extent of herniation.
- **Oligohydramnios**: Oligohydramnios, a condition characterized by low amniotic fluid levels, can lead to lung hypoplasia due to restricted fetal lung growth. Insufficient amniotic fluid decreases the mechanical forces necessary for lung expansion and development. The underdeveloped lungs have fewer alveoli and blood vessels, leading to high PVR and PPHN after birth.
- **Perinatal Asphyxia**: Perinatal asphyxia, resulting from insufficient oxygen supply before or during birth, can cause PPHN. Hypoxia and acidosis during asphyxia lead to pulmonary vasoconstriction and increased PVR. This condition also results in the release of vasoactive substances that exacerbate pulmonary hypertension. The severity of PPHN depends on the duration and extent of hypoxic insult.
- **Chronic Intrauterine Hypoxia**: Chronic hypoxia during fetal development, often due to placental insufficiency, can result in structural and functional changes in the pulmonary vasculature. Persistent hypoxia induces pulmonary vascular remodeling, including thickening of the arterial walls and increased smooth muscle mass, which leads to elevated PVR and PPHN at birth.
- **Genetic and Developmental Conditions**: Certain genetic disorders and congenital malformations can predispose neonates to PPHN. Conditions such as alveolar capillary dysplasia, pulmonary vein stenosis, and other congenital heart defects with pulmonary vascular involvement can disrupt normal pulmonary circulation and lead to increased PVR. Genetic mutations affecting the nitric oxide pathway and other vasoregulatory mechanisms also contribute to PPHN.
- **Transient Tachypnea of the Newborn (TTN)**: TTN is caused by delayed clearance of fetal lung fluid, leading to temporary respiratory distress. While typically mild and self-limiting, severe cases can increase PVR and result in PPHN. The presence of excess lung fluid interferes with normal gas exchange, causing hypoxemia and triggering pulmonary vasoconstriction.
- **Maternal Factors**: Maternal conditions such as diabetes, hypertension can increase the risk of PPHN in newborns. These conditions may contribute to fetal hypoxia, inflammation, and impaired lung development. For instance, maternal diabetes can lead to hyperinsulinemia and increased glycogen deposition in fetal lungs, impairing surfactant production and increasing the risk of RDS and PPHN.
- **Other maternal factors**: include antenatal use of certain drugs; for example salicylates. 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. 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 **(11).**

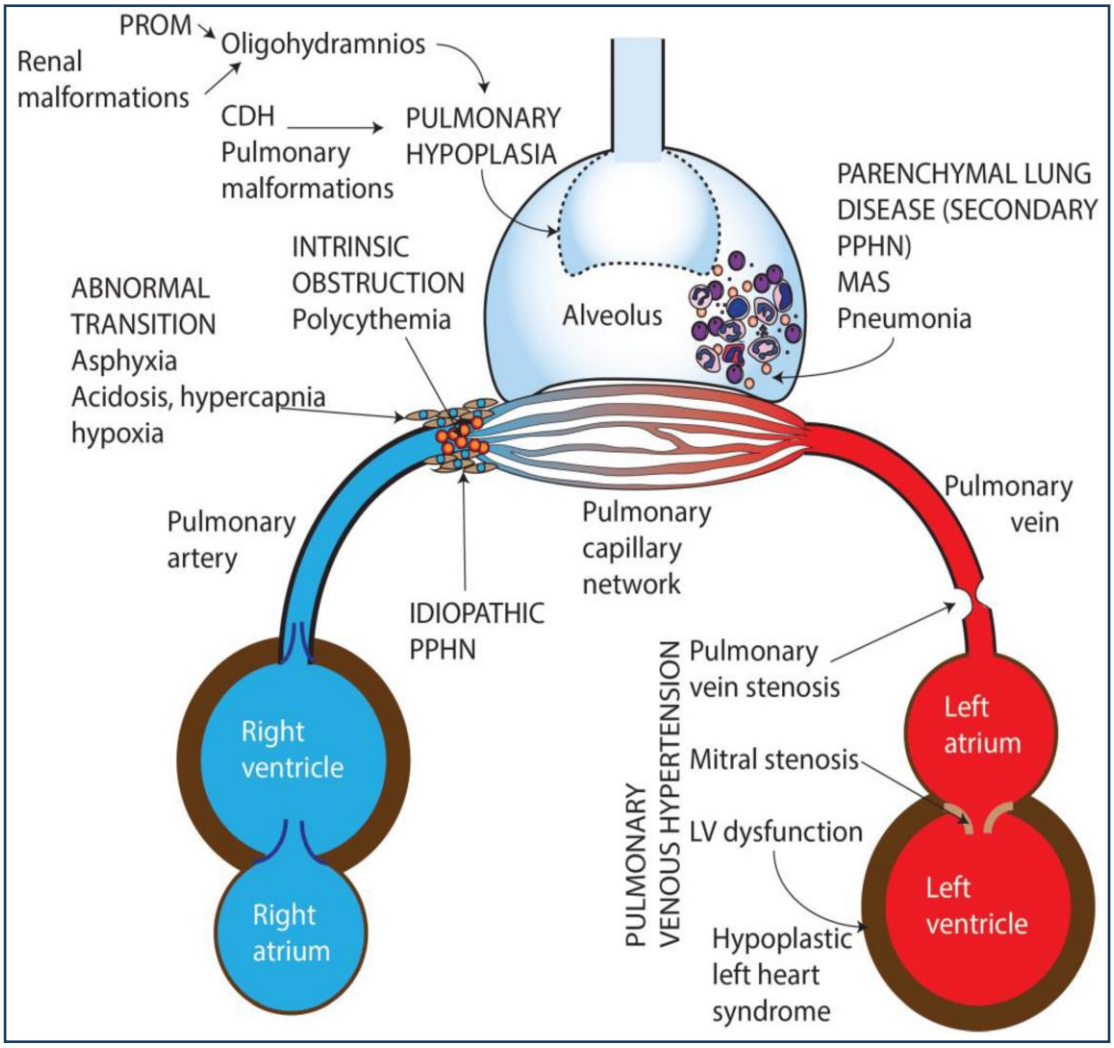

Figure (1): Causes of PPHN (12).

Pathophysiology:

The pathophysiology of Persistent Pulmonary Hypertension of the Newborn (PPHN) involves a complex interplay of several factors that ultimately lead to sustained high pulmonary vascular resistance (PVR) after birth, impairing the transition to normal postnatal circulation **(13).**

Normal Transition at Birth includes:

- Fetal circulation: In utero, high PVR directs blood away from the lungs through the ductus arteriosus and foramen oval.
- Postnatal Changes: At birth, the first breaths and the removal of the placenta lead to a significant drop in PVR due to lung expansion, increased oxygen tension, and the release of vasoactive substances like nitric oxide (NO) and prostacyclin, promoting vasodilation and establishing normal pulmonary circulation.
- Cyclooxygenase enzyme mediates the conversion of arachidonic acid to prostacyclin and is a rate-limiting enzyme. COX-1 is found in the lung and is upregulated when the fetus reaches term gestation. Prostacyclins increase cAMP levels which in turn cause vasorelaxation by decreasing intracellular calcium concentration **(14).**

- Nitric oxide-cyclic guanosine monophosphate (NO- cGMP) and nitric oxide-cyclic adenosine monophosphate (NO-cAMP) pathways are extensively studied in the pathophysiology of persistent fetal circulation. Subsequent clinical studies supported the widely accepted inhaled nitric oxide therapy in persistent pulmonary hypertension in newborns **(15).**

Pathophysiological mechanisms in PPHN includes:

- **Failure of Pulmonary Vasodilation:**
  - Endothelial dysfunction: Impaired production of vasodilators such as NO and prostacyclin, and/or increased production of vasoconstrictors like endothelin-1 and thromboxane. Endothelial Nitric Oxide Synthase (eNOS) catalyzes the production of NO from L-arginine. Reduced eNOS activity due to genetic mutations or inflammatory damage leads to decreased NO availability. ROS such as superoxide anions can react with NO, forming peroxynitrite, which is less effective as a vasodilator. This scavenging diminishes NO's vasodilatory effects. Cyclooxygenase (COX) enzymes, especially COX-1, are critical for converting arachidonic acid to prostacyclin. Reduced COX-1 activity or impaired prostacyclin synthesis impacts vasodilation. Dysfunction or downregulation of prostacyclin receptors can also impair the vasodilatory response. Endothelin-1 is a potent vasoconstrictor. Elevated endothelin-1 levels or receptor overactivity contribute to increased PVR. Thromboxane A2 is another vasoconstrictor that promotes pulmonary vasoconstriction, especially when produced in excess.
  - Decreased nitric oxide availability: Reduced expression or activity of endothelial nitric oxide synthase (eNOS) or scavenging of NO by reactive oxygen species (ROS).
  - Impaired response to oxygen: Persistent hypoxia impairs vasodilation mechanisms, maintaining high PVR.
- **Structural Remodeling of Pulmonary Vessels:**
  - Vascular smooth muscle hypertrophy: increased thickness of the muscular layer of the pulmonary arteries due to smooth muscle cell proliferation. Factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) stimulate smooth muscle cell proliferation and hypertrophy. Increased smooth muscle cell contractility due to altered calcium handling can contribute to sustained vasoconstriction.
  - Adventitial fibrosis: increased deposition of extracellular matrix proteins in the vessel walls. Increased deposition of collagen and elastin in the adventitia leads to vessel stiffening and reduced compliance. Inflammation activates fibroblasts to produce extracellular matrix components, contributing to fibrosis.
  - Decreased vascular density: reduced number of small pulmonary arteries and capillaries, seen in conditions like lung hypoplasia. Chronic fetal hypoxia can inhibit normal vascular growth, reducing the number of small pulmonary vessels. Conditions like congenital diaphragmatic hernia result in inadequate lung development and vascularization.
- **Increased Pulmonary Vascular Tone:**
  - Hypoxia-induced vasoconstriction: Chronic intrauterine hypoxia causes persistent vasoconstriction of the pulmonary arteries.
  - Acidosis: Perinatal asphyxia or severe respiratory distress can lead to acidosis, exacerbating vasoconstriction. Metabolic acidosis with accumulation of lactic acid due to hypoxia and respiratory acidosis with elevated CO_2 levels from respiratory distress
  - Inflammation and Oxidative Stress: Conditions such as MAS, RDS, and sepsis cause inflammation and oxidative stress, promoting vasoconstriction and vascular remodeling.
- **Extravascular Factors:**
  - Lung fluid clearance issues: Conditions like TTN lead to delayed clearance of fetal lung fluid, increasing intrapulmonary pressure and impeding pulmonary blood flow.

- Mechanical ventilation effects: Positive pressure ventilation can increase intrathoracic pressure, reducing venous return and right ventricular output, thereby affecting pulmonary circulation. Decreased venous return leads to reduced preload (the volume of blood in the ventricles at the end of diastole), potentially lowering cardiac output. Reduced right ventricular preload can exacerbate right ventricular dysfunction, which is already challenged by elevated pulmonary vascular resistance (PVR) in PPHN. Mechanical ventilation also alters hemodynamics as positive pressure ventilation can lead to decreased systemic blood pressure due to reduced cardiac output, and increased intrathoracic pressure can worsen right-to-left shunting of blood through the ductus arteriosus or foramen ovale, exacerbating hypoxemia.

- **Genetic and Molecular Factors:**
  - Genetic Predisposition: Mutations in genes involved in pulmonary vascular development and function (e.g., BMPR2, CAV1) can predispose infants to PPHN. BMPR2 is a receptor that is part of the bone morphogenetic protein (BMP) signaling pathway. This pathway regulates cell growth, differentiation, and apoptosis. It plays a critical role in the development and maintenance of pulmonary vasculature. Mutations in BMPR2 can be inherited in an autosomal dominant manner. However, not all individuals with BMPR2 mutations develop PPHN, indicating that additional factors may influence disease expression. Caveolin-1 is a protein involved in caveolae formation, which are small invaginations of the plasma membrane involved in endocytosis and signal transduction. It plays a role in modulating endothelial cell function and pulmonary vascular tone. Mutations in CAV1 can be inherited in an autosomal dominant manner, with variability in clinical presentation. Other genetic factors include ALK1 (Activin Receptor-Like Kinase 1) involved in the TGF-beta superfamily of receptors that regulate endothelial cell proliferation and angiogenesis, and Endoglin which is a co-receptor for TGF-beta, involved in endothelial cell proliferation and vascular remodeling.
  - Epigenetic Modifications: In utero exposure to adverse conditions may lead to epigenetic changes that affect pulmonary vascular reactivity and structure.
- **Clinical implications:**
  - Hypoxemia and cyanosis: cyanosis is due to right-to-left shunting of blood through the ductus arteriosus or foramen ovale, deoxygenated blood bypasses the lungs and enters the systemic circulation and is manifested as a bluish discoloration of the skin, lips, and mucous membranes. Hypoxemia is inadequate oxygenation of blood due to impaired pulmonary gas exchange and is manifested as low oxygen saturation levels (SpO_2) despite supplemental oxygen, and signs of respiratory distress.
  - Right ventricular strain and failure: persistent high PVR increases the workload on the right ventricle, potentially leading to right ventricular dysfunction. Symptoms include tachycardia, hypotension, and signs of poor perfusion, and may present with hepatomegaly, edema, and elevated jugular venous pressure.
  - Systemic hypoperfusion: impaired cardiac output can lead to inadequate perfusion of systemic organs. This can lead to decreased urine output and elevated creatinine levels, altered level of consciousness or seizures, and abdominal distension and feeding intolerance.

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) **(16).**

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 (PaO2). The appearance of the chest radiograph may be normal, unless there is underlying lung disease. The lung fields may be oligemic due to poor pulmonary blood flow **(17).**

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 **(18).**

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 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 **(19).**

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. However, BNP levels were not affected by inotrope administration and only weakly correlated with the oxygenation index. BNP levels, therefore, do not seem likely to become part of routine investigation of an infant with PPHN **(20).**

- History:

Infants usually present within a few days after birth. Prenatal history includes maternal health conditions including chronic illnesses: Diabetes, hypertension, lupus, and other chronic conditions can affect fetal development, or maternal infections, particularly during the third trimester, and use of certain medications (e.g., SSRIs, NSAIDs) or substances (e.g., tobacco, alcohol, illicit drugs) during pregnancy. Prenatal history also includes pregnancy complications (oligohydramnios, polyhydramnios, placental issues). Prenatal Ultrasound findings include congenital diaphragmatic hernia (CDH), and lung hypoplasia **(21).**

Perinatal history includes gestational age as preterm infants are at risk for respiratory distress syndrome (RDS), and term or post-term infants, often associated with conditions like meconium aspiration syndrome or birth asphyxia. Complications associated with cesarean section, especially without labor, can increase the risk of transient tachypnea of the newborn (TTN). Prolonged labor, fetal distress, meconium-stained amniotic fluid, or nuchal cord can lead to perinatal asphyxia and increase the risk of PPHN **(22).**

Neonatal history includes respiratory symptoms (tachypnea, retractions, cyanosis, and grunting), cardiac symptoms (heart murmurs, differential cyanosis), and response to oxygen therapy. Family history includes family history of congenital heart defects, and history of genetic conditions **(23).**

A history of fetal distress, severe metabolic acidosis in cord blood, low Apgar scores and/or the presence of meconium in amniotic fluid and/or in the neonate's larynx visualized on direct laryngoscopy along with typical chest X-ray findings suggest a significant perinatal hypoxic–ischemic event or series of events. Meconium aspiration syndrome may also occur in the setting of significant perinatal asphyxia; history of prolonged rupture of membranes, group B streptococcus colonization, or presence of chorioamnioitis suggest infection. In addition to the clinical features of septic shock or the presence of bronchopneumonia on chest radiograph, blood, urine or cerebrospinal fluid testing may reveal evidence of acute systemic inflammation **(24).**

A history of elective cesarean section and radiological finding of fluid in inter-lobar fissures suggests transient tachypnea of the newborn. Other, relatively less frequent etiologies include respiratory distress syndrome, especially in late-preterm and term neonates born to mothers with poorly controlled diabetes; antenatal drug exposure (e.g.

delayed transition from selective serotonin reuptake inhibitors, antenatal closure of ductus arteriosus from non-steroidal anti-inflammatory drugs); chromosomal anomalies; pulmonary hypo-plasia (secondary to congenital diaphragmatic hernia or severe long standing oligohydramnios) **(25).**

A family history positive for previous neonatal deaths from respiratory failure and/or a history of consanguinity may point towards surfactant protein deficiency. A neonate who appeared well at birth with normal Apgar scores but presents minutes or hours later with severe respiratory distress and HRF which is relatively unresponsive to medical management may suggest alveolar capillary dysplasia with misalignment of pulmonary veins, a rare genetic disorder characterized by maldevelopment of the capillary vascular bed around the alveoli in the lungs **(26).**

Enhanced appreciation of the likely etiology may enable a more focused and disease-specific approach to therapeutic interventions. This is highly relevant for unique situations such as hypoxic ischemic encephalopathy where the benefits of therapeutic hypothermia in minimizing the risk of brain injury need to be carefully balanced against the resultant aggravation of PVR. Regardless, therapeutic hypothermia is a post-stabilization intervention **(26).**

- Physical examination:

Newborn assessment usually occurs simultaneously with resuscitation in conditions such as meconium aspiration. On exam, an infant with persistent fetal circulation appears cyanotic. Respiratory distress can manifest as labored breathing with subcostal, suprasternal and intercostal retractions due to lung parenchymal disease **(8).**

Infants with congenital diaphragmatic hernia have a scaphoid abdomen on the exam. Septic infants can present with refractory hypotension, multiorgan failure, and easy bleeding due to disseminated intravascular coagulopathy (DIC) **(14).**

Hyperoxia-Hyperventilation test: Earlier, PPHN was diagnosed by hyperoxia-hyperventilation test in which a neonate will be subjected to 100% oxygen and hyperventilated with rates up to 100/min to achieve a partial pressure of CO2 (pCO2) of 20 to 25 mmHg and pH of 7.5. It was believed that hyperoxia and alkalosis produce vasodilation of pulmonary vessels and improve the partial pressure of oxygen (PaO2). A rise in PaO2 >30 mmHg is considered to be PPHN, whereas in cyanotic congenital heart diseases (CHDs) there will be no response in PaO2. However, this test has become obsolete nowadays because of the adverse effects associated with alkalosis **(27).**

- Complications:

Complications of persistent pulmonary hypertension of newborns are related to the underlying cause. In MAS, air leaks such as pneumothorax and pneumomediastinum occur very frequently due to the ball-valve phenomenon or the need for high ventilator settings. The long-term outcome of infants with PPHN may depend on their underlying conditions and the therapeutic interventions that they have received at birth. The rate of neurodevelopmental disabilities including cognitive delays and hearing deficit can be seen in 6.4% of PPHN survivors. Feeding problems and short-term respiratory morbidities can be seen also in 24% of PPHN survivors **(28).**

One of the primary complications of PPHN is hypoxemia, resulting from inadequate oxygenation of blood due to right-to-left shunting through the ductus arteriosus or foramen ovale. This can lead to significant cyanosis, particularly in peripheral tissues. Persistent hypoxemia can contribute to multi-organ dysfunction and exacerbate the infant's condition. Severe and prolonged hypoxemia may lead to neurological deficits, developmental delays, and increased mortality **(29).**

Elevated pulmonary vascular resistance places increased strain on the right ventricle, which must work harder to pump blood into the pulmonary arteries. This can lead to right ventricular hypertrophy and, ultimately, right ventricular failure. Signs of right ventricular failure include hypotension, edema, and a decreased cardiac output. This condition can further compromise systemic perfusion and exacerbate other complications associated with PPHN **(13).**

The high pressures in the pulmonary circulation can reduce blood flow to systemic organs, leading to systemic hypoperfusion. This can result in inadequate oxygen delivery to vital organs such as the brain, kidneys, and liver. Complications from systemic hypoperfusion include acute renal failure, hepatic dysfunction, and neurological impairment. Early recognition and management of systemic hypoperfusion are crucial to prevent irreversible damage **(30).**

Neonates with severe PPHN are at increased risk for neurological complications due to both hypoxemia and the potential for embolic events. These complications can include intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and developmental delays. The risk of these conditions underscores the importance of close monitoring and supportive care to minimize long-term neurological sequelae **(31).**

Renal and hepatic dysfunction can occur secondary to systemic hypoperfusion and hypoxemia. Reduced renal perfusion can lead to acute kidney injury (AKI), which may manifest as oliguria or anuria and electrolyte imbalances. Hepatic dysfunction can present as jaundice, elevated liver enzymes, and coagulopathy. Prompt identification and management of renal and hepatic issues are essential to improving outcomes in neonates with PPHN **(21).**

Gastrointestinal complications in PPHN may arise from systemic hypoperfusion and the use of certain medications. These can include necrotizing enterocolitis (NEC), feeding intolerance, and abdominal distension. The risk of NEC is particularly concerning due to its potential for severe morbidity and mortality. Ensuring adequate perfusion and careful management of feeding are critical components of care for affected neonates **(30).**

Neonates with PPHN are often more vulnerable to infections due to their compromised overall health and the potential use of invasive procedures. Infection risk can be exacerbated by the presence of central lines, mechanical ventilation, and other supportive measures. Prevention strategies, including stringent infection control practices and prophylactic antibiotics, are essential in minimizing this risk **(32).**

- Work-up:

Evaluation of an infant with suspected PPHN includes obtaining blood gas, chest X-ray, and echocardiogram. Sepsis should be ruled out with complete blood count with differential (CBC with diff), C- reactive protein (CRP), and blood culture. If ECMO support is anticipated, coagulation studies and a head ultrasound should be done before cannulation **(33).**

Arterial blood gas demonstrates low partial pressure of arterial oxygen (paO2). In sepsis, leucocytosis or leucopenia may be seen. CRP may be high in sepsis. Chest radiographs may show signs of underlying lung parenchymal disease **(15).**

ABG analysis is crucial in diagnosing and managing PPHN. It provides insight into the infant's oxygenation and acid-base balance. The key parameters measured include **(3)**:

- PaO_2 (Partial Pressure of Oxygen): Low PaO_2 levels indicate hypoxemia, a hallmark of PPHN. Persistent low oxygen levels despite supplemental oxygen may suggest severe pulmonary hypertension or inadequate ventilation.
- $PaCO_2$ (Partial Pressure of Carbon Dioxide): Elevated $PaCO_2$ levels can reflect inadequate ventilation or respiratory failure. In PPHN, there may be a mismatch between ventilation and perfusion, leading to elevated $PaCO_2$.
- pH (Hydrogen Ion Concentration): The pH level indicates the acid-base status. A low pH (acidosis) can result from either metabolic or respiratory causes. In PPHN, metabolic acidosis may be present due to lactic acid accumulation from hypoxia.

- HCO_3^- (Bicarbonate): This parameter helps in evaluating the metabolic component of acid-base disturbances. Changes in HCO_3^- levels can provide additional information about the infant's metabolic status and compensatory mechanisms.
- Base Excess: This value indicates the amount of excess or insufficient base in the blood, helping to identify the severity of metabolic acidosis or alkalosis.

Oxygenation Index (OI) = Mean airway pressure * FiO2*100/PaO2. OI >15, along with pre-post ductal saturation difference of >10%, are suggestive of high pulmonary vascular resistance. Also, echocardiography is the gold standard for confirming the diagnosis. It is also used to follow therapeutic efficacy. The direction of flow across PDA and PFO, interventricular septal deviation or flattening, and regurgitation across the tricuspid valve (TR jet) are used to estimate right ventricular and/or pulmonary vascular pressure **(13).**

TR jet may not be accurate in 30% of cases due to poor right ventricular dysfunction. Echocardiography also provides information about right and left ventricular function, which is vital in treating persistent pulmonary hypertension. Poor right ventricular function coupled with low right and left ventricular output is predictive of poor outcomes. Brain natriuretic peptide (BNP) is a hormone produced by stressed right ventricles. BNP levels are elevated in babies with PPHN. BNP level of more than 550pg/ml is predictive of persistent pulmonary hypertension **(34).**

Techniques such as cardiac catheterization and MRI for assessment of pulmonary vascular resistance, blood flow and myocardial function are currently not feasible in a sick newborn. Echocardiography is the only presently feasible bedside clinical investigation and is routinely used to confirm the diagnosis of PPHN and to monitor disease progression or response to therapies. It is a simple, non-invasive, bedside test, which can be performed even in the most unstable patients. For older children and adults, PHT is usually diagnosed by echocardiography if pulmonary artery peak systolic pressure is > 35 mmHg **(35).**

Although this definition may be useful for infants with late-onset, acute or chronic PHT, it is not applicable for diagnosing acute PPHN during the early neonatal period. This is because even under physiological conditions, pulmonary pressures are expected to be high at birth and decline thereafter. The decline is likely to be most rapid over the first few hours to days of age. A number of echocardiography indices of PVR and PHT have been validated in adult patients **(36).**

Enhancements in imaging techniques and wide dissemination of echocardiography equipment allow timely assessment of these indices in neonates; yet their clinical use in PPHN is limited by the relative paucity of normative neonatal data. Re-characterization of normal transitional physiology using echocardiography in a time-sensitive manner during early postnatal period can further inform its scientific use in management of neonates with PPHN. Nevertheless, echocardiographic findings consistent with suprasystemic pulmonary pressures, if present, are considered diagnostic of PPHN **(37).**

The most widely used measurements include peak systolic RV pressure calculated from measured velocity of tricuspid regurgitant jet, presence of pure right-to-left shunt at the ductal or atrial level, and paradoxical interventricular septal motion at end-systole. On the other hand, findings suggestive of high pulmonary pressures at levels which are not suprasystemic, such as bidirectional shunts or flat interventricular septal motion, should be considered supportive at best, of diagnosis of PPHN, especially when interpreted in context of the clinical symptoms **(38).**

- Differential Diagnosis:

Differential diagnosis includes cyanotic congenital heart disease, which presents with cyanosis. iNO treatment worsens the clinical condition in total anomalous pulmonary venous return and should be avoided. Infants with PDA, transposition of great vessels, and coarctation of the aorta can present with differential cyanosis **(13).**

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