Hypoxic Respiratory Failure (HRF) and Persistent Pulmonary Hypertension of the Newborn (PPHN)

Overview of Pathophysiology and Diagnostic Tools

This overview is intended as an educational background reference for healthcare providers. It is not a comprehensive presentation of symptoms, unanticipated causes, goals of therapy and benefits and limitations of diagnostic measures. It is not intended to replace clinical judgment. You are advised to use your own medical judgment when diagnosing and treating patients.

Pathophysiology of PPHN

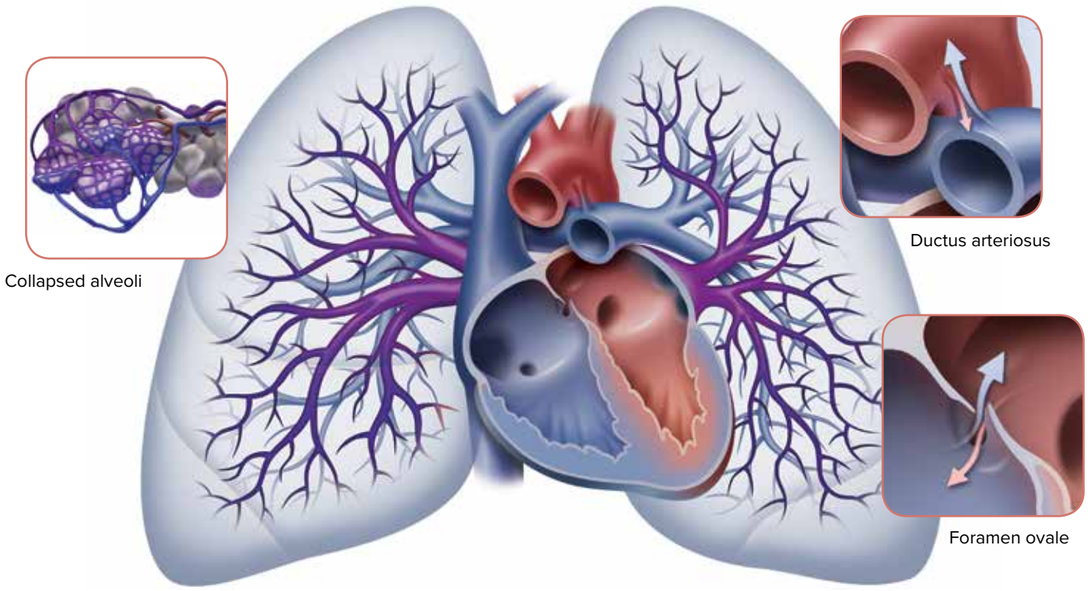
- Atelectasis causes intrapulmonary shunting[1]
- Pulmonary vascular resistance remains high[2,3]
- Blood shunts away from lungs to the systemic circulation (right to left) through one or both fetal shunts[2,3]
- The right ventricle compensates to manage the pressure to push blood to the lungs (RV dilatation, tachycardia)[2,3]

Intrapulmonary Shunt

Pulmonary arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lungs.

Extrapulmonary Shunt

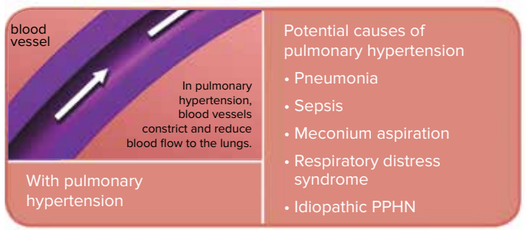
Right to left shunting where the blood bypasses the lungs through fetal channels (PDA and/or PFO).



Collapsed alveoli

Ductus arteriosus

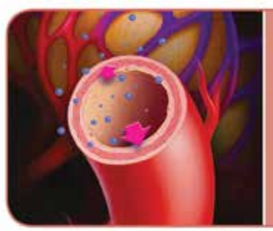
Foramen ovale



With pulmonary hypertension

Potential causes of pulmonary hypertension

- Pneumonia
- Sepsis
- Meconium aspiration
- Respiratory distress syndrome
- Idiopathic PPHN

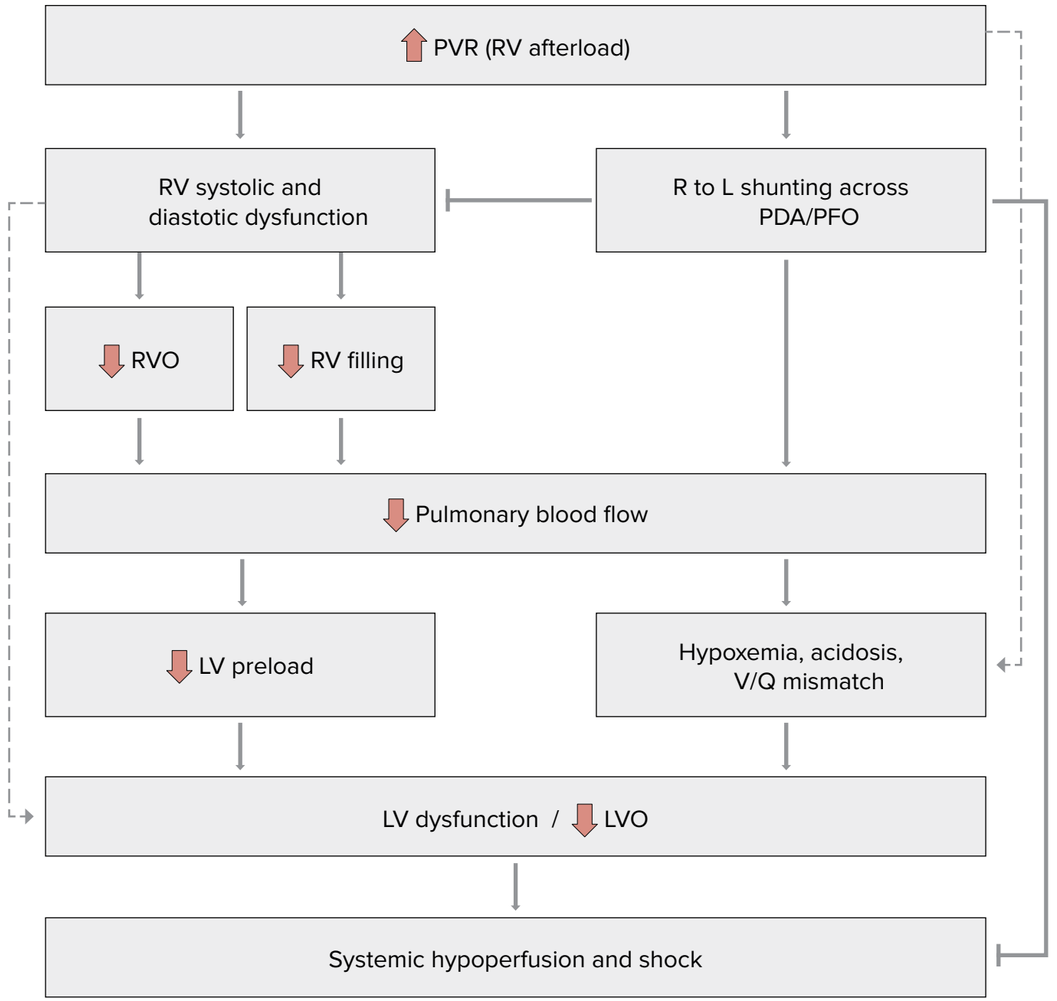


Treating pulmonary hypertension relaxes blood vessels and allows more blood to enter the lungs

PDA, patent ductus arteriosus; PFO, patent foramen ovale; PVR, pulmonary vascular resistance; RV, right ventricle.

The Cardiopulmonary Cascade

- If left untreated, the impact of PPHN on the right side of the heart begins to impact the left side[2]
- Insufficient blood and oxygen delivery from the left heart to the systemic circulation leads to systemic hypoperfusion and shock[2]



LV, left ventricle; LVO, left ventricular overload; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PVR, pulmonary vascular resistance; R to L, right to left; RV, right ventricle; RVO, right ventricular overload; V/Q, ventilation/perfusion.

Common Signs and Symptoms

Oxygenation failure associated with PPHN can manifest itself through a number of symptoms:[4,5]

B Blue (cyanosis)

A Accelerated rate (tachycardia)

B Breathing (tachypnea)

I Inadequate oxygenation

E Effort (retractions)

S Saturations (5–10% gradient)

Echocardiography: Standard of Care

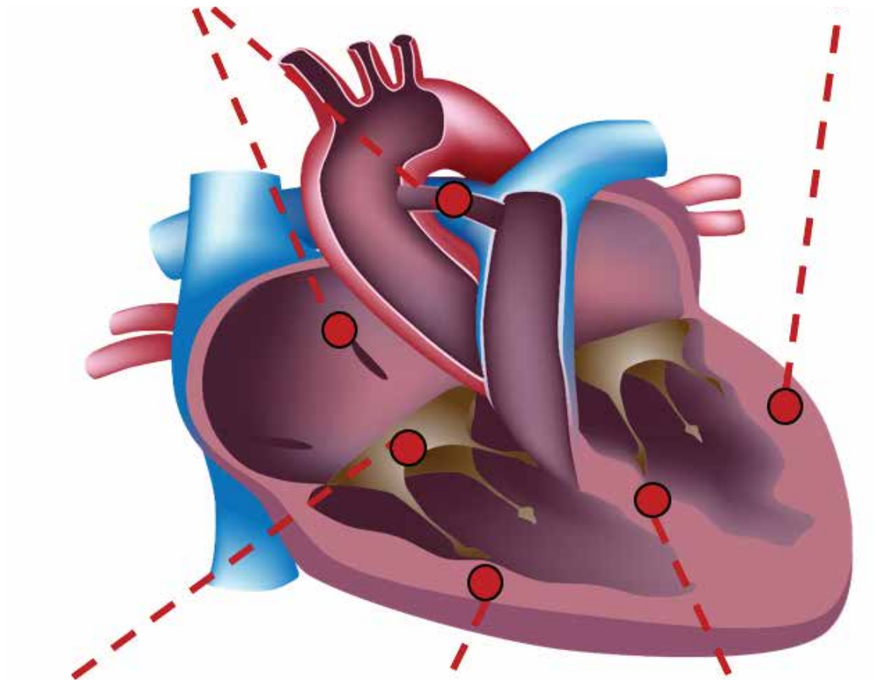
Echocardiography is considered the gold standard in the diagnosis of PPHN as catheterization and MRI are often not feasible for this population. Below are cardinal signs of PPHN that can be identified:[1]

R to L shunting across the PDA and PFO

Indicative of PVR > SVR[5]

LV filling, dilatation and contractility

Indicative of blood return from the lungs and the LV's ability to pump blood to the systemic circulation[3,5]



Tricuspid valve regurgitation

Indicative of RV pressures > RA pressures, demonstrating high RV afterload[5]

RV filling, dilatation and contractility

Indicative of the RV's ability to pump against the PVR and pump blood to the lungs[3,5]

Bowing of the intraventricular septum into the LV

Indicative of heart remodelling and compensation due to pumping against high PVR[3]

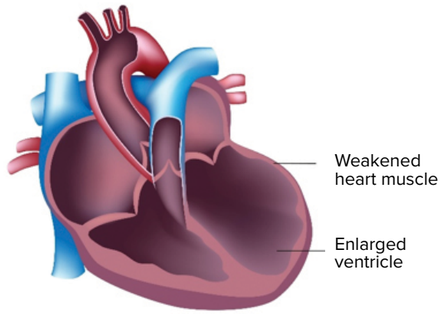
LV, left ventricle; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; SVR, systemic vascular resistance.

Diseases Often Mistaken for PPHN

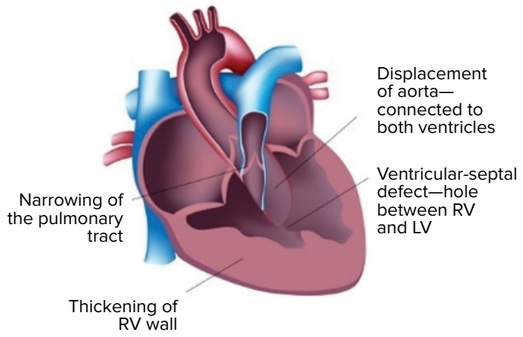
PPHN symptomology can occur as a result of other physiologic conditions for which treatment is different from PPHN:

Left Ventricular Dysfunction

Compromised LV contractility and output can also create high PVR as a result of pulmonary venous hypertension.[6] Symptoms can mimic those seen in PPHN.



Congenital heart disease
Tetralogy of Fallot



Congenital Heart Disease

About 1 in every 4 babies born with a heart disease has a critical congenital heart disease.[7] Examples include hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, TAPVR, transposition of the great arteries, tricuspid atresia, and truncus arteriosus.[7] Symptoms can mimic those seen in PPHN.

Arteriole-Venal Malformation Outside the Heart

In neonates, the most common type of arteriovenous shunts is the VGAM.[8] Neonates with VGAM present with a variety of systemic and pulmonary cardiovascular symptoms as a result of high-volume preductal left-to-right shunt. Inadequate development of the pulmonary vascular bed *in utero* caused by this over-circulation may cause severe PH, which presents as hypoxic respiratory failure at birth.[9] As a result, symptoms can mimic those seen in PPHN.

LV, left ventricle; PH, pulmonary hypertension; RV, right ventricle; TAPVR, total anomalous pulmonary venous return; VGAM, vein of Galen aneurysmal malformation.

Indirect Causes of Pulmonary Hypertension

Pulmonary hypertension can occur as a result of other indirect factors in the neonate's condition, management in the neonatal intensive care unit, or their mother's condition and management prior to birth.

Cooling-Induced Pulmonary Hypertension

Neonates with HIE will receive therapeutic hypothermia as part of a brain-protective strategy. The asphyxial event and cooling can cause acute pulmonary hypertension in these patients so optimal management of pulmonary hypertension is important prior to the initiation of cooling.[10]

Congenital Diaphragmatic Hernia (CDH)

Affecting approximately one in every 3000 babies, neonates with CDH may present with acute pulmonary hypertension due to defects in lung growth and morphogenesis such as pulmonary hypoplasia which result from herniation of the abdominal organs into the chest.[4,10]

Drug-Induced Pulmonary Hypertension

Maternal antenatal use of NSAIDs and SSRIs have demonstrated some association to the presence of pulmonary hypertension in neonates.[3,6]

Diabetes-Induced Pulmonary Hypertension

Neonates who experience fetal hyperinsulinemia as a result of maternal hyperglycemia are at risk of acute pulmonary hypertension. These neonates may have retarded surfactant production and secretion which increases their risk for RDS. RDS may consequently increase their risk for acute pulmonary hypertension.[10]

Infection-Induced Pulmonary Hypertension

Neonates with infections such as those whose panels indicate a GBS infection are also at risk of PPHN. GBS phosphatidylglycerol and cardiolipin are the dominant phospholipids associated with PPHN.[3]

GBS, Group B Streptococcus; HIE, hypoxic ischemic encephalopathy; NSAIDs, non-steroidal anti-inflammatory drugs; RDS, respiratory distress syndrome; SSRIs, selective serotonin reuptake inhibitors.

Common Goals of Therapy

To effectively and efficiently manage neonates with PPHN, understanding of the therapeutic goals, diagnostic measures and appropriate interventions is crucial.

Goal	Measures	Interventions	Intervention rationale
Improve oxygenation and achieve FRC[1,10,11]	• FiO_2 requirement[3] • Oxygenation index[1,12] • Arterial blood gases[3] • Pulse oximetry (pre-/post-ductal saturations)[1]	• Ventilatory support[3,10] • Supplemental oxygen[1,10] • Pulmonary vasodilators[1,3,10] • Surfactant[1,3,11]	• Support adequate lung inflation[1,3,6,10,11] • Facilitate oxygenation through open lung fields[1,3,6,10,11] • Reduce PVR to facilitate blood flow to ventilated regions[3,6,8,10] • Aim for CO_2 of 40–60 mm Hg to reduce pulmonary vasoconstriction[3]
Improve V/Q matching[1]	• FiO_2 requirement[3] • Oxygenation index[1,12] • Arterial blood gases[3] • Pulse oximetry (pre-/post-ductal saturations)[1]	• Surfactant[1,3] • Pulmonary vasodilators[1,3]	• Support adequate alveolar inflation[1,3] • Facilitate oxygenation through blood flow to ventilated regions[1,3,10]
Improve heart function (as required) and facilitate transition[1]	• ECHO (contractility, cardiac output, direction/presence of shunt, presence/absence of a PDA)[1,3] • Pulse oximetry (pre-/post-ductal saturations, heart rate)[1] • Urine output[5] • 4-limb blood pressure[1] • Arterial blood gases and lactate[5] • Capillary refill time[2]	• Inotropes[1,3,6] • Pressors[1,3,6] • Chronotropes[1,3,6] • Pulmonary vasodilators (shunt only)[1,3] • Prostaglandin[3]	• Support adequate heart rate and contractile function[1] • Facilitate post-transition pressure norms for PVR and SVR[1] • Optimize systemic hemodynamics[1,6]
General supportive care[1,3,6]	• Temperature[3,5] • Irritability[3,5] • Urine output[2,5] • Blood pressure[5]	• Temperature management[3,5,6] • Nutrition[5,6] • Minimal handling[3,5,6] • Glucose[3,6] • Sedation[5,6] • Volume[5,6] • Minimize noise and stimulation[3]	• Maintain patient stability[1,3,5,6] • Reduce agitation and act as a vasodilator[3]

ECHO, echocardiograph; FiO2, fraction of inspired oxygen; FRC, functional residual capacity; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; V/Q, ventilation/perfusion.

Benefits and Limitations of Diagnostic Measures

To effectively and efficiently manage neonates with PPHN, understanding of the benefits, limitations and considerations of available diagnostic measures is crucial.

Measure	Benefits	Limitations/Considerations
TNE (neonatologist-performed)	• Assessment of heart function combined with clinical picture provides advanced diagnostic clarity and therapeutic targeting of preload, afterload, and contractility[13] • Gold standard for diagnostic confirmation of PPHN[5] • Confirmation of cardinal signs of PPHN is relatively fast[1] • Offers ability to monitor response to and titrate dosing of interventions[13]	• Access to TNE-trained clinicians is still limited in many centres to one or a few staff members[5]
Echocardiography (cardiologist-performed)	• Assessment of heart structure and function • Gold standard for diagnostic confirmation of PPHN[5] • Confirmation of cardinal signs of PPHN is relatively fast[1]	• Access to cardiology, especially during off-hours, may limit the availability and opportunity for use[5] • Conduct of a full echocardiogram requires time to complete • Cardiology may not have clinical picture to connect echocardiographic findings for diagnostic purposes—important as patency and direction of shunts may be life-saving[13]
Pulse oximetry (pre-/post-ductal saturations)	• Easily applied to demonstrate labile saturations—identifying R to L shunting and heart rate[1]	• Absence of a gradient does not rule out pulmonary hypertension[5,10] • Skin temperature may impact oximeter reading of rate and saturations
Arterial blood gases	• Helps trend progress or further deterioration • Identifies respiratory and metabolic acidosis/alkalosis to narrow causes and diagnostic differential[1] • Preductal PaO_2 accurately predicts oxygen delivery to vital organs such as the brain and heart and is not altered by right to left shunting at the PDA[1]	• Requires arterial access[1] • Potential for infection and pain • Many patients with PPHN have umbilical arterial access (post-ductal blood gases) resulting in lower PaO_2 and higher OI and lower P/F ratio compared to preductal evaluation[1] (if inappropriately assessed prior to placement of an arterial line or arterial stab, can cause significant vascular compromise to the distal extremities)
Blood pressure	• Indicator of cardiac output • Analysis of systolic and diastolic blood pressure may offer insight on the location of the problem (right versus left heart);[14] 4-limb pressure gradient difference can be seen in some causes for PPHN such as VGAM • May offer insights on the presence of shunts[14]	• Pressure changes may be a result of volume bolus, introduction or removal of therapy, or changes in the patient condition which may impact sensitivity of measure[1] (non-invasive cuff monitoring vs invasive; medications [opiates, benzos all act as vasoplegics])
FiO_2 requirement	• Clear indicator of challenge with oxygenation and characteristic of PPHN[1] • Often available for monitoring due to frequency of oxygen use as a therapeutic intervention	• FiO_2 provision above 60% may have downstream consequences due to free radical and reactive oxygen species generation[1,6,15] • FiO_2 provision to increase PaO_2 >50–60 mm Hg is unlikely to have further impact on oxygenation, but may have deleterious impacts on outcome and inhibit response to pulmonary vasodilator therapy[1,6] • Labile hypoxemia (marked change in oxygen saturation with minimal or no change in ventilator settings or FiO_2) is characteristic of PPHN so FiO_2 should not be used as an independent measure[1]
Oxygenation index	• Used to measure lung disease severity in HRF/PPHN[1] • Accounts for patient's interventional requirement and output[1]	• Systemic or suprasystemic PVR can exist early in patient's course without high MAP or oxygen requirement—may impact the measure sensitivity[10] • As most arterial lines are placed in the post-ductal umbilical artery, consider monitoring implications[10] • In the presence of a high-volume R to L ductal shunt, post-ductal systolic arterial pressure may be higher leading to underestimation of pre-ductal perfusion pressure[10] • Knowledge of or access to the equation is required for calculation • Less predictive of outcome within the first hours of invasive positive pressure ventilation than later in the course of disease
Chest X-ray	• Clarify the underlying cause of HRF and response to ventilation therapy[1] • Show oligemic lung fields in primary PPHN and be helpful in diagnosing lung disease[3]	• Diaphragm position in relation to posterior ribs lacks precision for assessment of lung volume[10]
Urine output	• May be a marker of renal perfusion pressure • Sign of shock and circulatory failure[2]	• Urine output is also a function of kidney performance which may impact measure sensitivity[2]

FiO_2, fraction of inspired oxygen; HRF, hypoxic respiratory failure; MAP, mean airway pressure; OI, oxygenation index; P/F, partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO_2); PaO2, partial pressure of oxygen; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; R to L, right to left; TNE, targeted neonatal echocardiography; VGAM, vein of Galen aneurysmal malformation.

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