Persistent Pulmonary Hypertension of The Newborn

Khalid Ahmed Khalid

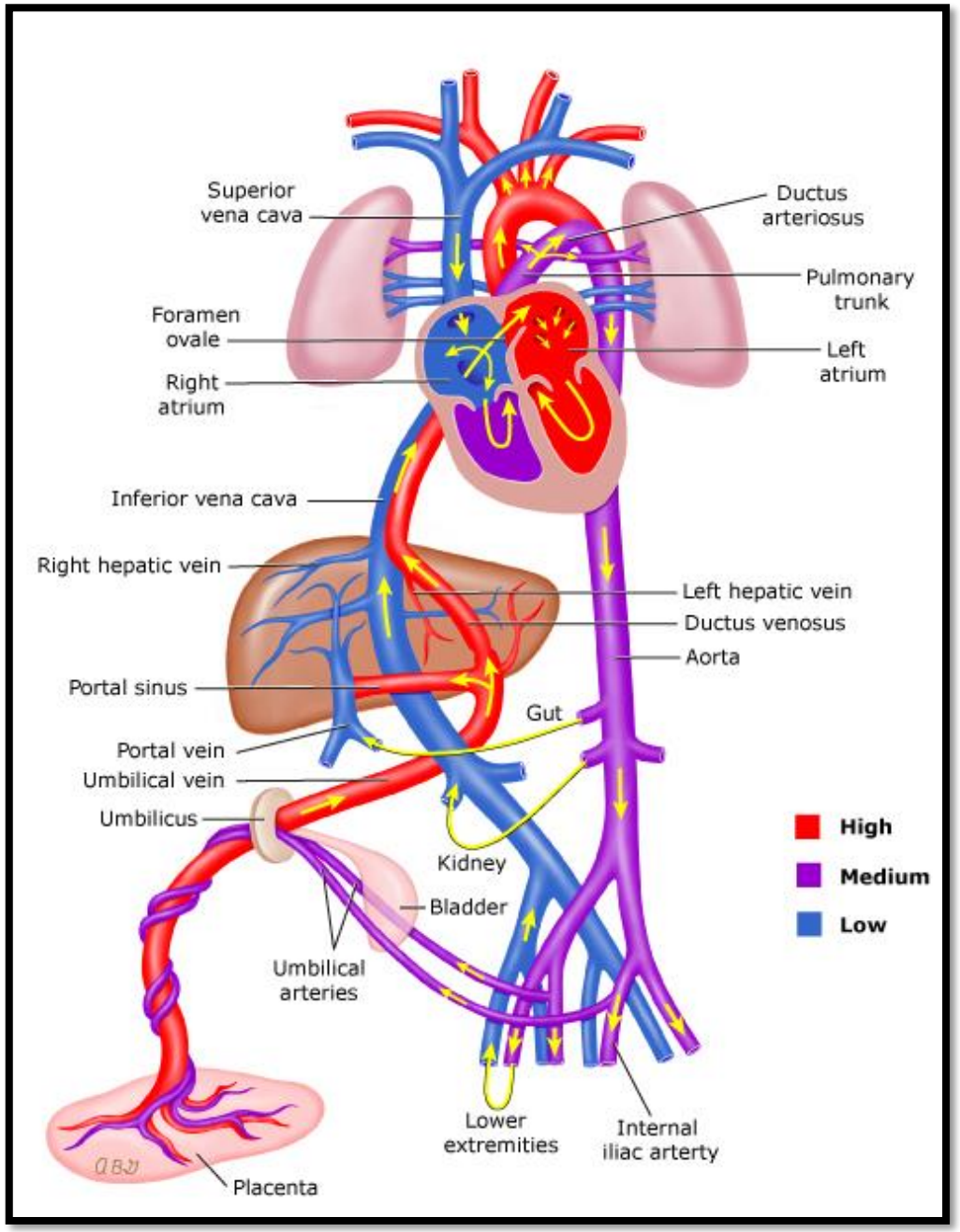
Congenital and Structural Interventional Cardiologist

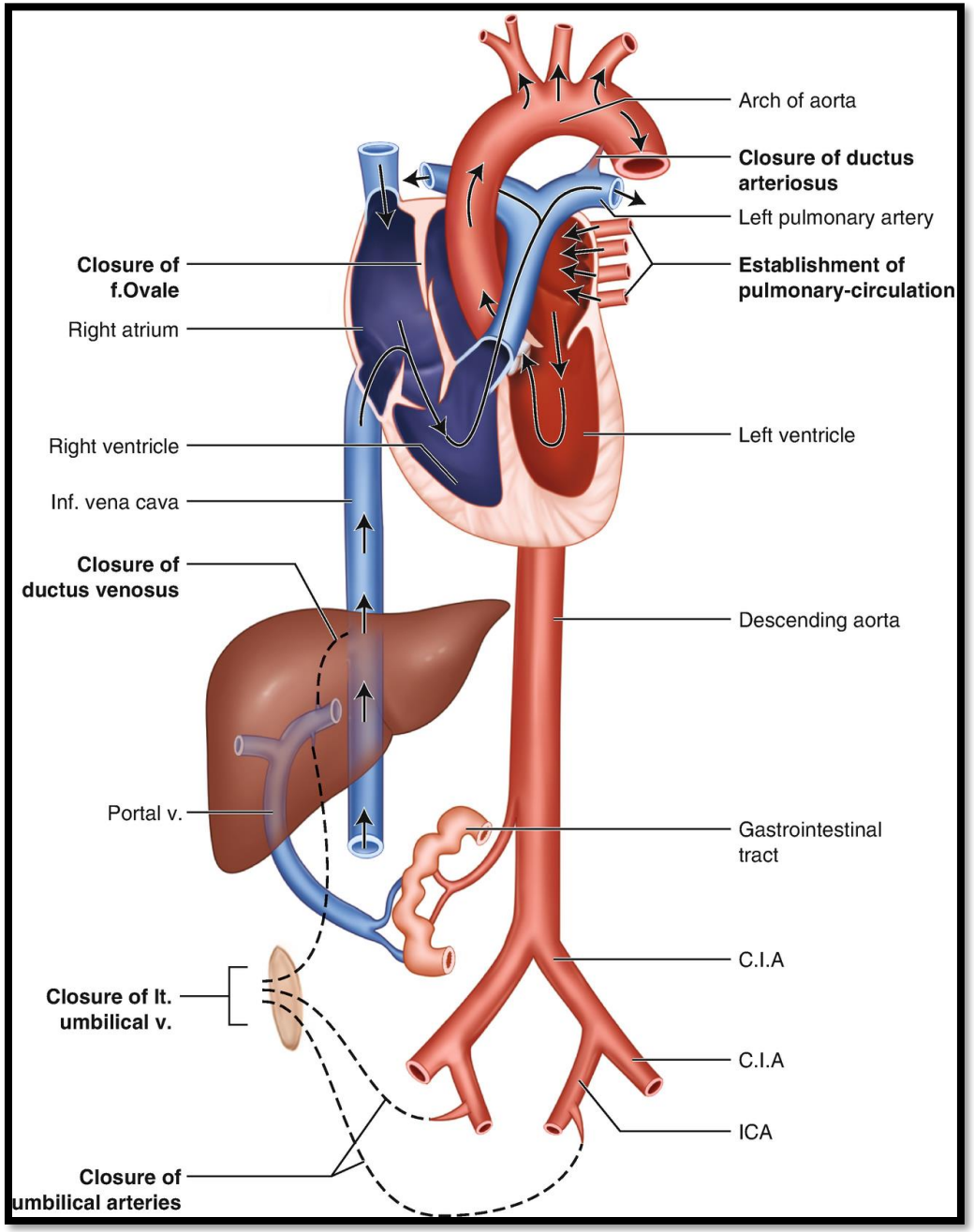
Basra Medical College

Basra Cardiac Center

Definition

- Defined as the failure of the normal circulatory transition that occurs after birth. It is a syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus.


Superior vena cava
Ductus arteriosus
Pulmonary trunk
Foramen ovale
Left atrium
Right atrium
Inferior vena cava
Right hepatic vein
Left hepatic vein
Ductus venosus
Aorta
Portal sinus
Gut
Portal vein
Umbilical vein
Umbilicus
Kidney
Bladder
Umbilical arteries
Lower extremities
Internal iliac arterty
Placenta
High
Medium
Low


Arch of aorta
Closure of ductus arteriosus
Left pulmonary artery
Closure of f.Ovale
Establishment of pulmonary-circulation
Right atrium
Right ventricle
Left ventricle
Inf. vena cava
Closure of ductus venosus
Descending aorta
Portal v.
Gastrointestinal tract
C.I.A
Closure of lt. umbilical v.
C.I.A
ICA
Closure of umbilical arteries

Transitional circulation

- Major circulatory adjustments occur at birth as the organ of gas exchange changes from the placenta to the lung. Under normal circumstances, a progressive fall in (PVR) accompanies the immediate rise in (SVR) that occurs after birth.
- For a short period, a transitional circulatory pattern exists that combines features of both the fetal and adult circulatory patterns. The decline in the PVR/SVR ratio results in a steady increase in pulmonary blood flow and oxygen uptake in the lung.

- The process of transition depends upon several factors. Factors that contribute to the postnatal increase in SVR include removal of the placenta, the catecholamine surge associated with birth, and the relatively cold extrauterine environment. Factors that promote the postnatal decrease in PVR include expansion of the lung to normal resting volume, establishment of adequate alveolar ventilation and oxygen tension, and successful clearance of fetal lung fluid.
- Conditions that interfere with the normal postnatal decline in the PVR/SVR ratio cause the transitional circulation to persist and result in PPHN.

Mechanisms of PPHN

	Underdevelopment	Maldevelopment	Maladaptation
Pathology	Decreased vascular growth	Abnormal vascular structure	Normal vasculature with hypoxia induced vasospasm
Examples	Pulmonary hypoplasia: • CDH • Oligohydramnios • Renal agenesis • Rare causes, e.g. alveolar capillary dysplasia	Idiopathic/ primary PPHN Chronic fetal hypoxia Fetal anaemia Premature closure of ductus arteriosus	Asphyxia Parenchymal diseases: • MAS • RDS • Sepsis/pneumonia

- The incidence of PPHN is approximately 0.2 percent.
- The following risk factors for PPHN:
  - Gestational age 34 to <37 weeks (ie, late preterm infants).
  - Black maternal race.
  - Infants who were either large or small for gestational age.
  - Mothers with pre-existing and gestational diabetes, obesity, and advanced age.
- Factors associated with a lower risk of PPHN included:
  - Female sex.
  - Hispanic ethnicity.
  - Multiple gestation.

CLINICAL MANIFESTATIONS

- Most neonates with PPHN present within the first 24 hours of life with signs of respiratory distress (eg, tachypnea, retractions, and grunting) and cyanosis.
- More than half of the infants had low Apgar scores and almost all of the patients received delivery room interventions including oxygen therapy, bag and mask ventilation, and endotracheal intubation.

Pulse oximetry assessment

- A difference of greater than **10%** between the pre- and postductal oxygen saturation.
- It is important to recognize that the absence of a pre- and postductal gradient in oxygenation does **not** exclude the diagnosis of PPHN, since right-to-left shunting can occur predominantly through the foramen ovale rather than the PDA.

Arterial blood gas

- An arterial blood gas sample typically will show low PaO_2 below 100 mmHg in patients receiving 100% inspired oxygen concentration), particularly samples that are postductal.
- The arterial $PaCO_2$ is normal in infants without accompanying lung disease.
- The right-to-left shunting of blood through the PDA can also be documented in differences in PaO_2 between samples obtained from the right radial artery (preductal sample) and the umbilical artery (postductal sample).

Chest radiograph

- The chest radiograph is usually normal or demonstrates the findings of an associated pulmonary condition (eg, parenchymal disease, air leak, or CDH).
- The heart size typically is normal or slightly enlarged.
- Pulmonary blood flow may appear normal or reduced

Echocardiography

- The definitive diagnosis of PPHN is made by echocardiography.
- Echocardiography is an essential test in any infant with unremitting cyanosis that is unexplained by parenchymal lung disease, to exclude structural heart disease and confirm a diagnosis of PPHN.

Severity of PHT

- Estimation of right ventricle pressure (RVp), using assessments of TR jet and/or changes in septal position, is compared with systemic blood pressure (BP), and the degree of atrial and/or patent ductus arteriosus shunting is determined.
- Estimations of severity are as follows:
  - ***Mild to moderate PPHN*** – Estimated RVp is **50-75%** of systemic BP
  - ***Moderate to severe PPHN*** – Estimated RVp is greater than **75%** of systemic BP but less than systemic BP
  - ***Severe PPHN*** – Estimated RVp greater than systemic BP
- Evidence of RV dysfunction suggests severe PH
- Evidence of biventricular dysfunction may represent global insult (eg, perinatal depression)

Table 5. Classification of PPHN severity[3]

Severity	OI*†
Mild	≤15
Moderate	>15 - 25
Severe	25 - 40
Very severe	>40

OI = oxygenation index; MAP = mean airway pressure in cmH_2O; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen in mmHg; OSI = oxygenation saturation index.

*$OI = MAP \times FiO_2 \times 100/PaO_2$.
†$OI = OSI \times 2$; $OSI = MAP \times FiO_2 \times 100$/pre-ductal saturation (no intravenous access required).

MANAGEMENT

General supportive care

- Supplemental oxygen
- Mechanical ventilation
- Fluid therapy and inotropic agents for circulatory support
- Correction of acidosis

Oxygen

- Oxygen is a pulmonary vasodilator and it should be **initially** administered in a concentration of 100% to infants with PPHN in an attempt to reverse pulmonary vasoconstriction. However, because the administration of high oxygen concentrations, even for a short time period, may cause lung injury and there is no advantage to maintaining an elevated PaO_2, oxygen concentration should be adjusted to maintain preductal oxygen saturation target of 90 to 95 percent. Although uncommon in PPHN, persistent hyperoxemia should be avoided.

- If the oxygen saturation cannot be maintained above 90 percent, other interventions to preserve adequate tissue oxygenation include maintenance of a Hemoglobin concentration between 15 and 16 g/dL and optimizing circulatory function.
- If these measures do not result in adequate oxygenation (assessed by calculating the oxygenation index), more directed/invasive measures (eg, iNO or ECMO) are required.

Assisted ventilation

- Because hypercarbia and acidosis increase PVR, initially attempt to establish and maintain normal ventilation ($PaCO_2$ 40 to 45 mmHg).
- As the infant's oxygenation and ventilatory status become more stable, maintain $PaCO_2$ in the range of 40 to 50 mmHg to minimize lung injury associated with high tidal volumes.
- In infants with **no** associated lung disease, hypoxemia is caused by right-to-left shunting rather than ventilation-perfusion imbalance. As a result, hypoxemia may not respond to conventional ventilator maneuvers. In this circumstance, strategies that elevate MAP may actually impede cardiac output and increase PVR. Thus, minimize MAP by using low inspiratory pressures and short inspiratory times or volume targeted ventilation. However, it is essential to maintain adequate lung recruitment with modest levels of positive end-expiratory pressure (PEEP).

- The aim of mechanical ventilation should be to maintain a $PaCO_2$ of 40-60 mmHg and PaO_2 of 60–90 mmHg by using gentle ventilation to optimise lung volume.
- High-frequency oscillatory ventilation (HFOV) can minimise lung injury, but has not been proven to have a clear benefit over conventional ventilation, except when used in combination with inhaled NO (iNO) in the treatment of MAS.

Sedation

- Pain and agitation cause catecholamine release, resulting in increased PVR and increased right-to-left shunting.
- In addition, agitation may result in ventilator asynchrony which can worsen hypoxemia.
- Therapeutic choices include intravenous **morphine sulfate** (loading dose of 100 to 150 mcg/kg over one hour followed by a continuous infusion of 10 to 20 mcg/kg per hour) or **fentanyl** (1 to 5 mcg/kg per hour).

Circulatory support

- In patients with PPHN, right-to-left shunting increases as cardiac output and systemic blood pressure (BP) decrease. Thus, maintaining optimal cardiac output and systemic BP is important to reduce the right-to-left shunting and to maintain adequate tissue oxygenation.
- Systemic BP targets are set at the upper limits of normal (mean BP 45 to 55 mmHg; systolic BP 50 to 70 mmHg) because the pulmonary arterial pressure in patients with PPHN is at or near normal systemic levels. This is accomplished by:
- Adequate vascular volume should be maintained with IV fluids.
- Transfusion of packed red blood cells usually is required to replace blood lost from sampling and to optimize tissue oxygen delivery, especially in patients with marginal oxygenation. In general, maintain hemoglobin concentration above 15 g (

- Vasopressor support usually is needed in patients with PPHN. Dopamine has been the most commonly used medication in neonates requiring pharmacologic inotropic support.
- IV infusion of dopamine at a starting dose of 2.5 mcg/kg per minute and titrate the infusion rate to maintain the mean arterial BP at a targeted level that minimizes right-to-left shunting. Little evidence exists comparing the effects of dopamine with other alternative inotropic agents in PPHN.
- IV milrinone in conjunction with iNO may facilitate reduction in PVR while enhancing myocardial performance and forward flow of blood.

Correction of acidosis

- Acidosis increases PVR and attempts should be made to maintain PCO_2 values between 40-50 mmHg and improve metabolic acidosis by cautious correction of a severe base deficit, if present.
- Sodium acetate may be added to infused IV fluids at a dose of 2 to 3 mEq/kg per day. Rapid infusion of sodium bicarbonate in face of impaired ventilation may worsen intracellular acidosis and is not recommended.

Inhaled NO

- iNO is a potent and selective pulmonary vasodilator that leads to improved oxygenation and reduced need for ECMO
- The use of iNO was FDA approved in 1999 for term and near-term infants with PPHN
- the most effective starting dose of iNO is 20 ppm, and response should be seen within 30 - 60 minutes.
- The use of iNO has significantly reduced the mortality of PPHN; however, ~40% of patients will not respond to iNO.
- Methaemoglobinaemia and increased nitrogen dioxide are known side-effects that occur more frequently at dosages greater than 20 ppm.

Table 6. Recommendations for use of iNO[3,4,6]

Starting dose	20 ppm
Consider weaning when	FiO_2 <60% PaO_2 >60 mmHg (>8 kPa) Preductal saturation >90% Above maintained for >60 minutes
Weaning procedure	Wean by 5 ppm every 2 - 4 hours till 5 ppm is reached Then wean by 1 ppm every 2 - 4 hours
Contra-indications	Hypoplastic left heart Interrupted aortic arch

ppm = parts per million.

Surfactant

- Surfactant therapy does **not** appear to be effective when PPHN is the primary diagnosis. However, it should be considered in patients with associated parenchymal lung disease, in whom there is either a suspected surfactant deficiency (eg, neonatal RDS) or impairment (meconium aspiration syndrome [MAS])

Interventions for severe cases

- In severe cases, general supportive care is often insufficient to maintain adequate oxygenation.
- Infants with OI greater than 25 despite the use of HFOV are candidates for iNO therapy or other vasodilatory agents that decrease PVR. Patients who fail to respond to these agents may require ECMO.

Sildenafil

- Sildenafil, a PDE5, is an agent that has been shown to selectively reduce PVR in both animal models and adult humans. It has also been reported to be successful in the treatment of infants with PPHN.
- In a systematic review, meta-analysis of three studies that included 77 patients showed **enteral** sildenafil therapy compared with placebo was associated with a reduction in mortality and improved oxygen levels.
- Enteral sildenafil, dose range 1-3 mg/kg every 6 hours

Other agents

- The following agents have been used in the management of PPHN, but are not recommended.
- Inhaled or IV prostacyclin is a potential intervention in patients who fail NO therapy, but is no longer commonly used.
- Bosentan, an ET-1 receptor antagonist, are conflicting regarding efficacy.
- A single trial of 47 neonates with PPHN in a setting where iNO and ECMO are unavailable showed bosentan (1 mg/kg given through orogastric tube twice a day) was more effective than placebo in improving OI and oxygen saturation, and in decreasing the time of mechanical ventilation.

FOLLOW-UP

- All infants with severe PPHN who have been treated with iNO and/or ECMO should have neurodevelopmental follow-up.
- Assessment should be performed through infancy at 6-12 month intervals, and longer if abnormalities are present.
- Hearing should be tested prior to hospital discharge and at 18-24 months corrected age.