Acute Pulmonary Hypertension: Pathophysiology, Clinical Presentation and Management

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Disclosure

• I have no actual or potential conflict of interest to declare
Objectives

1) Know the impact of acute pulmonary hypertension on neurodevelopmental outcomes
2) Describe the 3 major physiological changes that occur during normal neonatal transition
3) Describe the etiological classification of PPHN
4) Understand the pathobiology of PPHN and potential therapeutic targets (inhaled nitric oxide, sildenafil, milrinone, bosentan, epoprostenol)
5) Know that PPHN (↑PVR) is the pathophysiology of a subset (but not all) acute pulmonary hypertension and know the other contributors to increased pulmonary artery pressure
Why is Persistent Pulmonary Hypertension of the Newborn Important?

• Consider the following case:
  - Newborn term infant with severe hypoxic respiratory failure
  - FiO₂ 1.0; mean airway pressure ≥ 10cmH₂O; PaO₂ 40 – 100mmHg (from UAC)
  - No congenital anomalies (e.g. diaphragmatic hernia)

What is the risk of any* neurodevelopmental impairment (NDI) among survivors at 1 year?

A) 5%
B) 10%
C) 25%
D) 50%

* NDI defined as at least 1 mild impairments = MDI < 85 / PDI < 85 / abnormal tone/reflexes [or worse]

Lipkin et al. Neurodevelopmental and medical outcomes of PPHN. J Ped 2002
Rosenberg et al. Longitudinal follow-up of a cohort of newborn infants treated with iNO for PPHN. J Ped 1997
Quiz: High pulmonary artery pressure and reduced pulmonary blood flow is a .....

A) Normal physiological state for the human fetus
B) Normal physiological state for the term infant at 15 min after birth
C) Normal physiological state for the preterm infant at 60 min after birth
Fetal Circulation

- High Pulmonary Vascular Resistance (non-aerated lungs)

- Low Systemic Vascular Resistance (placenta in parallel with systemic circulation)
Quiz: What % of blood flow goes to the lungs in the healthy fetus / newborn?

• A) Fetus 10% / Newborn 100%
• B) Fetus 25% / Newborn 75%
• C) Fetus 40% / Newborn 100%
• D) Fetus 15% / Newborn 125%
Fetal Circulation

Pulmonary Artery

PDA

Pulmonary Veins

RA

LA

RV

LV

PVR HIGH

SVR LOW

10%

60%

30%

10%

‘Pre-ductal’

‘Post ductal’

Lungs

High PVR:
- Fluid filled lungs
- Lack of rhythmic lung distension
- Cuboidal configuration of endothelium
- Low PAO2 and PaO2
- High concn of LT, TXA2, Endthelin-1
What are the three normal transitional physiological events at birth?

• A) Ventilation in air, ↑ ventricular function, ↓ total cardiac output

• B) Ventilation in air, ↑ systemic vascular resistance, ↑ total cardiac output

• C) Ventilation in 100% oxygen, ↑ systemic vascular resistance, ↓ cardiac output
Transitional Circulation

Neonatal Circulation

- Low Pulmonary Vascular Resistance
- Higher Systemic Vascular Resistance
PVR Low

SVR Normal

‘Post ductal’

‘Pre-ductal’

Pulmonary Artery

100%

Aorta

100%

LUNGS

PDA

RA

LA

RV

LV
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PPHN/aPH

Serious cardiopulmonary disorder characterized by elevated mean pulmonary artery pressure (mPAP) and prolonged exposure of the right ventricle to high afterload

Jain A. PPHN SFNM 2015
Etiological Classification of PPHN ("Where Transition Goes Wrong")

- Pulmonary **Underdevelopment**
  (Lung parenchyma AND vasculature develop abnormally)

- Pulmonary **Maldevelopment**
  (Lung with normal parenchyma but abnormal vasculature)

- **Maladpatation**
  (Lung parenchymal disease but developmentally normal vasculature)
Example 1: Preterm Infant With Unusual Lungs

- Newborn at 28+1 weeks via spontaneous vaginal delivery
- Mother had PPROM at 20 weeks with subsequent anhydramnios
- Severe hypoxic respiratory failure at birth:
  - PCAC Rate 40 PIP25 PEEP 8 (VT 5mls/kg)FiO\textsubscript{2} 1.0
  - SpO2 90% and no improvement with surfactant
  - UAC ABG 7.32 / 49 / 34 / 19 / -7

A) Pulmonary Underdevelopment?  
B) Pulmonary Maldevelopment?  
C) Maladaptation?
Pulmonary Underdevelopment

- Hypoplastic pulmonary vasculature occurring WITH parenchymal underdevelopment
- Decreased number of pulmonary arteries per unit lung volume and peripheral muscularization of small pulmonary arteries
- Examples:
  - Congenital diaphragmatic hernia
  - Pulmonary hypoplasia secondary to early onset and prolonged oligohydramnios (e.g. Potter’s sequence, renal disease, chronic PPROM)
Example 2: Term baby with a ‘difficult start’

- 39+2 week newborn male, uncomplicated pregnancy and spontaneous labour
- Cord prolapse and fetal bradycardia; emergency C-section (meconium in amniotic fluid)
- Intubated due to apnea, HR 60, no chest compressions
- Apgars 1, 1, 5, 7 (at 1, 5, 10, 15 min)
- Cord Gases: UA 6.98 / 84 / 15 / 9 / -16
- Severe hypoxic respiratory failure

A) Pulmonary Underdevelopment?  
B) Pulmonary Maldevelopment?  
C) Maladaptation?
Maladaptation

• Inadequate neonatal ventilation and failure of decrease in pulmonary vascular resistance in the setting of otherwise normal pulmonary parenchymal and vascular development

• Examples:
  - Parenchymal lung disease that interferes with transition:
    - Meconium aspiration syndrome
    - Sepsis/pneumonia
    - Respiratory distress syndrome
    - ‘Malignant’ transient tachypnea of the newborn
  - Perinatal hypoxic ischemic encephalopathy
Example 3: Unexpected Illness

- 39+2 week newborn male, uncomplicated pregnancy and spontaneous vaginal delivery
- Respiratory distress at birth and low SpO2
- Started on mask CPAP in 100% oxygen and intubated at 30 min when not improved
- AC PEEP 6cmH_2O, Vt 5cc/kg, measured PIP 12, Rate 40, T_i 0.35 in 100% oxygen
- Pre/post SpO2 90% / 75%
- UAC gas at 1 hour: 7.32 / 38 / 40 / 22 / -4

A) Pulmonary **Underdevelopment?**
B) Pulmonary **Maldevelopment?**
C) Maladpatation?
Pulmonary Maldevelopment

• Lung with normal parenchyma but REMODELED pulmonary vasculature

• Smooth muscle hyperplasia and extension of smooth muscle in intra-acinar arteries

• Examples:
  • “Idiopathic PPHN” (Black Lung PPHN)
  • High PBF states in utero
    • Arterio-venous malformations
    • Twin-to-twin transfusion recipient
    • In-utero premature closure of ductus arteriosus
## Categories/Etiologies of PPHN

<table>
<thead>
<tr>
<th>Category</th>
<th>Lung parenchyma development?</th>
<th>Lung vasculature development?</th>
<th>Transition?</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underdevelopment</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Impaired</td>
<td>Pulmonary hypoplasia due to early PPROM and oligohydramnios</td>
</tr>
<tr>
<td>Maldevelopment</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Impaired</td>
<td>Fetal closure of ductus arteriosus or Idiopathic PPHN</td>
</tr>
<tr>
<td>Maladaptation</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>HIE, MAS</td>
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</table>
aPH Timeline: When does it happen

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress at birth</td>
<td>Birth - 12 hrs</td>
</tr>
<tr>
<td>Pneumothorax / Malignant TTN</td>
<td>24 hrs - 48 hrs</td>
</tr>
<tr>
<td>Late onset sepsis / pneumonia</td>
<td>72 hrs - 1 week</td>
</tr>
<tr>
<td></td>
<td>2 weeks - 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Lung disease without PPHN</td>
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<tr>
<td>---------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>History</td>
<td>Fetal distress, PROM, chorioamnionitis</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Present</td>
</tr>
<tr>
<td>Oxygen saturation on pulse ox</td>
<td>Improves with supplemental oxygen</td>
</tr>
<tr>
<td>Hyperoxia test</td>
<td>PaO2 often &gt; 150 mm Hg</td>
</tr>
<tr>
<td>PaCo2</td>
<td>Elevated</td>
</tr>
<tr>
<td>Hyperoxia-Hyperventilation</td>
<td>PaO2 &gt; 150 mm Hg</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Abnormal</td>
</tr>
<tr>
<td>ECHO</td>
<td>Normal</td>
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</table>
Hyperoxia Test

PaO₂ after administration of 100% oxygen

- >300 mmHg: Normal
- >150 but <300 mmHg: Pulmonary disorders, CNS disorders, Methemoglobinemia
- >100 but <150 mmHg: PPHN, Cardiac mixing lesions with increased PBF
- <100 mmHg: Cardiac condition with parallel circulation, Cardiac mixing lesions with restricted PBF
PPHN

- Labile hypoxemia
- Differential cyanosis: Pre-post ductal sat difference > 10%
Why is the lower limb $\text{SpO}_2$ far lower than the right upper limb $\text{SpO}_2$?

• A) Deoxygenated blood crosses the atrial septum (RA to LA) decreasing the $\text{SaO}_2$ in blood pumped to the body

• B) Deoxygenated blood crosses the ductus arteriosus (pulmonary artery to aorta)

• C) Oxygenated blood crosses the ductus arteriosus (aorta to pulmonary artery) resulting in lower $\text{SpO}_2$ in lower limb
PVR HIGH

LV

RA

LA

RV

SVR LOW

PDA

LUNGS

‘Pre-ductal’

‘Post ductal’
PDA is a Window to the Circulation

The direction of flow across the PDA indicates the relative difference in pressure in the pulmonary artery and aorta.

Large SpO2 pre/post difference indicates PA pressure >> Aorta pressure.
Postductal

Pre-ductal

PVR HIGH

SVR LOW

RA → LA

RV → LV

PDA

LUNGS

‘Post ductal’

‘Pre-ductal’
PPHN Physiology

Classic acute pulmonary hypertension after birth is characterized by
“persistent fetal circulation”:

* Atrial shunt: R to L (right atrium to left atrium)
* DA shunt: R to L (pulmonary artery to aorta)
* Don’t forget about possible co-existing intrapulmonary shunting and ventilation perfusion mismatch
Absence of pre-post ductal sat difference doesn’t rule out PPHN
Supportive Management

• Maintaining normal body temperature
• Normal glucose level
• Optimal sedation/ analgesia, minimal handling protocol
• Adequate lung recruitment: Preferential use of HFOV
• Maintain oxygen in the normal target zone
• Avoid acidosis, hypo/hypercarbia
Lung Recruitment

Optimal lung recruitment (8- to 9-rib expansion on an inspiratory chest radiograph) decreases PVR.
Both underinflation and overinflation of the lung will lead to elevation of PVR.
Atelectasis: Inc intrapulmonary Rt->Lt shunting leading to worsening hypoxia and hypercarbia.
Overinflation can impede venous return and cause systemic hypotension.
HFOV+iNO: Best response in neonates with PPHN sec to MAS and RDS.
IF HFOV not available be sure to OPTIMIZE MAP and utilizing your PEEP.
Oxygen Therapy

Pre-Ductal Sats target: 90-97%

Pre-Ductal PaO2 target: 50-80 mm Hg

Pрудuctal SPO2 >95% : No evidence to support its use

Lakshminrusimha S et al. Ped Research 2009
Acidosis vs Alkalosis

- Acidosis: Exaggerates vasoconstrictor response to hypoxia in PPHN
- Alkalosis: Reduces PVR, decreases CBF
  - Inc use of ECMO and O2 at 28 days of age
  - Poor neurodevelopmental outcomes and hearing loss in survivors

Target: pH > 7.30 preferentially between 7.35-7.45
iNO Non Responders

25-30% cases are iNO non responders
- CDH, chronic oligo/anhydramnios, sepsis: Possible poor response to iNO
- Strategies for management: Vasopressin, milrinone, Epinephrine, PGE1
- Close surveillance warranted-> ECMO
PPHN -> Shock
Not All Acute Pulmonary Hypertension At Birth is PPHN

\[
P\text{Ap} = (P\text{BF} \times P\text{VR}) + P\text{CW}\]

<table>
<thead>
<tr>
<th>Pulmonary artery pressure</th>
<th>↑ Pulmonary blood flow</th>
<th>↑ Pulmonary vascular resistance</th>
<th>↑ Pulmonary capillary wedge pressure (“back pressure in pulmonary veins”)</th>
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**RARE**
- Large arteriovenous malformations (e.g. vein of Galen)
- Unobstructed TAPVD

**VERY COMMON**
- “Classic PPHN”
- Lung disease (e.g. meconium aspiration)
- Idiopathic

**INFREQUENT**
- Obstructed TAPVD
- Left heart obstruction (HLHS, mitral stenosis)
- LV dysfunction
Pulmonary Hypertension in Neonates

↑ PBF
- In-utero shunt (AVM, TTTS)
- Pulmonary overcirculation (eg. PDA, TAPVR)

↑ PVR
Acute
- Reversible
  - Pulmonary
    - RDS
    - Pneumonia
    - MAS
    - Structural lesion (CDH, CPAM)
    - SIRS
  - Extrapulmonary
    - HIE
    - Medications (eg. SSRI, NSAID)
    - Severe acidemia (IEM)
- Irreversible
  - Pulmonary
    - Hypoplasia
    - Agenesis
    - Oligohydramnios
    - CDH / CPAM
    - Lymphangiectasis
    - ACD
  - Extrapulmonary
    - Genetic (eg. Trisomy 21)
    - Adrenal insufficiency
    - SIRS

↑ PCWP
Chronic
- Left heart obstruction
- LV diastolic dysfunction (eg. HCM, ischemia)

Weisz and McNamara. Assisted Ventilation of the Neonate 2016
Take Home Points II

Rule out CCHD
Follow ABC in management
Supportive management strategies are key to successful outcome
Establishing optimal FRC -> First step in management
Once available via ACTS for example, Use iNO once presumptive diagnosis is established after optimal recruitment on MV
Take Home Points I

1) Neurodevelopmental impairment occurs in 25% of term and late preterm newborns with PPHN

2) Transitional Physiology
   • Ventilation in air: ↓PVR  ↑ Pulmonary blood flow
   • Cord clamping: ↑ Systemic vascular resistance (shunt reversal in PDA/PFO)
   • Increase in cardiac output

3) Etiological Classification of PPHN

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Take Home Points III

• 4) Persistent fetal circulation (PPHN) is the most common circulatory physiology associated with severe hypoxic respiratory failure in the newborn

• 5) Caution: Not all acute pulmonary hypertension in newborns is PPHN. Beware alternative pathology when the atrial and ducal shunts are NOT ‘right to left’

\[ PAp = (PBF \times PVR) + PCWP \]