Pulmonary Hypertension Rx
Neonate to Infant

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Definition

• PPHN is defined as the failure of the normal circulatory transition that occurs after birth.
• Regardless of the PA pressure, as long as it is accompanied by right-to-left shunting and the absence of congenital heart disease.

Pathophysiology

• Elevated pulmonary vascular resistance (PVR) leads to right-to-left shunting across PFO / PDA.
• Inadequate pulmonary perfusion leads to severe, refractory hypoxemia, respiratory distress, and acidosis.

Fetal PHT

• PHT is a necessary state for the fetus
• Mechanisms that keep PVR high include:
  – low fetal oxygen content
  – lack of a gas-liquid interface
  – presence of vasoconstrictor mediators:
    • endothelin-1
    • Leukotrienes
    • Rho kinase
  – low production of vasodilators:
    • Prostacyclin
    • Nitric oxide (NO)

Normal Cardiopulmonary transition

• Pulmonary blood flow increases 8 to 10 x at birth
• PA pressure halves within 24 hours.

• This is due to:
  – increase in PaO2
  – decrease in PaCO2
  – establishment of an air-liquid interface
  – rhythmic distention of the lungs
  – In late gestation the fetus increases pulmonary expression of NO synthases and soluble guanylate cyclase - important for later pulmonary vasodilation.
Failure of transition

- Normal decrease in pulmonary vascular tone does not occur, resulting in PPHN.
- This results in shunting of blood away from the lungs and severe central hypoxemia.
- Severe PPHN can be associated with poor cardiac output and shock, oliguria, hypotension, and lactic acidosis.

Increased Risk

- Down Sd
- Black and Asian maternal race
- Male gender
- Genetic factors: link between PPHN and polymorphisms of the carbamoyl phosphate synthase gene
- Exposure to SSRIs during the third trimester of pregnancy

Common Etiologies

PPHN usually due to 1 of 3 following:

1. Acute pulmonary vasoconstriction
2. Hypoplasia of the pulmonary vascular bed
3. Idiopathic pulmonary hypertension

Acute Pulmonary Vasoconstriction

- Due to acute perinatal events:
  - Alveolar hypoxia 2nd to parenchym lung disease:
    - Meconium aspiration
    - Respiratory distress syndrome
    - Pneumonia

Also:

- Hypoventilation from asphyxia or neurological conditions
- Hypothermia
- Hypoglycemia

Hypoplasia of the pulmonary vascular bed

- Congenital diaphragmatic hernia: the abdominal viscera enter the chest cavity and compress the lung, impairing growth.
  - Oligohydramnios
Idiopathic pulmonary hypertension

- 2nd most common cause
- Constriction / premature closure of the DA in utero, after exposure to NSAIDs during the 3rd trimester.
- Histology: remodeling of the pulmonary vasculature, with vascular wall thickening and smooth muscle hyperplasia.
- As a result, infants do not vasodilate their pulmonary vessels adequately in response to birth-related stimuli.

Diagnosis

Examination

- Cyanosis with tachypneoa and respiratory distress.
- Hypoxemia is out of proportion to severity of lung disease
- Loud, single S2
- Pansystolic murmur of tricuspid regurg.
- Systemic hypotension
- Shock, poor cardiac function and perfusion

Differential Diagnosis

- Congenital heart disease:
  - TGA, TAPVC, Pulmonary atresia/ IVS
- Primary parenchymal lung disease:
  - BPD, Neonatal pneumonia, RDS, Pulmonary sequestration, Pulmonary hypoplasia
- Sepsis
- Alveolar capillary dysplasia
- Surfactant protein B deficiency

Blood Tests

- FBC:
  - Hematocrit level: polycythemia with hyperviscosity may lead to or exacerbate PPHN
  - Assess for underlying sepsis or pneumonia
- Coagulation studies: platelet count, PTT, INR:
  - Assess for coagulopathy (increased disease severity)
- Serum electrolytes
- Glucose: hypoglycemia worsens PPHN
- Calcium: hypocalcemia worsens PPHN
critical cofactor for NO synthase

Imaging: CXR

- Assess parenchymal lung disease: MAS, pneumonia, surfactant deficiency
- Exclude underlying disorders: congenital diaphragmatic hernia
- In PPHN:
  - lung fields appear clear
  - decreased vascularity
  - heart size is normal
Imaging : Echocardiography

- Most reliable, convenient, and noninvasive test
- Assess presence / direction of the intracardiac shunt at the PDA and PFO
- Estimate the pulmonary arterial pressures
- Rule out associated anomalous pulmonary venous return before initiating ECMO

Imaging : Cardiac catheterization

- In rare cases where sonar findings are not definitive
- Exclude congenital heart disease: obstructed anomalous pulmonary venous return / pulmonary vein stenosis.
- A vasodilator trial using hyperoxia or inhaled nitric oxide (iNO), is used to identify those infants likely to have a favorable long-term response to pulmonary vasodilators.

Imaging : Other

- Skull sonar:
  - assess for IVH or infarct before initiating ECMO
- CT or MRI:
  - Evaluate for central nervous system injury
  - Lung disease
  - Complex cardiac anatomy (non-invasive)

Treatment

- PPHN

Treatment Aims

- Maintaining adequate systemic BP
- Decreasing PVR
- Ensuring oxygen release to tissues
- Minimizing lesions induced by high levels of inspired oxygen
- Minimizing barotrauma from ventilation

General management principles

- Continuous monitoring of oxygenation, BP and perfusion
- Maintaining a normal body temperature
- Correction of electrolytes, glucose and metabolic acidosis
- Nutritional support
- Minimal stimulation / handling of the newborn
- Minimal use of invasive procedures / suctioning
**Pulse Oximetry**
- Continuously assess the patient’s oxygen saturation - guide to the adequacy of oxygen delivery at tissue level.
- Oximeter probes can be placed on pre-ductal (right hand) and post-ductal (feet) sites to assess for right-to-left shunting across the PDA.
- A difference > 10% between ductus arteriosus preductal and postductal oxygen saturations correlates to right-to-left ductal shunting.

**Arterial blood gas**
- Place umbilical or peripheral arterial line.
  - Frequent sampling needed
  - Avoid painful stimulation
- Choice of sampling site will affect the ABG results:
  - right-to-left shunting over the PDA will lead to lower post-ductal sats
- Assess: pH, PaCO2, PaO2

**Arterial blood gas**
- Calculate alveolar-arterial (A-a) difference in the PaO2 to assess oxygenation.
- Oxygenation index (OI): \[\frac{\text{mean airway pressure} \times \text{FiO2}}{\text{postductal PaO2}}\]
- An OI > 25 indicates need for iNO
- An OI > 40 indicates need for ECMO

**Ventilatory Support**
- Achieve / maintain optimal lung distention (app 9 ribs on CXR)
- Recruit areas of atelectasis
- Avoid overexpansion:
  - elevates PVR: worsens right-to-left shunting
  - increases risk for pneumothorax.
- Step up to HFV if:
  - require PIP >30 cm H2O
  - mean airway pressures >15 cm H2O

**Target PaO2**
- Little is known about what oxygen concentrations maximize benefits and minimize risks.
- PaO2 levels of > 50 mm Hg provide adequate oxygen delivery.
- Aiming for higher PaO2 leads to:
  - increased ventilator support and barotrauma
  - formation of reactive oxygen radicals which are toxic to the developing lung
Sedation

- Minimize agitation which increases PVR
- Dormicum ± Fentanyl infusion

- Induced paralysis (Controversial)
  - Reserved for newborns who cannot be treated only with sedatives
  - especially with pancuronium, may promote atelectasis of dependent lung regions and promote ventilation-perfusion mismatch
  - increased risk of death

Surfactant

- Not effective when PPHN is the primary diagnosis.
- Should be considered in patients with parenchymal lung disease - often associated with surfactant deficiency, inactivation, or both.
- Improves oxygenation, reduces air leak, and reduces the need for ECMO in infants with meconium aspiration and sepsis

ECMO

- Used when optimal ventilatory support fails to maintain oxygenation and perfusion
- Can now be provided using a double-lumen catheter in the internal jugular vein; thus ligation of the right common carotid artery avoided.
- Although inhaled NO (iNO) is an effective pulmonary vasodilator, ECMO remains the only therapy that has been proven to be life-saving for PPHN.
- Timely transfer to an ECMO center is vital for newborns with severe PPHN.

ECMO

- Evaluate risk factors: invasive, heparinize

- Criteria for consideration for ECMO
  - OI consistently > 40 or higher
  - Gestation > 34 weeks
  - Weight > 2000 g
  - No IVH > grade II
  - Reversible lung disease
  - No evidence of lethal congenital anomalies or inoperable cardiac disease

Circulatory Support

- Aim to maintain adequate perfusion and maximize tissue oxygenation.
- Place a CV catheter in the umbilical or other vein for inotropic drugs / hypertonic solutions
- Avoid CV placement into the neck vessels – save for ECMO, if available.
- Correct acidosis and alkalosis
Circulatory Support

- Avoid rapid boluses of fluid, unless there is evidence of intravascular depletion
- Results in further increase in RA pressure and worsens right-to-left shunting across the PFO.
- Inotropic support with Dopamine, Dobutamine and/or Milrinone maintains adequate cardiac output and systemic BP while avoiding excessive volume administration.
  - Dopamine is used as first-line agent
  - Dobutamine and Milrinone are used when myocardial contractility is poor.

Acidosis vs. Alkalosis

- Acidosis acts as a pulmonary vasoconstrictor and should be avoided.
- Currently, there is no evidence suggesting that using sodium bicarbonate infusions to induce alkalosis provides any benefit:
  - Pulmonary vascular response to alkalosis is transient
  - Prolonged alkalosis may paradoxically worsen pulmonary vascular tone, reactivity and pulmonary oedema
  - Alkalosis causes cerebral constriction and reduces cerebral blood flow and oxygen delivery to the brain - thus associated with worse neurodevelopmental outcomes.

Pharmacotherapy

- Pulmonary vasodilation with:
  - Inhaled nitric oxide
  - Sildenafil
  - Milrinone

iNO

- NO is a rapid and potent vasodilator
- Selective for the pulmonary circulation.
- Indicated for an OI > 25.
- Can be delivered through a ventilator because of its low molecular weight.
- Once in the bloodstream, it binds to Hb, thus limiting its systemic vascular activity.
- Combine with HFV to optimize lung recruitment and expansion.

iNO

- **Dose**: Start at 20 ppm
  (higher concentrations are not more effective and are associated with a higher incidence of metHbemia and formation of nitrogen dioxide).
- In infants who respond, an improvement in oxygenation is evident within few minutes.
- Continuous monitoring of nitrogen dioxide and daily serum levels of methemoglobin should be obtained
  (methemoglobin levels should be kept at < 5%).

iNO Problems

- In 2 large randomized trials, iNO reduced the need for ECMO support by 40% but did not reduce mortality, length of hospitalization, or the risk of neurodevelopmental impairment.
- Contraindicated in CHD with LVOT: AS, coarctation, HLHS and in severe left ventricular dysfunction.
- iNO should be gradually weaned to prevent rebound vasoconstriction.
- Up to 40% will not respond to iNO.
Sildenafil

• Vasodilation via PDE5 inhibition
• Selectively reduces PVR.
• **Dose:** start at 0.3 mg/kg/dose 6 hry po increase gradually to 3 mg/kg/dose
• Monitor BP
• Additional studies are needed to assess the safety and efficacy of sildenafil compared with treatment with the more costly iNO.

Milrinone

• Vasodilation via PDE3 inhibition
• Improves cardiac output without increasing heart rate
• **Dose:** 50 mcg/kg loading IV over 10-60 min then 0.25-0.75 mcg/kg/min IV
• Monitor electrolytes, renal function, blood pressure - may drop BP if given too quickly

Referrals in Recovery

• Paeds Neurologist:
  – 25% incidence of significant neurodevelopmental impairment
  – Evaluation for CNS injury with Brain CT or MRI
• Audiologist:
  – Test Hearing - prevalence of hearing loss is high.
• Speech therapist:
  – Newborns recovering from PPHN often feed poorly and need nasogastric feeding
  – Oral feeding has to be re-established

Treatment

Beyond the Neonatal Period
Prostanoids

= Prostacyclin analogs
  • Induce vasodilatation
  • Inhibit platelet aggregation
  • Limitation of a short half-life
  • Varying response to
    • E.g. epoprostenol, treprostinil, iloprost.

<table>
<thead>
<tr>
<th>Prostanoids</th>
<th>1/2 Life</th>
<th>Route</th>
<th>Dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>3-5 min</td>
<td>IV</td>
<td>2-4 ng/kg/min</td>
<td>Diarrhoea, flushing, headache, arthralgia, local site infection</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>60-80 min</td>
<td>IV/SC infusion</td>
<td>1-2 ng/kg/min</td>
<td>Flushing, headache, local pain over pump</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Aerosol</td>
<td>6-9 puffs/day</td>
<td>Flushing, cough</td>
<td></td>
</tr>
<tr>
<td>Beraprost</td>
<td>Oral</td>
<td>Limited results</td>
<td></td>
<td></td>
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Endothelin Receptor Antagonists (ERA)

• Vasodilation
• Prevent smooth muscle migration
• HEPATOTOXICITY: monthly LFTs
• Teratogenic: monthly pregnancy tests
• E.g. Bosentan

<table>
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<tr>
<th>ERAs</th>
<th>Route</th>
<th>Dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>po</td>
<td>&lt; 20kg: 31.25 mg bd</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 – 40kg: 62.5 mg bd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 40 kg: 125 mg bd po</td>
<td></td>
</tr>
<tr>
<td>Sitaxentan</td>
<td>po</td>
<td>WITHDRAWN</td>
<td>Fatal liver injury</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>po</td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
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Phosphodiesterase Inhibitors

• Inhibit cGMP, cAMP degradation
• Increase NO
• Vasodilation
• E.g. Sildenafil (PDE5-I)
  Milrinone (PDE3-I)
Rho-Kinase Inhibitors

- Rho-kinase enhances the contraction of the vascular smooth muscle cells through inhibition of myosin phosphatase
- When inhibited:
  - endothelial ↑ NO synthase (eNOS)
  - ↓ migration of inflammatory cells
  - ↓ smooth muscle proliferation
- E.g. Fasudil

Stimulator / Activator of Soluble Guanylate Cyclase

- eNOS synthetizes NO
- The downstream effector of NO is sGC, which synthetizes the secondary messenger cGMP.
- Increased cGMP:
  - Acute vasodilatation
  - Reduction in platelet aggregation
  - Prevention of the pulmonary vascular remodeling
  - Reduction in the RV afterload.
- E.g. Riociguat

Serotonin Antagonists

- Serotonin synthetized in the pulmonary endothelium
- Passes into the underlying pulmonary smooth muscle cells through the serotonin transporter (SERT) to initiate proliferation
- Serotonin re antagonists and Serotonin transporter inhibitors are in development

Vasoactive Intestinal Peptide

- Neurotransmitter - acts as a potent systemic and pulmonary vasodilator
- Deficiency of VIP found in serum and lung tissue of patients with idiopathic PAH
- VIP results in improved haemodynamic parameters without significant side effects

Magnesium Sulfate

- Promotes vasodilatation by antagonizing the entry of calcium ions into the smooth muscle cells.
- Pulmonary vasodilator properties need further study.
Combination therapy

- Enhanced pulmonary vasodilatation compared with monotherapy.
- E.g.
  - iNO and Sildenafil to increase cGMP
  - prostacyclin (PGI2) which enhances c-AMP can work synergistically with iNO which enhances c-GMP
  - endothelin receptors antagonists and iNO.

Follow-up Care

- Infants should be monitored at Neurodevelopmental clinic for first 2 years of life: high prevalence of both expressive and receptive language problems.
- Complete screening again before entering school for any subtle deficits that may predispose them to learning disabilities.
- Late sensorineural hearing loss has been reported in a high percentage of patients thus reassess the infant’s hearing at 6 months and again as needed.
- Patients with persistence of any PHT must be followed up at PHT clinic.

Outcomes

- Mortality rate for PPHN as high as 40%
- Up to 25% have significant neurodevelopmental impairment
- Rapid stabilization and initiation of vasodilators is necessary

Practice Essentials

- High index of suspicion – early echo
- Support ventilation and circulation
  - HFV
  - Inotropes
- Start iNO if OI > 25 ± Sildenafil
- Accept PaO2 > 50
- Wean slowly
- Follow up ND and hearing

Thank you for your attention