Persistent Pulmonary Hypertension of the Newborn

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Disclosures

The portion of this lecture dealing with investigational treatments for PPHN will include the discussion of several “off-label” and experimental uses of medications which should not be used outside of experimental protocols with informed consent of the parents.
Objectives

1: To understand the pathophysiology and clinical presentation of pulmonary hypertension

2: To identify the rationale for the current and experimental treatments for persistent pulmonary hypertension of the newborn.
Persistent Pulmonary Hypertension

- Mainly a disease of term and late-preterm infants
- Normal transition from intrauterine life is disrupted
  - Pulmonary vascular resistance remains elevated during the newborn period with varying degrees of respiratory distress.
- The treatment for PPHN is often quite different from that of other respiratory diseases.
PPHN

- First described in 1969 by Gersony#
- Also called Persistent Fetal Circulation (PFC)
- Affect 1-4% of live births*
  - Actual incidence is difficult to measure
    - No strict criteria for the diagnosis
- Elevated pressure in the pulmonary vascular bed.
- Hypoxemia out of proportion to radiographic findings

* Emmanouilides GC. *Fetal Neonatal and Infant Cardiac Disease* 1990:chpa 38 pp777-786.
Fetal vs. Adult Circulation

![Diagram showing fetal vs. adult circulation](image-url)
Transition from Fetal to Extrauterine Life

Cardiovascular Changes

Increased pulmonary circulation
Closure of the ductus venosus, foramen ovale and ductus arteriosus
Changes in systemic circulation
Physical Factors act alone and through vasoactive mediators to induce cardiovascular changes.

**Constrictors**
- Norepinephrine
- A-adrenergic stimulation
- Hypoxia
- Endothelin
- Thromboxanes
- Leukotrienes
- Platelet activating factor
- PGF$_{2a}$

**Dilators**
- PGI$_2$, PGD$_2$, PGE$_2$
- Nitric Oxide
- Cyclic GMP
- ATP / Adenosine
- Bradykinin
- Rhythmic Distension
- Oxygen
- Decreased lung fluid
- Cessation of umbilical blood flow
Pulmonary Hypertension

Primary-Persistent Fetal Circulation
- Following slides

Secondary
- Elevated pulmonary pressure as a result of a structural defect that allows transmission of the systemic pressure to the pulmonary vascular bed.
  - Infant with large VSD → High pressure in the LV transmitted to the RV and on to the lungs → Elevated pressure interferes with the normal drop in pulmonary vascular resistance → Pulmonary hypertension.
  - AV canal
  - Result of chronic lung disease
Persistent Pulmonary Hypertension

- Transition from intra- to extra-uterine life
  - Circulatory changes—most dramatic is the fall in pulmonary vascular resistance.
- Delayed fall in PVR is associated with
  - Lung hypoplasia
  - MAS
  - Asphyxia
  - Pneumonia
  - Sepsis
  - No Identifiable Inciting Event
Categories

- Maladaptation
  - Blood vessels have normal structure but abnormal vasoreactivity

- Excessive Muscularization
  - Increased smooth muscle thickness and/or extension of smooth muscle into distal airway

- Underdevelopment
  - Lung hypoplasia

- Not mutually exclusive
  - Maladaptive process can lead to tissue remodeling with excessive muscularization
Pathogenesis

**Multifactorial**

- Interference with normal transition at birth
  - Predelivery Factors
    - Precipitous delivery, C-section with no labor, Difficult extraction, Hypoxic-ischemic injury. Acute or Chronic
  - Post-delivery Stress
    - *The ECMO bath*
  - Sepsis
    - Particularly GBS
    - +/- pneumonia
- About half the time there is no identifiable inciting event
Presentation

- Similar to cardiovascular shock
- Respiratory distress
- Differential includes
  - Cyanotic heart lesions
  - Infection
  - RDS
  - TTN
Diagnosis

Difficult by clinical criteria due to similar symptoms to other respiratory and cardiovascular diseases

- Hypoxemia out of proportion to x-ray findings

Cardiac Catheterization

- Unrealistic
Diagnosis

- Recognize Risk Factors
- Clinical Exam
- Response to treatment, clinical course
- B-type Natriuretic Peptide Levels
BNP in PPHN

- Initial BNP levels are predictive of PPHN.
  - A BNP level greater than 550 pg/mL is predictive of PPHN. (p < 0.001, Fischer’s Exact Test)
  - Alll infants with BNP levels >835 had PPHN
  - But, level does not correlate with “degree of sick”

- Similar results with recent studies of older children.
  - BNP levels helpful monitoring PAH in children age 5-14.

*Pediatrics* Nov 2004;114(5):1297-1304
*Chest* Mar 2009;135(3):745-751
Diagnosis

- Echocardiography
  - Rule out structural heart disease
  - Physiologic measurement/estimate
  - Elevated TR gradient
  - Evidence of right-to-left shunting at the PDA or PFO
  - Septal flattening or bulging into the left ventricle
Shunting occurs at the ductus arteriosus and foramen ovale.

- Causes hypoxemia (*out of proportion to radiographic findings*).
- Shunting is promoted by:
  - Fetal RV is less compliant than LV.
  - High pulmonary pressure can compromise the diastolic function of the RV.
Shunting

Shunting is protective for infants with PPHN.

- Allows continued perfusion and oxygen delivery (albeit, decreased pO$_2$) to systemic circulation.
  - Without shunting, increased RA pressure would lead to decreased LA filling and decreased cardiac output resulting in worse perfusion and even more severe hypoxemia and hypotension with eventual death
Shunting

- Blood returning to the heart encounters increased pressure on the right side of the heart stemming from the elevated PVR.
- Atrial-level R-to-L shunting causes LA, LV and systemic desaturation.
Shunting

леч

R-to-L shunting at the PDA occurs during systole.

- During diastole, there is L-to-R shunting, unless pulmonary pressure is very high, then R-to-L shunting continues.

If shunting is only occurring at the PDA, desaturation is limited to the descending aorta and the preductal saturation is normal.
Treatment

- Treat any underlying lung disease.
- Oxygen
  - Increased tissue oxygenation in the pulmonary vascular bed is a vasodilator. In other beds it is a constrictor.
  - Oxyhood cannot deliver 100% oxygen in the standard configuration.
Treatment

- Treat any underlying lung disease.
- Oxygen
- Ventilation
  - Conventional Vent or HFOV
  - Surfactant Replacement
    - Deficiency or Inactivation
    - Increase alveolar ventilation
  - Induce mild alkalosis
    - pH = 7.43-7.48  pCO₂ = 28-33  BE = +3-+5
## Target Blood Gases

<table>
<thead>
<tr>
<th>Disease</th>
<th>PPHN</th>
<th>RDS</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>7.43-7.48</td>
<td>7.23-7.28</td>
</tr>
<tr>
<td>pCO₂</td>
<td>28-33</td>
<td>50-55</td>
</tr>
<tr>
<td>pO₂</td>
<td>&gt;150</td>
<td>70-100</td>
</tr>
<tr>
<td>BE</td>
<td>0 - +5</td>
<td>-7 - -4</td>
</tr>
</tbody>
</table>
Effect of pH on PVR
Treatment

Normalize/Elevate systemic blood pressure
- Volume expansion, dopamine, dobutamine
- Minimizes shunting
Pulmonary and Systemic Pressures

Shunting
Treatment

Normalize/Elevate systemic blood pressure
- Volume expansion, dopamine, dobutamine
- Minimizes shunting

Environmental Control
- Minimal Stimulation
- Sedation
Treatment

 Nitric oxide

- Messenger molecule involved in diverse physiologic processes
  - Smooth muscle contractility, platelet activity, neurotransmissions, cytotoxic actions of immunity
- Induces endothelium-derived relaxing factors
- When inhaled, selectively dilates the pulmonary vasculature
- Number of babies requiring ECMO has decreased by nearly half since the wide acceptance of NO.
Nitric Oxide

NO is formed endogenously by nitric oxide synthases (NOS).

- Three distinct forms of NOS
  - Neuronal (nNOS)
    - Constitutive, activity regulated by Ca$^{2+}$ and Calmodulin, also found in epithelium of bronchi and trachea and skeletal muscle
  - Vascular endothelial (eNOS)
    - Constitutive, Ca$^{2+}$ and Calmodulin requiring, also found in platelets and neuronal populations, inducible in certain circumstances
  - Inducible (iNOS)
    - Induced by inflammatory mediators and bacterial products, found constitutively in bronchial epithelium, rat kidney, ovine lung
Nitric Oxide

Physiologic actions via activation of soluble guanylate cyclase (sGC)

- NO induces a 400-fold increase in sGC activity
  - GTP $\rightarrow$ cGMP
- Increasing cGMP causes relaxation of vascular smooth muscle
  - cGMP-gated ion channels
  - cGMP regulated phosphodiesterases
  - cGMP-dependent protein kinases
- Acts via modulation of calcium homeostasis by more than one mechanism and phospholipase C
NO and PPHN

- Evidence of impaired NO/cGMP pathway
  - Decreased urinary metabolites of NO in PPHN
  - cGMP concentrations lower in PPHN than healthy newborns
  - Decreased arginine utilization during acute phase of PPHN
  - Decreased eNOS gene expression in umbilical vein of patients with PPHN
Using NO Therapy

- Add NO to the ventilator circuit
- No consensus regarding order of adding NO vs. HFOV, combination is more effective than either alone
- Usually use between 5 and 20 ppm
  - If no response at 20 ppm, the infant is not likely to respond to higher doses (increased toxicity).
- Monitor NO$_2$ in the inspired gas
  - Formation is proportional to FiO$_2$ and NO concentration
    - Irritant to eyes, nose and respiratory tract at 10-20 ppm
    - Chest pain after 60 minutes of 25 ppm
    - Pulmonary edema and death after 60 min @ 100 ppm
    - Toxic levels of NO$_2$ not seen at NO of up to 20 ppm
Using NO Therapy

Monitor methemoglobin levels

- Toxic levels not seen in experimental protocols using 5-20 ppm
- >7% methemoglobin in experiment using 80 ppm

Other potential (theoretical) toxicities include platelet dysfunction, lipid peroxidation via free radical generation, caregiver exposure.

- Studies of actual occurrence are mixed

Conventional wisdom versus emerging information
Using NO Therapy

40-50% of infants do not respond to NO

Differences may be due to:

- Inadequate lung volume recruitment
- Myocardial dysfunction
- Anatomic lesions of systemic or pulmonary circulation
- Severe airway inflammation
- Excess vasoconstrictive agents
- Incorrect dose of NO
  - Too High—Response @ 80 = Response @ 20 with less toxicity
  - Too Low—Starting @ 2 attenuates later response to 20
- Abnormal pulmonary vascular structure or altered smooth muscle responsiveness
Other Treatments

- Non-selective dilators
  - Tolazoline, Nitroprusside, Prostaglandin, Isoproterenol
  - Mg\(^{2+}\) and Mn\(^{2+}\) increase sGC and increase binding of GTP
Experimental Treatments

- Natriuretic Peptides
  - Increase cGMP via different receptor than NO

- Sildenafil
  - Blocks PDE-5, prevents clearance of cGMP

- SOD
  - Prevents inactivation of NO by superoxide

- Adenosine
  - Infusion improves oxygenation with no systemic hemodynamic effects in preliminary studies.
**Experimental Treatments**

**Endothelins**

- ET1 acts on ET-A and B
  - ET-A: vasoconstriction
  - ET-B: vasodilatation

- Increased ET1 clearance seen in patients with increased pulmonary pressure

- ? Role of endothelin antagonists in treatment
  - Bosentan: approved treatment for adult pulmonary hypertension, hepatotoxicity
Experimental Treatments

Prostacyclin

- PGI$_2$ is a potent nonselective vasodilator
- Actions mediated through cAMP.
- Nebulized, oral, continuous subcutaneous injection
- Little experience in neonates, favorable results in adults.
Experimental Treatments

Milrinone

- Inhibits PDE3
  - Resulting in accumulation of cAMP

Sheep Model

- Improved myocardial performance and vasodilation
- Synergistic effect with PGI₂

Case series reports

  - 9 patients…Oxygenation improved…Did not look at any other outcome or adverse effects.
- Bassler: Biol Neonate. 2006;89(1):1-5. Epub 2005 Sep 8
  - 4 patients…Oxygenation improved, 3 developed IVH, 2 Severe
- AAP statement (2007) treatment requires informed consent
Treatment...Don’t “Flip” the patient

When the patient is getting better...

- Don’t wean treatments too fast.
- **7.40 30 120**

  weaned something too fast and next gas was

  **7.04 120 30**

Select reasonable goals

- Wean O₂ 2% per hour
  - 100% to 60% in 20 hours
- Wean NO 1-2 ppm per hour
  - 20 to 10 ppm in 1 day, 10 to 5 in 1 day, 5 to OFF in 1 day
  - Often easier to go from 20 to 3 than 3 to OFF
- Wean pressor support slowly
  - Dopamine or Dobutamine in 2.5 mcg/kg/min increments
Treatment (Failed Medical Management)

Extra-corporeal Membrane Oxygenation (ECMO)

- “Esperanza”
  - 1976, baby girl with meconium aspiration
  - Dr. Robert Bartlett, Southern California

- Cardio-pulmonary bypass
- Allows lungs to rest and recover
- Serious inherent risks
  - Systemic and intracranial hemorrhage
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
  - Increased risk of IVH in smaller, younger infants
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
- No IVH
  - Risk of catastrophic extension of existing IVH
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
- No IVH
- No congenital heart disease

- Infants require prompt surgical intervention, not ECMO. ECMO can be used as a bridge to definitive surgery if patients has reversible disease that makes him/her temporarily a poor surgical candidate.
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
- No IVH
- No congenital heart disease
- Fewer than 10-14 days of assisted ventilation
  - ECMO can not reverse severe lung disease resulting from barotrauma or oxygen toxicity
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
- No IVH
- No congenital heart disease
- Fewer than 10-14 days of assisted ventilation
- Reversible lung disease
  - Not for severe pulmonary hypoplasia that is not compatible with life
Eligibility Criteria

- GA of 34 weeks or older, >2000 grams
- No IVH
- No congenital heart disease
- Fewer than 10-14 days of assisted ventilation
- Reversible lung disease
- Failure of maximum medical therapy
Failure of Maximal Medical Therapy

Oxygenation Index (OI)

$$OI = 100 \times \frac{MAP \times FiO_2}{PaO_2}$$

$OI > 40$ on $3$ of $5$ consecutive blood gases within $5$ hours correlates with $80\%$ mortality
Failure of Maximal Medical Therapy

- Alveolar-Arterial Oxygen Gradient ($AaDO_2$)

  Assuming $FiO_2 = 100\%$, Barometric Pressure at sea level is 760, Partial pressure of $H_2O$ vapor is 47, and $P_{ACO_2} = PaCO_2$ …

  $$AaDO_2 = 713 \times FiO_2 - (PaO_2 + PaCO_2)$$

- $AaDO_2 > 620$ correlates with 80% mortality
Failure of Maximal Medical Therapy

- Pa$_{O_2}$ < 50 for 4 hours on Fi$_{O_2}$ = 100%

- Acute deterioration with Pa$_{O_2}$ < 30-40 on Fi$_{O_2}$ = 100%

- Intractable hypotension with poor cardiac output unresponsive to volume expansion and pressors.
The Circuit

- Baby
- Venous reservoir
  - 3-4 feet below the level of the heart
- Pump
  - Roller
  - Centrifugal
- Artificial lung
  - 0.6-0.8 m² thin, gas-permeable, silicone membrane
- Heater
ECMO

- Provide 90-120 mL/kg per minute of flow
- Pressor support, vasodilators and paralytic agents usually not needed while the child is on ECMO
- Systemic anticoagulation therapy
- Activated clotting times are measured hourly and maintained in the range of 180 to 240 seconds
ECMO

❖ Reduce assisted ventilation
  ❖ PIP 14-20 cm  Rate 12-20
    • Maintains lung expansion and pulmonary toilet
  ❖ Mixed venous saturation of 65% or greater reflects adequate oxygen delivery.

❖ As mixed venous saturation rises above baseline, flow through the circuit can be decreased
  ❖ When flow is 10 to 20 mL/kg per minute, the infant can be weaned from the circuit.
Outcomes

Prior to ECMO—Death rates were reported between 12-50%

Post-ECMO 85% survival
- Significant morbidity in 10-15% of patients
- NO has cut in half the number of infants requiring ECMO

Survivors have exaggerated response to adverse pulmonary stimuli in later life.
- Increased likelihood of asthma
- Difficulty with altitude
Summary

- Pulmonary hypertension causes some of the sickest babies in the NICU.
- Ventilation strategies, blood pressure management and hyperoxia are the standard first line treatments.
- Inhaled nitric oxide is an effective vasodilator for 50% of affected infants.
- ECMO cases have decreased since the wide acceptance of NO therapy.
- Experimental treatments may be able to keep some infants off of ECMO.
<table>
<thead>
<tr>
<th>Things You Should Do Initially</th>
<th>Things We May Do For Really Sick Babies</th>
<th>Things you Should Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Hyperoxia</td>
<td>Nitric Oxide</td>
<td>Too Much Activity</td>
</tr>
<tr>
<td>pO₂ = HIGH</td>
<td>Standard of Care</td>
<td>Never wean anything</td>
</tr>
<tr>
<td>Blood Pressure Management</td>
<td>Nonselective Dilators</td>
<td>until you are sure</td>
</tr>
<tr>
<td>MBP 50-60</td>
<td>Old school</td>
<td>it is safe!</td>
</tr>
<tr>
<td>Normal pH or mild Alkalosis</td>
<td>ECMO</td>
<td></td>
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<tr>
<td></td>
<td>For those who fail NO</td>
<td></td>
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<tr>
<td>For Intubated Patients:</td>
<td>Experimental Treatments</td>
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<tr>
<td>Relative Hypocarbia</td>
<td>Sildenafil</td>
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<td>Surfactant Replacement</td>
<td>Natriuretic Peptides</td>
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<tr>
<td>If indicated.</td>
<td>Endothelin Antagonists</td>
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<td>Milrinone</td>
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