Neonatal Hypoxemic Respiratory Failure and Refractory PPHN

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Hypoxemic Respiratory Failure in the Term Newborn

Idiopathic PPHN
Meconium Aspiration

Pneumonia
Congenital Diaphragmatic Hernia

Persistent Pulmonary Hypertension of the Newborn: Failure of Postnatal Adaptation

Fetus (Birth) - Neonate
PVR

Normal

PPHN

Pathogenesis of PPHN

Injury

- Hypertension
- Hypoxia
- Inflammation
- Genetic Factors
- Other Stimuli:
  - NSAIDs
  - SSRI
  - Smoking
  - Maternal diabetes
  - Abnormal placenta

Altered Structure

- SMC Hyperplasia
- Fibroblast Proliferation
- Altered Matrix Production
- Impaired angiogenesis (hypoplasia)

Altered Function

- Dilators
- Constrictors
- Altered SMC Responses
**Hypothesis:** Endothelial Cells Modulate Vascular Growth and Function in the Developing Lung

- Nitrile Oxide
- Endothelium-1
- Smooth Muscle Cell

- Vasodilation
- Angiogenesis
- Survival
- Growth
- SMC Proliferation
- Matrix Production

**Role of NO in the Perinatal Lung**

- Endogenous NO at Birth
- Inhaled NO

**Inhaled NO in PPHN**

- Sustained Improvement in Oxygenation
- Reduced ECMO Use (Denver)

**Inhaled NO Reduces the Need for ECMO Therapy in Term Newborns with PPHN**

- "…………an apparent 40% treatment failure rate…………"

**Mechanisms Underlying Poor Responses to Inhaled NO**

- Primary Disease and Pathophysiology
- Poor Lung Inflation
- Anatomic Cardiac Disease
- Right Ventricular Failure
- Left Ventricular Dysfunction
- Structural Disease (developmental lung disease, pulmonary venous obstruction, severe remodeling)
- Biochemical: Increased PDE5 activity, increased $O_2^-$ and ET production, others.

**Cardiopulmonary Interactions in PPHN**

- Pulmonary Vascular Disease
- Right-to-left shunting at DA and FO
- Hypoxia, acidosis
- RV pressure overload
- LV dysfunction
- Hypothesis: Endothelial Cells Modulate Vascular Growth and Function in the Developing Lung

- Endothelial Cell
- Nitrile Oxide
- Endothelium-1
- Smooth Muscle Cell

- Vasodilation
- Angiogenesis
- Survival
- Growth
- SMC Proliferation
- Matrix Production

- Vasoconstriction
- SMC Proliferation
- Matrix Production

- Nitric Oxide
- Angiogenesis
- Survival
- Growth
- SMC Proliferation
- Matrix Production

- Endothelin-1
- Angiogenesis
- Survival
- Growth
- SMC Proliferation
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PVR Increases at Lung Volumes Below and Above FRC

HFOV Augments the Response to Inhaled NO in Neonatal Hypoxemic Respiratory Failure and PPHN

Improved Lung Recruitment with HFOV in a Newborn With CDH

Changes in PaO₂ in Severe PPHN in CDH: Combined Effects of iNO with HFOV

Pulmonary Edema During Inhaled NO Therapy in an Infant with BPD and LV Dysfunction

Abnormal NO-cGMP Cascade in PPHN

Birth-Related Stimuli:
(O₂, Ventilation, Shear Stress)
Pulmonary Vascular Effects of Acetylcholine, BAY 41-2272 and Sildenafil in PPHN

![Graph showing percent change in PVR for Acetylcholine, Sildenafil, and BAY 41-2272](image)

*P < 0.05 and **P < 0.01 between Day 1 & Day 5; #P < 0.01 between BAY 41-2272 day 5 & sildenafil day 5.

(Steinhorn et al, J Pediatr, 2009)

Intravenous Sildenafil Improves Oxygenation in Neonates with PPHN

![Graph showing change in oxygenation](image)

Intravenous Sildenafil Improves Oxygenation in Neonates with PPHN

Non-cGMP Signaling: Therapeutic Targets in PPHN

![Diagram showing endothelial cell, GTP, cGMP, PDE, Sildenafil, and vasodilation](image)

Alveolar Capillary Dysplasia

![Image of alveolar capillary dysplasia](image)

Pulmonary Vein Stenosis

![Image of pulmonary vein stenosis](image)

ATP Binding Cassette Protein (ABCA3) Deficiency

![Image of ABCA3 deficiency](image)
Developmental Lung Diseases and Refractory Pulmonary Hypertension

- Bronchopulmonary Dysplasia
- Alveolar Capillary Dysplasia (ACD)
- ACD with Misalignment of Veins
- Lung Hypoplasia (“primary” or “secondary”)
- Surfactant Protein Abnormalities(*)
  - SPB deficiency
  - SPC deficiency
  - ABCA3
  - TTF-1/Nkx2
- Pulmonary Intertstitial Glycogenosis
- Pulmonary Alveolar Proteinosis
- Pulmonary Lymphangiectasia
- Pulmonary Alveolar Proteinosis
- Pulmonary Venous Obstruction (PVS, PVOD, associated with anatomic heart disease)

Diagnostic Approach

- Aggressive management of respiratory disease
- Complete pulmonary evaluation:
  - Radiographic
    - Chest x-ray
    - Chest CT
  - Bronchoscopic (structural, dynamic obstruction, BALF)
  - Aspiration Evaluation (pH and impedance probes, barium studies)
- Genetic studies
- Cardiac Catheterization
- Lung Biopsy

Diagnosis-Related Mortality in ILD

<table>
<thead>
<tr>
<th>Category</th>
<th>Age at Biopsy, mo</th>
<th>Mean ± SD (range)</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse developmental disorders</td>
<td>0.7 ± 0.2 (0.1-1.2)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Lung growth abnormalities</td>
<td>2.33 ± 0.3 (0.3-22)</td>
<td>3%</td>
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<tr>
<td>Pulmonary interstitial glycogenosis</td>
<td>1.9 ± 0.6 (0.0-3.0)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Nonspecific cell hypoplasia of infancy</td>
<td>1.6 ± 0.7 (0.1-7.0)</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Sulfuric dysfunction (all)</td>
<td>3.8 ± 0.6 (2.2-22)</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>ABCA3 mutations</td>
<td>8.8 ± 3.0 (0.0-22)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Disorders of the normal host</td>
<td>1.7 ± 1.2 (0.2-24)</td>
<td>5%</td>
<td></td>
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<tr>
<td>Disorders resulting from systemic disease processes</td>
<td>10.5 ± 3.6 (1-22)</td>
<td>20%</td>
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<tr>
<td>Disorders of the immature-primed host</td>
<td>15.4 ± 1.3 (1.3-24)</td>
<td>30%</td>
<td></td>
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<tr>
<td>Disorders manifesting as ILD</td>
<td>7.3 ± 2.3 (0.2-24)</td>
<td>28%</td>
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Conclusions

- Impaired NO-cGMP signaling contributes to the pathophysiology of PPHN;
- Although inhaled NO therapy is an effective therapy for PPHN, success is dependent on ventilator strategies and cardiac performance;
- Adjunct therapies (eg, sildenafil, bosentan) to augment NO responsiveness or to treat severe PH needs further study;
- Novel interventions are needed to enhance lung vascular and alveolar growth in PPHN associated with lung hypoplasia.

Pediatric Heart Lung Center

Clinical Team

Lab Group