PPHN: A Pathophysiological Update

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with companies or the manufacturer(s) of any commercial product/service that will be discussed as part of this presentation.

Session Summary

During this session Dr. Moore will review the physiology, cellular signaling mechanisms, different treatment strategies, and drugs for the management of primary pulmonary hypertension in the neonate.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- define PPHN;
- discuss etiology, incidence and prevalence of PPHN;
- describe current pathogenesis models related to PPHN development;
- explain appropriate pharmacologic and interventions for PPHN.

References


Session Outline

See handout on the following pages.
Pulmonary Hypertension: A Pathophysiological Update

FANNP’s 23rd National Neonatal Nurse Practitioner Symposium October 18, 2012

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Disclosures

Dr. Moore has nothing to disclose

Pulmonary Hypertension

- Definition
- Etiology
- Treatment

Definition

- Mean pulmonary artery pressure >25 mmHg
- Normal pulmonary capillary wedge pressure (≤15 mmHg)
- Increased pulmonary vascular resistance

Pulmonary Artery Hypertension

- PPHN syndrome may occur as often as 3-6 cases per 1000 live births.
- In the term newborn with parenchymal lung disease, such as MAS or pneumonia, PPHN is a significant complication (25,000-30,000 infants and 1000 deaths).

Causes of PPHN

1) Conditions leading to acute pulmonary vasoconstriction:
   - RDS
   - asphyxia
   - hypothermia
   - MAS
   - sepsis

2) Idiopathic PPHN (black lung PPHN): results from abnormal vascular remodeling, can be due to prenatal NSAIDS or chronic stress in utero (IUGR).

3) Newer reports are in the literature for PPHN developing in infants whose mothers who use selective serotonin reuptake inhibitors (SSRIs) during the last half of their pregnancies (Chambers et al NEJM 2006)
Less than 25 years ago, the mortality rate reached 40%, and the prevalence of major neurologic disability was 15–60% in PPHN.

ECMO reduced mortality by 50% and combining all of today’s therapies, the mortality from PPHN is < 10%.

Rates for major neurologic disability still remain high at 12–20%.

Classifications that do not fit standard definition

- Congenital diaphragmatic hernia
- Bronchopulmonary dysplasia
- Linked to lung growth and development with abnormalities of alveolarisation and vascular development

Pathologic Changes

- Remodeling of pre-capillary resistance pulmonary arteries with
  - Thickening of intima, media, adventia
  - Intimal fibrosis
  - Thrombosis
  - Development of plexiform lesions
- Adults more often develop severe intimal fibrosis, plexiform lesions, “fixed” irreversible pulmonary vascular changes
- Children more often develop pulmonary vascular medial hypertrophy, less intimal fibrosis, fewer plexiform lesions

Mechanism

- Unclear
- Endothelial cell dysfunction
- Smooth muscle cell migration and dysfunction
  - Smooth muscle de-differentiate
- Abnormal apoptosis
- Mediators involved: thromboxane A2, endothelin-1, prostacyclin, nitric oxide

Echocardiogram
Endothelin-1

- Potent vasoconstrictor
- Mitogen for smooth-muscle cells and fibroblasts

Thromboxane A₂

- Potent pulmonary vasoconstrictor
- Stimulus for platelet aggregation

Prostanoids

- Prostacyclin, prostaglandin, thromboxane families
- Prostacyclin I₂ (PGI₂), prostaglandin E₁ (PGE₁),
- Potent vasodilators, anti-platelet aggregation
- Pulmonary vasodilation results in decreased workload to the right ventricle, increases pulmonary blood flow, decreases pulmonary artery pressure
Prostanoids
- Eposprostenol (Flolan): synthetic PGI₂, needs
  continuous infusion, half-life 2–3 minutes,
  inhalation form under investigation
- Treprostinil (Remodulin): PGI₂ analog, needs
  continuous IV or subQ infusion, now can be inhaled
- Iloprost (Ventavis): PGI₂ analog, can be inhaled (6–9
  times a day), fewer systemic side effects
- Beraprost: oral prostacyclin analog under
  investigation
- Side effects: headache, flushing, hypotension, jaw
  pain with initial chewing, diarrhea, nausea,
  erythematous rash, muscle aches

Medications
- Anticoagulation: coumadin
- PAH disease specific therapy:
  - Endothelin receptor antagonist: Bosetan,
    ambrisentan (ET₄ selective)
  - Phosphodiesterase 5 inhibitors: sildenafil,
    tadalafil
  - Prostacyclin analog
    - epoprostenol
    - inhaled iloprost
    - IV or subQ treprostinil

Inhalable Nitric Oxide
- Rapid and avid binding of NO to
  hemoglobin resulting in
  inactivation
- Preferential delivery to better
  ventilated lung units optimizing
  V/Q matching and reducing
  intrapulmonary shunting

Nutric Oxide
- Endothelium-derived
  vasorelaxant
- Inhibitor of smooth muscle
  growth

iNO: Mechanism of Action
- Rapid and avid binding of NO to
  hemoglobin resulting in
  inactivation
- Preferential delivery to better
  ventilated lung units optimizing
  V/Q matching and reducing
  intrapulmonary shunting

Wessel DL et al. Advances in Pharmacology, 1995
**Inhaled Nitric Oxide: V:Q Matching**

**Effects of O₂ on iNO Response**

**Hyperoxia Increases PDE5 Expression**

**iNO and O₂, to Much of a Good Thing?**

**Conventional Management and Treatment of PPHN**

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Oxygen

Pain Relief/Sedation/Paralysis

Fentanyl, morphine, lorazepam, midazolam, vecuronium, pancuronium etc

Volume Status and need for systemic vasopressors

Alkalosis ????????
### Lung-Protective Mechanical Ventilation Strategies

- ARDS Network trial, 2000
  - Compared 2 different CV strategies in ARDS
  - 6 mL/kg TV vs 12 mL/kg TV
  - N=861
  - Trial stopped early, with lower mortality in low TV group (31% vs 40%)
  - Higher PEEP in low TV group


### HRF: Impact of Alkalosis

![Graph showing mortality and ECMO usage with alkalosis](image)


### Lung Recruitment With HFOV and iNO Response in Neonates with HRF

![Graph showing responders in various conditions](image)


**P<0.05**

### Milrinone and PPHN

- Milrinone is a phosphodiesterase III Inhibitor
- Cardiologist use it to improve inotropy and reduce afterload
- Two trials to date have shown benefit
- Concern however about IVH in preterm population


### Milrinone Improves Oxygenation in Neonates with PPHN

![Graph showing oxygenation improvement](image)


**P<0.05** vs baseline

### And if all else fails...

ECMO is a procedure that takes over the work of the lungs. This allows the lungs to heal from the underlying pathology, to help break the cycle of hypoxic vasoconstriction.
Summary

- There is no perfect therapy for PPHN
- Multiple approaches are available and when used appropriately have improved outcome
- iNO has been a valuable addition to our tool box, and there are newer therapies evolving which will add to our treatment strategies
- The need for ECMO has declined, but it is still an extremely effective therapy

Questions
Thank you for your attention