Respiratory Failure / Persistent Pulmonary Hypertension (PPHN) in Neonates
Syed K. Shah, MD
Assistant Professor, Division of Neonatology
Department of Pediatrics

Disclosure
I have no actual or potential conflict of interest in relation to this presentation.

Outline
- Lung and Vascular Development
- Fetal Circulation and Postnatal Transition
- Pathophysiology of Neonatal Respiratory Failure / PPHN
- Management of PPHN
  - Conventional Mechanical Ventilation
  - High Frequency Ventilation
  - Medications; Inotropes & Vasodilators
  - Nitric Oxide
  - Surfactant
  - ECMO

Lung Development
Stages of lung development
- Day 26 gestation- lung bud begins from foregut
- Embryonic stage: Sacules develop 2 on left, 3 on right
- Pseudoglandular stage: budding and branching to terminal bronchioles
- Canalicular stage: Capillaries develop close to airway epithelium and respiratory bronchioles form

Lung Development
Saccular stage:
- Primitive alveoli form, become lined by type 1 alveolar cells which allow gas exchange
- Sacules subdivide into terminal airway clusters
- Increased vascularization of alveoli

Alveolar stage:
- Type II cells surfactant production
- Further alveolar development- secondary septae, alveolar ducts

Lung Development Timeline

Timeline:
- TE Fistula
- CDH
- Lung Hypoplasia
- Lung Development

Timeline:
- 4-7 weeks
- 8-13 weeks
- 13-28 weeks
- 28 weeks
- Postnatal
Lung Development - Vascularity

Double capillary network fails to fuse → Alveolar-Capillary Dysplasia

Fetal Circulation

Pulmonary Vascular Transition

Fetal Circulation: PPHN

Potential Causes of Respiratory Failure:
- Congenital Diaphragmatic Hernia (CDH)
- Meconium Aspiration Syndrome (MAS)
- Sepsis / Pneumonia
- PPHN
- RDS in late preterm/term
- Air leak
**Diagnosis of PPHN**

- Pulmonary hypoplasia
  - Severe on ipsilateral side
  - Variable on contralateral side
  - Immature, abnormal lung
- Vascular complications

**Congenital Diaphragmatic Hernia**

- High mortality = historically 50%, now much less
- ECMO survival = 54%
  - Non-transient, underlying abnormal lung

**Meconium Aspiration Syndrome**

- Most common reason for neonatal ECMO overall, highly successful (94% ECMO survival)
  - Referred early
  - Non-homogeneous disease—areas of atelectasis mixed with over-distention
  - Hypoxia/Acidosis/PPHN/Air leak

**Meconium Aspiration Syndrome**

- Etiology/physiology
  - Chronic asphyxia
  - Surfactant dysfunction – toxic pneumonitis
  - Air trapping
- Treatment
  - Suctioning decreases incidence of mild & moderate cases, but not severe MAS
  - Management of PPHN
  - ECMO if pre-ECMO therapies fail
**Pneumonia**
- Much less common reason for ECMO referral
- Viral and bacterial
- Long runs
  - Average length = 210 hours
- Survival poor for referrals
  - Often identified late in course
  - ECMO survival = 58%

**Respiratory Distress Syndrome**
- Potential ECMO candidate down to 35 weeks GA
- Surfactant deficiency +/- immature lung structure
- Homogeneous disease, generally responds to surfactant, HFV, or in rare event short ECMO run
  - 84% ECMO survival

**Persistent Pulmonary Hypertension**
- End result of MAS, CHD, sepsis, RDS
- Oligohydramnios/pulmonary hypoplasia, asphyxia...or idiopathic primary issue
- 5-10% require ECMO
  - 79% survival
  - Need to treat underlying cause, if known

**Air Leak Syndrome**
- Uncommon reason for requiring ECMO
- Non-homogeneous disease
  - But responds well to HFOV/Jet, which allows ventilation without high PIP
- Intermediate success
  - ECMO survival = 68%

**Management of PPHN**
- Mechanical Ventilation
  - SIMV modes
  - HFV
- Medications
  - Inotropes
  - Vasodilators
  - Surfactant

**Mechanical Ventilation**
Escalation of Resp Management

- Mainstay of treatment of neonatal respiratory failure
- Improved CO₂ removal by increased minute ventilation
- Improved O₂
  - Increased FiO₂
  - Increased Paw

But...it may cause
- Oxygen / inflammation injury
- Pressure / volume injury

Mechanical Ventilation

Conventional Ventilation

- "Old School"
- Hyperventilation to induce respiratory alkalosis
  - Well known to decrease pulmonary vasoconstriction
  - Mechanism unclear, but independent of NO
  - Short term benefit
  - Aggressive use of pressors and volume
  - 100% FiO₂

Conventional Ventilation

- Adverse outcome in PPHN significantly related to duration of hyperventilation
- Hyperventilation associated with sensorineural hearing loss
- Oxygen toxicity
  - Direct injury

Oxygen Toxicity

- Permissive hypercapnia/normocapnia
- Decreased duration of ventilation
- Lower tidal volume strategies
- Acceptance of low/normal pO₂ levels
- Lower PIP and higher PEEP
- Avoid reduction/swings in cerebral blood flow

Current Practice
SIMV in Neonates

- Theoretical advantage
  - Decreased air leak
  - Decreased work of breathing
  - Improved stability of BP, CBF, minute ventilation

- However
  - Mostly extrapolated from adult literature
  - Few small suggestive “trend” studies only

High Frequency Ventilation

- More successful with RDS or pneumonia than CDH or MAS
- Responders usually demonstrate response within 2-4 hours
- Among ECMO candidates:
  - Carlo: HFJV reduced $P_{aw}$ and PaCO$_2$, but no difference in outcomes vs CMV
  - Clark: 31% vs 60% failure for HFOV vs CMV
  - May offer additional benefit with NO

High Frequency Ventilation

- HFJV, HFOV
- Theoretical advantage
  - Animal literature
    - Decreased HMD, lung injury in surfactant deficient models (baboon, rabbit)
  - Premature infant
    - When used correctly, may decrease CLD
    - Concern over IVH risk
  - Extrapolate to older patient, other diseases?
    - Adequate ventilation without high PIP

Medical Therapy: Inotropes

- Raises systemic MAP, reduces $R \rightarrow L$ shunt
- Dopamine
  - Increases SVR and PVR
  - May lead to decreased LV output
- Dobutamine
  - Inotrope + vasodilator
    - May increase LV output by decreasing afterload
Medical Therapy: Inotropes

- Epinephrine
  - Shown to increase BP & decrease PA pressure at low dose
  - At 0.2-0.8 mcg/kg/min may cause both systemic and pulmonary vasodilation
  - May have greater effect on SVR than PVR

Medical Therapy: Nitric Oxide

- Produced by NO synthase from L-arginine
- Activates guanylate cyclase by binding to heme component
- C-GMP binds to potassium channels
- Blocks influx of calcium

Medical Therapy: Nitric Oxide

- High affinity for heme proteins
  - When delivered by inhalation, acts selectively on pulmonary vasculature
- Well studied in animals and term infants
  - Dose range 5-80 ppm
  - Rapid pulmonary vasodilation

Medical Therapy: Nitric Oxide

• Meta-analysis of 9 randomized trials:
  - 58% of hypoxic near-term infants responded
  - Response within 30-60 minutes
  - PaO2 increased average of 45 torr
  - Risk of death or need for ECMO: 66% RR
• Concerns
  - Methemoglobinemia
  - Increased bleeding time?
  - Rebound effect (induction of phosphodiesterase V)
  - Long term unknown – neurodevelopment?

Flolan (Epoprostenol, PG I2)

- Prostacyclin, IV infusion
- Being used more in neonates, potential complement to nitric oxide
- More extensive experience with pulm HTN in adults
- Very short half-life

Vasodilators for PPHN
Medical Therapy: Surfactant

- **Without Surfactant**
  - Airways stay open
  - Higher pressure due to smaller radius
  - More likely to collapse and get harder to inflate

- **With Surfactant**
  - Airways stay open
  - Lower pressure due to larger radius
  - Less likely to collapse and easier to inflate

Surfactant Use

- Standard therapy for primary surfactant deficiency
  - Improved survival and decreased morbidity
  - Incidence of BPD unchanged?

- Surfactant deficiency/dysfunction in other disease states
  - MAS: direct chemical effect
  - CDH: immature lung function

Summary of Management

Extra Corporeal Membrane Oxygenation (ECMO)

- Form of cardiopulmonary bypass that provides support for patients with reversible respiratory and/or cardiac failure

**Modes of ECMO:**
- Venoarterial (VA)
- Venovenous (VV)

ECMO Indications

- Neonatal Respiratory Failure:
  - Congenital Diaphragmatic Hernia (CDH)
  - Meconium Aspiration Syndrome (MAS)
  - Sepsis/pneumonia
  - PPHN
  - RDS in late preterm/term
  - Air leak

- Oxygenation Index
  - \[\frac{(Paw \times FIO2)}{PaO2}\] x 100
  - OI > 40 x 3 hrs
  - Post ductal
  - AaDO2
    - \[\frac{(Patm – 47 \times FIO2)}{p a O 2 – p C O 2}\]
    - AaDO2 > 610 x 8 hours or > 600 x 12 hours
**ECMO Contraindications**

- Significantly premature (<34 weeks, < 2 kg)- Risk for IVH
- Severe asphyxia with multi-organ system injury
- Prolonged vent course
- Certain congenital malformations
- Ongoing hemorrhage or bleeding diathesis

**ECMO Complications**

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<th>Physiologic Complications</th>
<th>Mechanical Complications</th>
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<td>Arrhythmia</td>
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<td>Pneumothorax</td>
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**Potential ECMO Candidate**

- Post term, BG delivered via stat C-section for failure to progress and persistent late fetal decelerations
- Pregnancy was complicated with meconium stained amniotic fluid and chorio. at OSH
- Severe perinatal depression, intubated at 11 minutes of life and received surfactant after that

**Potential ECMO Candidate**

- NEURO: Placed on cooling protocol due to severe hypoxic ischemic encephalopathy
- RESP: Initial blood gas pH 6.92 and BE -23.5. LA 10.7. Oxygen Index: rapidly increased from 58 to 80 by 12hrs of life. A chest tube was placed for a left pneumothorax
- CV: Hypotension: on dopamine, dobutamine, epi and hydrocortisone
- ID: Blood and trach culture positive for E.coli at 6hrs of life
- Heme: Anemic and coagulopathic

**Potential ECMO Candidate**

- UHS transport team was called at around 12 hours of life and arrived at ~ 16 hrs of life. Upon arrival, infant oxygen saturations were in 60’s on 100 % FIO2
- During the whole course (24 hours of life), blood gases showed persistent acidosis (ph < 6.97) and worsening of respiratory failure
  - **Did the baby meet the ECMO criteria?**
  - **Would you place the baby on ECMO?**

**Summary**

- Newborn Lung is still developing when newborn lung disease occurs
- Disease states are generally complicated by pulmonary hypertension, exacerbating the hypoxic respiratory failure
- Large number of ventilatory strategies, devices, and medical therapies are available
- Needs more studies to find out the un-answered questions
Questions, Comments?

References

- ELSO Neonatal Respiratory Failure Supplement to the ELSO General Guidelines 2013.
- University of Rochester Medical Center, Rochester, NY, Neonatal ECMO guidelines 2014.