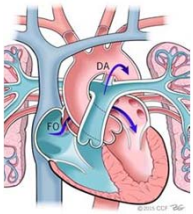

Respiratory Failure / Persistent Pulmonary Hypertension (PPHN) in Neonates

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Disclosure

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

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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

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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

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Lung Development

Saccular stage:

- Primitive alveoli form, become lined by type 1 alveolar cells which allow → gas exchange
- Saccules subdivide into terminal airway clusters
- Increased vascularization of alveoli

Alveolar stage:

- Type II cells → surfactant production
- Further alveolar development- secondary septae, alveolar ducts

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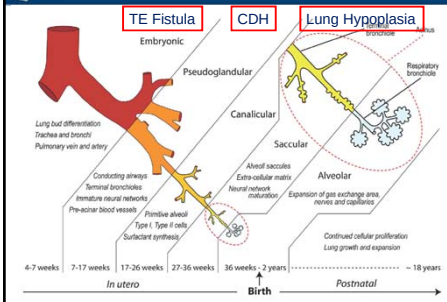
Lung Development Timeline



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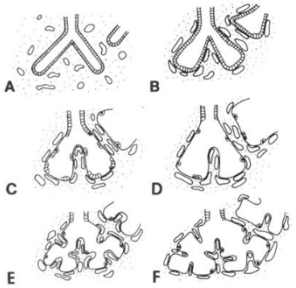
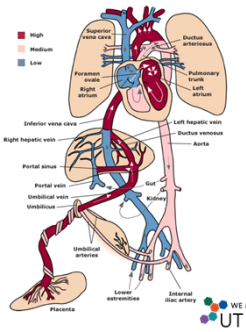
Lung Development - Vascularity

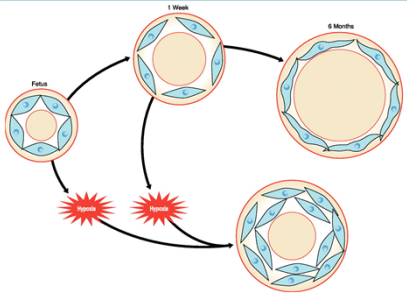


Double capillary network fails to fuse → Alveolar-Capillary Dysplasia

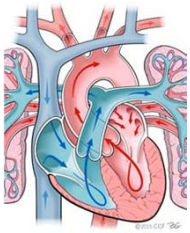
Fetal Circulation



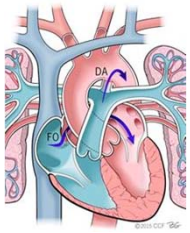
Pulmonary Vascular Transition



Fetal Circulation: PPHN



Normal

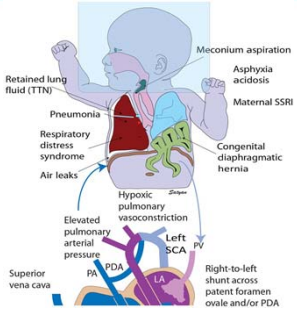


PPHN

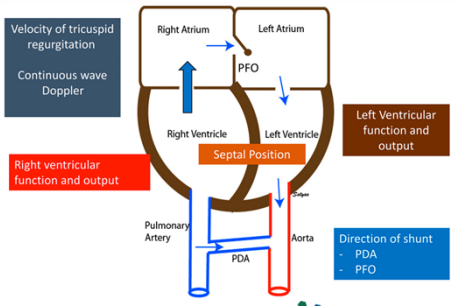
Pathophysiology

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

Pathophysiology

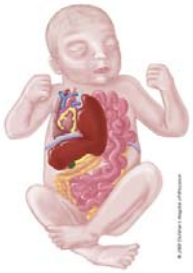


Diagnosis of PPHN



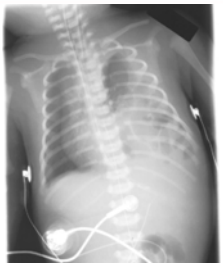
Congenital Diaphragmatic Hernia

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



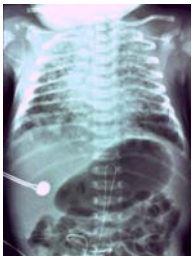
Congenital Diaphragmatic Hernia

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



Meconium Aspiration Syndrome

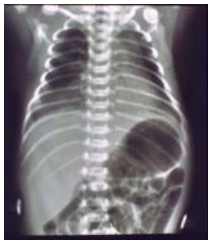
- Most common reason for neonatal ECMO overall, highly successful (94% ECMO survival)
  - Referred early
- Non-homogeneous disease—areas of atelectasis mixed with over-distention
- Hypoxia/Acidosis/PPHN/Air leak

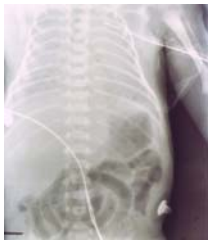


Meconium Aspiration Syndrome

- 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



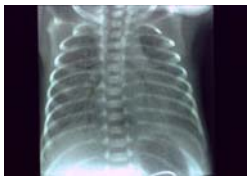


Pneumonia

- 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%

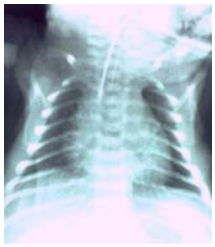
Respiratory Distress Syndrome

- 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



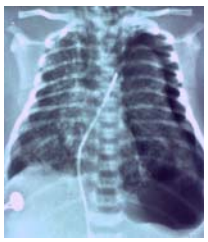
Persistent Pulmonary Hypertension

- 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%

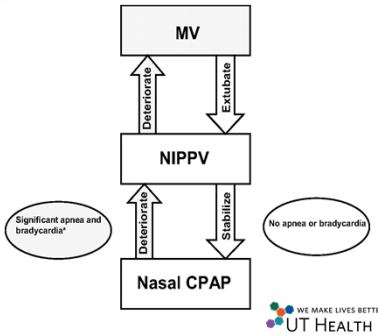


Management of PPHN

- Mechanical Ventilation
  - SIMV modes
  - HFV
- Medications
  - Inotropes
  - Vasodilators
  - Surfactant

Mechanical Ventilation

Escalation of Resp Management



Mechanical Ventilation

- Mainstay of treatment of neonatal respiratory failure
- Improved CO_2 removal by increased minute ventilation
- Improved O_2
  - Increased FIO_2
  - Increased Paw

But…it may cause

- Oxygen / inflammation injury
- Pressure / volume injury

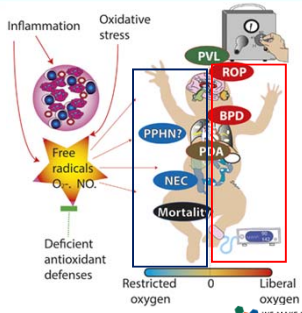
Conventional Ventilation

- "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

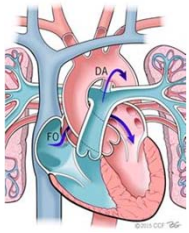
- Adverse outcome in PPHN significantly related to duration of hyperventilation
- Hyperventilation associated with sensorineural hearing loss
- Oxygen toxicity
  - Direct injury

Oxygen Toxicity



Current Practice

- Permissive hypercapnia/normocapnia
  - Decreased duration of ventilation
  - Lower tidal volume strategies
- Acceptance of low/normal pO_2 levels
  - Lower PIP and higher PEEP
  - Avoid reduction/swings in cerebral blood flow

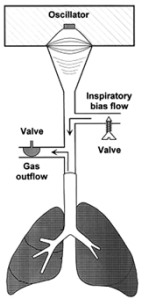


SIMV in Neonates

- 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

High Frequency Ventilation



High Frequency Ventilation

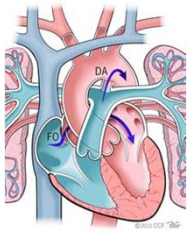
- More successful with RDS or pneumonia than CDH or MAS
- Responders usually demonstrate response within 2-4 hours
- Among ECMO candidates:
  - Carlo: HFJV reduced P_{aw} and $PaCO_2$, but no difference in outcomes vs CMV
  - Clark: 31% vs 60% failure for HFOV vs CMV
  - May offer additional benefit 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 → L shunt
- Dopamine
  - Increases SVR and PVR
  - May lead to decreased LV output
- Dobutamine
  - Inotrope + vasodilator
    - May increase LV output by decreasing afterload

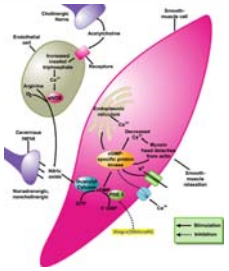


Medical Therapy: Inotropes

- 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

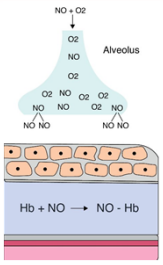
Medical Therapy: Nitric Oxide

- 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



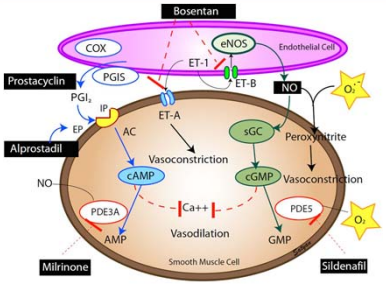
Medical Therapy: Nitric Oxide

- 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?

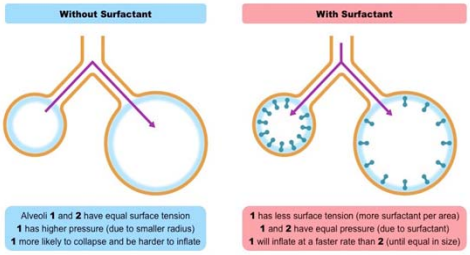
Flolan (Epoprosterenol, PG I2)

- 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

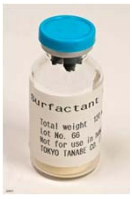


Medical Therapy: Surfactant

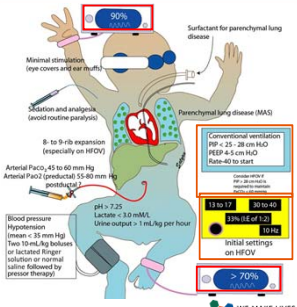


Surfactant Use

- 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

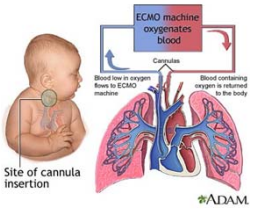


Extra Corporeal Membrane Oxygenation (ECMO)

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

ECMO Respiratory Criteria

- Oxygenation Index
  - [(Paw x FIO2)/PaO2] x 100
  - OI > 40 x 3 hrs
  - Post ductal
- AaDO2
  - [(Patm – 47) x FIO2] – paO2 – pCO2
  - 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

Physiologic Complications	Mechanical Complications
Intracranial Bleeding	Failure of oxygenator
Bleeding from surgical site	Pump failure
Hemolysis	Tubing rupture
Seizures	Cannula
Neurologic Complications	
Arrhythmia	
Pneumothorax	

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 ?

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References

- S Lakshminrusimha. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates. *Journal of Perinatology* (2016) 36, S12–S19. doi:10.1038/jp.2016.44
- S Lakshminrusimha. The fetal circulation, pathophysiology of hypoxemic respiratory failure and pulmonary hypertension in neonates, and the role of oxygen therapy. *Journal of Perinatology* (2016) 36, S3–S11. doi:10.1038/jp.2016.43.
- ELSO Neonatal Respiratory Failure Supplement to the ELSO General Guidelines 2013.
- Zwischenberger JB, Bartlett RH . "ECMO: Extra corporeal cardiopulmonary support in critical care", Extra corporeal life support organization, 2nd edition 2000.
- University of Rochester Medical Center, Rochester, NY, Neonatal ECMO guidelines 2014.
- Revenis ME, Glass P, Short BL: Mortality and morbidity rates among lower birth weight infants (2000 to 2500 grams) treated with extracorporeal membrane oxygenation. J Pediatr 1992, 121(3):452-458.
- Hardart GE, Hardart MK, Arnold JH. Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptional age. J Pediatr 2004, 145(2):184-9.

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