Persistent Pulmonary Hypertension of the Newborn (PPHN)

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Disclosure

- I have nothing to disclose.

Introduction

- Achieving successful transition from intrauterine to extrauterine life is dependent upon significant physiologic changes in cardiopulmonary function that occur at birth. In majority of infants, these changes are successfully completed at the time of delivery without requiring any special assistance.

- 10% of neonates will need some intervention, and <1 % will require extensive resuscitative measures at birth.

- The most critical period during this transition are the first few hours after birth when multiple organ systems adapt.

- The vulnerable newborn is particularly at risk during this period, and early signs of clinical instability need to be recognized early not only to ensure immediate survival but also to prevent morbidities that will have life-long consequences.

Objectives

1. Review fetal circulation

2. Stress the importance of the processes involved in neonatal transition from intrauterine to extrauterine environment

3. Review the pathophysiology and management of persistent pulmonary hypertension of the newborn

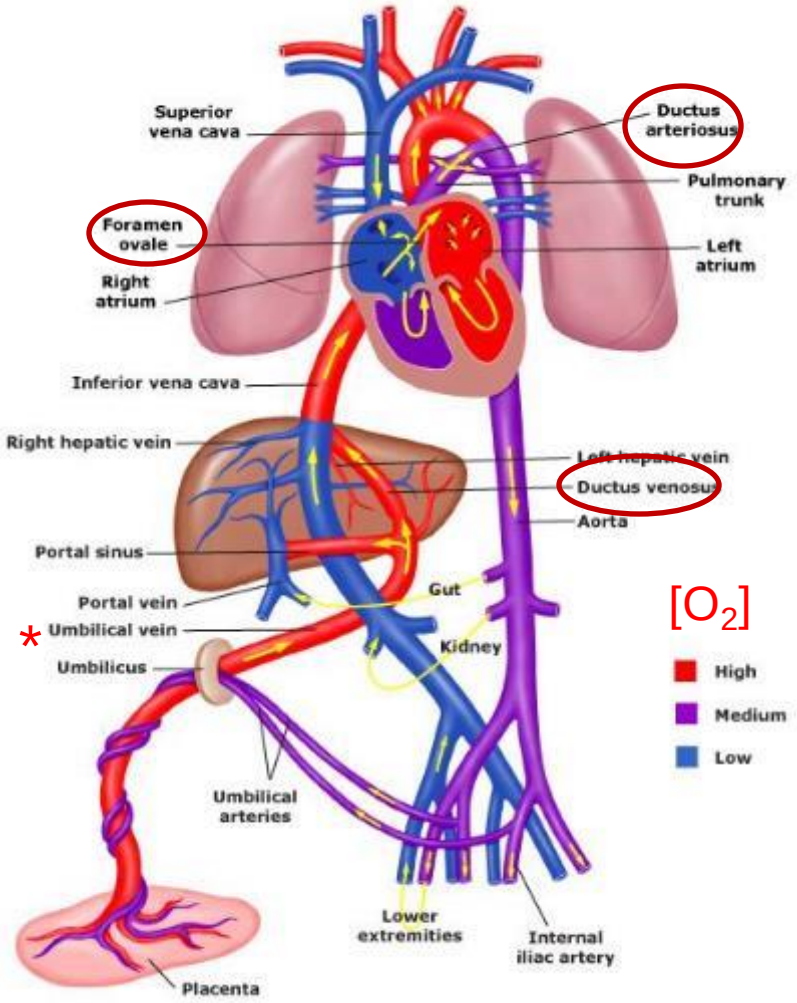
Neonatal Transition

- "Switch"
  - Fetal → Neonatal circulation

- Clearance of lung fluid

Background: Fetal to Neonatal Circulation

Fetal circulation



- Fetal shunts: (R to L shunt)
  - DV; DA; FO; high PVR (Lung)
- * Umbilical vein delivers oxygenated blood
  - Mixing from IVC and SVC in RA → LA (50-60%) via FO
- RV → PA
  - 90% shunted via DA to Aorta → distributed systemically
  - 10% perfuses Lung (8% of fetal cardiac output); increases with advancing gestational age
- At birth: cord clamping → inc SVR (along with lung expansion and dec PVR)

Kiserud. The fetal circulation. *Prenatal Diagnosis* 2004

Background (Fetal to Neonatal Circulation)

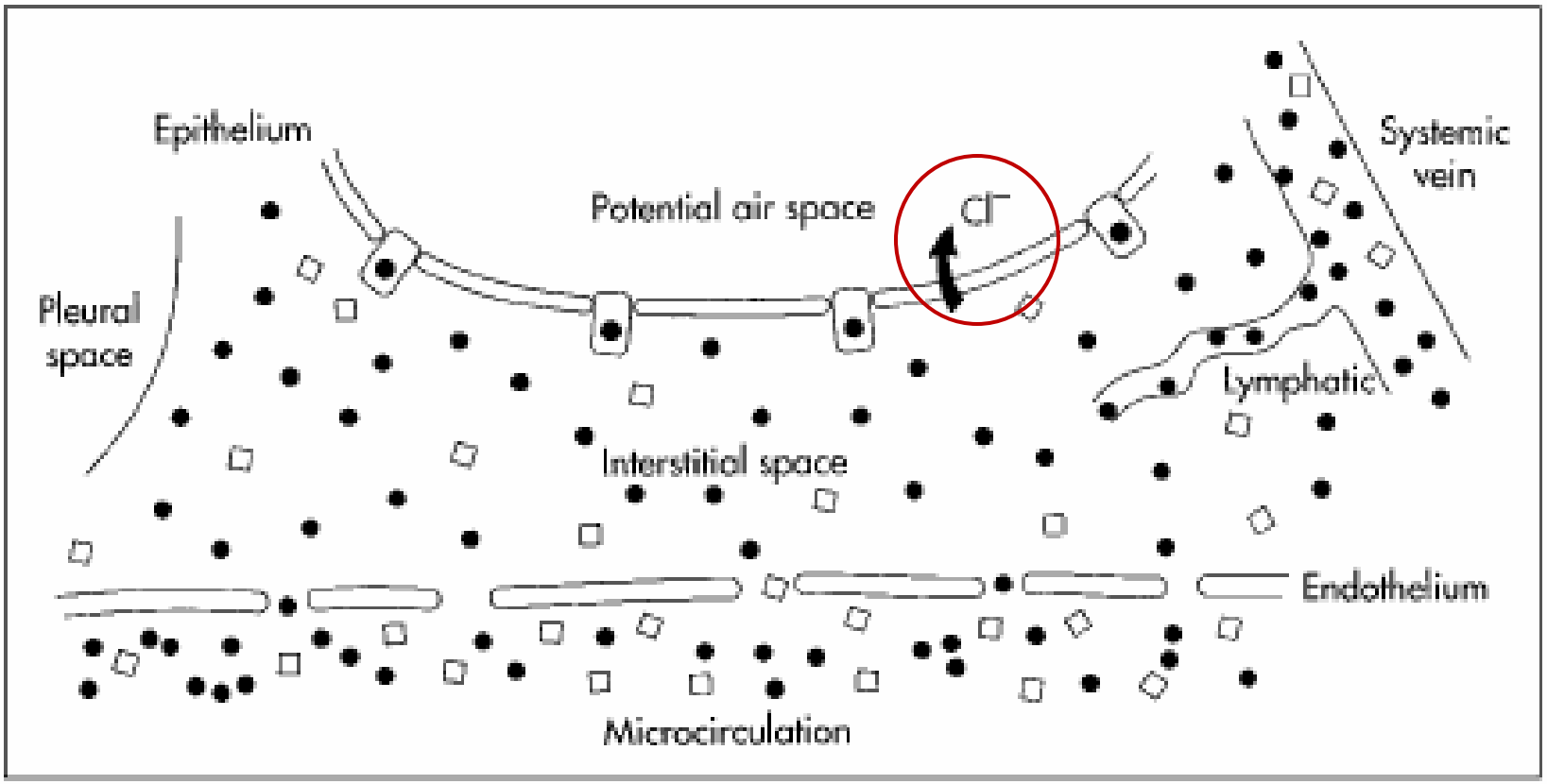
- At birth:
  - O_2 enters lungs → dec PVR → dec RA pressure
  - Inc pulm blood flow → inc venous return to LA → functional closure of FO
  - SVR rises, and with dec PVR → DA reverses flow
  - DA closure due to rising O_2 in the blood
    - Prostaglandin level drops with removal of placenta
  - Conditions such as hypoxia, acidosis, hypothermia, persistence of inc PVR → R to L shunt
    - **PPHN**
    - **Hypoxic Respiratory Failure**

Background: Fetal Lung Fluid

- Fetal lung, not the amniotic sac, is the source of fluid that fills the lung during development.
  - Fetal lung is physiologically (breathing movements) and metabolically active (surfactant, secrete liquid into potential air spaces).
  - Intrauterine lung growth depends on balance between adequate production and controlled drainage of (lung) luminal fluid.
  - Switch from placental to pulmonary gas exchange at birth requires rapid removal of fluid from the lung lumen.

Secretion of fetal lung fluid

- Schematic diagram of the fluid compartments in the fetal lung



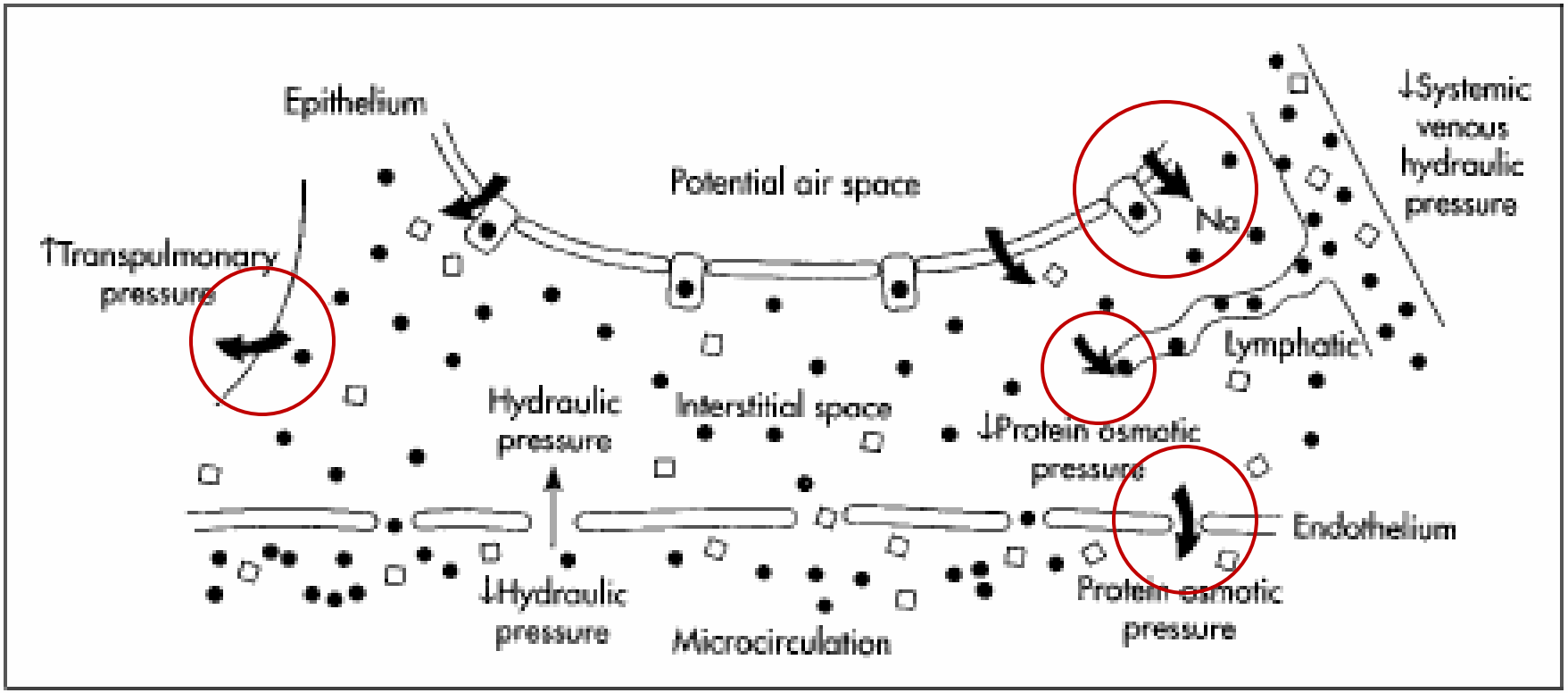
Composition and dynamics of fetal lung fluid

Table. Composition of Lung Luminal Liquid, Lymph, Plasma, and Amniotic Liquid of Fetal Lambs Late in Gestation*

	Sodium (mEq/L) [mmol/L]	Potassium (mEq/L) [mmol/L]	Chloride (mEq/L) [mmol/L]	Bicarbonate (mEg/L) [mmol/L]	pH	Total protein (g/dL) [g/L]
Luminal liquid	150±1	6.3±0.7	157±4	2.8±0.3	6.27±0.01	0.03±0.002 [0.3±0.02]
Lung lymph	147±1	4.8±0.5	107±1	25±1	7.31±0.02	3.27±0.41 [32.7±4.1]
Plasma	150±1	4.8±0.2	107±1	24±1	7.34±0.04	4.09±0.26 [40.9±2.6]
Amniotic liquid	113±7	7.6±0.8	87±5	19±3	7.02±0.09	0.10±0.01 [1.0±0.1]

*Values are mean ± SEM and are taken from the work of Adamson et al (21) and Humphreys et al (88).

(Postnatal) Clearance of fetal lung fluid



Neonatal Transition

- 2-6 hours (h)
  - Clearance of lung fluid (crackles on PE/auscultation)
  - Establish FRC (+/- barrel-chest)
  - Cardiovascular adaptation → normal pattern of oxygenation (pre-ductal O_2 sat); +/- murmur (TR)
  - Impt to maintain normothermia

  - PE: (normal pattern) Initial period of reactivity → somnolence → reactivity
    - HR changes (tachycardia → bradycardia → labile heart rates)
    - Initial grunting and nasal flaring/irregular respirations → rapid, shallow breathing → resolution of grunting and nasal flaring
    - Acrocyanosis
    - Improved muscle tone

Postnatal adaptations: what can go wrong?

- Respiratory
  - Failure to clear lung fluid
  - Failure to establish a regular pattern of respiration (failure of effective ventilation)
  - Failure to establish oxygenation ("persistent fetal circulation" → **PPHN**)

- Thermal regulation
  - Hypothermia
- Metabolic regulation
  - Hypoglycemia

Neonatal Transition "Red Flags"

- Persistence (and progression) of symptoms **>2h** duration

- Worsening respiratory distress
  - Moderate-to-severe respiratory distress: grunting, nasal flaring, marked retractions and need for supplemental O_2 beyond 2h of age

- Apnea in a late preterm (PT) or term newborn
- Central cyanosis
- Poor muscle tone

Problems During Neonatal Transition (DDx)

- Respiratory:
  - TTN; **RDS**; MAS; **PPHN**; Pneumonia/Sepsis; Air leak syndrome; Pulmonary hypoplasia; Congenital lung anomalies
- Cardiovascular
  - CCHD (PDA-dependent lesions)
- Metabolic
  - Hypoglycemia (IDM; LGA; SGA; Prematurity, etc)
- Hypothermia
- Infection
  - Early-onset sepsis (EOS) (GBS, E coli, etc)

What can "derail" normal transition?

- Maternal:
  - Gestational Diabetes; Hypertensive Disorders of Pregnancy; Infection; Cardiac and Respiratory Disorders; Anemia
- Fetal/Neonatal:
  - Prematurity; Postmaturity; Congenital Anomalies; Birth Trauma
- Antepartum:
  - IUGR; Multiple Gestation; Malpresentation; PIH; Illicit Drug Use; Placenta Previa/Abruption
- Intrapartum:
  - Fetal Distress; PROM/PPROM/PPPROM; Chorioamnionitis; Maternal Fever; MSAF; Operative Delivery (C/S +/- labor; Vacuum; Forceps); Malpresentation (Breech, Shoulder Dystocia); MSAF; Narcotics and Magnesium Sulfate administration

"Transition" Disorders: Common Thread

- Respiratory distress:
  - Apnea, cyanosis, grunting, inspiratory stridor, nasal flaring, tachypnea, retractions (intercostal, subcostal, suprasternal)
  - ± O2 requirement
  - ± Ventilatory support

PPHN

Persistent Pulmonary Hypertension of the Newborn

- With lung expansion (first breaths) after birth, pulmonary vascular resistance (PVR) dec, and systemic vascular resistance (SVR) inc.

- **PPHN** occurs when PVR remains elevated after birth, resulting in R->L shunting of blood through fetal circulatory pathways (PFO and PDA), leading to severe hypoxemia that may not respond to conventional respiratory support.
  - PVR dec: lung expansion (adequate ventilation and oxygenation); lung fluid clearance
  - SVR inc: removal of placenta, catecholamine surge at birth, cold environment

PPHN

Persistent Pulmonary Hypertension of the Newborn

- Prevalence: ~ estimated 1.9/1000 live births
- Conditions that interfere with normal postnatal decline in the PVR/SVR ratio cause fetal/transitional circulation to persist and result in PPHN.
- Occurs primarily in term or late preterm infants ≥34wks gestation.
- Abnormalities of the pulmonary vasculature underlie the disorder: underdevelopment, maldevelopment, and maladaptation.

PPHN

- Abnormalities of the pulmonary vasculature: underdevelopment, maldevelopment, and maladaptation.
  - **Underdevelopment**: pulmonary hypoplasia (relatively fixed elevation of PVR)
    - Associated with: congenital diaphragmatic hernia (CDH), congenital pulmonary (CPAM) malformation, renal agenesis, oligohydramnios (renal/obstructive uropathy), and fetal growth restriction.
  - **Maldevelopment**: abnormal muscle layer thickening of pulmonary arterioles in a normally developed lung; extracellular matrix that surrounds the pulmonary vessels also is excessive. Remodeling of the pulmonary vascular bed is thought to occur during the first 7-14d after birth leading to fall in PVR.
    - Associated with: postterm delivery, MSAF/MAS; premature DA closure (e.g., caused by nonsteroidal anti-inflammatory drugs [NSAIDs]) or FO closure, high placental vascular resistance, and TAPVR.
  - **Maladaptation**: active pulm bed vasoconstriction in a normally developed lung that interfere with the normal postnatal fall in PVR.
    - Associated with: perinatal depression, pulmonary parenchymal diseases, and bacterial infections (esp GBS sepsis → mechanism of increased PVR is activation of vasoactive mediators by bacterial phospholipid components).

PPHN: Clinical Features

- Prenatal factors
  - Signs of intrauterine and perinatal asphyxia: fetal HR abn (bradycardia and tachycardia)
  - MSAF (Mec-Stained Amniotic Fluid)
  - In utero exposure of selective serotonin reuptake inhibitors (SSRIs) during second half of pregnancy (associated with a sixfold inc risk of PPHN)
  - PPROM

- Neonatal findings
  - Present within the first 24h of life with signs of respiratory distress (e.g., tachypnea, retractions, and grunting) and cyanosis)
  - Low APGAR scores
  - Received DR interventions incl O_2, bag/mask vent, and endotracheal intubation

Walsh-Sukys *Pediatr* 2000

PPHN: Clinical Features

- PE: characterized by cyanosis and signs of resp distress; mec-staining (indicative of intrauterine stress); prominent precordial impulse, narrowly split and accentuated S2; harsh systolic murmur (tricuspid insufficiency)

- Other accompanying diagnosis(es): (NICHD Cohort)
  - MAS (41);
  - Pneumonia (14);
  - RDS (13);
  - CDH (10);
  - Pulmonary hypoplasia (4)
  - Idiopathic (17)

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PPHN: Diagnostic Tests

- **Pulse oximetry:**
  - >10% difference between the pre- and postductal O_2 sat (due to R->L shunt through PDA). NOTE: absence of a pre- and postductal gradient in oxygenation does **not** exclude the Dx of PPHN, since R->L shunting can occur predominantly through the FO rather than the PDA.

- **Arterial blood gas:**
  - Low PaO_2 (<100 mmHg on 100% FiO_2), esp postductal samples. However, vs infants with cyanotic CHD, many PPHN infants have at least one measurement of PaO_2 >100 mmHg early in the course of their illness.
  - $PaCO_2$ is normal in infants without accompanying lung disease.
  - The R->L shunt through PDA can also be documented in differences in PaO_2 between samples obtained from the R radial artery (preductal sample) and the UAC (postductal sample).

- **Chest XR:**
  - Usually normal or demonstrates findings of an associated pulmonary condition (e.g., parenchymal disease, air leak, or CDH); heart size typically normal or slightly enlarged; pulmonary blood flow may appear normal or reduced.

- **Echocardiogram:** definitive diagnosis of PPHN

Walsh-Sukys *Pediatr* 2000

PPHN: Echocardiogram

- Definitive diagnosis of PPHN; essential in any infant with unremitting cyanosis unexplained by parenchymal lung disease, and to exclude structural heart disease.
  - Normal structural cardiac anatomy with evidence of pulmonary hypertension (PH), (e.g., flattened or displaced ventricular septum)
  - Doppler studies show R->L shunting through PDA and/or PFO. Continuous-wave Doppler measurement of the velocity of a tricuspid regurgitation (TR) jet (if present) using a modified Bernoulli equation can be used to estimate RV systolic pressure (RVp). In the absence of RV outflow obstruction, PA systolic pressure can be calculated (peak pressure difference = 4 x [peak TR velocity]^2), which is elevated in patients with PPHN.
  - Assess ventricular function
  - Provide estimation of PH severity

PPHN: Echocardiogram

- Estimation of RVp, using assessments of TR jet and/or changes in septal position, is compared with systemic BP, and the degree of atrial and/or PDA shunting is determined.

- Estimations of severity of PPHN:
  - Mild-moderate PPHN – Est RVp between 1/2 to 3/4 syst BP
  - Moderate-severe PPHN – Est RVp > 3/4 syst BP but < syst BP
  - Severe PPHN – Est RVp > syst BP
  - Evidence of RV dysfunction suggests severe PH
  - Evidence of biventricular dysfunction may represent global insult (e.g., perinatal depression)

PPHN: DDx

- 1. Cyanotic congenital heart disease (CHD) - distinguished from PPHN by echo.
- 2. Primary isolated parenchymal lung disease (e.g., neonatal Pneumonia, MAS, TTN, and RDS - differentiated from PPHN by the clinical setting and chest radiography. Note: most patients with PPHN will also have an associated lung disorder. In these patients, echo confirms PPHN.
- 3. Sepsis - distinguished by the clinical setting, positive blood cultures, and echo. PPHN may occur as a component of sepsis in a neonate.
- 4. Alveolar capillary dysplasia - misalignment of the pulmonary veins (ACD-MPV)
  - Rare disorder; may have similar presentation as severe PPHN (severe hypoxia that is refractory to general supportive care).
  - However, ACD-MPV pts typically have initial period of stability and develop severe hypoxemia later than PPHN after the first few hours or days of life.
  - If ACD-MPV is suspected, further eval incl catheterization and lung biopsy to confirm Dx.

PPHN: Management

- General supportive cardiorespiratory care.
- (Pulmonary) Vasodilators (e.g., [iNO]) to reduce the ratio of PVR/SVR; provide adequate tissue oxygenation until PVR falls
- ECMO
- Specific Rx for any associated parenchymal lung disease (e.g., antibiotic therapy for pneumonia, or surfactant for RDS, etc)

PPHN: Management

- **Assessment of severity of hypoxemia:**
  Oxygenation Index (OI):
  - Guides the timing of interventions (iNO or ECMO)
  - OI calculation:
    - **OI = [mean airway pressure x FiO_2 ÷ PaO_2] x 100**
  - High OI indicates severe hypoxemic respiratory failure. A term or late PT infant with an OI ≥25 should receive care in a center where HFOV, iNO, and ECMO are readily available.
  - For OI <25, general supportive care is typically adequate and no further invasive intervention is usually required.

Chest XR (CXR)

- **CXR**: differentiating various causes of respiratory distress
  - **RDS**: low lung volume, ground glass appearance, air bronchograms, reticulo-granular pattern and white out lung
  - **TTN**: prominent central perihilar vascular markings, edema of the interlobar septae, fluid in the interlobar fissures, mild cardiomegaly, minimal pleural effusion, and hyperinflation
  - **MAS**: diffuse, asymmetric patchy infiltrates, areas of consolidation, often worse on the right, hyperinflation and sometimes + air leak syndrome
  - **Pulmonary hypoplasia**: low lung volume on the affected side with mediastinal shift to the same side (esp in CDH)
  - **Air leak syndrome**: extra-alveolar air - pneumothorax (air collection in pleural space), pneumomediastinum (collection of air in mediastinum), pneumopericardium (collection of air around heart in pericardium), and pulmonary interstitial emphysema (PIE - presence of air in the lung interstitium)
  - **CDH**: + chest bowel loops; hints about severity of lung compromise and help in prognostication

Summary

- Resuscitation and stabilization
  - Achieve FRC and facilitate lung fluid clearance
  - Teamwork and effective communication
  - Prevent hypoxia
  - Delayed cord clamping
- Prevent hypothermia
  - Maintain neutral thermal environment
- Prevention of sepsis

Physiologic effects of Hypothermia

- Hypoxia
  - Inc O_2 need for thermogenesis which can lead to hypoxia, results in inc resp distress and inc O_2 requirements, desaturations
  - Can lead to anaerobic metabolism and pulm vasoconstriction
  - Can lead to SA inactivation, pulm hge, and resp failure
  - Twice as much O_2 is needed when an infant's temperature is 35^0C vs 37^0C
- Hypoglycemia
  - Inc metabolic demand to produce heat
  - Poorly timed increased glucose need - stores are diminished and may have a delay in glucose delivery depending on vascular access
- Respiratory and metabolic acidosis
  - Anaerobic metabolism and continued hypoxia can lead to lactic acidosis which can compromise cardiac output and worsen the acid/base balance
- Cardiovascular compromise
  - Bradycardia, hypotension, dec perfusion → impaired contractility and function
- Neurologic compromise
  - Inc permeability of the blood-brain barrier
  - Could increase risk for IVH, with alteration in SVC flow and hypoperfusion

Bibliography

- References will be provided upon request.

Thank you!

Questions?