Persistent Pulmonary Hypertension of the Newborn

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Baby L

- Born at 31 weeks via induced vaginal delivery after mom presented and suspected DKA in the setting of type 1 diabetes and suspected preterm labor.
- Pregnancy further complicated by PPROM noted on admission (30w 4d)
- Mom developed worsening respiratory distress and eventual respiratory failure.
- Given clinical deterioration, cervical change on exam and new presence of MSAF, and new concern of IAI, decision made to augment labor. Full course of betamethasone completed 2 days prior to delivery
- 2120g (LGA) infant delivered; Required PPV; transitioned to CPAP and transferred to NICU in 50% FiO2. APGARs: 2/8

In the NICU

- Admitted on nCPAP 6/50% FiO2 -> increased to nCPAP 7 shortly after arrival
- Steady increase in FiO2 despite in … ductal monitoring was initiated; s… times)
- Infant was intubated and subsequ… persistent FiO2 requirement great…
  - VCAC –5 ml/kg; PEEP: 6; RR: 30
    - 7.17/68/-5 -> TV increased to 6 ml/kg;
    - Inhaled nitric oxide started (CV); s/p E…
    - PIPs: 25-30; Fio2: 100% to maintain sa…

00-06	06-12	12-18	18-00	00-06	06-12	
90	100+					FiO2
VC-AC	STAN… +					Mode
30	40+					Rate
10.6	12.6					Vt
0.3	0.35+					I-Time
0.05	0+					Slope
6	7					PEEP
	0.2+					Trigger
	42	34	36	36+	46	AMP (OSC)
	100	40+	55	48+	75+	FiO2 (OSC)
	12	12+	12+	12+	12+	Freq (OSC)
	0.33	0.33+	0.33+	0.33+	0.33+	%I: Time (…
	Y	Y+	Y+	Y+	Y+	Piston Ce…
	20	20+	20+	20+	20+	Flow (OSC)
	18	20	20+	20+	20	MAP/PAW…

In the NICU

- Fio2 requirement improved with transition to HFOV, iNO, and most notably with adequate sedation; labile hypoxemia for several days
- Neuro: Infant noted to be intermittently agitated; responded well to intermittent fentanyl boluses thus fentanyl drip was initiated; Precedex added due to ongoing agitation; gradually weaned while back on CV
- Cardiovascular: Required BP support (Epi -> Norepi) in first day of life; Weaned off and remained hemodynamically stable afterwards

- We will circle back to Baby L at the end...

Objectives

- Review of fetal circulation and transitional physiology
- Pathophysiology of PPHN
- Managment of PPHN

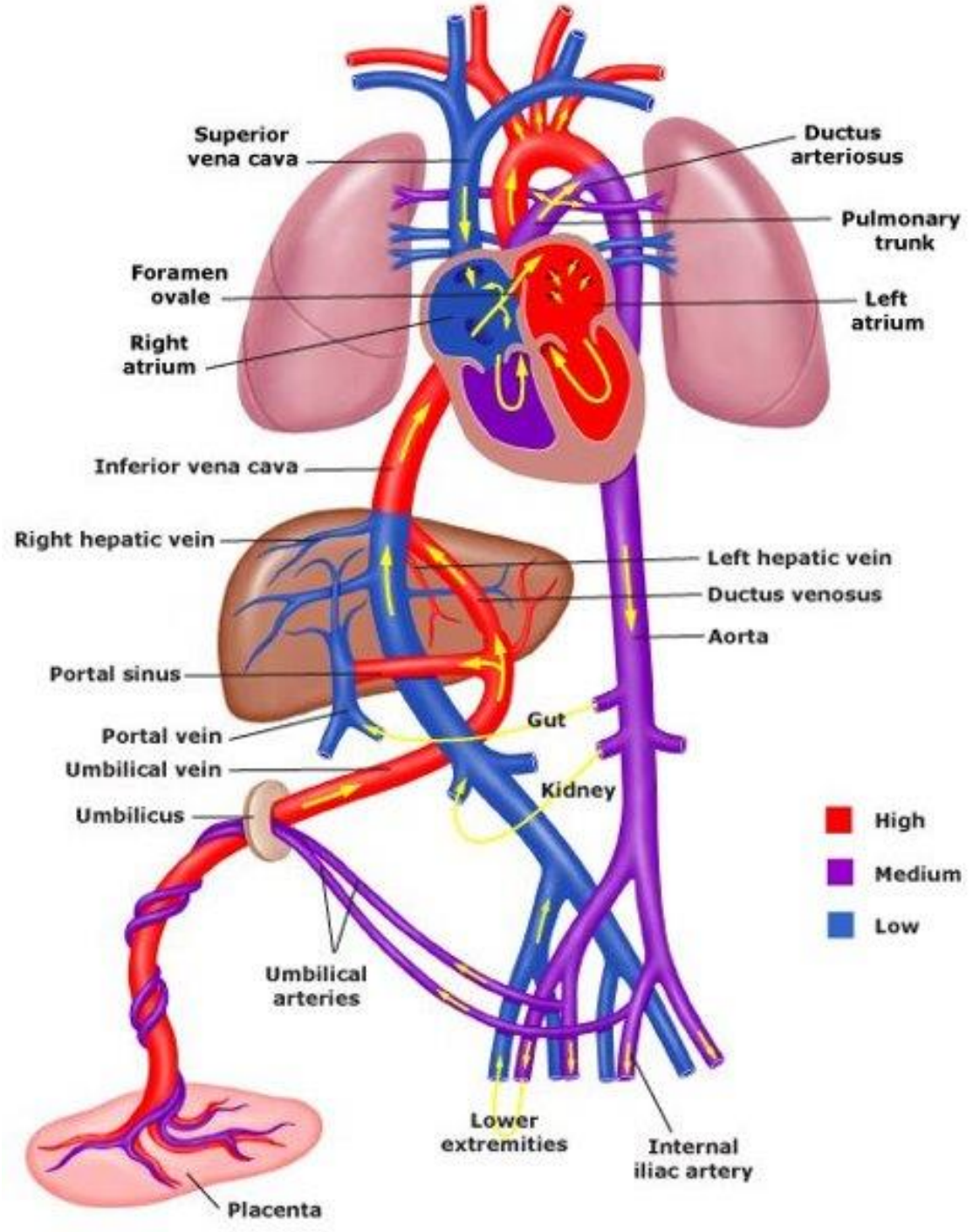
Epidemiology of PPHN

- Affects ~2 / 1,000 live births
- Risk factors:
  - maternal diabetes
  - maternal obesity
  - AMA
  - SSRI exposure
  - LGA, SGA,
  - meconium-stained fluid (directly or due to perinatal stress)
  - PPROM in preterm infants

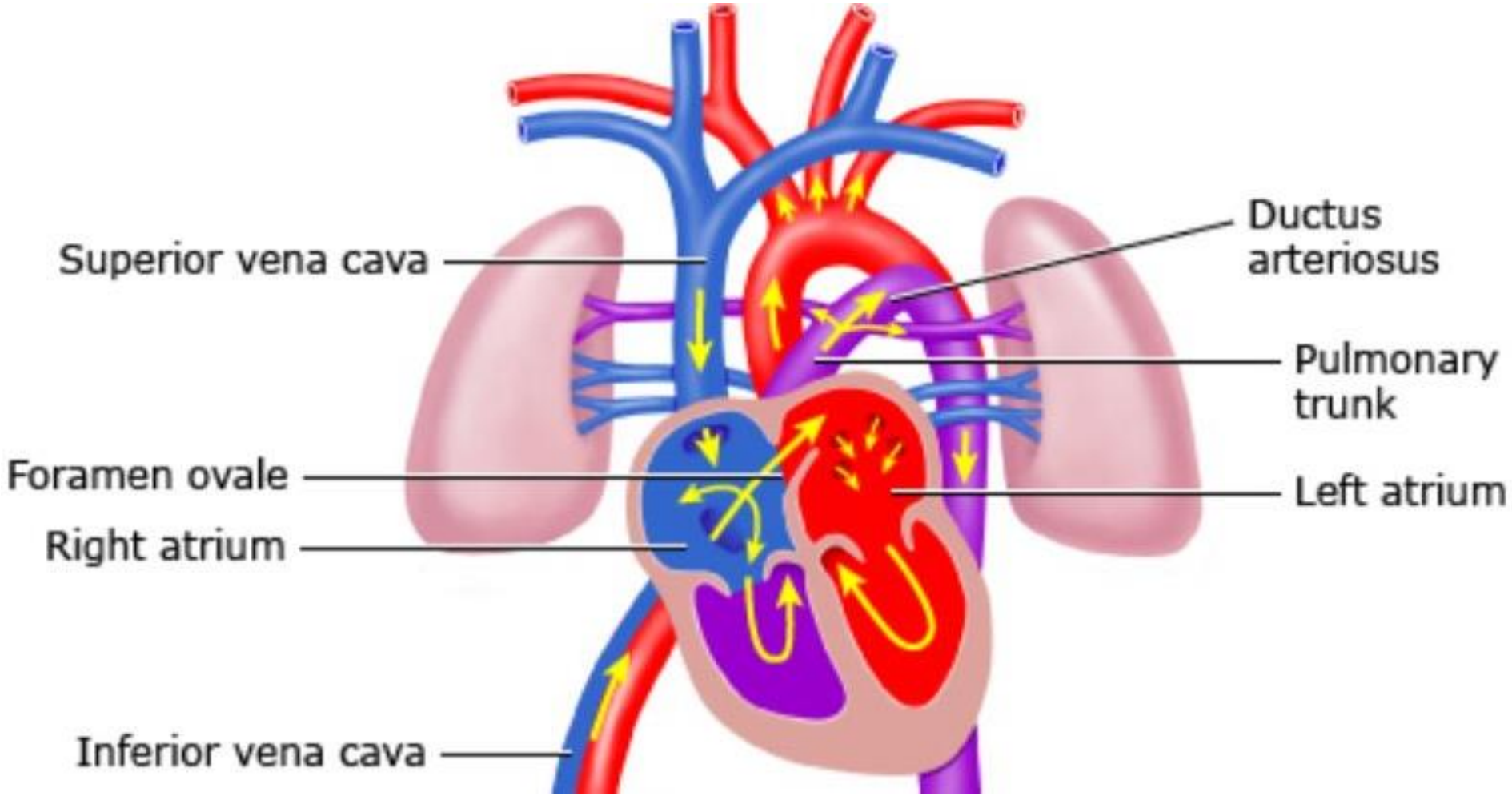
What is PPHN?

Fetal Circulation

- Placenta serves as site for gas exchange
- Oxygenated blood travels from UV→Ductus Venosus→IVC→RA

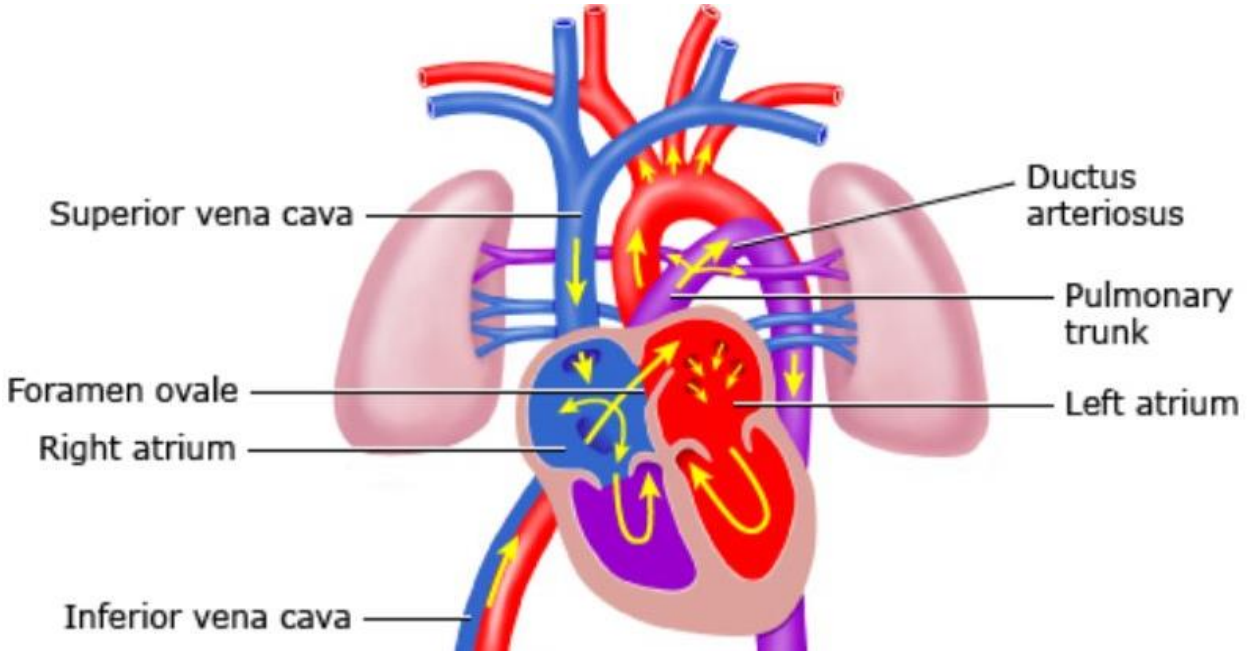


Fetal circulation



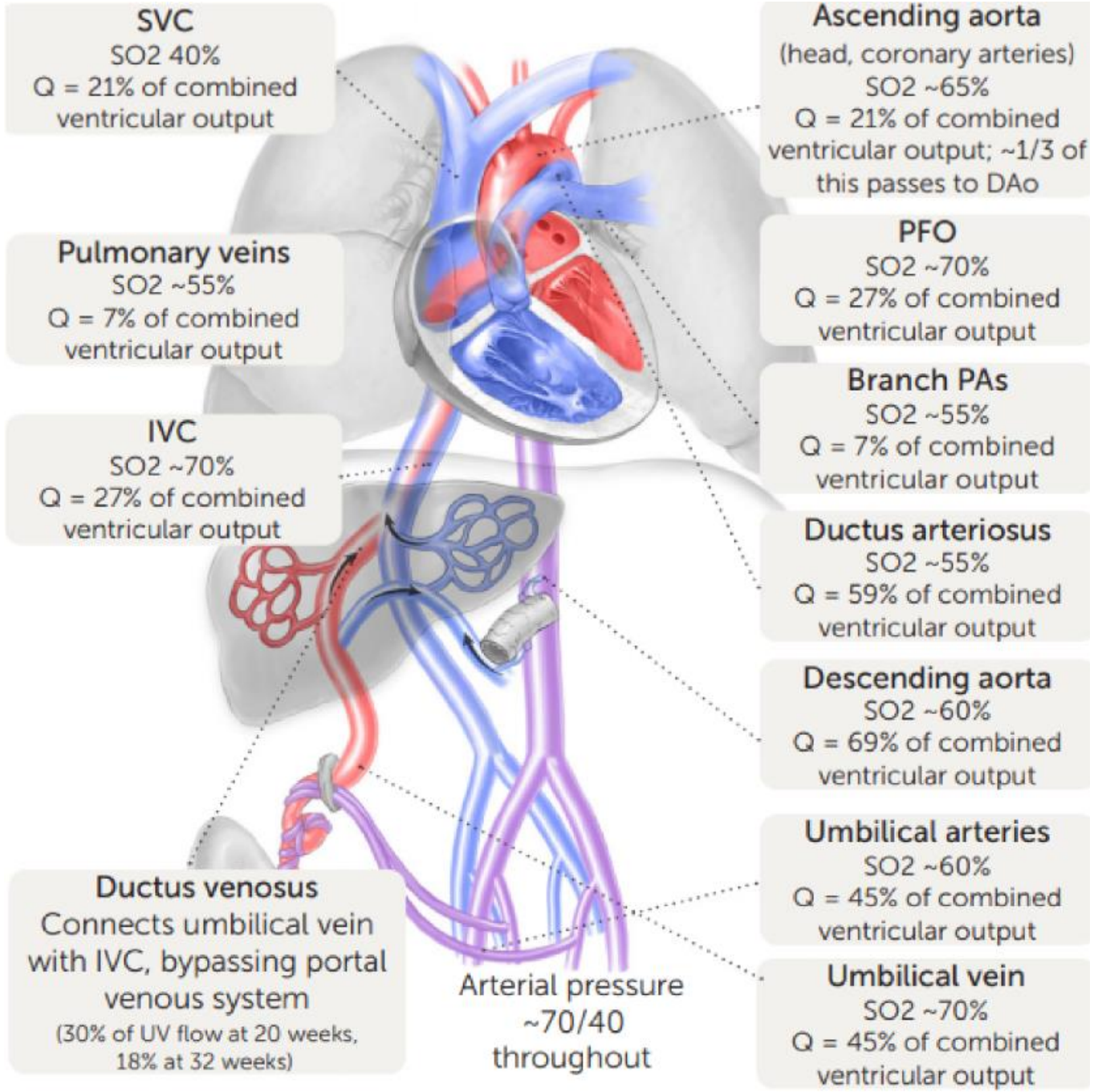
Fetal circulation

- High PVR with decreased PBF is normal fetal physiology
  - hypoxic pulmonary vasoconstriction
  - Fluid filled lungs
  - High levels circulating Vasoconstrictors:
    - Endothelin 1, Leukotriene and Thromboxane
  - Low levels of circulating vasodilators:
    - Nitric oxide, prostaglandins
- Pulmonary reactivity to vasodilators increases with increasing gestational age



Fetal Circulation

- Low blood oxygen content (placental PO2 of 30 mmHg)
  - Fetal hemoglobin becomes ~70% saturated
  - ‘Left shift’ of Hgb F permits oxygen offloading from mother to baby



Transitional Circulation

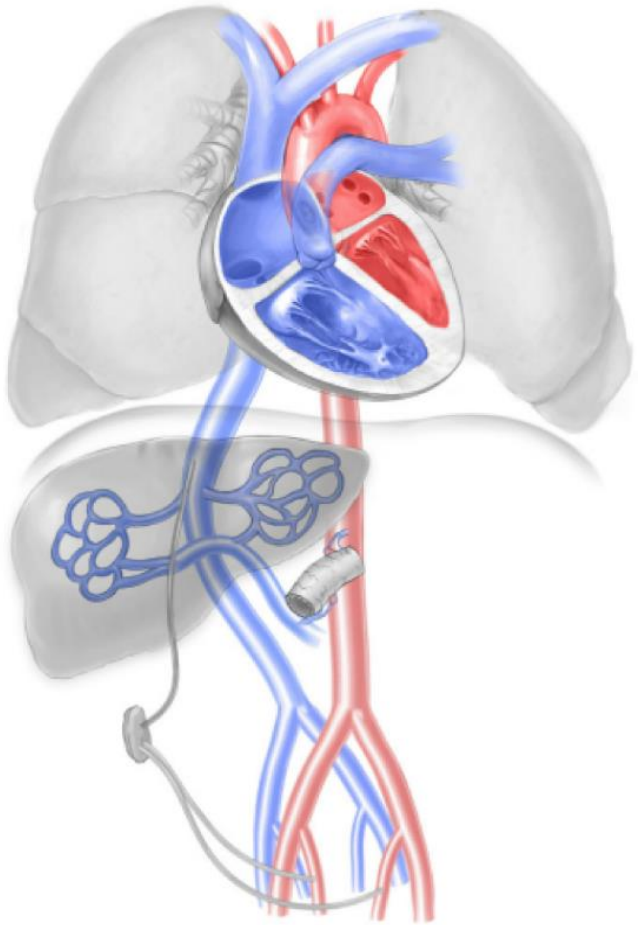
PVR decreases
as lungs fill with air, oxygen vasodilates, atelectasis resorbed

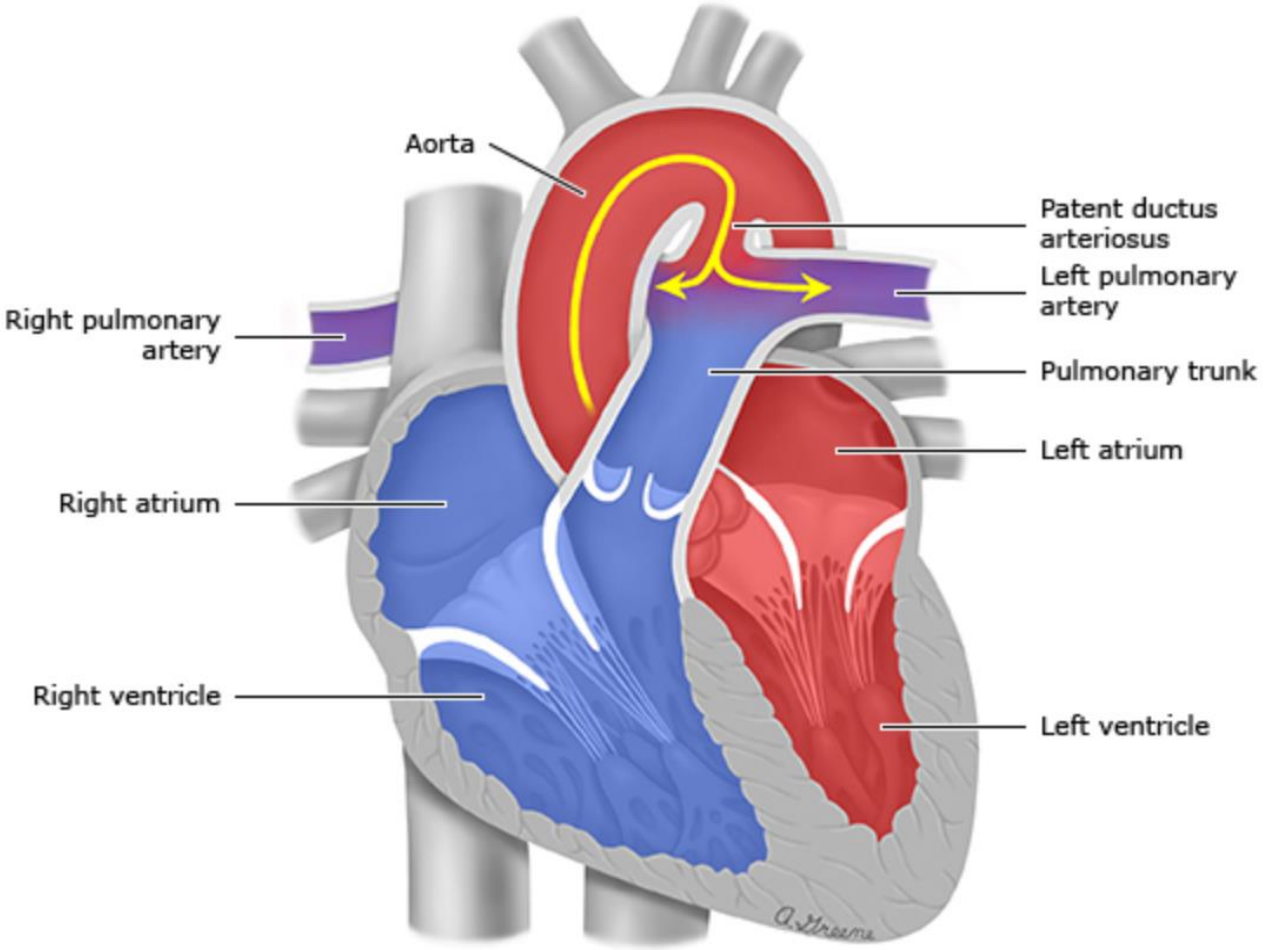
PFO closes
LAP > RAP due to increased PBF and decreased SBF

Placenta excluded
from circulation, removing a low resistance component of systemic circulation, raising SVR

PDA closes
due to hyperoxia and other hormal factors

Ductus venosus closes
within minutes-hours of birth due to hyperoxia and other hormal factors

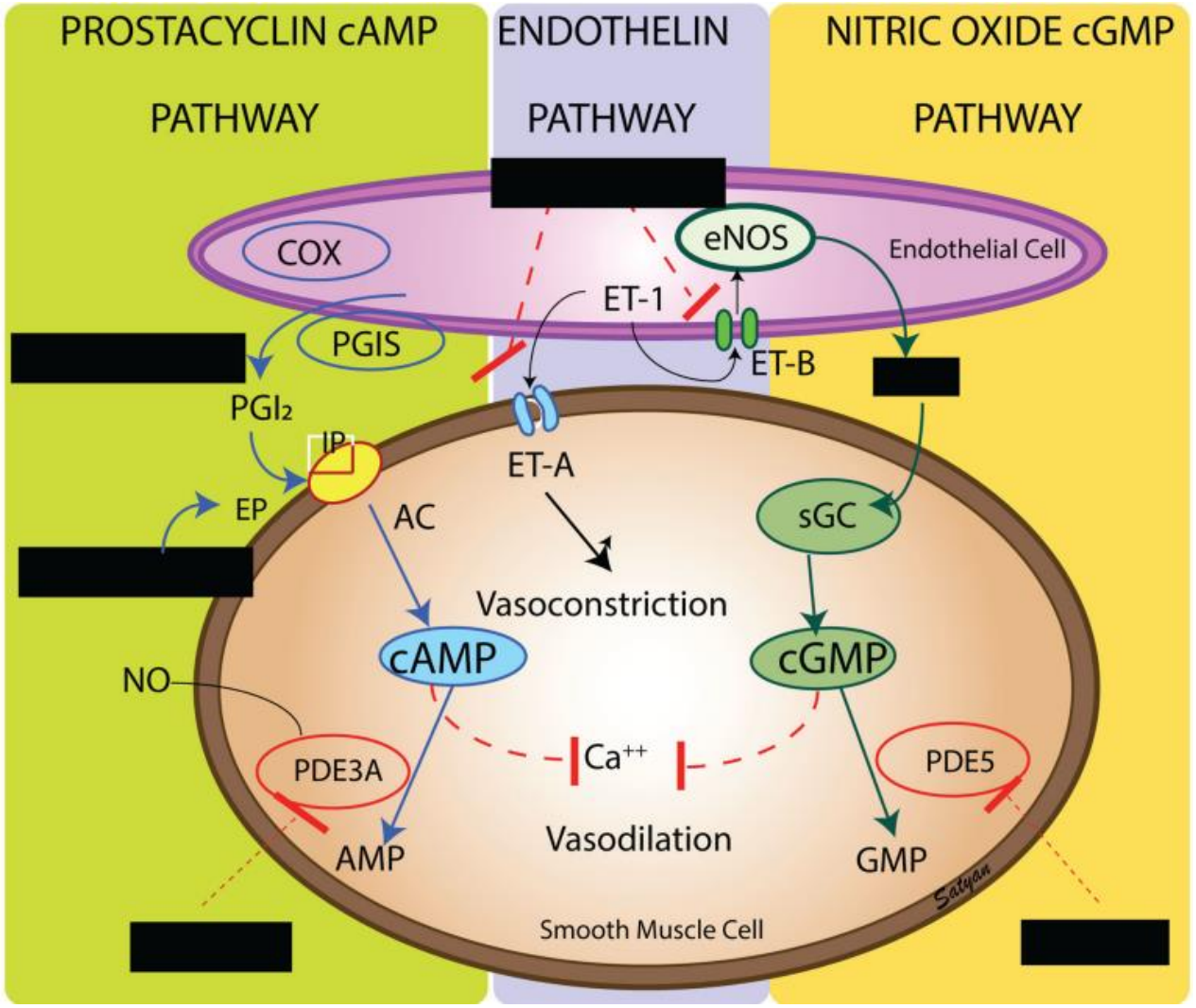




Transitional Circulation: Endothelial Mediators

- Increased oxygenation and shear stress from increased PBF activates pathways

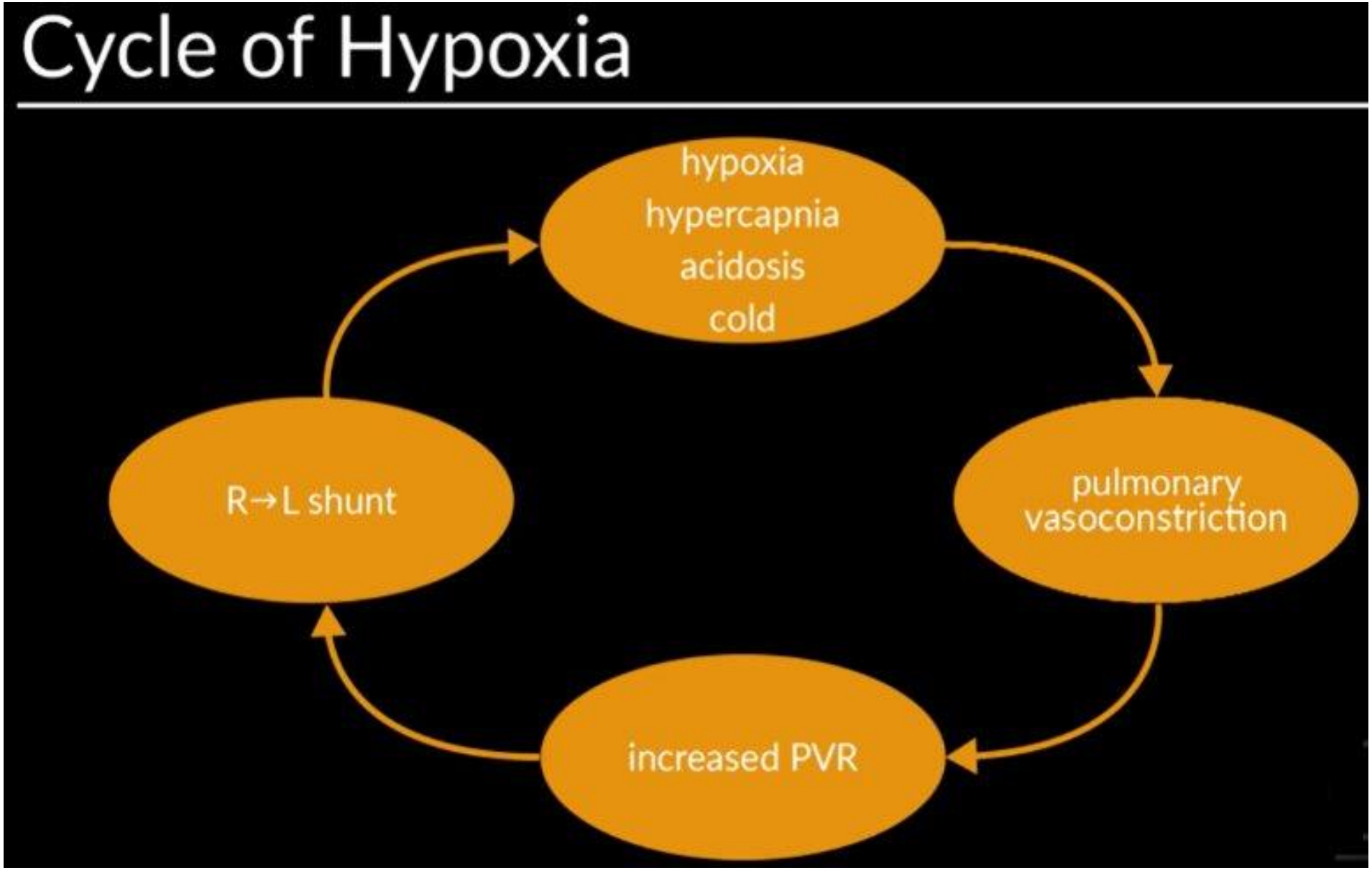
- NO increases cGMP; Prostacyclin increases cAMP
  - Both reduce Ca^{2+} in smooth muscle cells leading pulmonary vasodilation

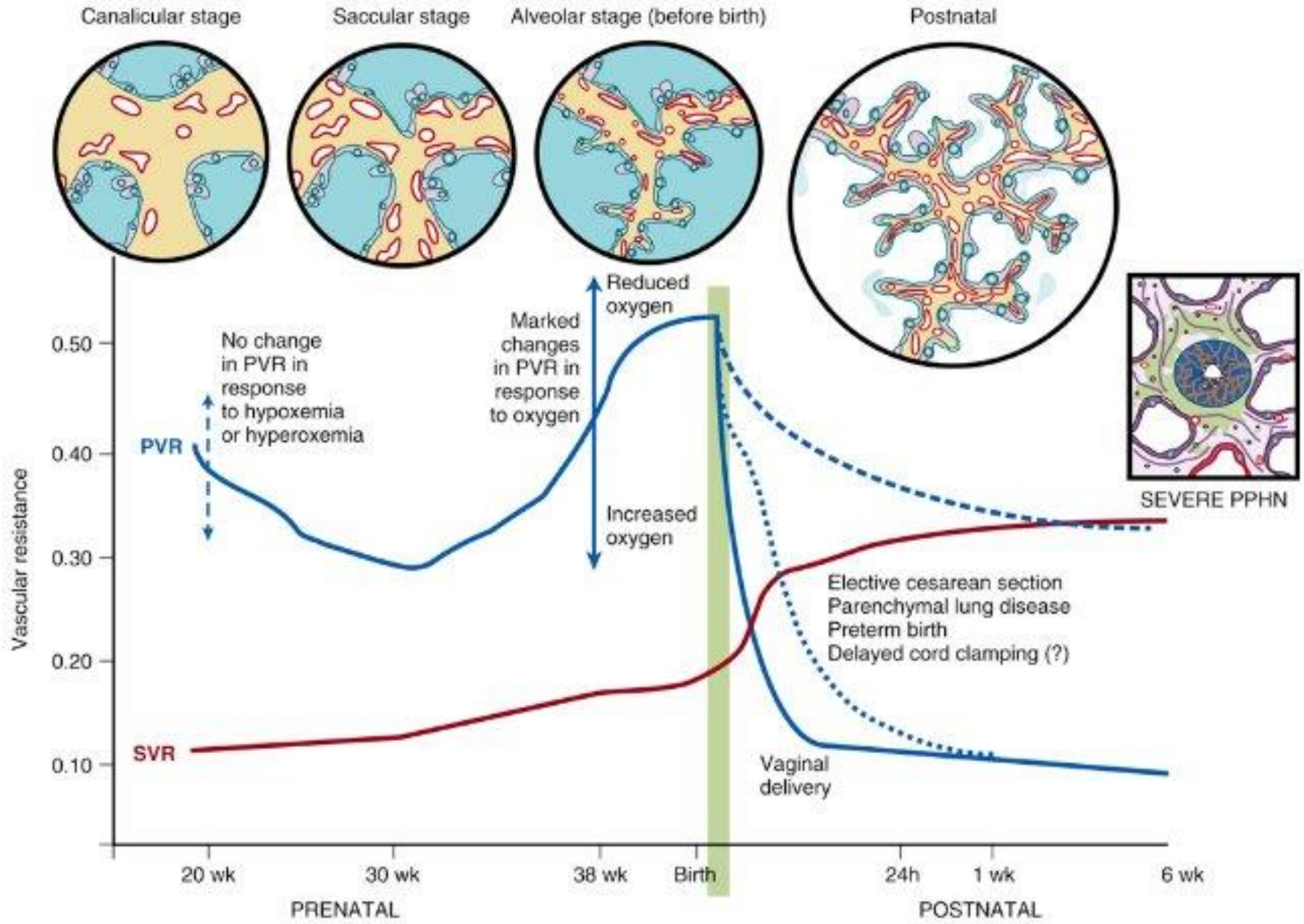


Pathophysiology

- Complex, multifactorial and dynamic – it evolves with time and is significantly affected by the intervention and disease process
- Hallmark:
  - Persistently increased PVR -> Decreased Pulmonary blood flow and right-to-Left shunting across PDA and PFO -> hypoxia, decreased end organ perfusion, acidosis and cyanosis
- Hypoxemia and acidosis are potent vasoconstrictors leading to increase in PVR and worsening of PPHN

Cycle of Hypoxia




Canalicular stage
Saccular stage
Alveolar stage (before birth)
Postnatal
Vascular resistance
0.50
0.40
0.30
0.20
0.10
PVR
SVR
No change in PVR in response to hypoxemia or hyperoxemia
Marked changes in PVR in response to oxygen
Reduced oxygen
Increased oxygen
Elective cesarean section
Parenchymal lung disease
Preterm birth
Delayed cord clamping (?)
Vaginal delivery
SEVERE PPHN
20 wk
30 wk
38 wk
Birth
24h
1 wk
6 wk
PRENATAL
POSTNATAL

Etiology

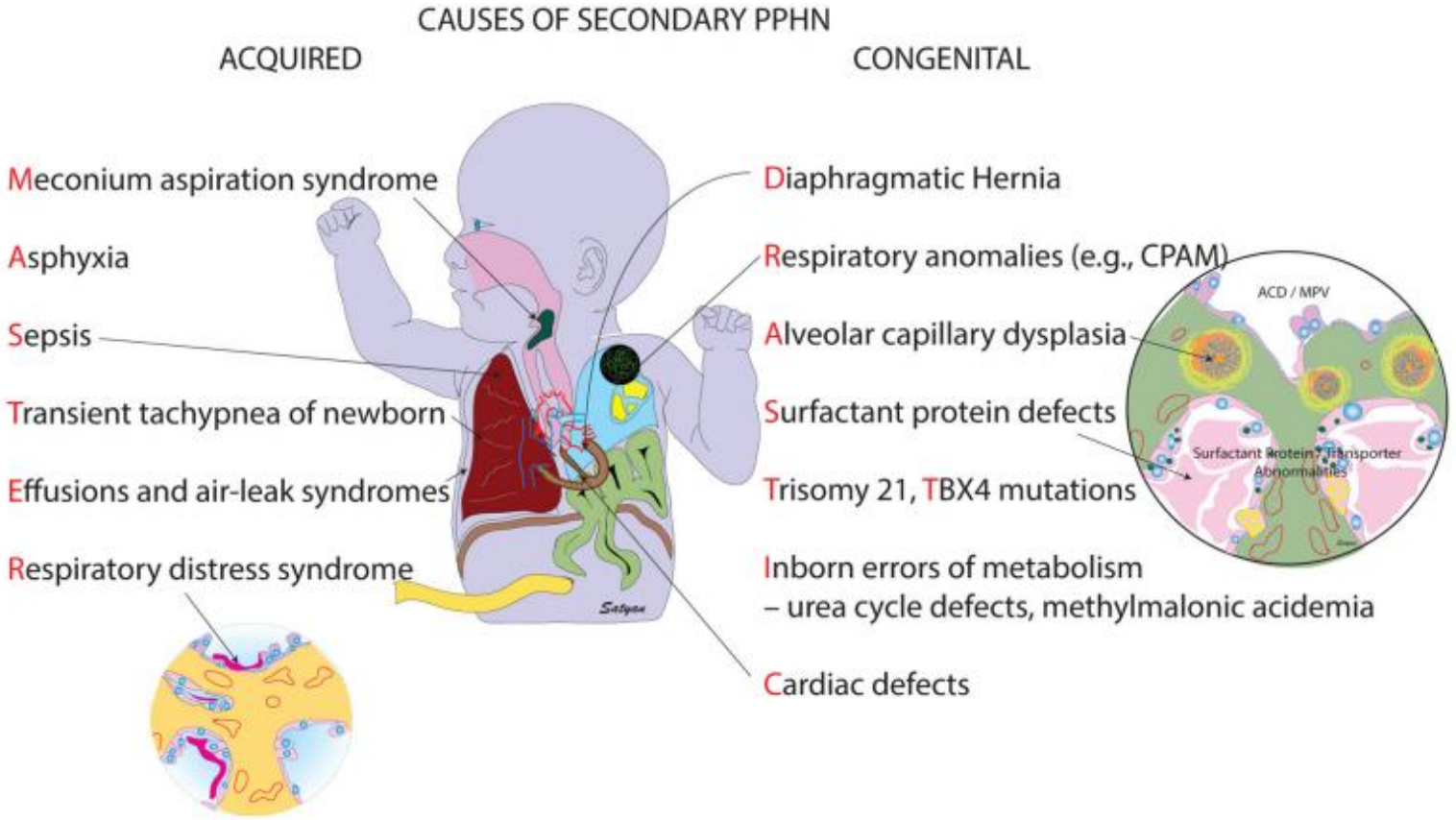
- Primary vs Secondary
- 5 Leading causes of PPHN
  - Infection (30%)
  - MAS (24%)
  - Idiopathic (20%)
  - RDS (7%)
  - CDH (6%)

SECONDARY

Parenchymal Lung Diseases:
- Meconium aspiration syndrome (MAS)
- Respiratory distress syndrome (RDS)
- Pneumonia
- Transient tachypnea of the newborn (TTN)
- Sepsis

Mal-/Underdevelopment of Lungs:
- Pulmonary hypoplasia (due to oligohydramnios)
- Congenital diaphragmatic hernia (CDH)

Intrinsic Obstruction:
- Polycythemia (leading to hyper-viscosity)

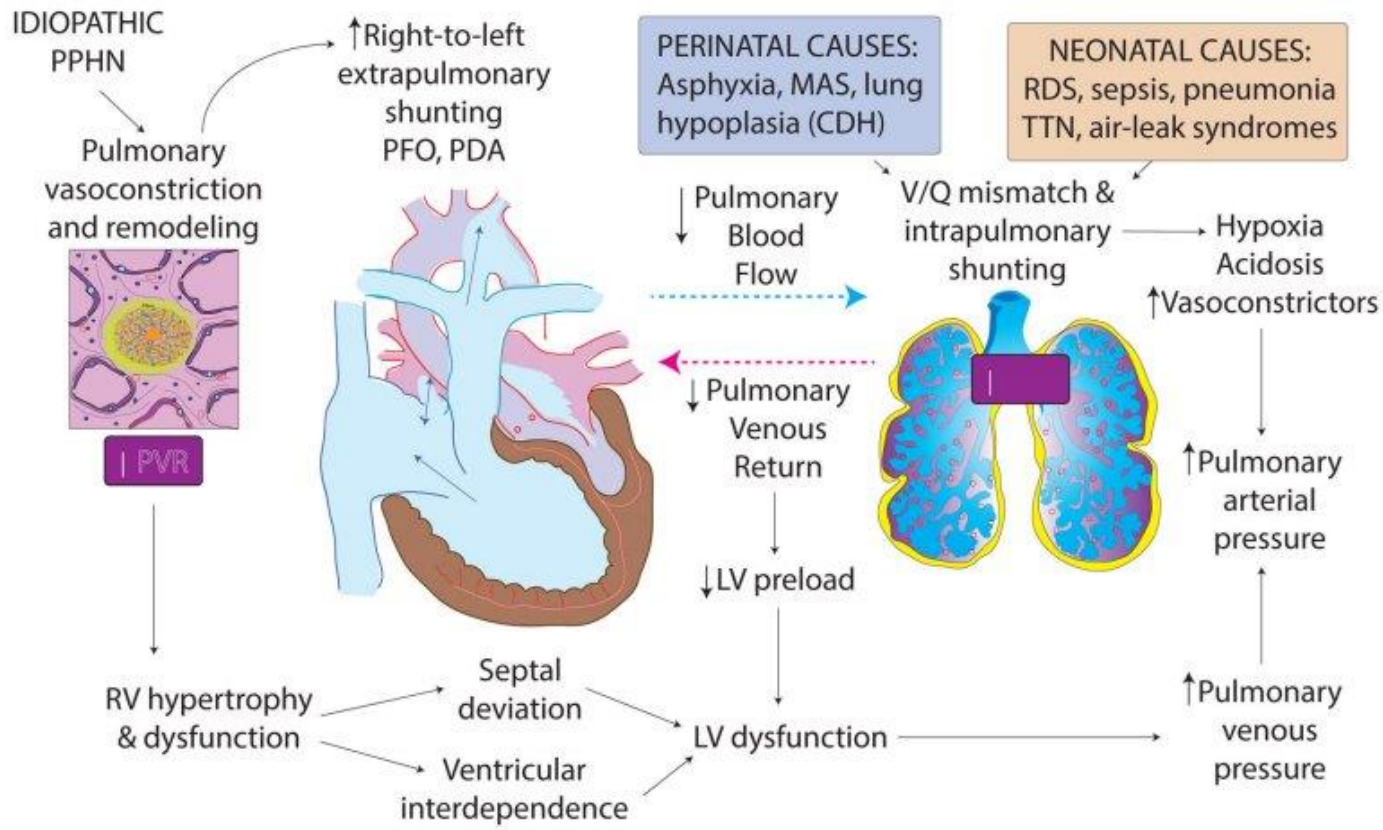


PPHN is a MASTER of disguise and can be associated with many common perinatal conditions

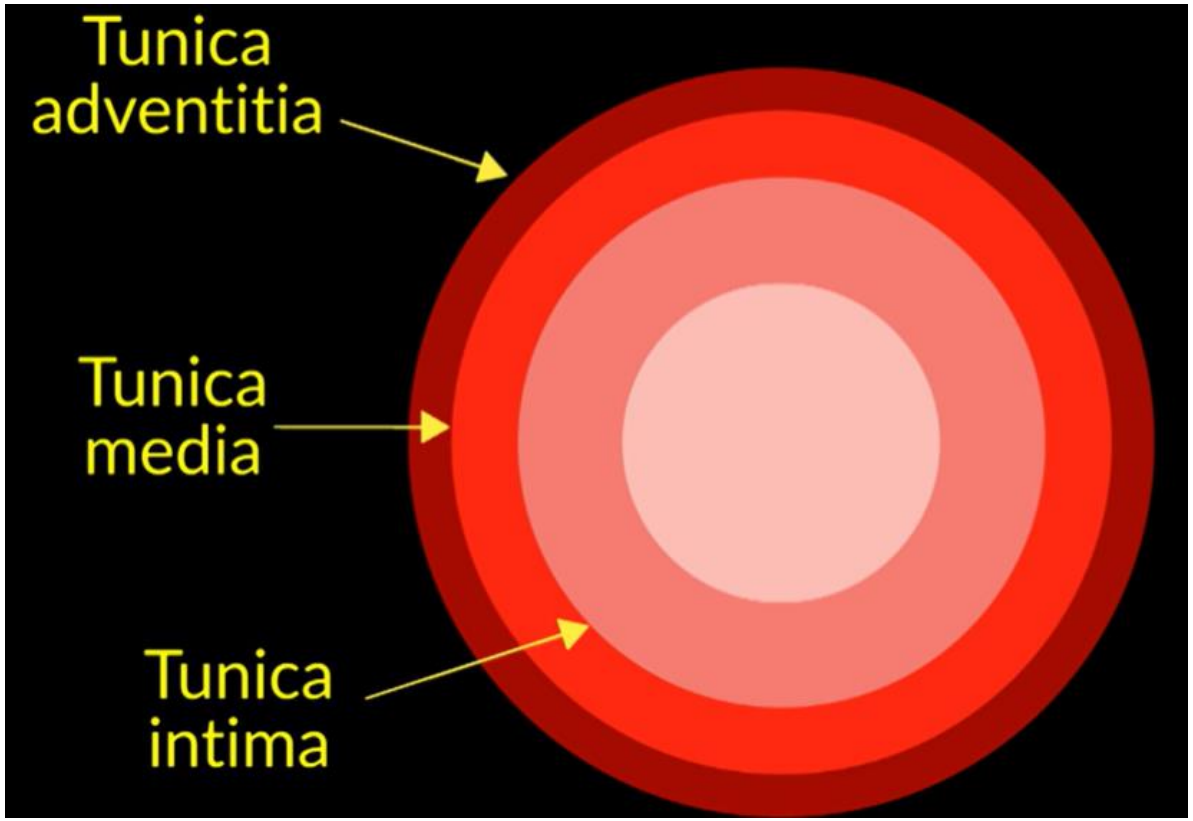
Congenital causes of PPHN, if not recognized early, can be associated with DRASTIC consequences

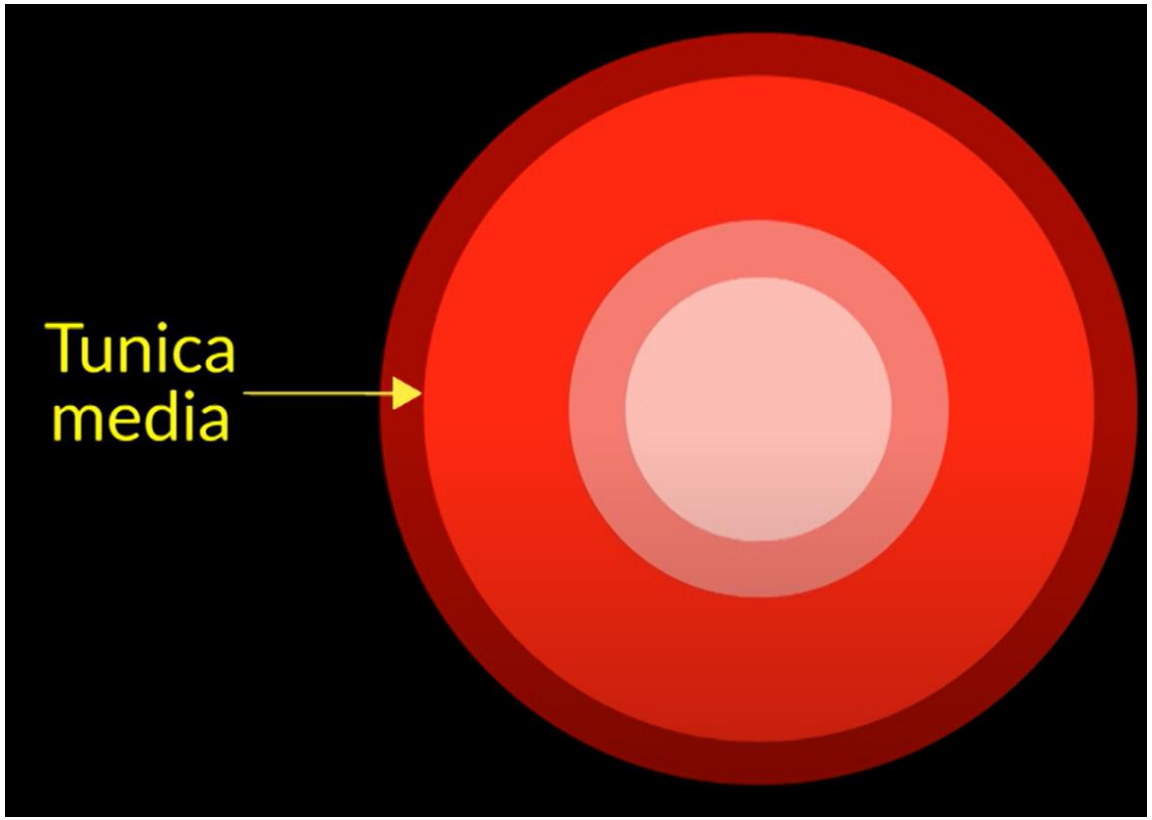
Primary or Idiopathic PPHN

- Refers to the absence of parenchymal lung disease to explain elevated pulmonary arterial pressure
- Implies intrauterine pulmonary vascular remodeling
- 10–20% of cases of PPHN are idiopathic

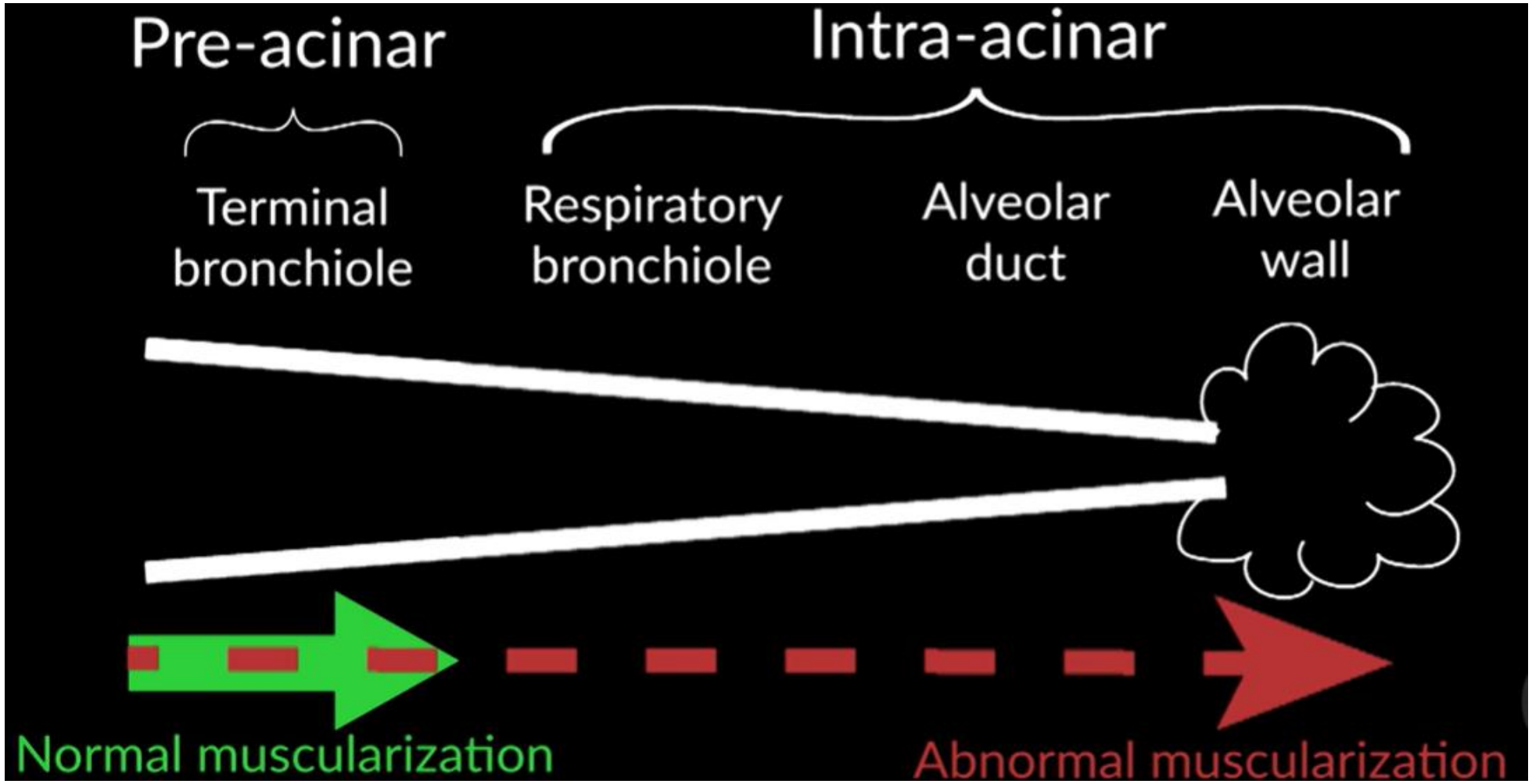


Vascular remodeling



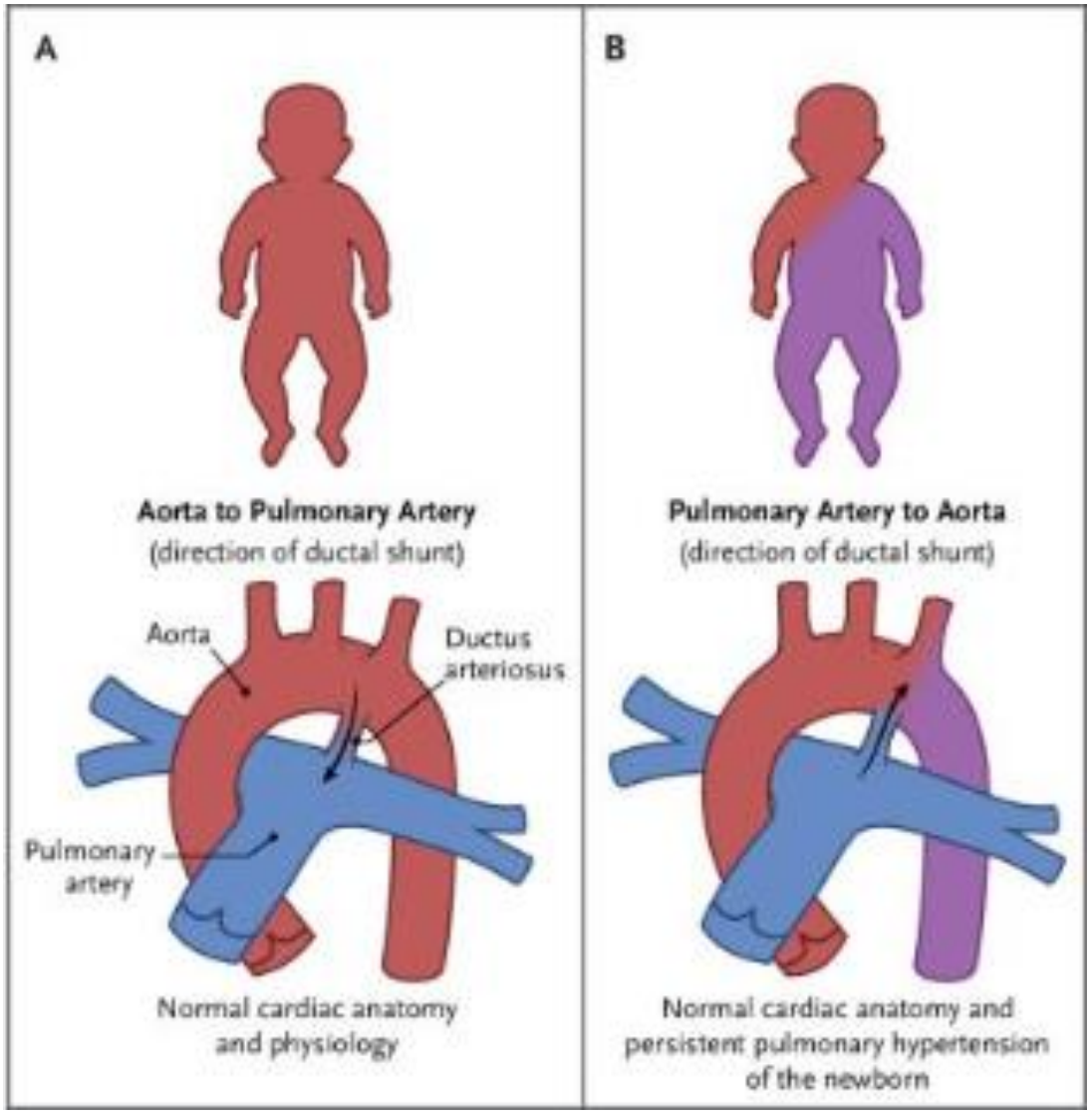


Extension of muscularization at the intra-acinar level



Clinical Findings

- Differential cyanosis
  - Post-ductal saturations >5-10% lower than pre-ductal
  - Note: if PDA is closed, the shunt is exclusively via the PFO, and thus degree of cyanosis is similar in both upper and lower extremities
- Labile hypoxemia
  - Dramatic change in O2 saturations with movement or minimal change in FiO2
- Acidosis
- Tachypnea



Extra-cardiac shunting across PDA results in more than a 10% differential between pre and post-ductal saturations

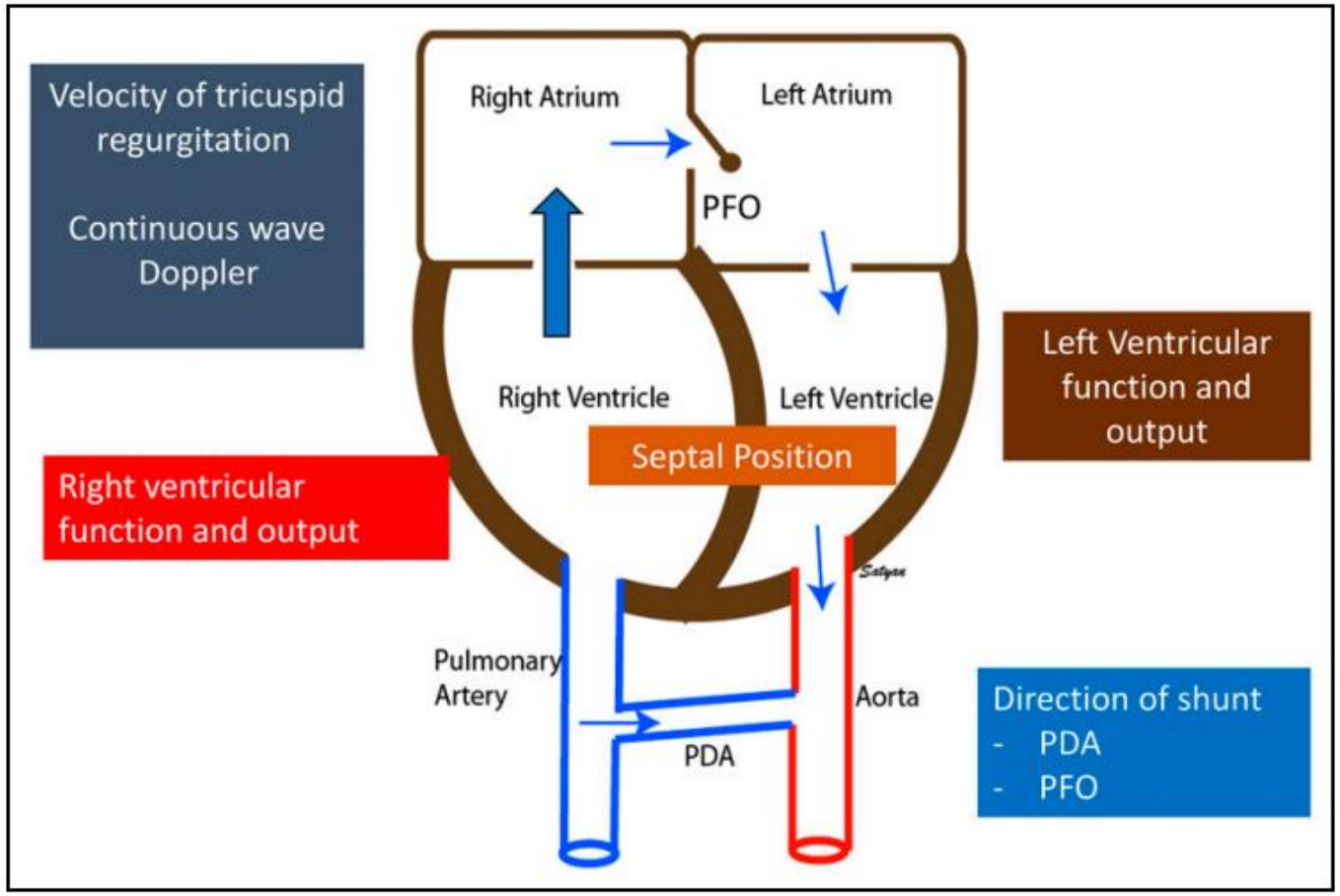
Diagnosis of PPHN

- Pre/post ductal saturation difference
  - >10%, suggestive of PPHN
  - The bigger the split, the higher the pulmonary pressure
- Hypoxemia
  - Increasing fio2 needs to maintain saturations
    - Start thinking PPHN
- Echocardiogram
  - Not measuring direct pressure in the NICU (cath)
  - Look for indirect signs - (next slide)

Oxygenation Index = (FiO_2 x P_{AW}) / PaO_2

- FiO_2 = fraction of inhaled oxygen, %
- P_{AW} = mean airway pressure, mm Hg
- PaO2 = Partial pressure of arterial oxygen, mm Hg

Echo Findings



- Leftward deviation of the interventricular septum
- Right-to-Left shunt of PFO and/or PDA
- High RV pressures lead to tricuspid regurgitation (TR)
- +/- Decreased RV/LV function

Severity Assessment

- The OI is used to categorize the severity of hypoxemia as follows:
  - Mild hypoxemia: OI <15
  - Moderate hypoxemia: OI ≥15 and <25
  - Severe hypoxemia: OI ≥25 and <40
  - Very severe hypoxemia: OI ≥40

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- FiO_2 = fraction of inhaled oxygen, %
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- Serial measurements are more informative than a single assessment

Severity of pulmonary hypertension (PH)

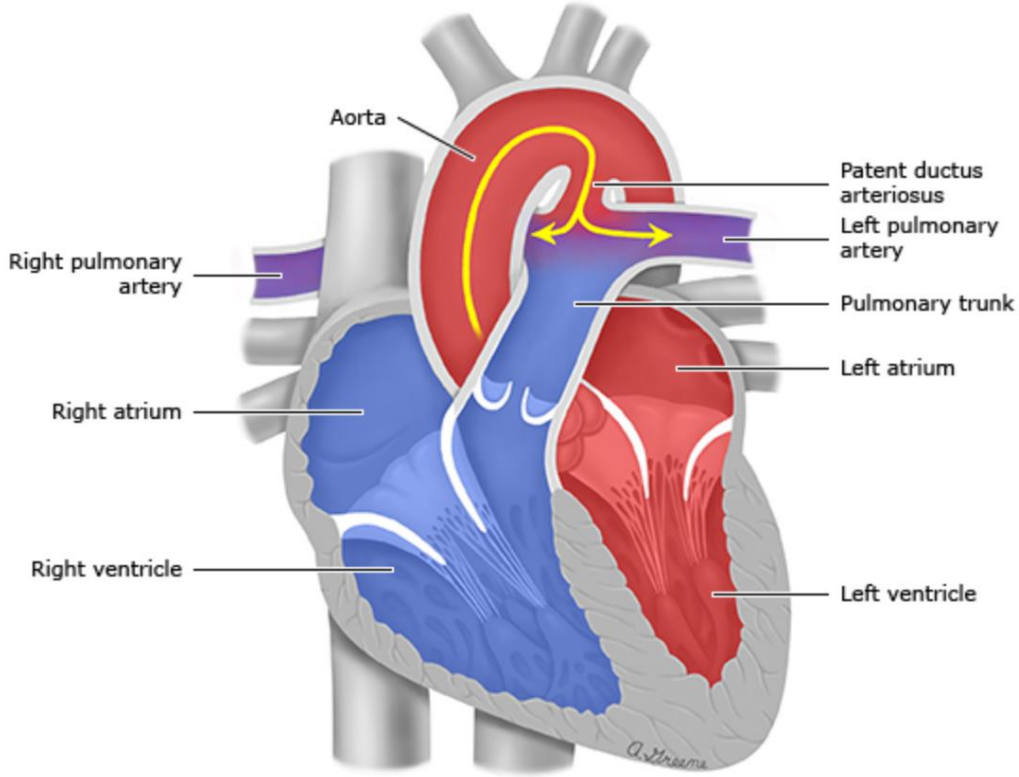
- PH severity is categorized based upon the estimated RVp relative to the systemic blood pressure (BP) as follows:
  - Mild to moderate PPHN – Estimated RVp between one-half to three-quarters systemic BP
  - Moderate to severe PPHN – Estimated RVp greater than three-quarters systemic BP but less than systemic BP
  - Severe PPHN – Estimated RVp greater than systemic BP

Goals of Management

- Treat underlying cause
- Expected to be transient, so goal is to maintain cardiopulmonary function while awaiting improvement
- Titrate ventilators, especially in preterm population, to minimize lung injury
- Maintain adequate systemic perfusion (to allow oxygen delivery)
- Avoid acidosis (as worsens pulmonary vasoconstriction)

Cardiovascular management

- Monitor blood pressure
- Increase systemic vascular resistance (SVR) to push blood through pulmonary circulation
  - Epinephrine, norepinephrine
  - NOT dopamine
  - Can target MAPs higher than norm for age
- Give additional LR boluses for hypovolemia
- Monitor urine output, lactate after admission



Neurologic Management

- Agitation and dyssynchrony with the ventilator can increase PVR and worsen hypoxemia:
  - Management aimed Improve ventilator function and decrease O2 demand
- Sedation
  - Opiate (fentanyl/morphine)
  - Benzo (midazolam if >35 weeks)
  - Precedex
- Muscle relaxation
  - Reserved for neonates with dyssynchronous breathing and persistent severe hypoxemia
  - Vecuronium/rocuronium
- Decrease stimulation

Pulmonary Management

- Oxygen – target pre-ductal saturation
- Mechanical Ventilation
- Inhaled nitric oxide
- Maintain normal carbon dioxide (pCO2) to prevent acidosis
- Monitor Oxygenation index

Oxygenation Index = (FiO_2 x P_{AW}) / PaO_2

- FiO_2 = fraction of inhaled oxygen, %
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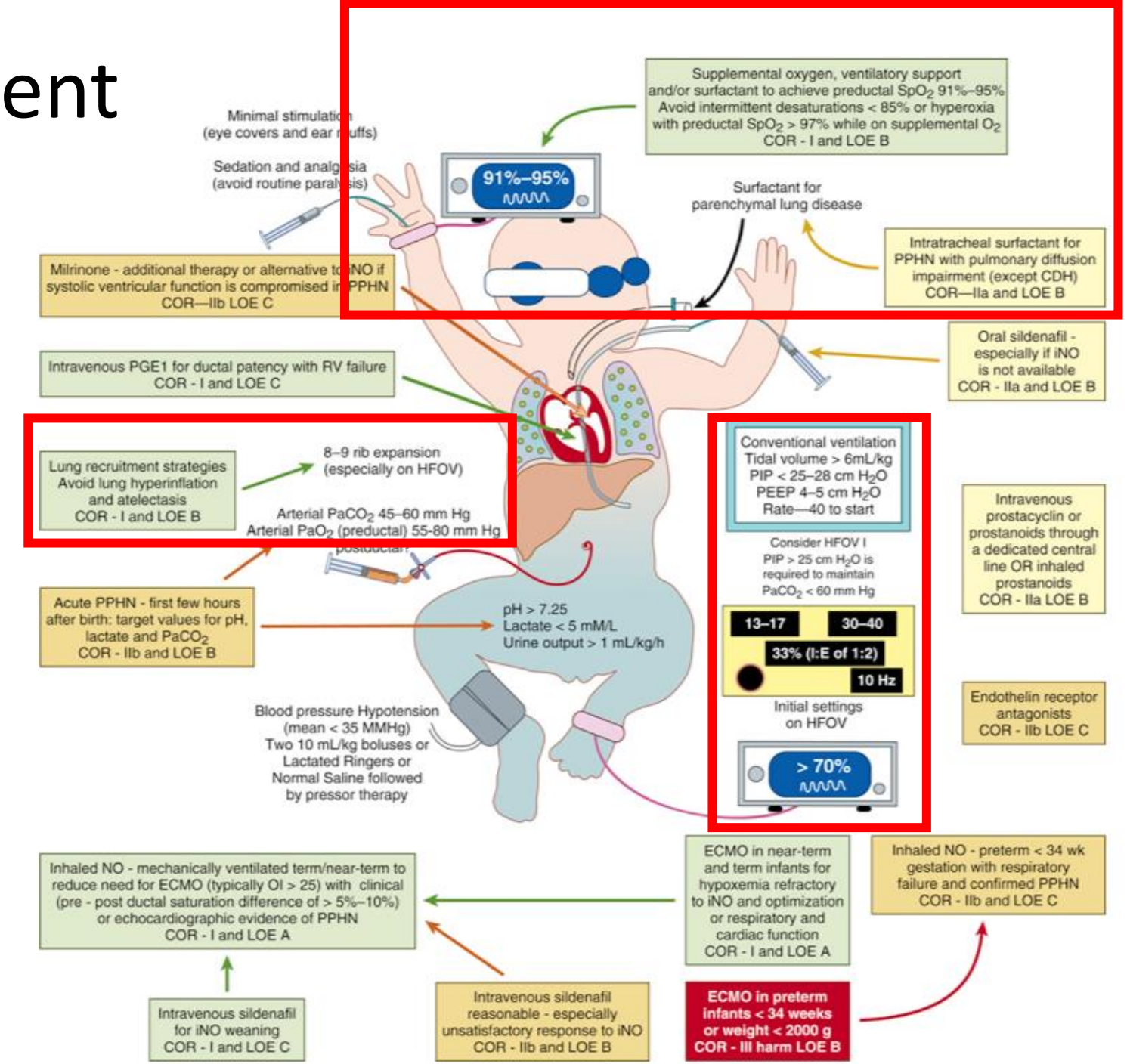
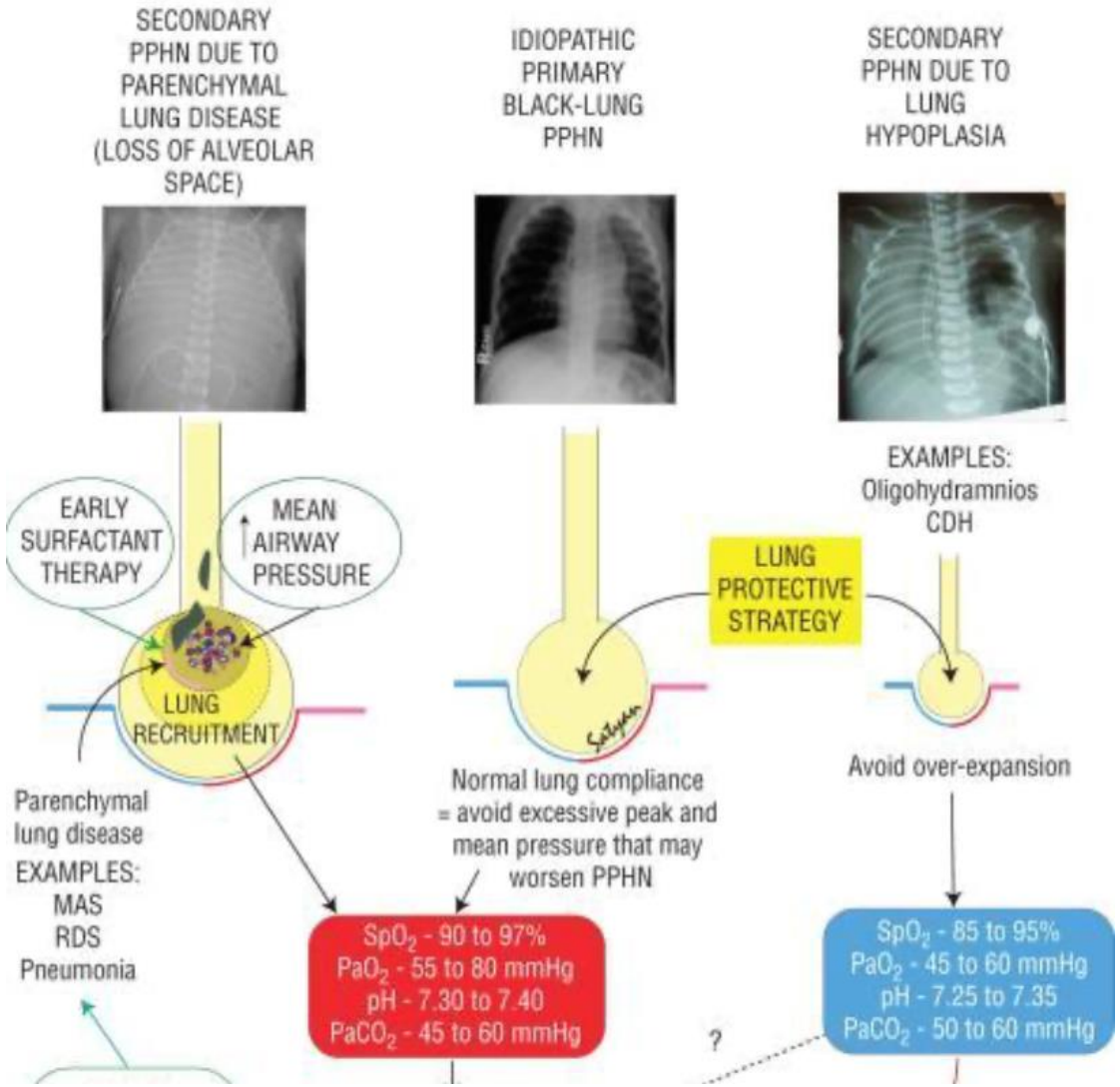
Management



Lakshminrusimha, 2020

- Loss of alveolar space
  - MAS
  - RDS
  - TTN
  - Pneumonia
  - Goal = lung recruitment



Lung hypoplasia

- CDH
- Oligohydramnios
- Goals = lung protection and gentle ventilation
- Volume recruitment may make things worse

- Conventional with volume targeted ventilation
  - Goal TV 5-6 ml/kg
  - Change to HF if can't resolve respiratory acidosis with PIPs of 25-28

Oxygenation targets

- Goal SpO2 of 90-95%
  - Associated with, decreased PVR, lower FiO2 requirement and best PaO2/FiO2 ratio
  - Hyperoxemia suppresses normal postnatal increase in eNOS expression in pulmonary arteries and may cause lung injury

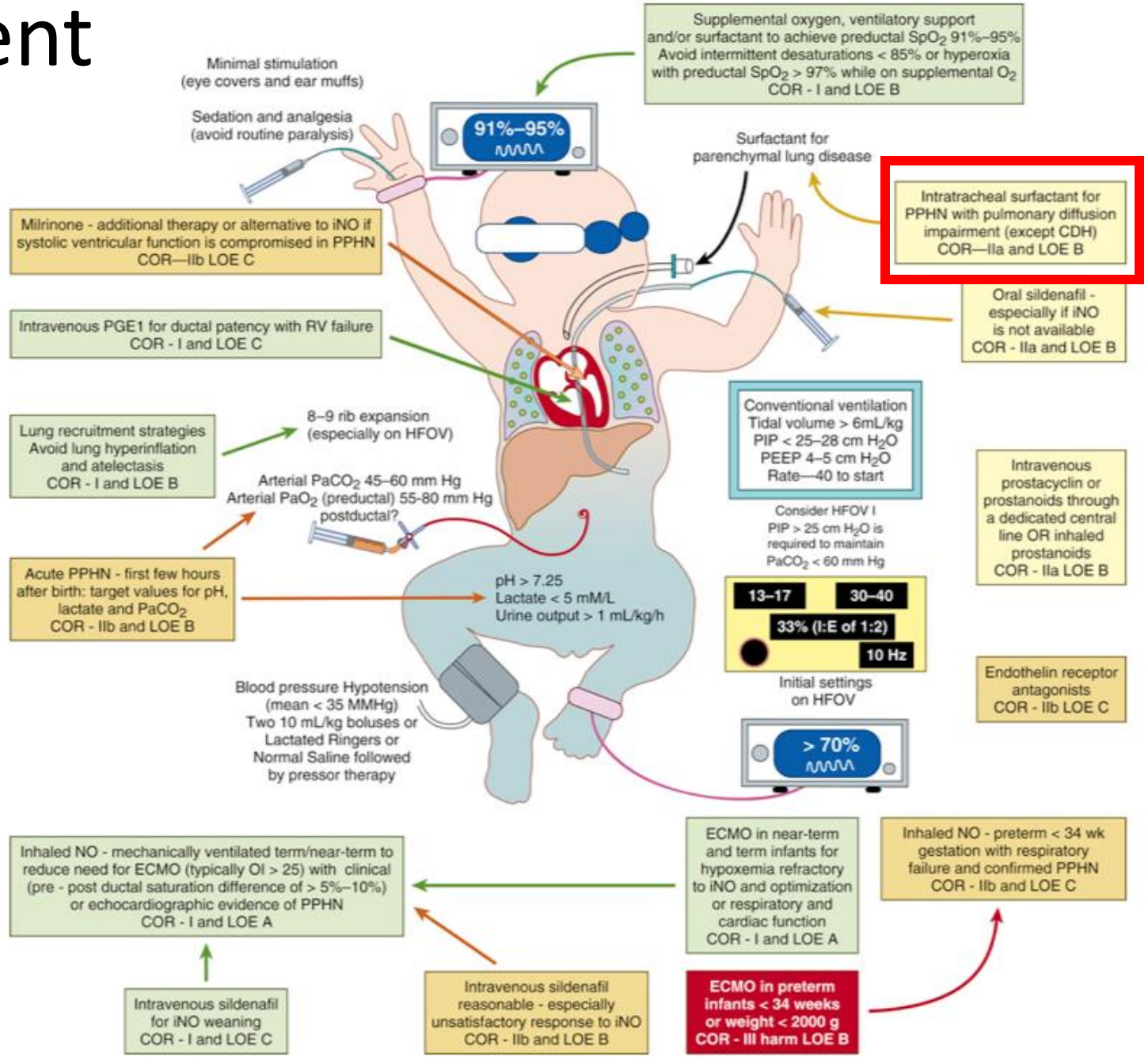
- Goal pre-ducal PaO2: 55-80 mmHg
  - PaO2 below 45-50 -> increased PVR
  - PaO2 >80 does not result in additional decrease in PVR*
    - Increased PDE5 activity -> limits NO-induced vasodilation

- Need higher targets during whole body cooling because of shift in hemoglobin oxygen dissociation curve (aim for mid-high 90s)

Goal $PaCO_2$ (40-50 mmHg)

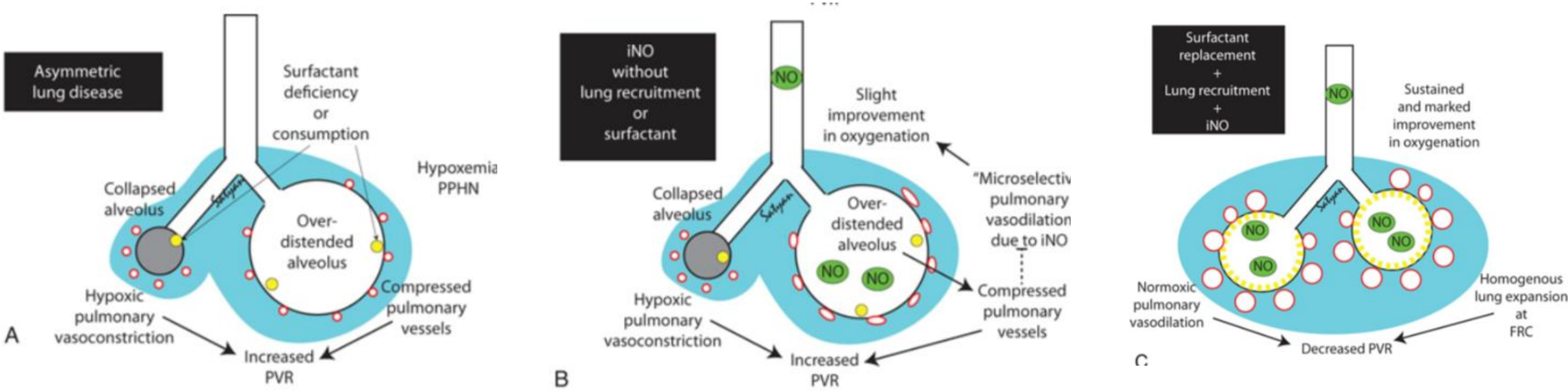
- Historically had aimed for alkalosis, however..
  - Associated with increased ECMO and chronic lung disease
  - Metabolic acidosis usually resolves once poor tissue prefusion is fixed
  - Hyperventilation and alkalosis increased risk of sensorineural deafness
  - With moderate to severe HIE $PaCO_2$ under 35 associated with lower survival without NDI
- Current practice to aim for permissive hypercapnia with tolerance of $PaCO_2$ to 50 mm Hg (60 mm Hg)
  - To minimize lung injury
- Still should avoid acidosis <pH 7.25
  - (acidosis -> Pulm vasoconstriction -> increased PVR)

Management

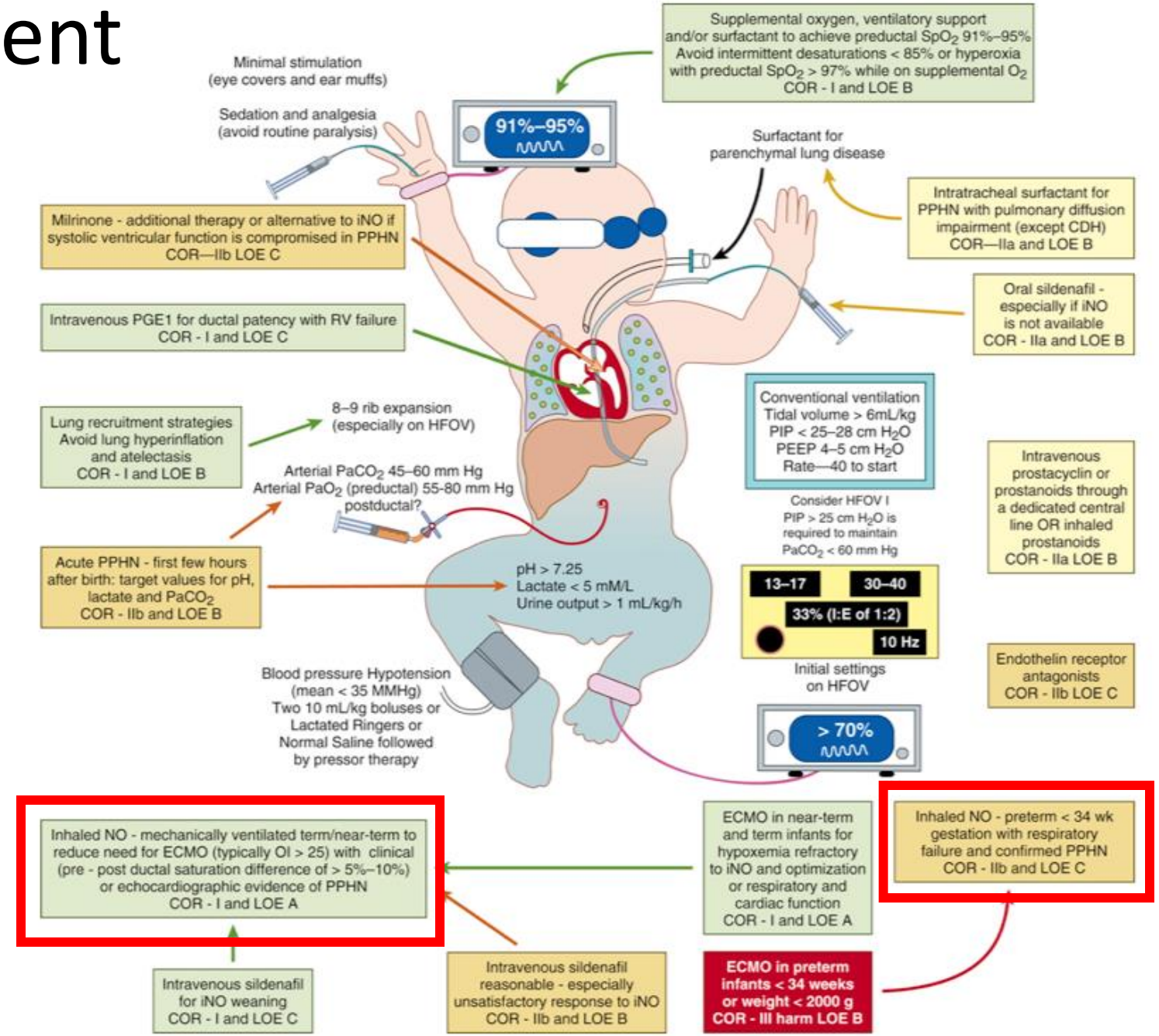

Supplemental oxygen, ventilatory support and/or surfactant to achieve preductal SpO_2 91%–95% Avoid intermittent desaturations < 85% or hyperoxia with preductal SpO_2 > 97% while on supplemental O_2 COR - I and LOE B
Minimal stimulation (eye covers and ear muffs)
Sedation and analgesia (avoid routine paralysis)
91%–95%
Surfactant for parenchymal lung disease
Intratracheal surfactant for PPHN with pulmonary diffusion impairment (except CDH) COR—IIa and LOE B
Milrinone - additional therapy or alternative to iNO if systolic ventricular function is compromised in PPHN COR—IIb LOE C
Oral sildenafil - especially if iNO is not available COR - IIa and LOE B
Intravenous PGE1 for ductal patency with RV failure COR - I and LOE C
Conventional ventilation Tidal volume > 6mL/kg PIP < 25–28 cm H_2O PEEP 4–5 cm H_2O Rate—40 to start
Lung recruitment strategies Avoid lung hyperinflation and atelectasis COR - I and LOE B
8–9 rib expansion (especially on HFOV)
Arterial $PaCO_2$ 45–60 mm Hg
Arterial PaO_2 (preductal) 55-80 mm Hg
postductal?
Consider HFOV I PIP > 25 cm H_2O is required to maintain $PaCO_2$ < 60 mm Hg
Intravenous prostacyclin or prostanoids through a dedicated central line OR inhaled prostanoids COR - IIa LOE B
Acute PPHN - first few hours after birth: target values for pH, lactate and $PaCO_2$ COR - IIb and LOE B
pH > 7.25
Lactate < 5 mM/L
Urine output > 1 mL/kg/h
13–17
30–40
33% (I:E of 1:2)
10 Hz
Initial settings on HFOV
Endothelin receptor antagonists COR - IIb LOE C
Blood pressure Hypotension (mean < 35 MMHg) Two 10 mL/kg boluses or Lactated Ringers or Normal Saline followed by pressor therapy
> 70%
Inhaled NO - mechanically ventilated term/near-term to reduce need for ECMO (typically OI > 25) with clinical (pre - post ductal saturation difference of > 5%–10%) or echocardiographic evidence of PPHN COR - I and LOE A
ECMO in near-term and term infants for hypoxemia refractory to iNO and optimization or respiratory and cardiac function COR - I and LOE A
Inhaled NO - preterm < 34 wk gestation with respiratory failure and confirmed PPHN COR - IIb and LOE C
Intravenous sildenafil for iNO weaning COR - I and LOE C
Intravenous sildenafil reasonable - especially unsatisfactory response to iNO COR - IIb and LOE B
ECMO in preterm infants < 34 weeks or weight < 2000 g COR - III harm LOE B

Surfactant

- Used in PPHN associated with MAS or RDS; considered in situations w/ significant lung disease (even if not clearly MAS/RDS)
- Inconclusive evidence: RCT (2) of iNO vs surf+iNO found combo slowed progression of hypoxic respiratory failure and reduced ECMO/death - MAS in majority of infants



Management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iNO

- Only FDA approved treatment
- >34 weeks gestation w/ hypoxemic respiratory failure with clinical or echo evidence of PPHN
- Considered first-line therapy in infants w/ PPHN needing mechanical ventilation
  - Usually started when OI reaches ~20
  - "20-20-20" rule
    - Complete response to iNO is defined as an increase in Pao2/Fio2 ratio of 20 mm Hg or more
- 2 RCTs – iNO reduced need for ECMO
  - Led to FDA approval for use in PPHN
  - Did NOT reduce mortality, length of hospitalization, risk of NDI

Roberts et. al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med. 1997 Feb 27;336(9):605-10

Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, Roy BJ, Keszler M, Kinsella JP. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med. 2000 Feb 17;342(7):469-74

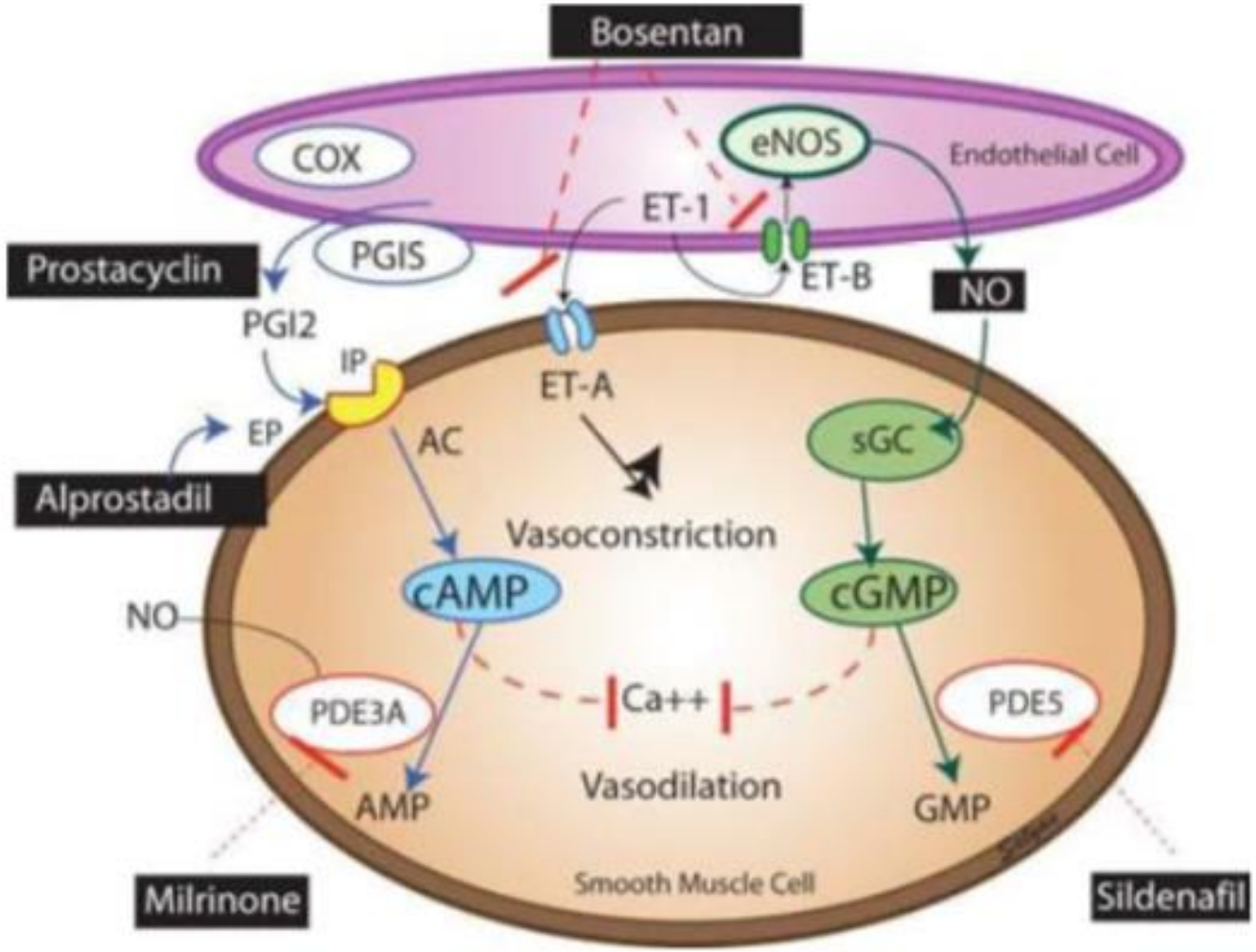
iNO

- Potent and selective pulmonary vasodilator
- Oxygenation improves as vessels are dilated in well-ventilated parts of the lung
  - Thereby redistributing blood flow from regions w/ decreased ventilation and reducing intrapulmonary shunting
- In circulation – avidly binds to Hgb and is rapidly converted to methemoglobin and nitrate
- As a result, there is little effect on SVR and systemic BP

- Contraindications:
  - Ductal dependent CHD
    - IAA, Critical AS, HLHS
  - Severe L. ventricular dysfunctions

iNO: mechanism

- Stimulates sGC to make cGMP
  - reduces cytosolic concentration of ionic calcium
  - Vasodilation



iNO: Methemoglobinemia

- Dose-related methemoglobinemia may occur and lead to hypoxemia
- Monitor methemoglobin concentrations within 4 to 8 hours of starting nitric oxide treatment and then periodically – usually daily

- Treated by reducing the dose of or discontinuing nitric oxide
- Methemoglobinemia that does not resolve with dosage reduction or discontinuation of therapy may require
  - IV vitamin C, IV methylene blue, or blood transfusion

iNO use in extremely early LBW infants

- Infants <26 weeks born in the setting of PPROM and IAI at high risk for PPHN
- Use of iNO has resulted in contradictory responses but overall has not improved mortality or neurologic outcomes

- AAP does not recommend use of iNO for infants at this gestational age with iNO for rescue or routine use to improve survival
  - Still very commonly used: 7-8% of infants
  - Infants with pPROM and oligo and pulmonary hypoplasia do seem to respond well to iNO

Weaning iNO – protocols can vary

- Gradual process to minimize the risk of rebound vasoconstriction
- "60-60-60" rule
  - Start weaning once FiO2 is ≤0.6
  - wean iNO only if PaO2 maintained >60 mmHg for 60 mins
    - (or pre-ductal sats >/= 90% maintained for 60 mins)

- Wean by 5 ppm every 2 to 4 hours as tolerated until reaching a dose of 5 ppm
  - Wean by 1 ppm every 2 to 4 hours as tolerated until reaching a dose of 1 ppm
  - If the neonate is stable on 1 ppm, discontinue iNO and monitor for rebound PH

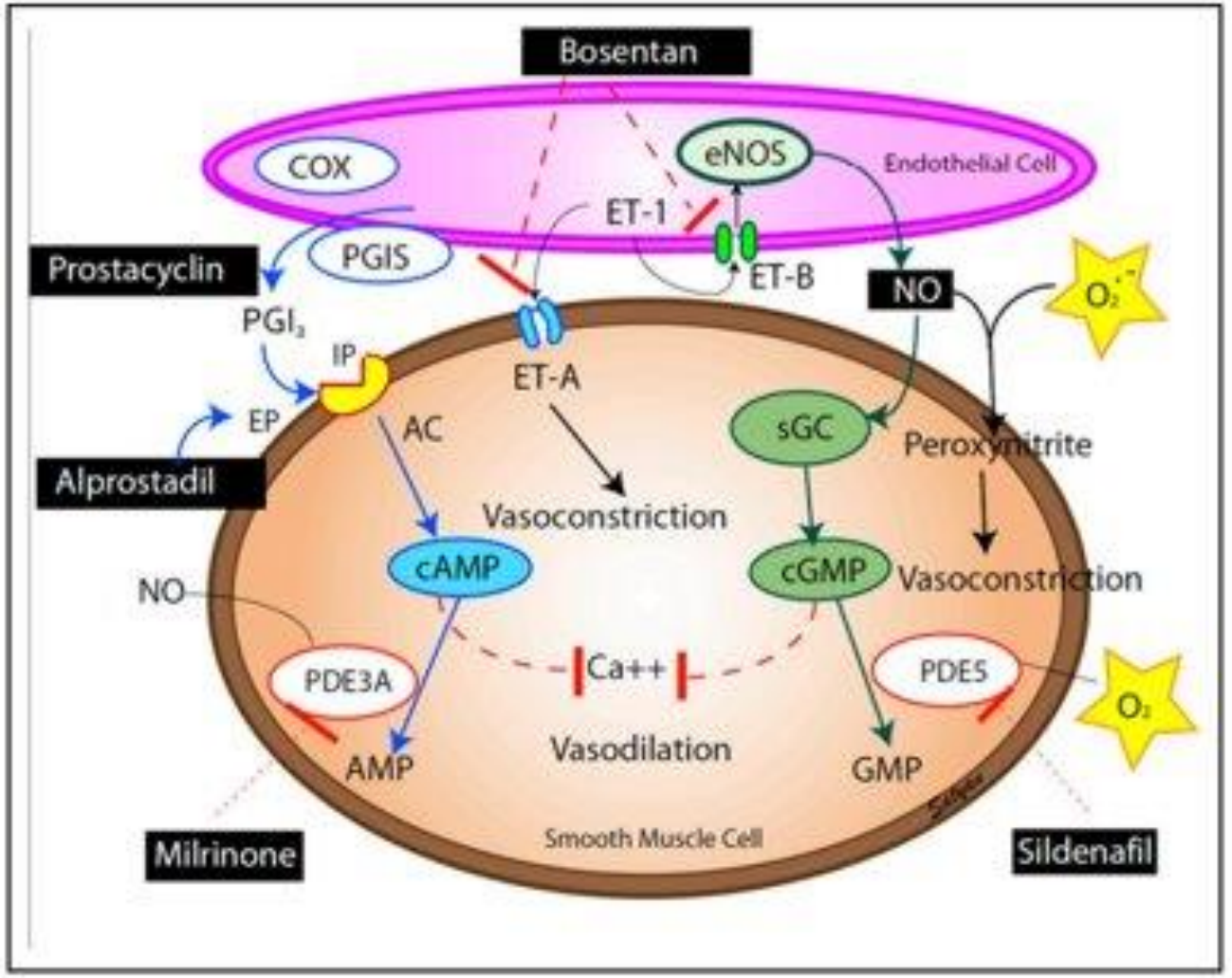
- Continuing iNO in infants unresponsive to iNO or failure to wean iNO can potentially lead to prolonged dependence on iNO due to suppression of endogenous eNOS

Pharmacologic Therapy

- If blood pressure is relatively stable but hypoxemia persists, consider the use of phosphodiesterase (PDE) 5 inhibitors, especially in the presence of a R-to-L shunt at the PFO and/or PDA levels with good ventricular function

- IV Sildenafil is usually the first line agent
- Studies have found that oral sildenafil improves oxygenation and reduces mortality in centers where iNO/ECMO are not available

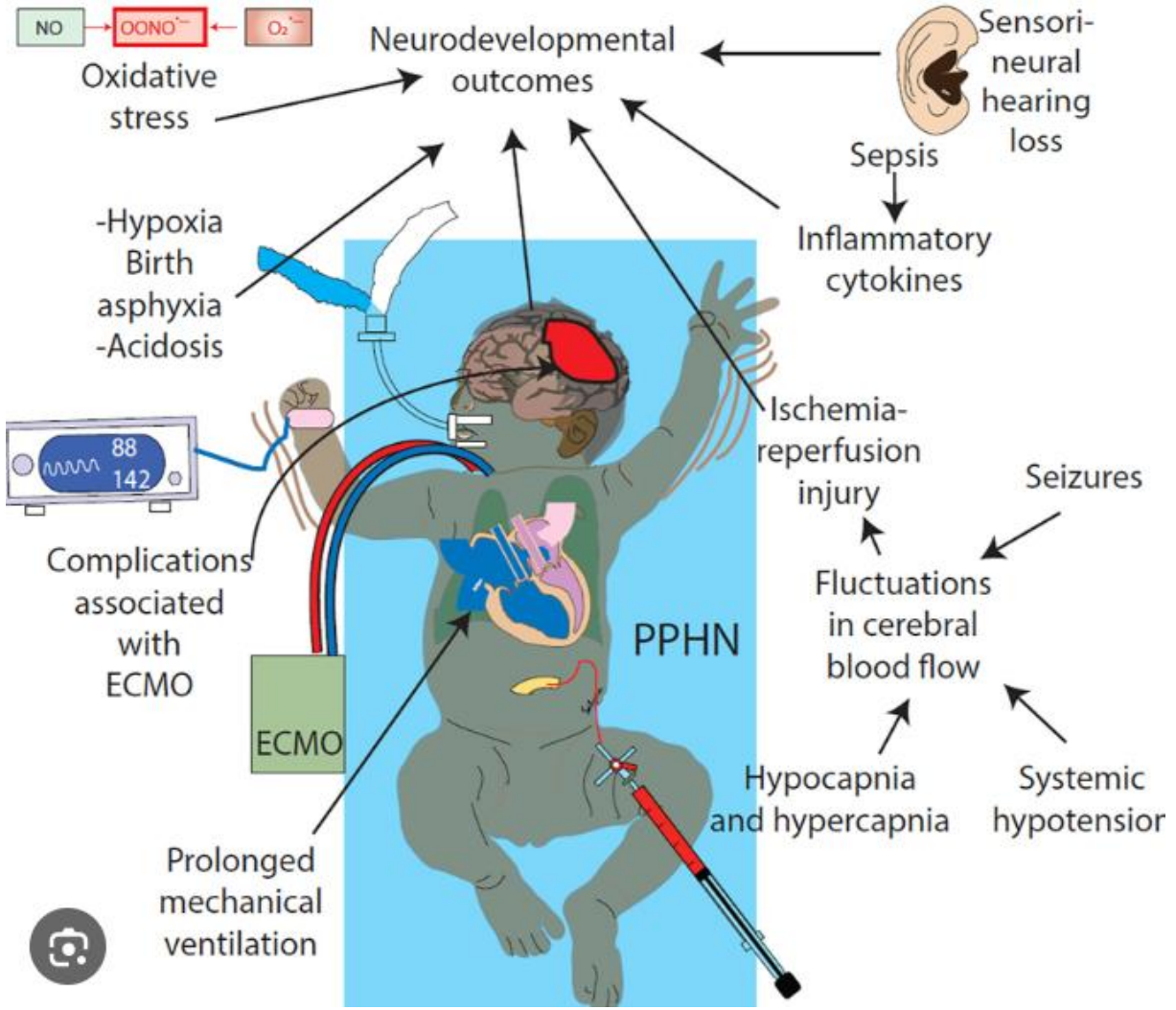
- Hypotension is associated with cardiac dysfunction, and rapid deterioration with hemodynamic instability should precipitate cannulation for ECMO (or immediate transfer to an ECMO center)



Neurodevelopmental Outcomes

- About 25% have neurodevelopmental impairment
- About 20% have hearing impairment
- Require long-term follow-up after discharge

- The presence of neurodevelopmental and medical disabilities may reflect the severity of the underlying illnesses experienced by these infants rather than complications of iNO or ECMO



Back to our case..

- Baby L
  - inhaled Nitric Oxide x7 days, and mechanical ventilation x10 days
  - Extubated to CPAP; RA by 1.5 months (chronological age)
  - Experienced slow development of feeding schools
    - Discharged home by 2 months of age (PMA: 42 weeks)
      - RA; POAL
  - Ongoing concern for abnormal neurologic exam at time of discharge
    - Will be followed closely for development in NICU follow up clinic

Thank you!

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