



Childrens Heart Center Nevada

continuous care for the fetus, child & adult with congenital heart disease

Persistent Pulmonary Hypertension of the Newborn

October 28, 2017

Abraham Rothman, MD

UNLV
School of MEDICINE



Topics

- ▶ Definition, causes, pathophysiology
- ▶ Diagnosis
- ▶ Management
- ▶ Prognosis



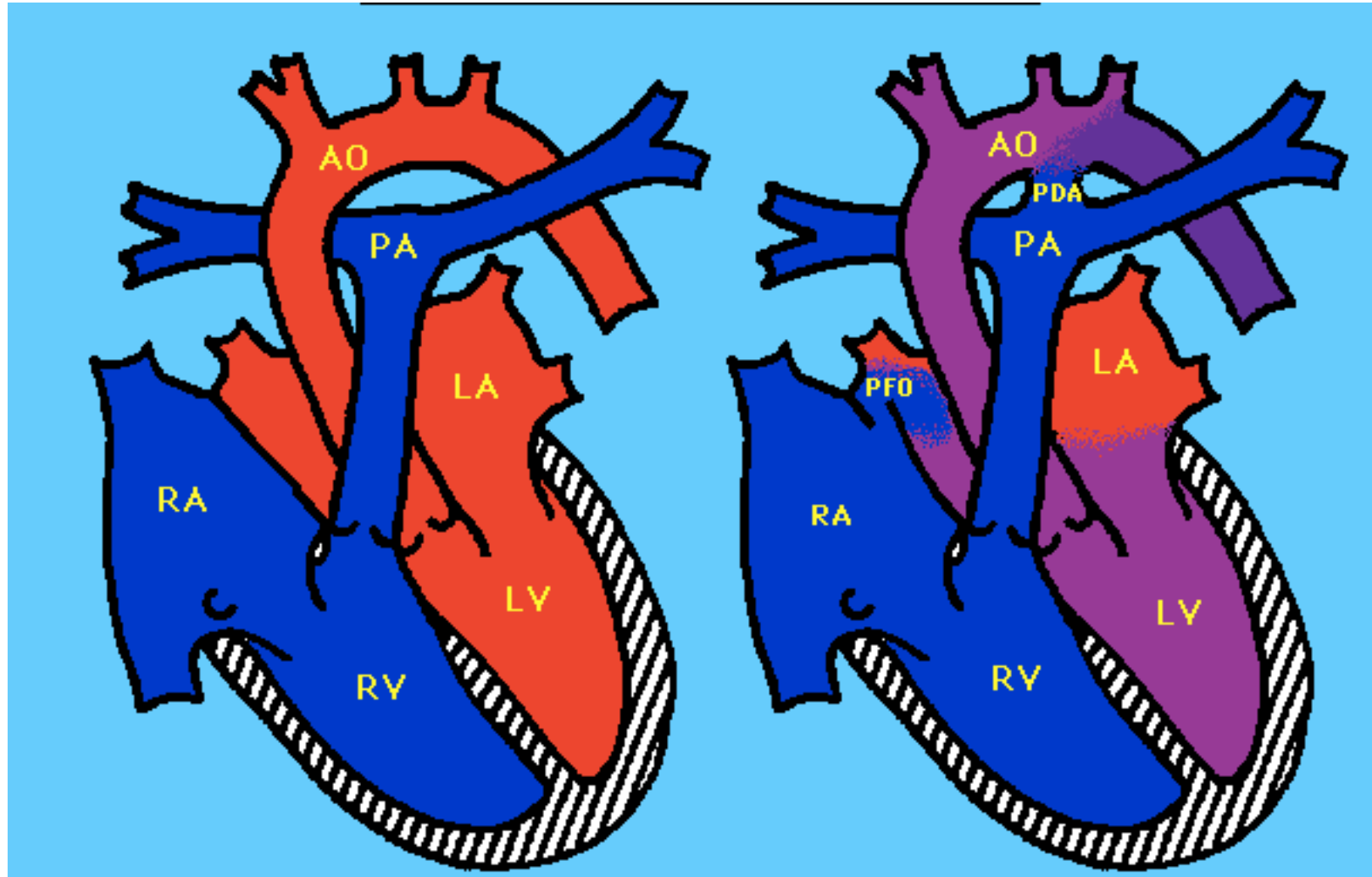
Disclosures

▶ None



Definition and incidence

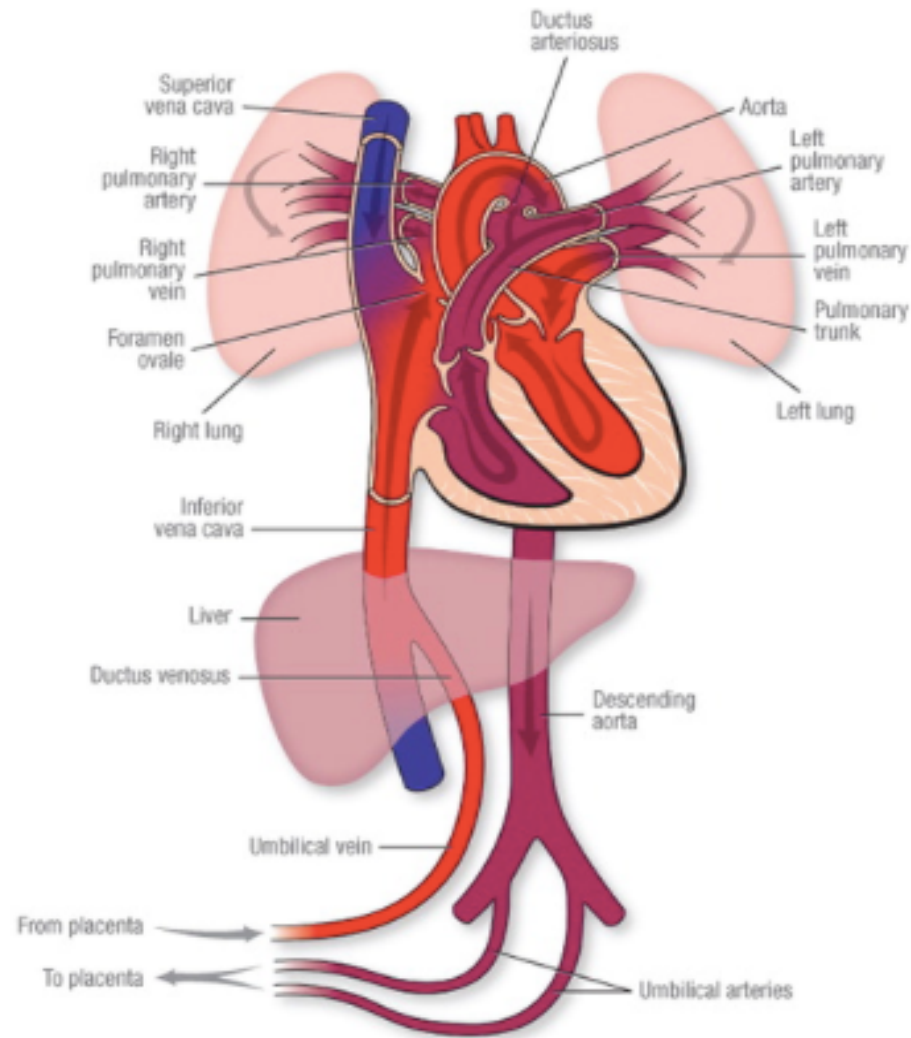
- ▶ Birth: Rapid decrease in pulmonary vascular resistance (PVR) and increase in pulmonary blood flow to attain effective gas exchange.
- ▶ Failure of pulmonary vascular adaptation results in PPHN: elevated PVR, with right to left shunting at PFO and or PDA and resultant hypoxemia.
- ▶ Incidence: 0.4 – 6.8 per 1000 live births in the US and 0.43 – 6 per live births in the UK.
- ▶ Early mortality (10%), serious morbidity, significant neurologic impairment (25% at 2 years).





Fetal Circulation

- ▶ High PVR, 13-21% of combined ventricular output perfuses the lungs.
- ▶ Factors causing high PVR: fluid filled lungs, hypoxic vasoconstriction and circulating vasoconstrictors:
 - ▶ Endothelin-1
 - ▶ Products of prostaglandin pathway, including thromboxanes and leukotrienes.





Birth

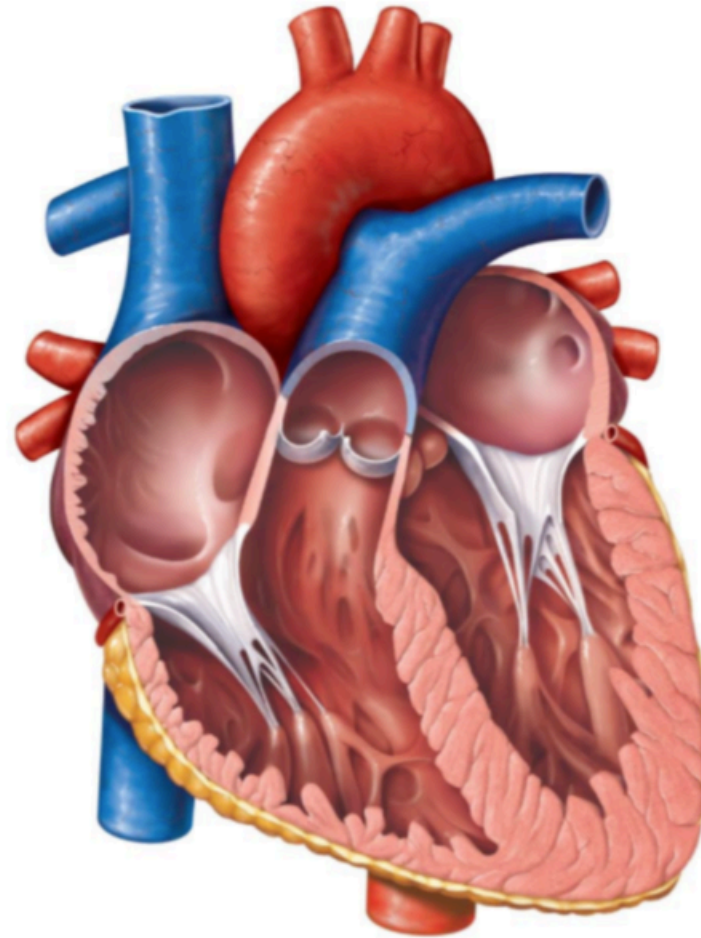
- ▶ Removal of low resistance placental circulation, increased SVR
- ▶ Expansion of lungs, decreased PVR, improved oxygenation, 8-10 fold increase in pulmonary blood flow, increased left atrial pressure, closure of the PFO, reversal of PDA flow, closure of the PDA.
- ▶ Further remodeling of the pulmonary vascular bed results in further decrease in PVR.
- ▶ Increased NO production -> increased cGMP; increased prostacyclin -> increased cAMP; both cause more vasodilation.



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Normal anatomy





PPHN- definition

- ▶ Elevation of pulmonary arterial pressure
- ▶ PA pressure normally decreases to $\frac{1}{2}$ systemic by 2 days and $\frac{1}{3}$ systemic by 3 weeks of life
- ▶ Normal mean PAp < 25 mmHg
- ▶ Normal PVRI < 3 Wood Units



Pathophysiology

- ▶ Maladaptation: vasoconstriction associated with parenchymal disease such as MAS, RDS, pneumonia and sepsis.
- ▶ Remodeled pulmonary vasculature with normal lung parenchyma = idiopathic = 10%
- ▶ Hypoplastic pulmonary vasculature secondary to lung hypoplasia (ex: diaphragmatic hernia or oligohydramnios)
- ▶ Increased PVR causes RV dysfunction, decreased PBF, LV dysfunction, systemic hypo-perfusion and shock



Pathophysiology – risk factors

- ▶ Male gender, C-Section, delivery < 37 weeks or > 41 weeks, SGA and LGA.
- ▶ Preterm: PROM, oligohydramnios, SGA, RDS.
- ▶ ? Non-steroidal anti-inflammatories
- ▶ SSRIs in the 3rd trimester of pregnancy
- ▶ Trisomy 21
- ▶ Surfactant function abnormalities
- ▶ Endothelin-1 mutation
- ▶ Other genetic defects



Causes

- ▶ RDS, TTN, MAS, infection, CDH, maternal diabetes, hypoglycemia, polycythemia, adrenal insufficiency
- ▶ “Irreversible:” pulmonary hypoplasia, alveolar capillary dysplasia with misalignment of pulmonary veins, pulmonary interstitial lymphangectasia, surfactant protein deficiency
- ▶ Chronic: chronic neonatal lung disease, CDH, cardiac lesions (ASD, VSD, PDA), pulmonary hypoplasia



Congenital Diaphragmatic Hernia

- ▶ Abnormal diaphragm, herniation of abdominal viscera into thoracic cavity
- ▶ Pulmonary hypoplasia
- ▶ Developmental arrest in the normal pattern of airway branching, impaired alveolar formation
- ▶ Impaired pulmonary arterial branching, reduced cross section of pulmonary vascular bed, thickening of media and adventitia of the arterioles.
- ▶ High mortality (up to 20-30%), depending on the severity of PH



Diaphragmatic hernia

- ▶ After repair of diaphragmatic hernia
- ▶ If normal PA pressure, survival 75%
- ▶ If systemic or suprasystemic pressure 3 weeks later, mortality 100%
- ▶ Dillon PW et al J Pediatr Surgery 2004

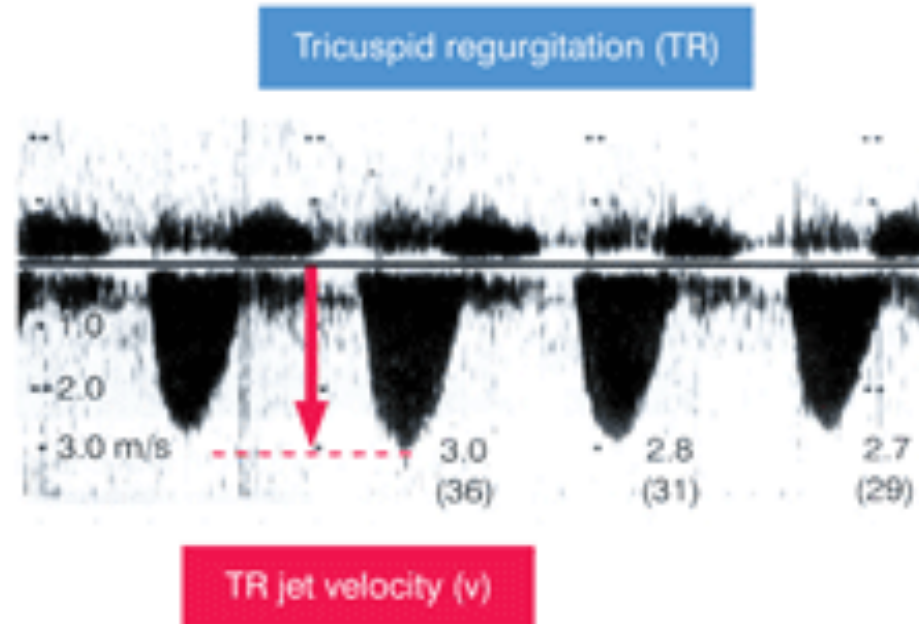
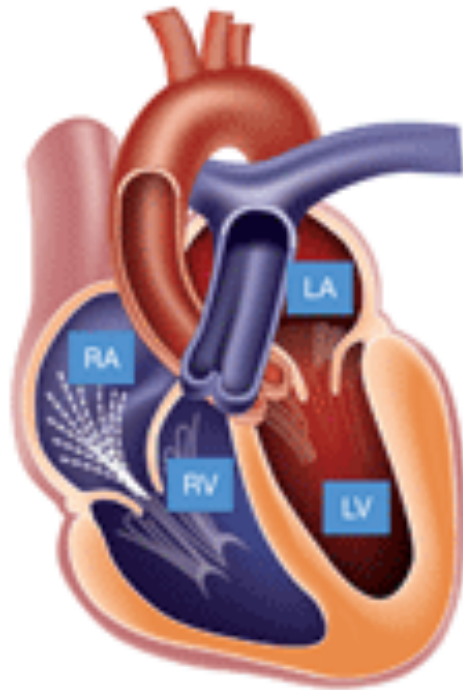


Diagnosis of PPHN

- ▶ Cyanosis, respiratory distress (acidosis, hypotension)
- ▶ Oxygen saturation difference larger than 5% between upper and lower body.
- ▶ CXR: normal or oligemic lungs or lung pathology
- ▶ Echocardiography (TR jet, PFO and PDA flow, IVS position, RV size and function, LV function)
- ▶ Rule out congenital heart disease
- ▶ RV and LV dysfunction related to need for HFV and ECMO, and prognosis



Echocardiographic estimation of PA pressure



Syst PAP = Right ventricular systolic pressure

(in absence of pulmonary outflow obstruction)

$$RVSP = 4v^2 + RAP^*$$



Classification (Nice, 2013)

1. Pulmonary arterial hypertension (PAH)

1.1 Idiopathic PAH (IPAH)

1.2 Heritable PAH

1.2.1 BMPR2

1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3

1.2.3 Unknown

1.3 Drug- and toxin-induced PAH

1.4 Associated PAH

1.4.1 Connective tissue disease

1.4.2 HIV infection

1.4.3 Portal hypertension

1.4.4 Congenital heart disease

1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1''. Persistent pulmonary hypertension of the newborn (PPHN)

2. PH due to left heart disease

2.1 LV systolic dysfunction

2.2 LV diastolic dysfunction

2.3 Valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia

3.1 COPD

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear multifactorial mechanisms

5.1 Hematologic disorders

5.2 Systemic disorders

5.3 Metabolic disorders

5.4 Others



Classification of Pediatric PH

The broad schema of 10 basic categories of Pediatric Pulmonary Hypertensive Vascular Disease

Category	Description
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders



Management

- ▶ Treat hypoxemia and any underlying condition
- ▶ Supportive care:
- ▶ Maintain normothermia
- ▶ Avoid stress, “low-noise” environment, gentle handling and sedation, careful suctioning
- ▶ Maintain adequate intravascular volume and BP
- ▶ Optimal nutritional support
- ▶ Avoid acidosis – pulmonary vasoconstriction
- ▶ Avoid alkalosis – cerebral vasoconstriction, reduced cerebral blood flow – CNS injury



Oxygen therapy and mechanical ventilation

- ▶ Oxygen – potent pulmonary vasodilator
- ▶ Animal studies: hypoxemia → vasoconstriction; normoxemia reduces PVR; hyperoxemia does not cause significant additional vasodilation.
- ▶ Oxygen may increase contractility of pulmonary arteries and decrease response to iNO
- ▶ Optimal lung recruitment with positive pressure ventilation, decreases PVR. HFV only in severe lung disease.
- ▶ If lung disease, best combination: HFV and iNO
- ▶ ? Optimal Saturation (90-95%), pO₂ (50-90)



Adjuvant therapy

- ▶ Surfactant. Surfactant deficiency in RDS, MAS and pneumonia. If parenchymal lung disease and PPHN, early administration of surfactant -> better lung recruitment, reduced need for ECMO and death
- ▶ Glucocorticoids. Have anti-inflammatory beneficial effects in MAS, pulmonary edema, vasoconstriction and inflammation. In animal models -> improved oxygenation, less oxidative stress, increased cGMP. In neonates -> decreased duration of oxygen therapy.



Other therapies

- ▶ Vasopressin, increases SVR, decreases PVR
- ▶ Dopamine
- ▶ Dobutamine, decreases SVR but increases contractility
- ▶ Epinephrine – if very hypotensive/shock
- ▶ Adenosine – increases cAMP to aid in vasodilation
- ▶ Drain pericardial effusion
- ▶ Low dose PGE1 if PDA is closed or restrictive – It causes pulmonary vasodilation and prevents suprasystemic PA pressure



Right Ventricle Dysfunction

- ▶ RV supports pulmonary blood flow. RV dysfunction is an important component of and prognostic factor in PPHN
- ▶ Caused by low RV preload: hypovolemia, arrhythmia, high airway pressures, vasodilator shock
- ▶ Impaired RV contractility: ischemia, cytokine-induced (sepsis, myocarditis), LV dysfunction
- ▶ High RV afterload: hypoxic or hypercarbic vasoconstriction, PH, pulm venous hyperension, high airway pressures
- ▶ Treat: Optimize preload (volume, lower airway pressure), contractility (dobutamine, milrinone, or epinephrine), reduce afterload (iNO, milrinone, PGE1 to keep PDA open)



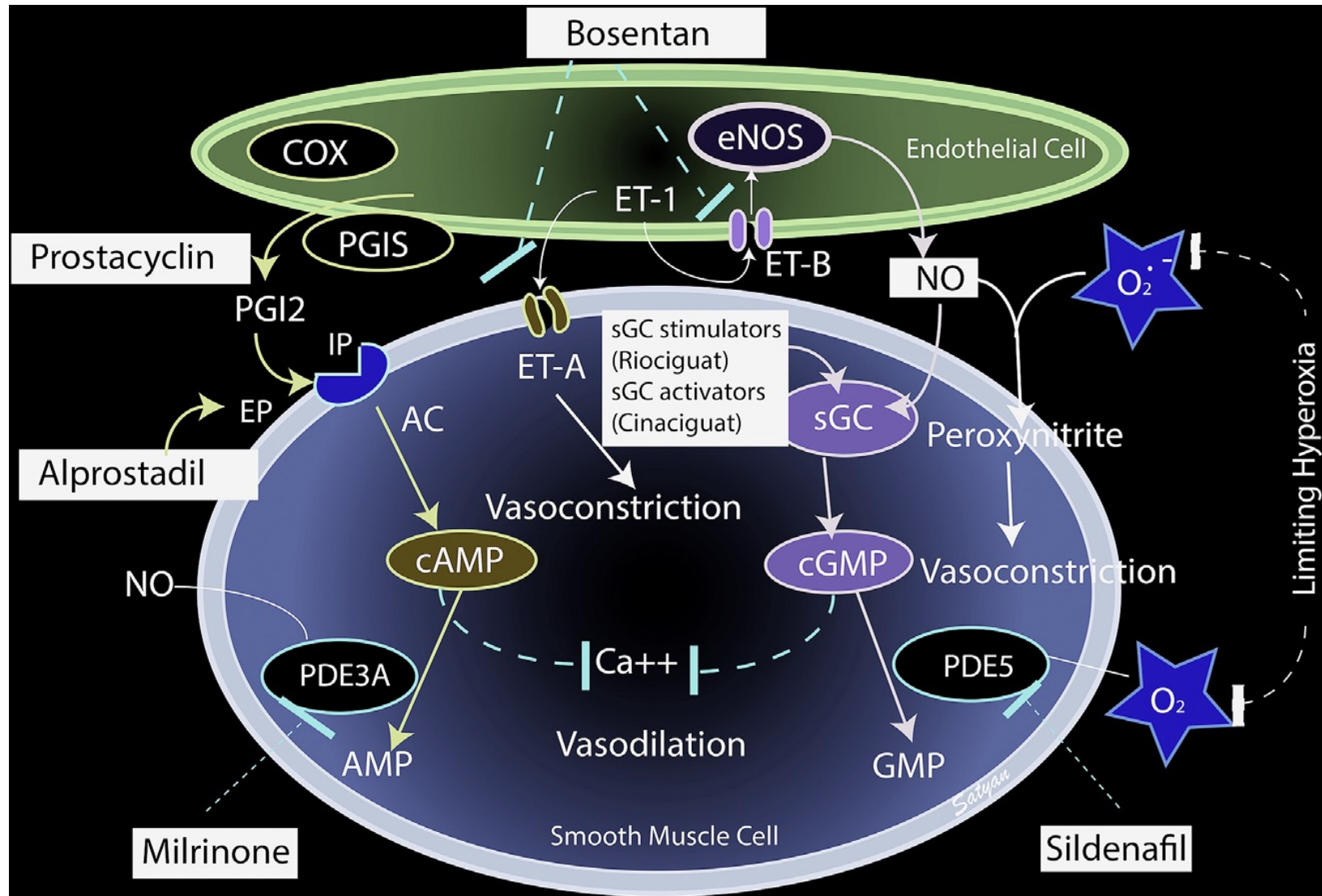
Other measures

- ▶ Avoid lung hyperinflation, atelectasis
- ▶ High frequency oscillation not routinely recommended over conventional ventilation.
- ▶ $\text{pH} > 7.25$, lactate < 5 , pCO_2 45-60
- ▶ ECMO not recommended < 34 wks gestation or weight < 2 Kg
- ▶ Use of iNO in very preterm infants is controversial
- ▶ In more chronic PPHN, consider intravenous prostanoids and diuretics



Pulmonary Vasodilators

- ▶ In PPHN, impaired endothelial cell function
- ▶ Altered balance of vasoconstrictors (endothelin-1) and vasodilators (NO and prostacyclin).
- ▶ Aim: pulmonary vasodilation and pulmonary vascular remodeling.
- ▶ Three main pathways targeted:
 - ▶ cGMP
 - ▶ cAMP
 - ▶ Endothelin





cGMP pathway

- ▶ iNO is a potent selective pulmonary vasodilator. NO activates soluble guanylate cyclase, increases cGMP, activates cGMP activated channels and cGMP dependent protein kinase.
- ▶ iNO decreases oxygen requirement and need for ECMO in term infants with PPHN.
- ▶ iNO does not reduce mortality, LOS, pulmonary function or neurodevelopmental outcomes at follow-up
- ▶ iNO dose 20 ppm (if higher, risk of methemoglobinemia and increased nitrogen dioxide levels)
- ▶ Careful use of iNO in premies, because they may have LV dysfunction, PV stenoses



Sildenafil

- ▶ Phosphodiesterase-5 (PDE-5) hydrolyzes cGMP to inactive GMP.
- ▶ Sildenafil is a selective PDE-5 inhibitor and enhances NO-mediated vascular relaxation
- ▶ Enteral or intravenous sildenafil facilitates weaning from iNO
- ▶ Useful for longer-term use (BPD and PH)
- ▶ Not FDA approved for neonates
- ▶ Dose 0.5 – 1.0 mg/kg every 4-8 hours



cAMP pathway

- ▶ Prostanoids. Prostacyclin (PGI₂) is produced by endothelial cells, is a potent vasodilator, activates adenylate cyclase to increase cAMP levels.
- ▶ Also a systemic vasodilator in infants with PPHN which limits its use. Inhaled epoprostenol has less systemic effects and can be beneficial.
- ▶ PGI₂ - IV or inhaled – improved oxygenation in pts with PPHN refractory to iNO therapy
- ▶ Inhaled iloprost more effective than sildenafil in one study



Milrinone

- ▶ Phosphodiesterase-3 (PDE-3) breaks down cAMP in arterial smooth muscle cells and myocardium.
- ▶ Milrinone is a PDE-3 inhibitor, increases cAMP levels which result in vasodilation. It also has inotropic effects and decreases systemic afterload.
- ▶ Case reports have described reduced oxygen requirement and improved pulmonary vasodilation in infants with PPHN.
- ▶ May be most beneficial if there is also significant LV dysfunction.



Endothelin pathway

- ▶ Endothelin-1 (ET-1) is a potent vasoconstrictor, is produced by endothelial cells and acts via ETA and ETB receptors. ETA receptors mediate vasoconstriction and ETB receptors mediate vasodilation.
- ▶ ET-1 is increased in infants with PPHN.
- ▶ In PPHN, bosentan (acts on both receptors) improved short- and long-term outcomes at 6 months compared with placebo. Bosentan had no additive effect on iNO treated infants with PPHN.



Oxygenation Index

- ▶ Mean airway pressure X FIO2 X100 / pO2
- ▶ > 25 (? > 15) -> NO
- ▶ > 40 -> ECMO



ECMO

- ▶ The only therapy known to be life-saving in infants with severe PPHN who fail to respond to medical management.
- ▶ ECMO vs medical management (relative risk of mortality 0.33-0.44).
- ▶ Follow-up at 7 years of infants treated with ECMO showed reduced risk of death without an associated increase in severe disability. However, in the UK study, nearly half of patients had died or were severely disabled at age 7 years.
- ▶ Improved medical management has resulted in a decreased need for ECMO in neonates with PPHN.



Summary

- ▶ Despite advances, morbidity and mortality associated with PPHN is still high
- ▶ Up to 1/3 of infants with PPHN fail to respond to iNO, so need new understanding or new therapies
- ▶ Overall management includes optimizing oxygenation and minimizing lung injury
- ▶ Optimize lung recruitment, judicious use of oxygen, and surfactant use in infants with parenchymal disease.
- ▶ Consider milrinone + iNO if ventricular dysfunction



BPD

- ▶ Bronchopulmonary dysplasia
- ▶ Chronic lung disease of infancy in premature infants after oxygen and ventilator therapy for acute respiratory disease after birth
- ▶ Estimated 10,000-15,000 infants per year in US
- ▶ Prolonged NICU stay, frequent readmissions in first 2 years of life, with respiratory infections and asthma
- ▶ Persistent lung function abnormalities and exercise intolerance as adolescents and young adults
- ▶ PH contributes to high morbidity and mortality in BPD



Pulmonary vasculature in BPD

- ▶ Reduction of small pulmonary arteries
- ▶ Reduction in alveolar-capillary surface area, reduced gas exchange, prolonged oxygen and ventilator need, hypoxemia, respiratory infections, -> PH
- ▶ Disruption of vascular growth and signaling
- ▶ Early signs of PH contribute to developing worse BPD and also subsequent PH
- ▶ Risk factors for PH in BPD: lower gestational age, birth weight, longer respiratory support, PDA, infections, oligohydramnios, SGA



PH in BPD

- ▶ Prenatal factors may worsen PH: placental dysfunction and genetic/epigenetic factors
- ▶ Increased vascular tone and reactivity -> worse PH
- ▶ Reduced lung vascular surface area results in left to right shunts such as PDA, ASD, VSD, Ao-PA collaterals, causing more hemodynamic injury or adverse effects (edema, oxygen need)
- ▶ PH contributes to the high mortality in BPD.
- ▶ PH beyond 3 months, 40% mortality. Infants with late severe PH may have as high as 70% mortality.



Diagnosis of PH in BPD

- ▶ ? Incidence of PH in BPD (estimated 25-37%)
- ▶ Early echocardiographic diagnosis, especially in severe prematurity (<26 weeks).
- ▶ Serial echocardiograms suggested (may not detect PH in some). Echo far from perfect, but still best available.
- ▶ Compared to cardiac cath, echocardiography identified presence or absence of PH in 79%, severity level in only 47%.
- ▶ Catheterization if persistent severe PH, suspected PH despite echo findings, candidates for chronic therapy, unexplained pulmonary edema.



Catheterization in BPD

- ▶ Assess severity
- ▶ Associated lesions: systemic-lung collaterals, PV stenoses, PA stenoses, left heart dysfunction
- ▶ Test vasoreactivity
- ▶ Assessment of severity of shunt lesions: ASD
- ▶ Wedge pressure or LVEDp
- ▶ Up to 25% of pts with BPD had signs of LV diastolic dysfunction at time of cath



Therapy of PH in BPD

- ▶ Treat underlying lung disease: airway obstruction, tracheomalacia, tonsillar and adenoidal hypertrophy, vocal cord paralysis, chronic reflux and aspiration, bronchoreactivity, pulmonary edema, sleep apnea and episodes of hypoxemia
- ▶ Target oxygen saturation 92-94%
- ▶ iNO
- ▶ Sildenafil
- ▶ Bosentan
- ▶ Prostacyclin analogues
- ▶ Milrinone



Follow-up

- ▶ How long to treat with medications?
- ▶ Frequent pulmonary follow-up
- ▶ Regular echocardiograms and occasional cardiac catheterizations
- ▶ Wean while following closely: clinically and with echocardiograms
- ▶ Regular BNP levels may be helpful
- ▶ Long-term effects of PH medications and prognosis in BPD still being studied



The Future

- ▶ Research
- ▶ Pulmonary vasculature
- ▶ Right ventricular function
- ▶ Identification of biomarkers to predict risk, and monitor progress and response to therapies
- ▶ Randomized studies: iNO, sildenafil, other vasodilators
- ▶ Vasodilation, vascular structural remodeling, angiogenesis
- ▶ “Precision medicine”
- ▶ My research

Acknowledgements

Children's Heart Center – Nevada Physicians and staff, Sunrise Hospital and other Nevada Hospitals NICU Physicians and staff