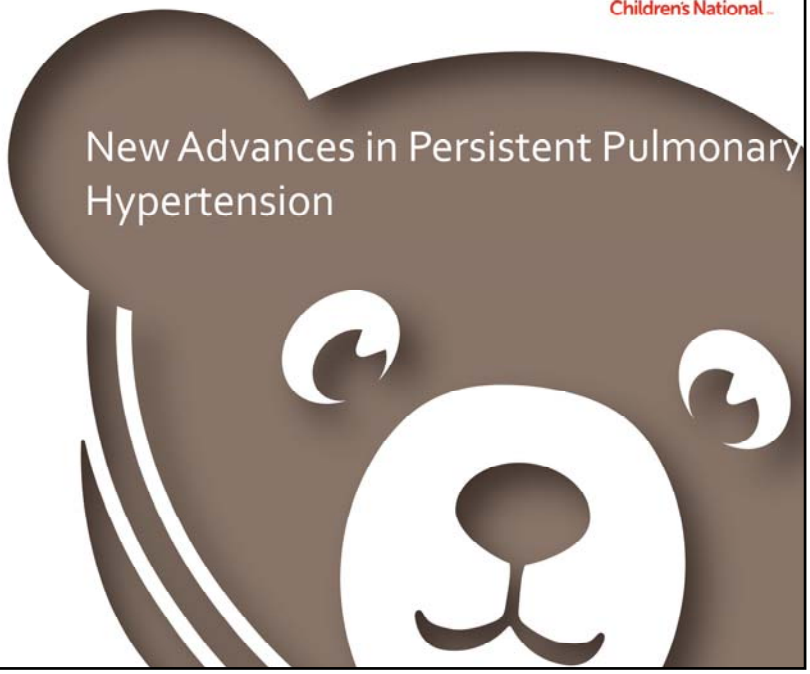
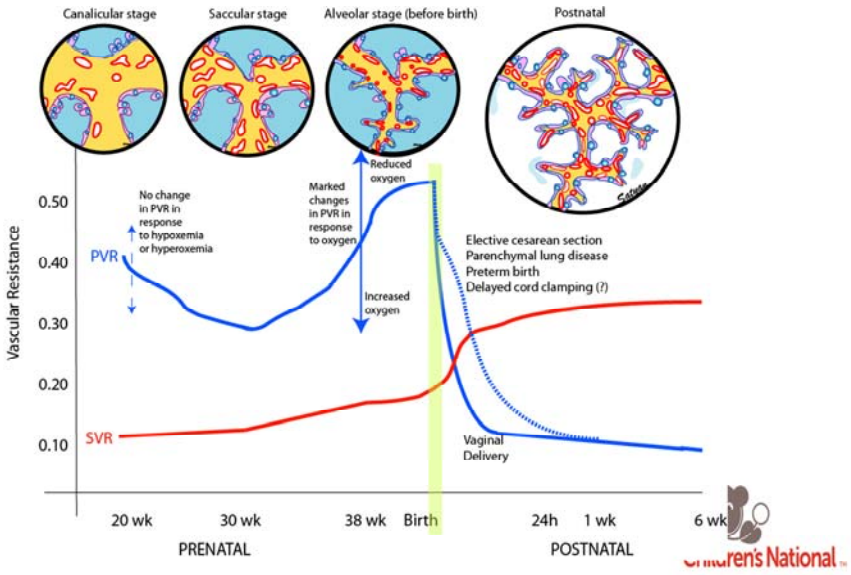
3º Congreso Argentino de Neonatologia

Children's National

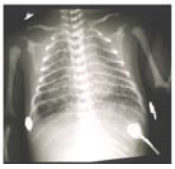
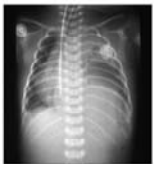
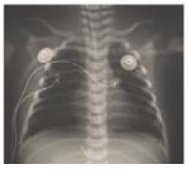
New Advances in Persistent Pulmonary Hypertension

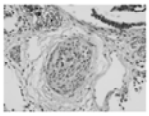


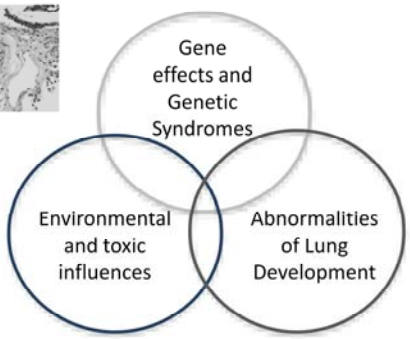
Fetal/Neonatal Vascular Development



Neonatal Pulmonary Hypertension





- Impaired pulmonary vascular adaptation during early neonatal period
- ~10% of all neonates with early respiratory failure
- Multiple underlying diseases
- Few genetic factors identified
- Reversibility and impact on adult pulmonary disease poorly understood

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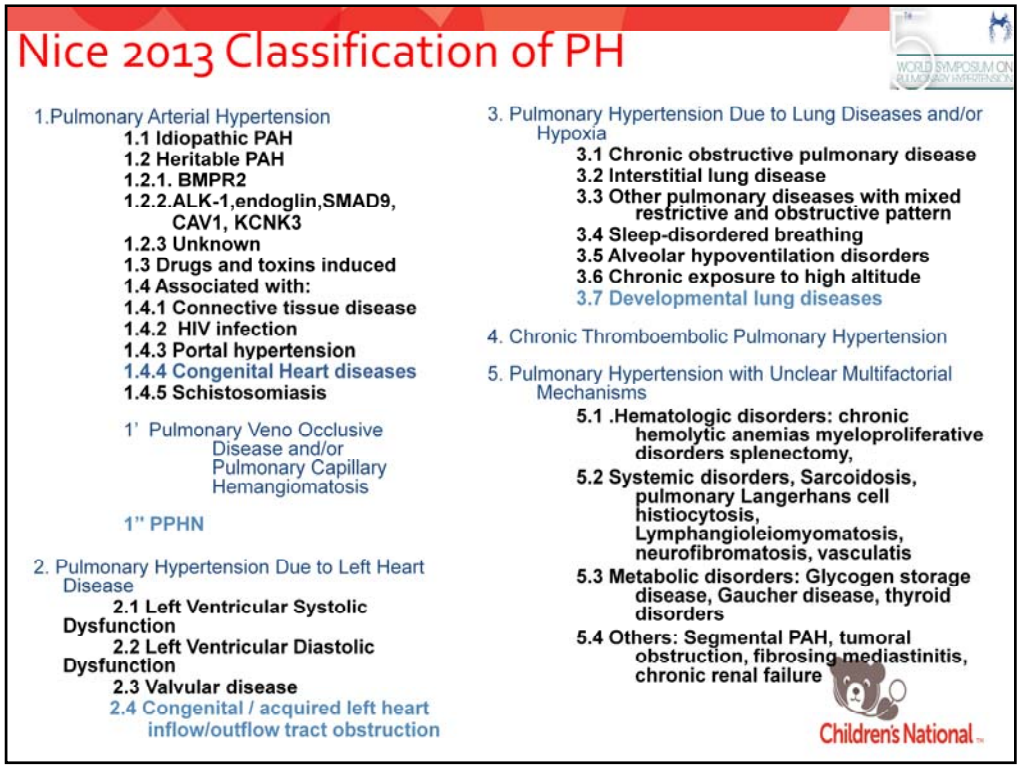
Nice 2013 Classification of PH
1.Pulmonary Arterial Hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1. BMPR2
1.2.2.ALK-1,endoglin,SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital Heart diseases
1.4.5 Schistosomiasis
1' Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis
1" PPHN
2. Pulmonary Hypertension Due to Left Heart Disease
2.1 Left Ventricular Systolic Dysfunction
2.2 Left Ventricular Diastolic Dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction
3. Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
3.1 Chronic obstructive pulmonary disease
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
5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms
5.1 .Hematologic disorders: chronic hemolytic anemias myeloproliferative disorders splenectomy,
5.2 Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculatis
5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure
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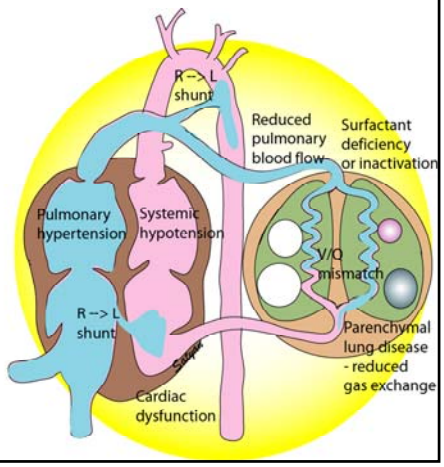
RIFAI

Circulation; December 2015

AHA/ATS Guideline

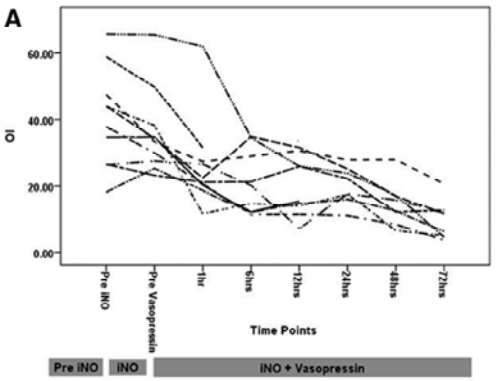
Pediatric Pulmonary Hypertension
Guidelines From the American Heart Association and American Thoracic Society

- Optimal lung recruitment
  - High frequency ventilation
  - Surfactant
- Cardiovascular support
  - Milrinone
  - Vasopressin
- Pulmonary Vasodilation:
  - Oxygen
  - Inhaled Nitric Oxide
- ECMO



Considerations for Vasopressor Support

- Pay attention to preloa
- Decrease PVR
  - High RV systolic pressu
    coronary artery, and lov
    coronary artery diastoli
- Examine direction of sh
  - L->R shunt across the PFC
    LV dysfunction
- Avoid tachycardia
- Consider vasopressin for refractory PPHN/hypotension
  - Constricts systemic vessels via V1 receptors; may dilate pulmonary vessels via eNOS



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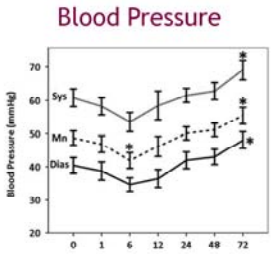
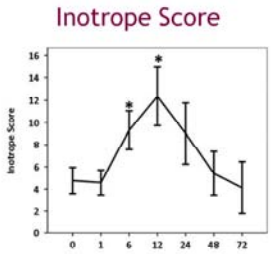
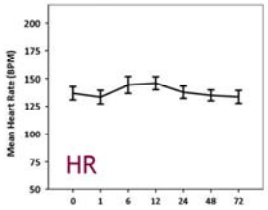
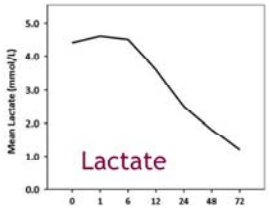
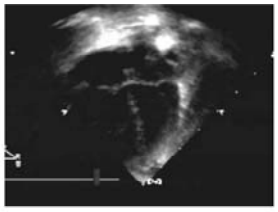
Milrinone: An Inodilator for PPHN











- Retrospective review of 17 iNO-nonresponsive infants treated with milrinone
- Dose 0.5 -0.75 mcg/kg/min (no loading dose)
- Increased right ventricular output, urine output, pH
- Improved oxygenation

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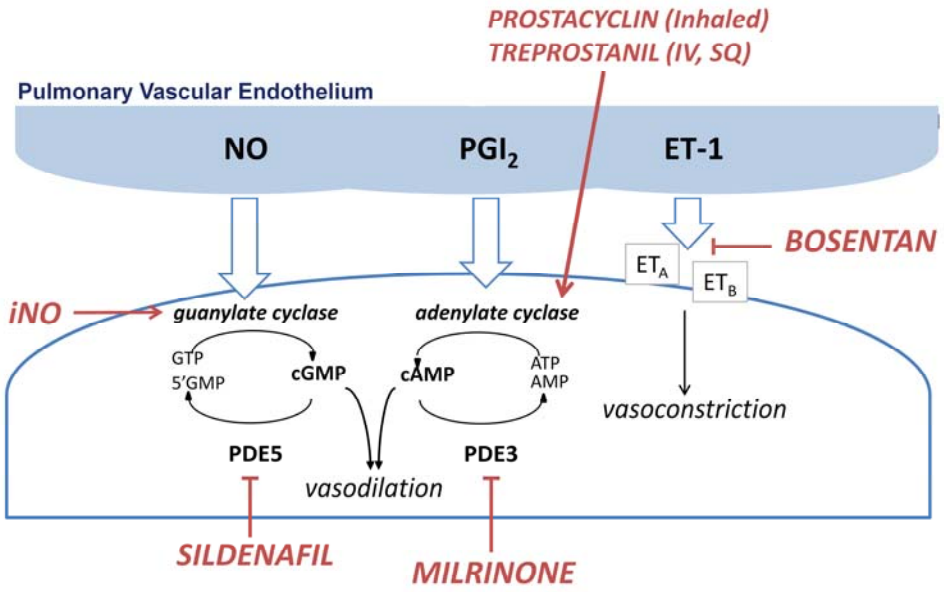
James et al; Cardiol Young 2015

Dublin cohort, retrospective review. Milrinone was commenced at an initial dose of 0.50 µg/kg/minute up to 0.75 µg/kg/minute and was continued depending on clinical response. No loading dose was used in this cohort in order to minimise the risk of hypotension. Administration of milrinone was associated with a

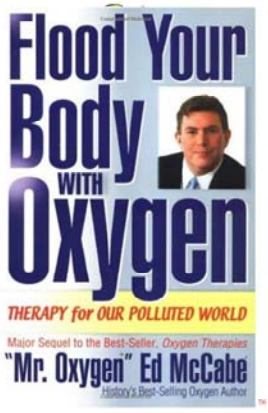
reduction in systolic, diastolic, and mean blood pressures (p=0.04), peaking at 6 hours after administration. This was associated with a significant increase in the use of vasopressor inotropes at 6 and 24 hours (Fig 2); however, blood pressure began to increase after 12 hours of milrinone administration with a peak at 72 hours (systolic p=0.02, mean p=0.03, diastolic p=0.02), in spite of a reduction in the use of vasopressor inotropes over the same time period.

Pharmacotherapy for PH

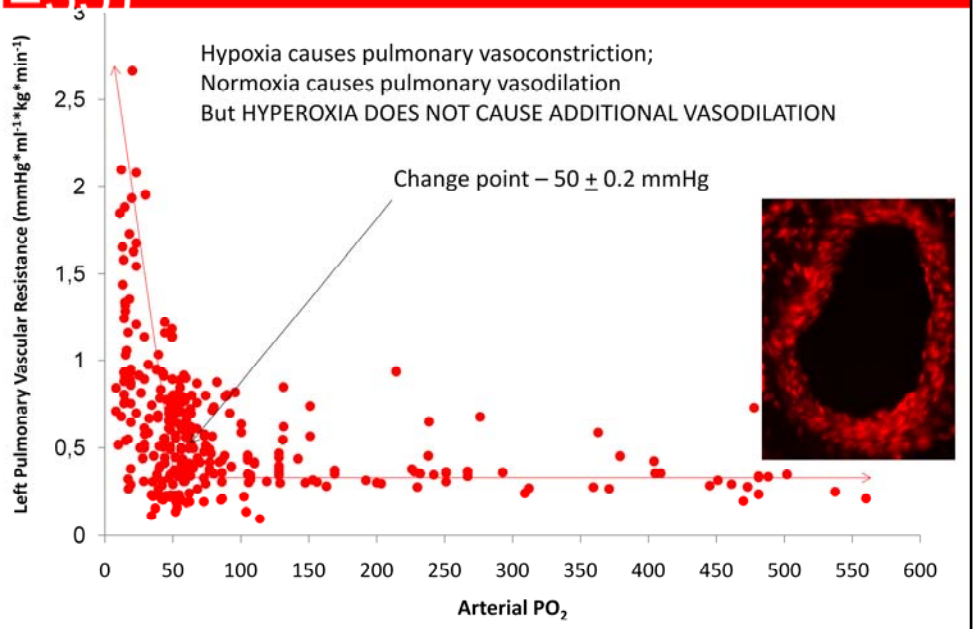


Goals of Oxygen Therapy

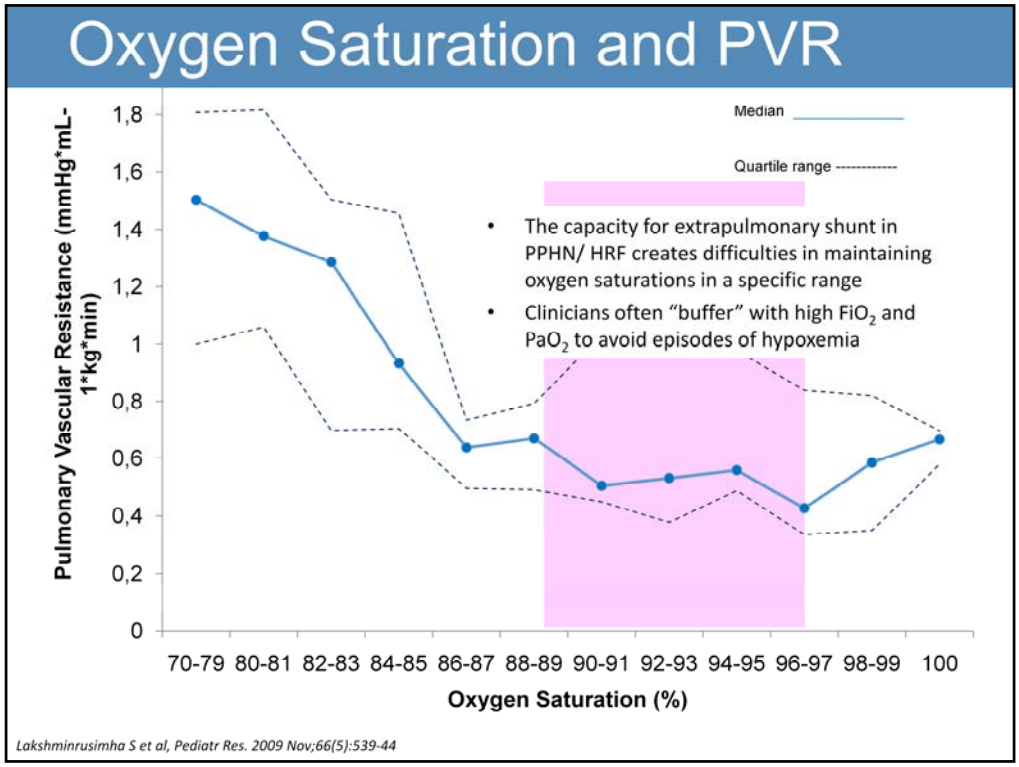
- Oxygen delivery
- Facilitate pulmonary vasodilation
- Improve outcomes



Healthy Neonatal Lambs (2h old n=35)



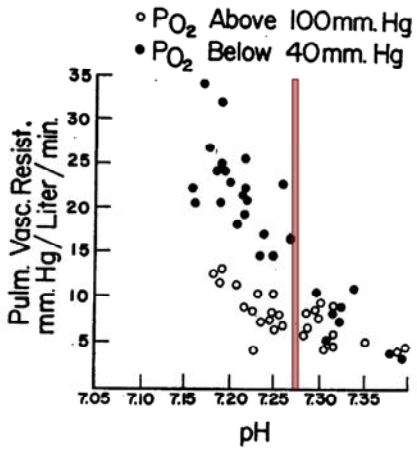
Lakshminrusimha et al, Pediatric Research 2009



Such a drop in oxygenation can result in hypoxic pulmonary vasoconstriction in babies with PPHN.

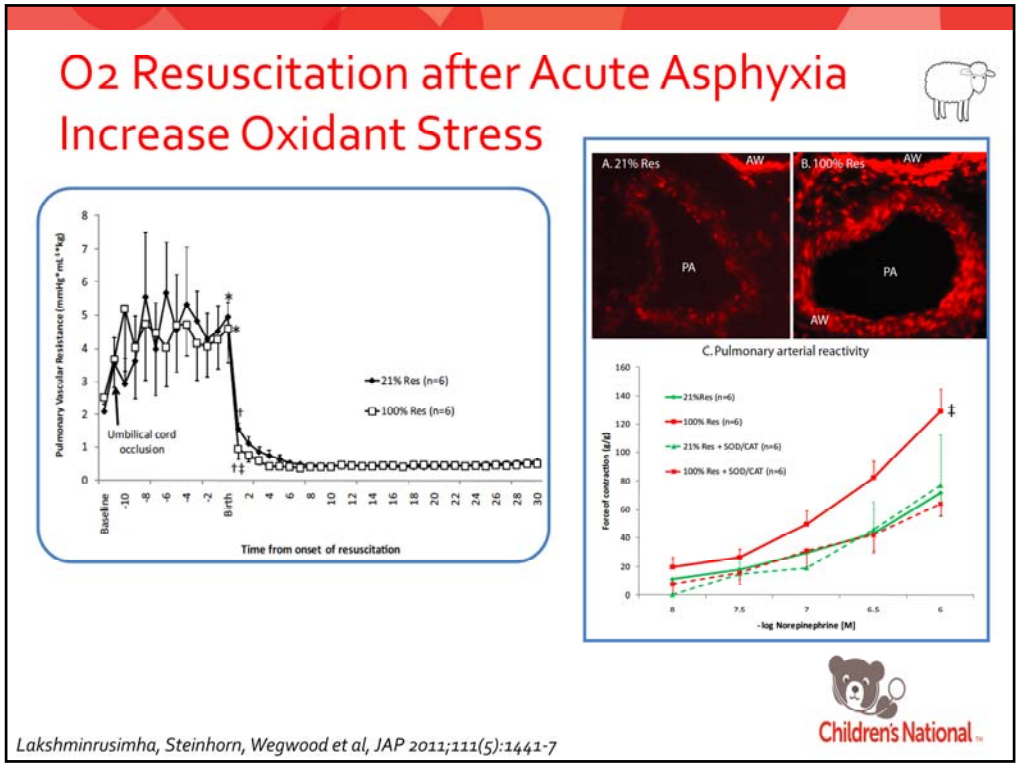
Interaction between Acidosis and PO_2

Respiratory and metabolic acidosis worsen HPV



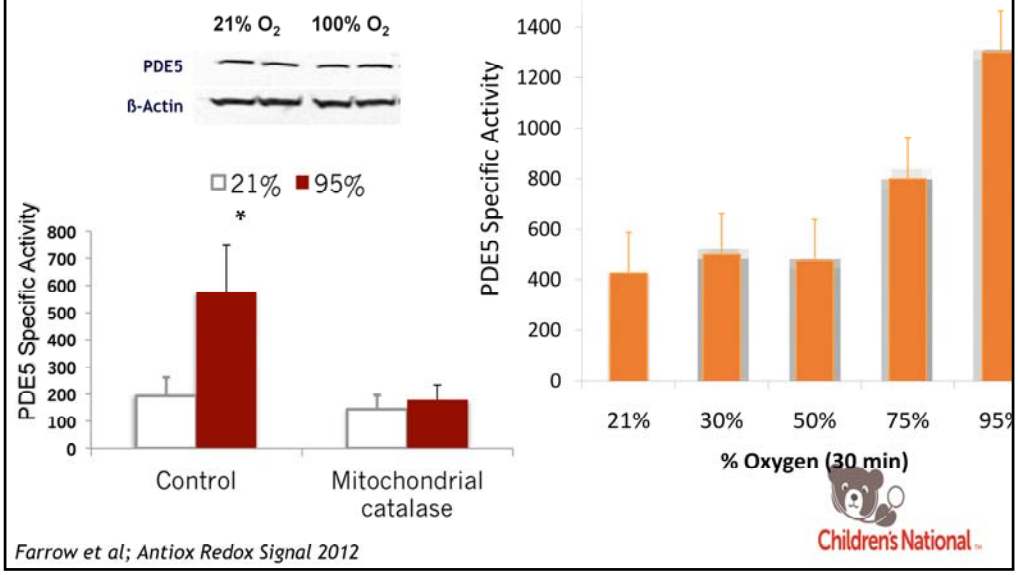
Normal pH partially protects against HPV

Rudolph AM, Yuan S: JCI 1966



intrauterine umbilical cord occlusion for 10min resulting in acidosis (pH-6.96±0.05 and pCO(2)-103±5mmHg), bradycardia, systemic hypotension and increased PVR

Brief Hyperoxia Increases PDE5 Activity in PASMC



Farrow et al; Antiox Redox Signal 2012

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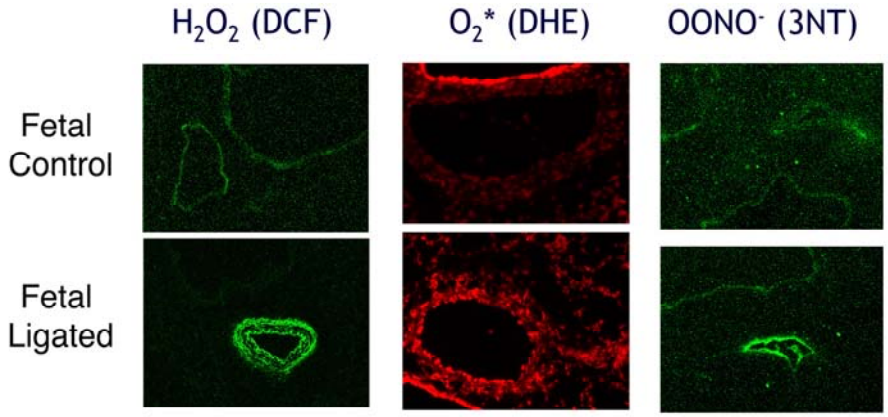
PPHN is a Disease of Vascular Remodeling and Oxidant Stress



Brennan, et. al. *Circ Res*. 2003
Lakshminrusimha, AJRCCM 2006
Wedgwood et al, AJP 2005

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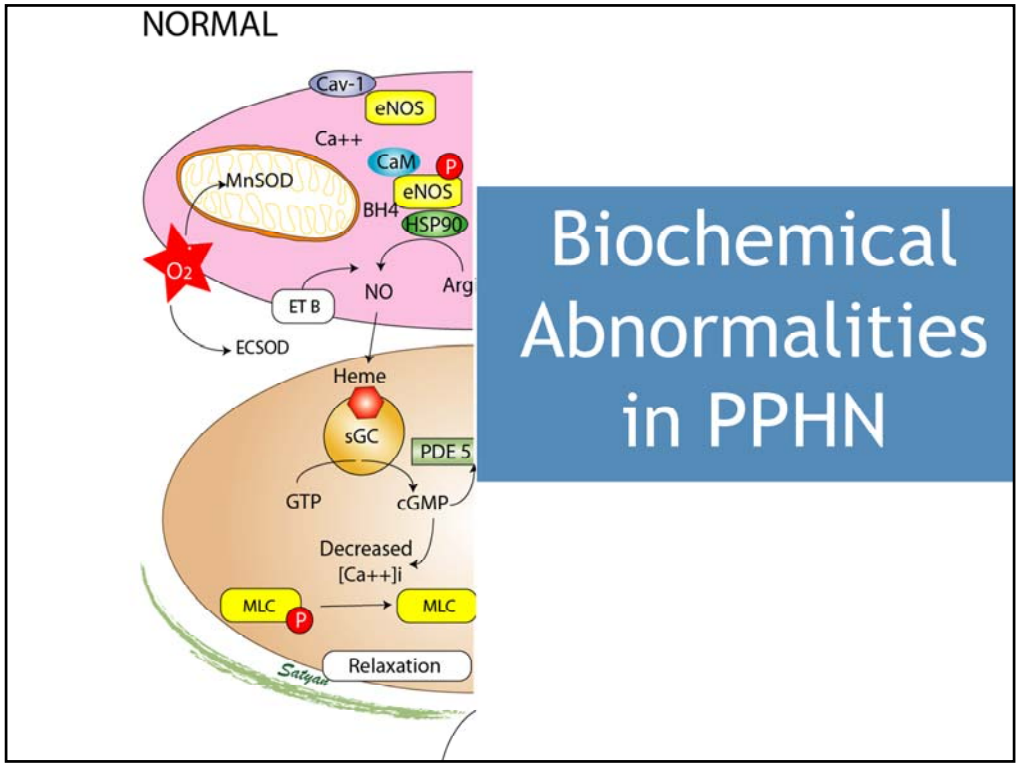
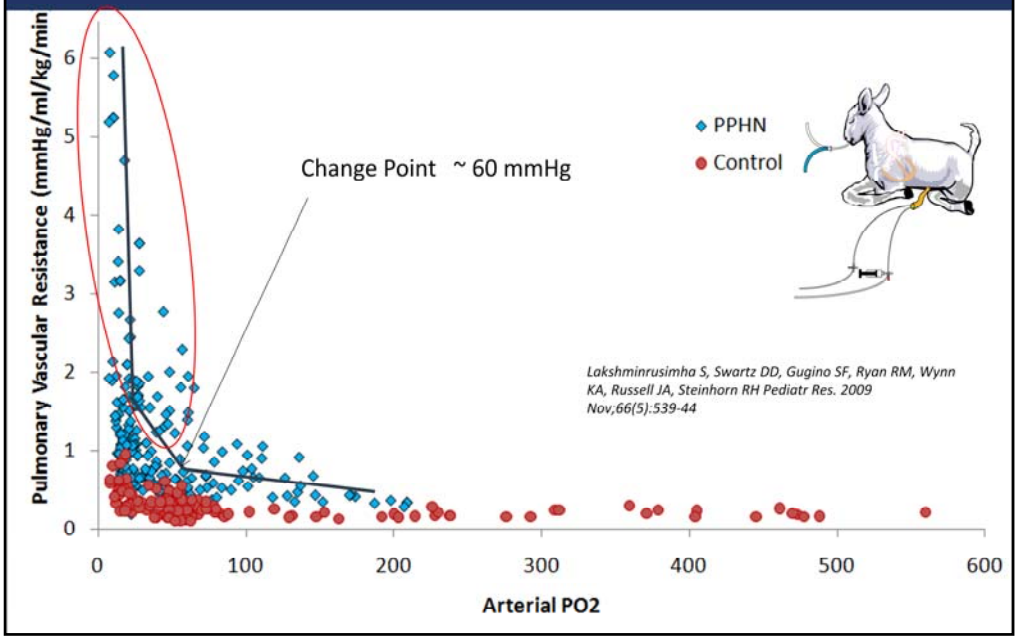

NORMAL
Cav-1
eNOS
Ca++
CaM
P
eNOS
MnSOD
BH4
HSP90
O2
NO
Arg
ET B
ECSOD
Heme
sGC
PDE 5
GTP
cGMP
Decreased
[Ca++]i
MLC
P
MLC
Relaxation
Biochemical Abnormalities in PPHN

Is the Response to O2 Different in PPHN?



Oxygen Recommendations for PPHN

- Avoid hypoxia and hyperoxia (Target PaO_2 55-75 or SpO_2 92-96)
- No evidence that pO_2>60 mm Hg or FiO_2>60% enhances pulmonary vasodilation
- Avoid acidosis
- Shunt across the PDA can be protective in some situations
- Wean FiO_2 before weaning iNO

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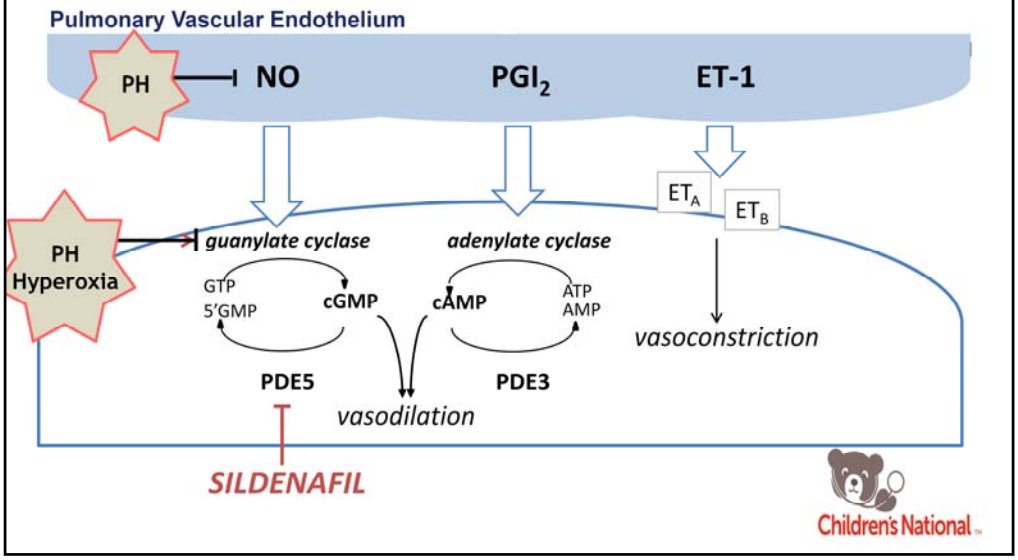
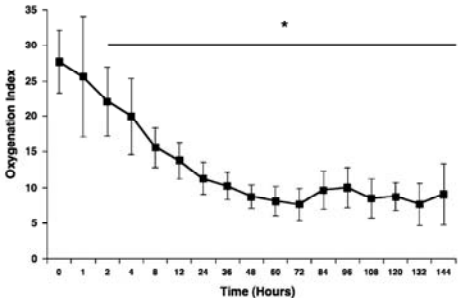
Pharmacotherapy for PH

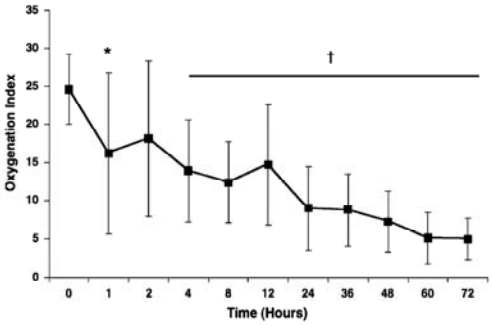


Intravenous Sildenafil Improves Oxygenation in PPHN

All Patients (n=36)



NO Naïve (n=7)



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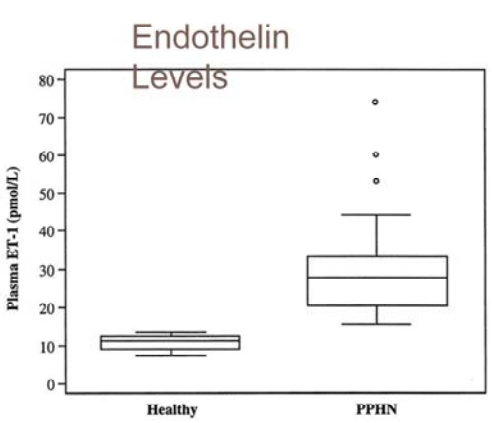
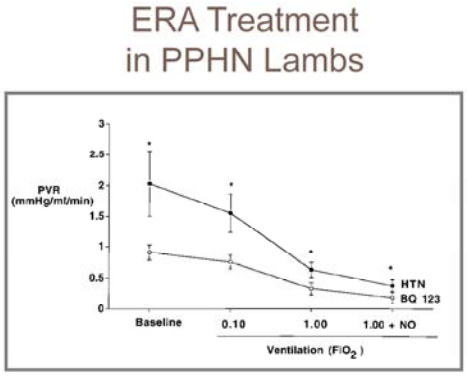
Steinhorn et al, J Pediatr 2009

Endothelin Levels in PPHN





Christou et al, J Pediatr 1997; Ivy DD, J Clin Invest 1997

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Plasma ET-1 concentrations were significantly higher in infants with PPHN at the time of entry into the study than in healthy term infants on the first day of life (median concentration, 28 pmol/L [range, 15 to 74 pmol/L] vs 11 pmol/L [range, 7 to 13 pmol/L], respectively; p = 0.0001)

Hemodynamic effects of BQ 123 on pulmonary vascular resistance during acute delivery after ductus arteriosus

ligation in the late-gestation fetal lamb. PVR was lower following BQ 123 treatment prior to ventilation (*Baseline*), and ventilation with

low FiO2 (0.10), high FiO2 (1.00), and during ventilation with high FiO2 and 20 ppm inhaled NO than control (*HTN*).

Bosentan in NO-Naïve Infants

- Mohamed et al, J Perinatol 2012
- Single site study
- 47 infants with PPHN and OI>25 randomized to bosentan (1 mg/kg/bid) or placebo
- iNO and ECMO not available

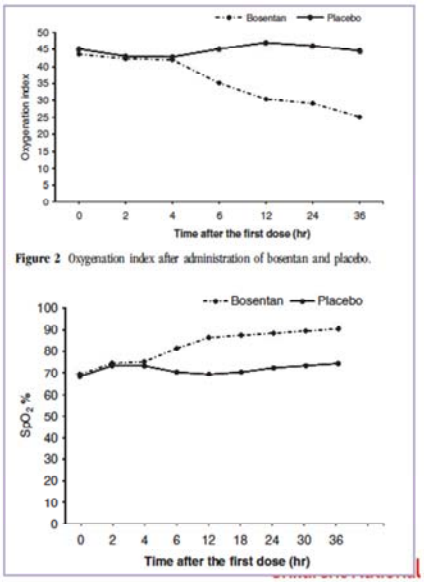
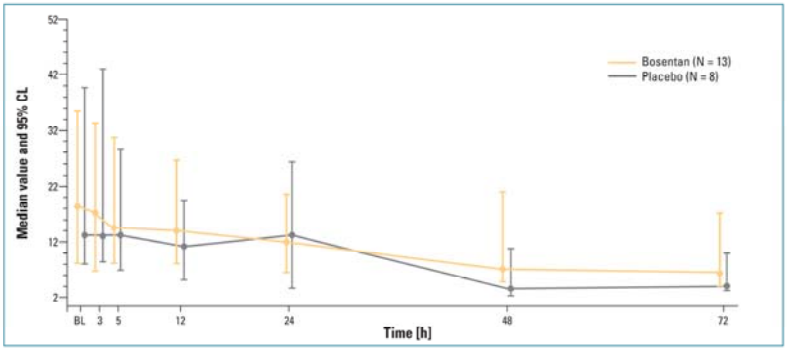


Figure 2 Oxygenation index after administration of bosentan and placebo.

FUTURE 4 Trial of Bosentan as Adjunctive Therapy to iNO

OI



	Bosentan (n=13)	Placebo (n=8)
Treatment failure (need for ECMO)	1 (7.7%)	0
Time to weaning from iNO (Days, median [95% CL])	3.7 [1.17, 6.95]	2.9 [1.26, 4.23]
Time to weaning from mechanical ventilation (Days, median [95% CL])	10.8 [3.21, 12.21]	8.6 [3.71, 9.66]

Steinhorn et al, J Pediatr in press

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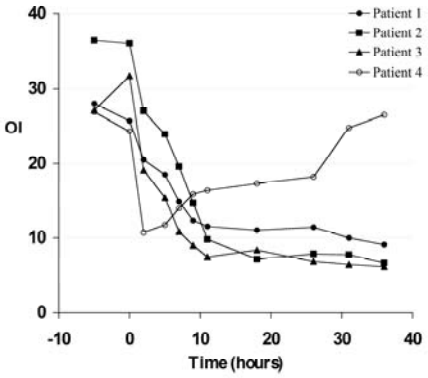
Prostanoids

- Intravenous prostanoids: short t1/2, require dedicated central line, high risk of line infections, site pain, thrombosis
- Inhaled epoprostanol: Standard in adult ICUs; no clinical trials in infants
- Iloprost or treprostinil – newer generation preparations for inhalation, longer t1/2
- Treprostinil can be delivered intravenously or subcutaneously



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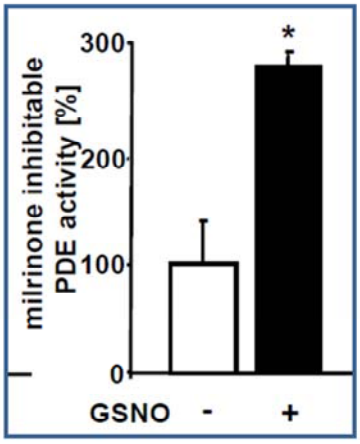
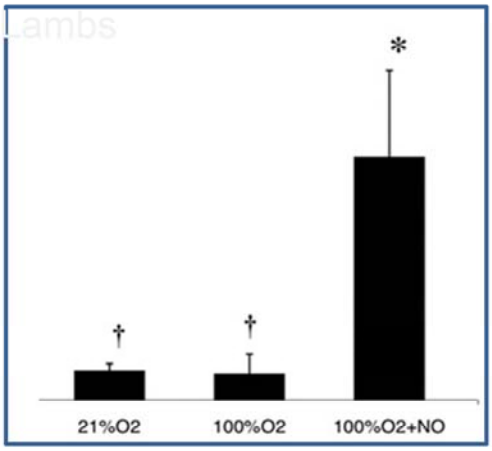
Ferdman et al, Pediatrics 2013

Exposure to NO Increases PDE3 Activity

Rat PASMC



Ventilated Neonatal Lambs



Busch CJ, et al J Physiol Pharmacol 61:663-669.
Chen et al, Ped Res 2009

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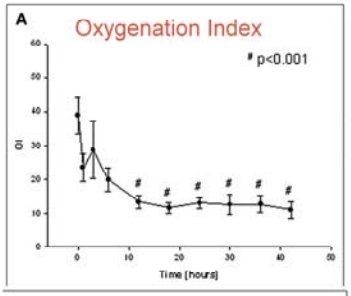
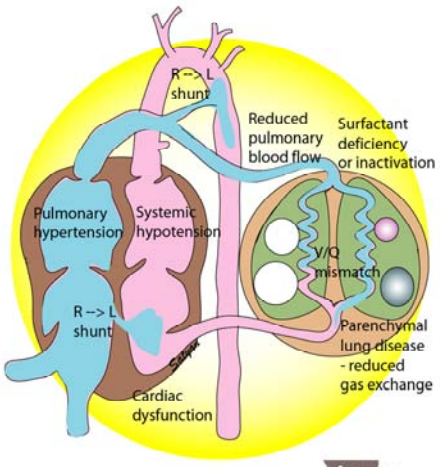
Milrinone Enhances Oxygenation in NO-resistant PPHN





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McNamara et al; Pediatr Crit Care Med 2013;14: 74

11 patients with iNO resistent PPH. Figure 2 . A, Interval changes in oxygenation index (OI); B, inhaled nitric oxide (iNO) before and after milrinone treatment. (6 patients at 30 and 36 hrs; 4 patients at 42 hrs).

Glucocorticoids and PPHN

- Reports of efficacy of hydrocortisone in neonatal cases of meconium aspiration syndrome
- Methylprednisolone improves oxygenation and attenuates pulmonary hypertensive response in porcine meconium aspiration
- Antenatal betamethasone attenuates oxidant stress and improves vasodilator response of pulmonary arteries in lambs with PPHN

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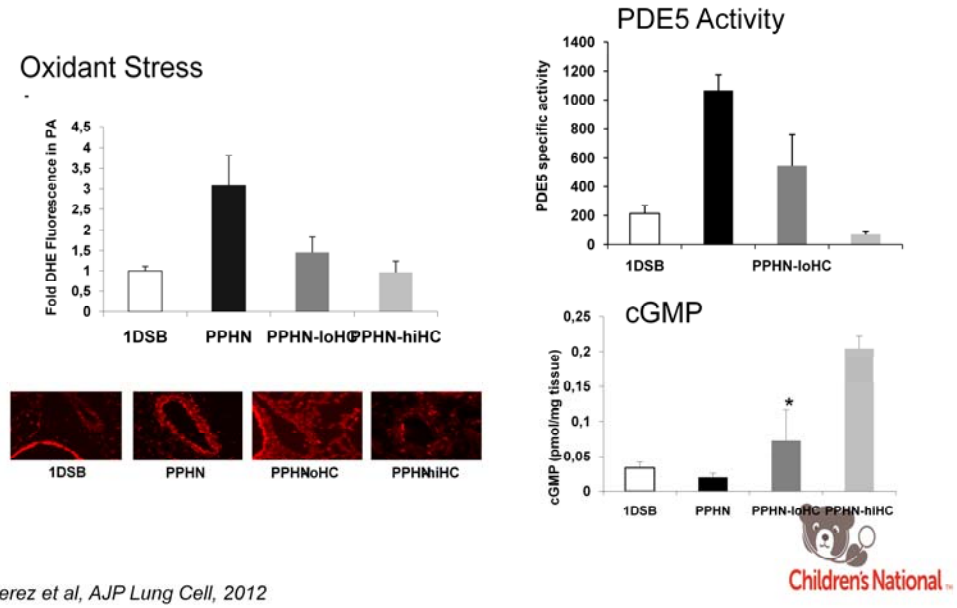
While glucocorticoids have been used in neonates for the treatment of adrenal insufficiency, pressor-resistant hypotension and BPD prophylaxis, there have been only few reports of efficacy of hydrocortisone in neonatal cases of meconium aspiration syndrome, a common cause of PPHN. Methylprednisolone was found to improve oxygenation and attenuate pulmonary hypertensive response in an animal model of meconium aspiration.

Antenatally-administered betamethasone attenuates oxidant stress and improves response to vasodilators in PPHN lambs.

Hydrocortisone Decreases Oxidant Stress and PDE5 Activity in PPHN Lambs



Perez et al, AJP Lung Cell, 2012

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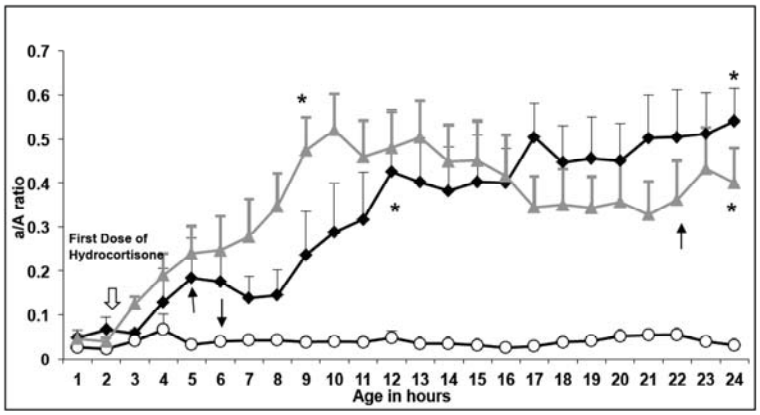
Hydrocortisone Improves Oxygenation in PPHN Lambs



High
5 mg/kg q6H

Low
3 mg/kg x 1, then
1 mg/kg q8H

Oxygen only

Perez et al, AJP Lung Cell 2012

Children's National

AHA/ATS Guideline

Pediatric Pulmonary Hypertension

Guidelines From the American Heart Association and American Thoracic Society

1. Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with PPHN or hypoxemic respiratory failure who have an oxygenation index that exceeds 25. (Class I, Level A).

2. Lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease. (Class 1, Level B)

3. ECMO support is indicated for term and near-term neonates with severe PH and/or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function. (Class I, Level A).

4. Evaluation for disorders of lung development, such as alveolar capillary dysplasia and genetic surfactant protein diseases, is reasonable for infants with severe PPHN who fail to improve after vasodilator, lung recruitment and/or ECMO therapy. (Class IIa, Level B)

5. Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to inhaled NO, especially with an oxygenation index that exceeds 25. (IIa,B)

6. Inhaled prostacyclin analogues may be considered as adjunctive therapy for infants with PPHN that are refractory to iNO and have an oxygenation index that exceeds 25.(IIb,B)

7. Intravenous milrinone is reasonable in infants with PPHN and signs of left ventricular dysfunction. (IIa, B)

8. Inhaled NO can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease. (Class IIa, Level B)

9. iNO and other PAH-targeted drug therapies should be used cautiously in subjects with CDH especially in those with confirmed or suspected left ventricular dysfunction. (Class IIa, Level B)

Conclusions and Future Directions

- Oxygen targeting is complex, but a target range of 92-95% is reasonable for both term and preterm babies
- Promising therapeutic approaches:
  - Hydrocortisone, sildenafil, treprostanil
  - Selective antioxidants
- We need adaptive designs and improved referrals of at-risk babies to successfully complete clinical trials

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Northwestern University
Paul Schumacker
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Nicolas Porta
Marta Perez
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Keng Jin Lee

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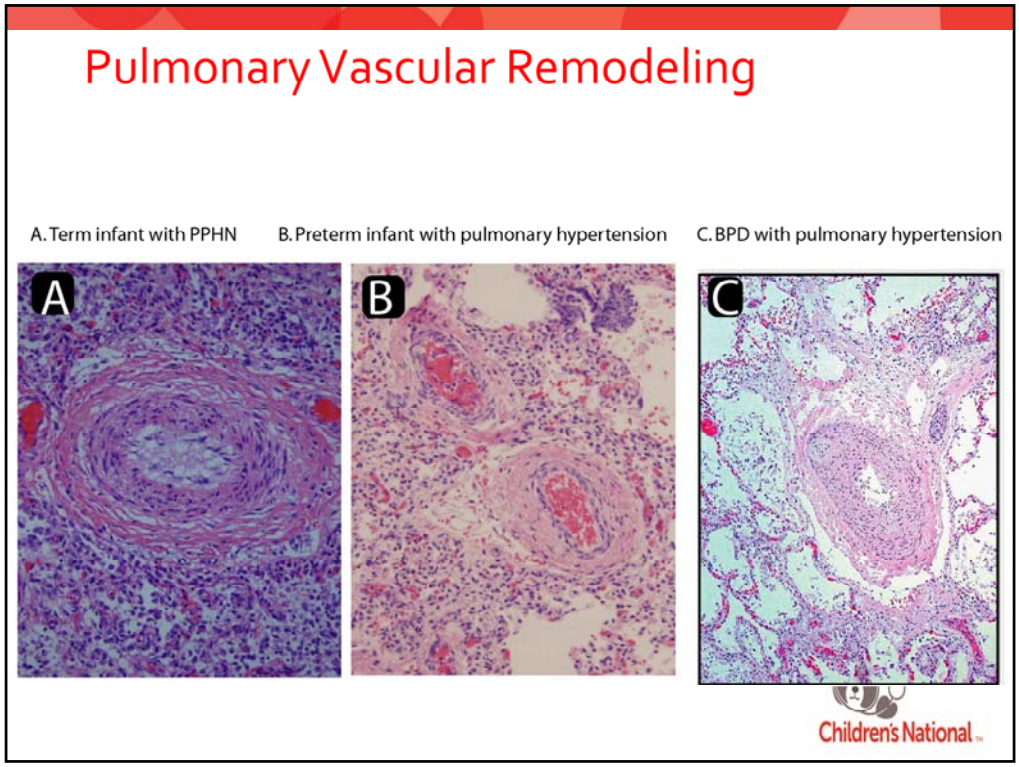
Satyan Lakshminrusimha
James A. Russell
Sylvia Gugino

Denver
John Kinsella
Stephen Abman



A. 14-day old 37 week gestation infant with trisomy 21 (Note the significant thickening of the medial and adventitial layers);

B. 5-day old 25 week gestation preterm infant with pulmonary hypertension and severe hypoxemic respiratory failure; and

C. 4-month old ex-23 week gestation infant with bronchopulmonary dysplasia and pulmonary hypertension.

There are two ways to live your life….

One is as though nothing is a miracle.

The other is as though everything is.

Albert Einstein

Clinical Trials: HRF in Term/Near-Term Infants

Trial	Recruitment Period	Sites	Enrollment Goal	Final Enrollment
PGE1 (NO naive)	4 months	NRN	50	0
PGE1	9 months	NRN	50	7
Sildenafil (NO naive)	18 months	5	50	4
Bosentan	24 months	25	30	21
Sildenafil	36+ months (ongoing)	50 (42 active)	64	(ongoing)
Remodulin	Launched 2015/2016			
MINT	Launching 2016			

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Why Does PPHN Remain High Risk in 2016?

- Surprisingly common but difficult to recognize
- High mortality
- High incidence of neurodevelopmental impairment
- Few evidence based treatments
- High degree of practice variation

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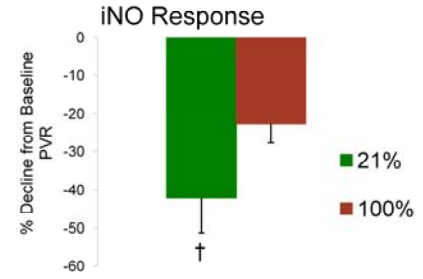
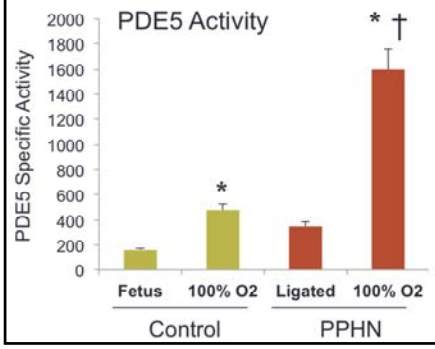
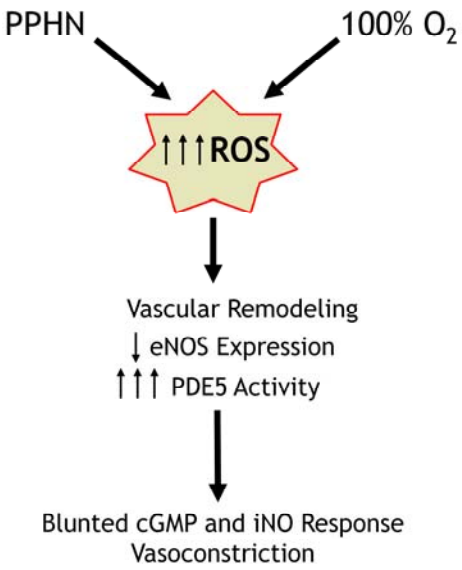
Hyperoxia Accentuates Vascular Dysfunction

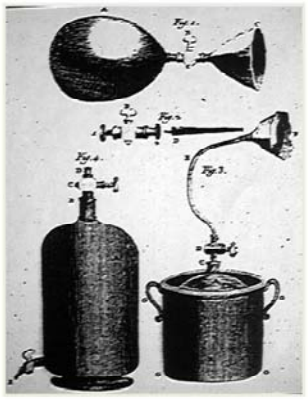






History of Supplemental Oxygen

- Appearance of cyanobacteria using photosynthesis ~2.5 billion years ago, eukaryotes begin to acquire mitochondria
- 1770's: Discovered as an element and component of air
- 1780: First administration of oxygen to a neonate
- 1798: Founding of the "Pneumatic Institute" in Bristol, using pure oxygen to treat disease
- 1890's: First descriptions of oxygen toxicity
- 1942: First description of retinopathy of prematurity due to oxygen toxicity
- 1950's: Description of oxygen-derived radicals



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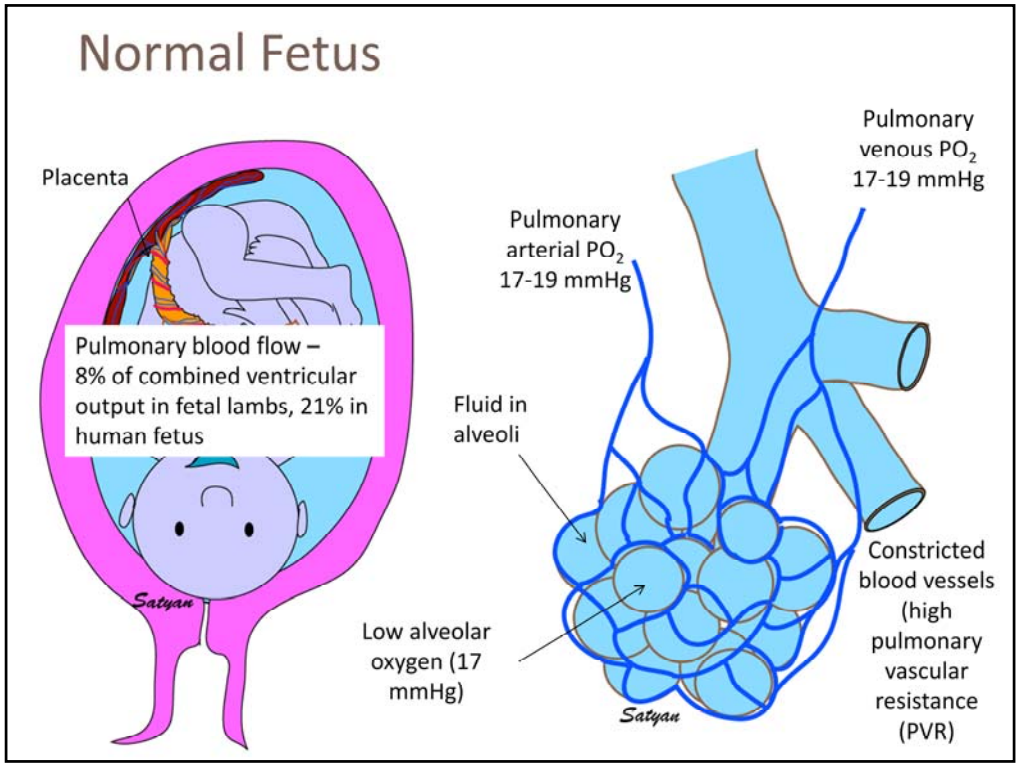
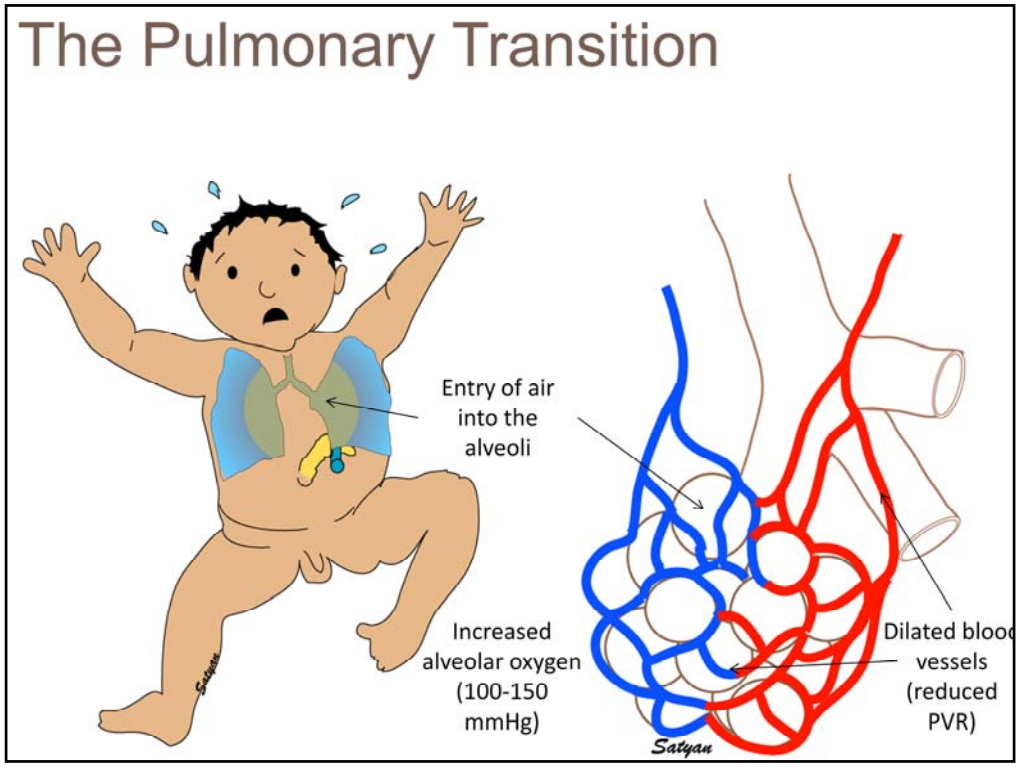
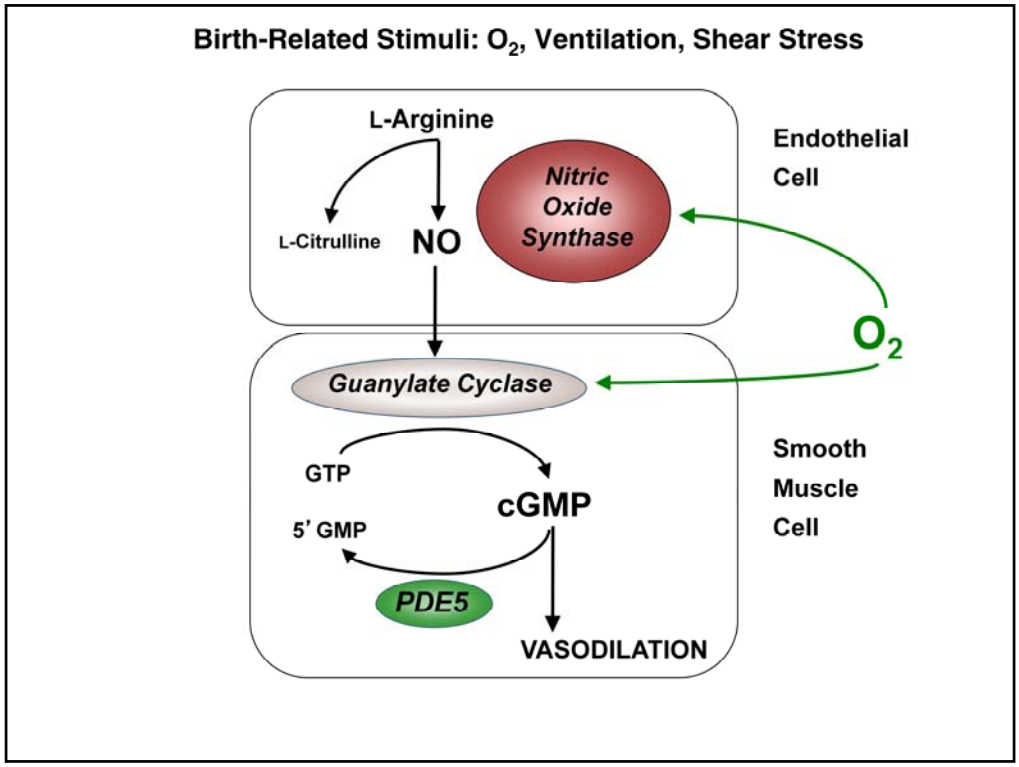
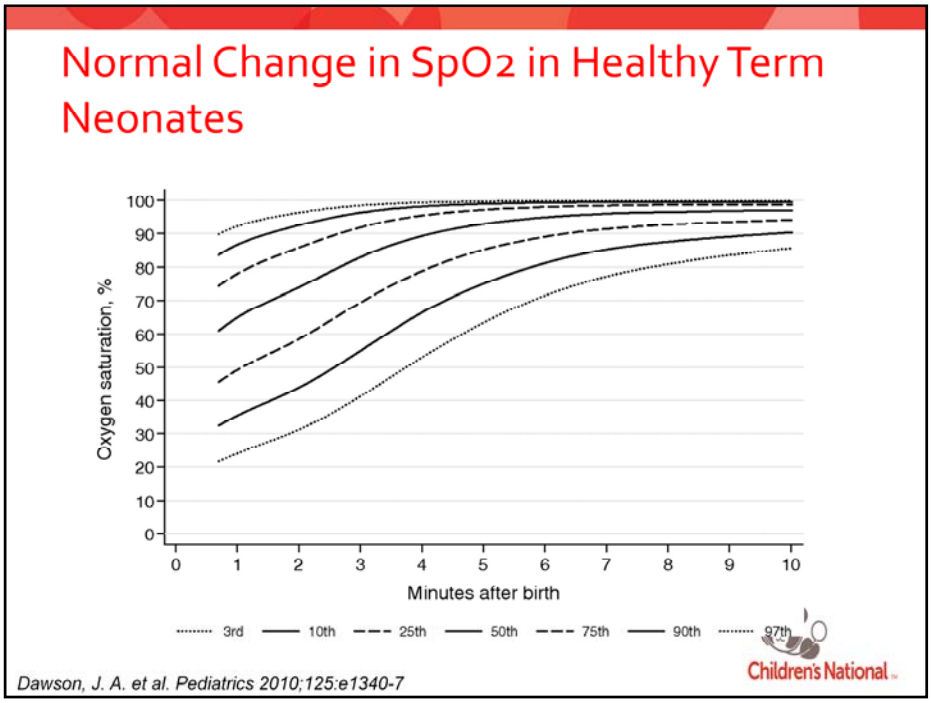


The fetal lungs are expanded in utero, but the alveoli are filled with fluid. The oxygen levels in the alveoli are low compared to postnatal levels. The arterioles that perfuse the fetal lungs are markedly consticted, partly due to the low pO2 resulting in high pulmonary vascular resistance. No significant change is observed in pulmonary arterial to venous PO2 as lungs are not the site of gas exchange.



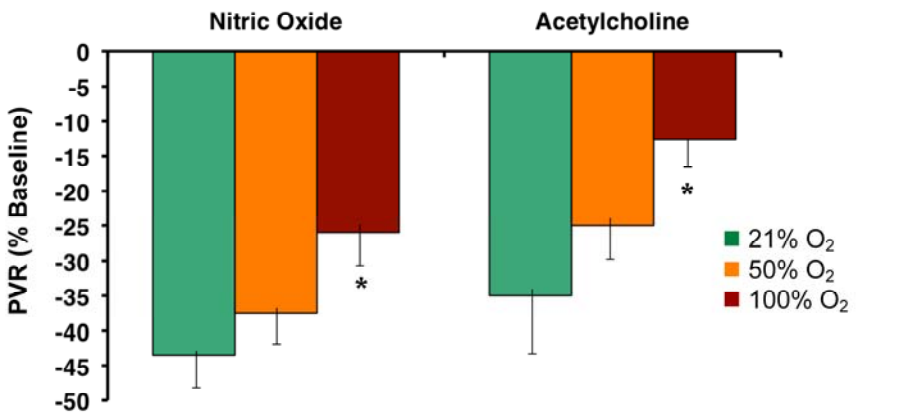
Soon after birth, fluid in the alveoli is absorbed and replaced by air. Because air contains 21% oxygen, filling the alveoli with air increases the alveolar oxygen levels. As a result of gaseous distension and increased oxygen in the alveoli, blood vessels in the lung dilate and pulmonary vascular resistance falls. Pulmonary blood flow increases, oxygen from the alveoli is absorbed by the blood in the pulmonary vessels, and oxygen-enriched blood (with pO2 in the 100 mmHg range) returns to the left side of the heart where it is pumped to the tissues of the newborn's body.


Birth-Related Stimuli: O_2, Ventilation, Shear Stress
L-Arginine
L-Citrulline
NO
Nitric Oxide Synthase
Endothelial Cell
O_2
Guanylate Cyclase
GTP
cGMP
5' GMP
PDE5
VASODILATION
Smooth Muscle Cell



Jennifer Dawson from Colin Morley's group in Australia. Studied 468 infants and recorded >60K SpO2 data points. The infants had a mean gestational age of 38 +/- 4 weeks and birth weight of just under 3 kg. It took a median of 7.9 minutes (interquartile range: 5.0 –10 minutes) to reach a SpO2 value of >90%

Resuscitation with 100% Oxygen Blunts Response to NO



Lakshminrusimha et al; Pediatr Res 2007

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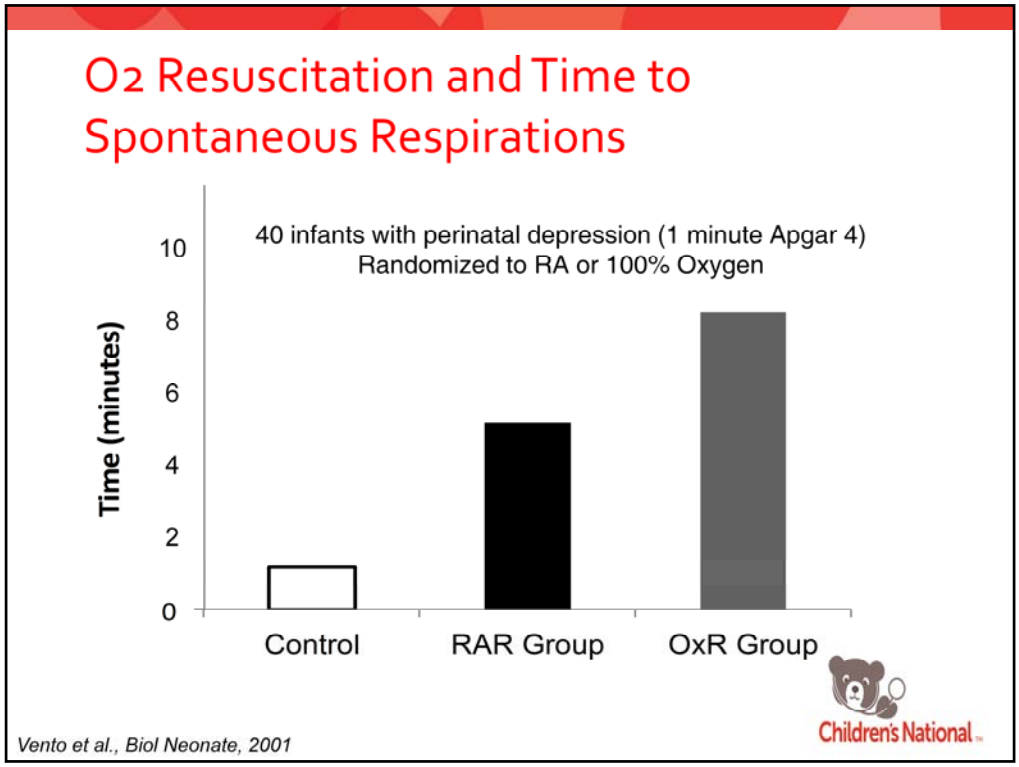
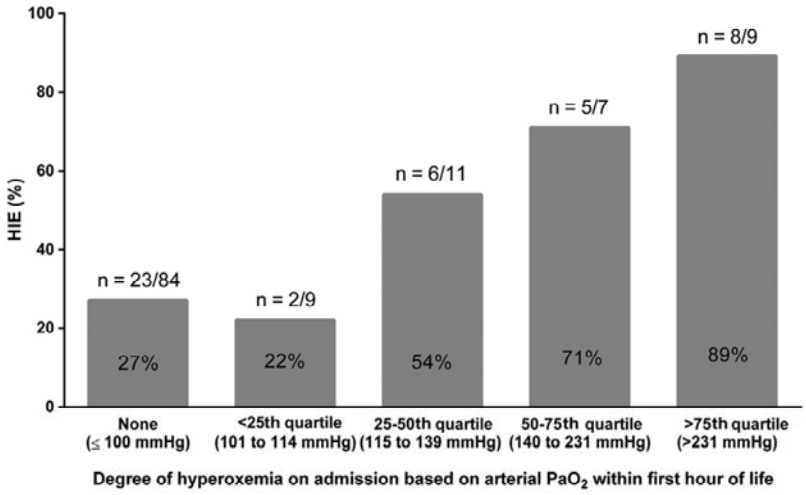


Controls consisted of 26 nonasphyxiated term neonates with a median Apgar score at 1 minute of 8 (7–9). All infants were born by vaginal delivery under epidural analgesia. Serum markers of oxidative stress elevated in the oxygen group, and this persisted for at least 4 weeks.

Hyperoxia worsens HIE



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Kapadia et al; J Pediatr 2013

Delivery Room Resuscitation and Childhood Cancers

- Naumburg, et al. 2002
  - Children born in Sweden between 1973 and 1989 and diagnosed with lymphatic leukemia (578 cases)
  - Delivery room resuscitation with 100% O2 was associated with an increased risk of lymphatic leukemia (OR=2.57, 95%CI=1.21-6.82)
  - Risk was further increased if ventilation with O2 lasted > 3 minutes (OR=3.54, 95%CI=1.16-10.8)
- Spector, et al. 2005
  - Delivery room O2 for greater than 3 minutes was associated with increased risk of any childhood cancer.

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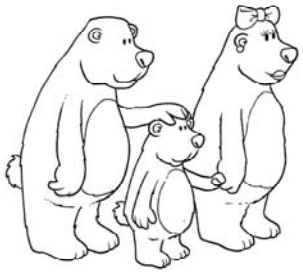
Naumberg-- Matched with randomly selected controls by gender and birth date

Trisomy 21 children were excluded

Spector – large database of over 55,000 children followed to age 8

Oxygen Therapy for PPHN

- Reverse critical hypoxemia
- Pulmonary vasodilation



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Oxygen Therapy for PPHN

- Pre-iNO era:
  - Superphysiological pO_2 targets were standard
  - Preference for weaning ventilator settings over FiO_2
  - Complacent attitude about tolerance of neonates to hyperoxia
  - Fear of labile PH and acute, life-threatening HPV
- Current era:
  - Better understanding of dose-response
  - Better understanding of pre- and post-ductal SpO_2s
  - Appreciation of potential injurious effects of hyperoxia and ROS-induced damage

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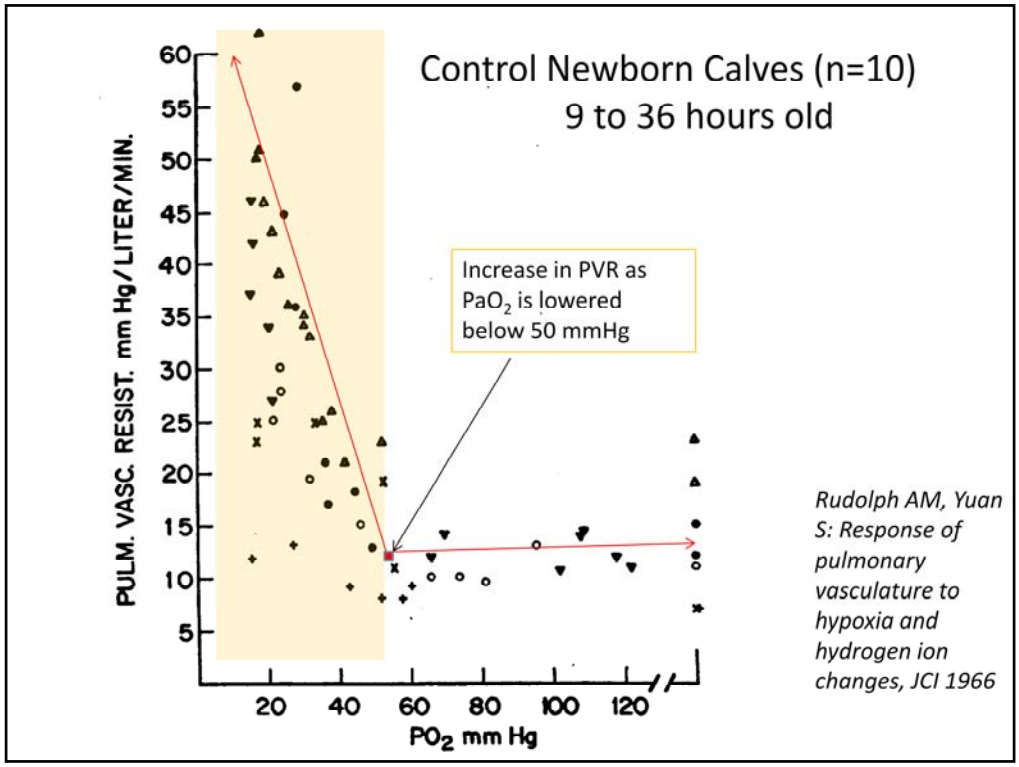

Those of us who have heard Dr. Aschner's talk on oxygen therapy in PPHN are familiar with this classic study done in the 60s by Dr. Abraham Rudolph looking at the relation between PVR and PaO2 in 9 – 36 h old normal newborn calves. He observed that when PO2 is decreased below 50 mmHg (CLICK), PVR increases significantly. However, if PaO2 levels are increased above 50 mmHg (CLICK), no further decrease in PVR is noted. These results were obtained in calves with normal pulmonary vasculature (click). The relationship between pO2 and PVR in animal models with remodeled pulmonary vasculature and pphn is not known.