Persistent Pulmonary Hypertension of the Newborn (PPHN)

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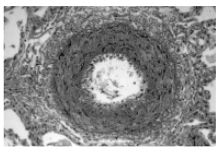
Pulmonary Circulation

- Low-pressure, high-flow system with a great capacity for recruitment of normally unperfused vessels
- Wall of PA are thin
- PAH is a disease of the small pulmonary arteries, characterized by vascular narrowing, leading to progressive increase in pulmonary vascular resistance

Pulmonary Hypertension

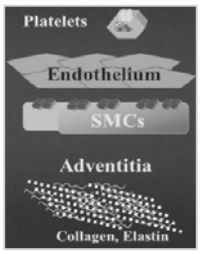
- Vasoconstriction
- Remodeling of the PA wall
- Thrombosis



Pulmonary arterial obstruction by vascular proliferation & remodeling is the hallmark for PAH pathogenesis

Pulmonary Hypertension

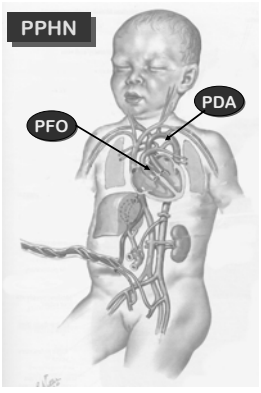
- Pulmonary vascular remodeling involves all layers of the vessel wall
  - Endothelial Cells
  - Smooth muscle cells
  - Fibroblasts - Adventitia
  - Inflammatory Cells
  - Platelets and thrombosis



Mediators of PAH

- Prostacyclin
- Vasoactive intestinal peptide
- Nitric oxide
- Endothelin-1
- Potassium Channels
- Serotonin

- **Clinical Syndrome**
  - **↑ PVR after birth**
  - **R → L shunting at the PDA &/or PFO**
  - **Resulting in persistent hypoxia**



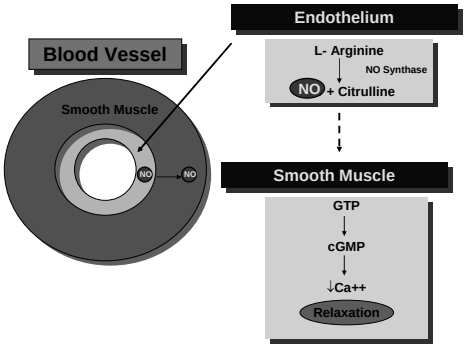
The Fetal Lung

- ***High Resting Vascular Tone - Causes***
  - Compression of PA by fluid filled alveoli
  - Low alveolar oxygen tensions, 17 – 20 mmHg
  - Different balance between the vasoconstrictors & vasodilators pre and post delivery

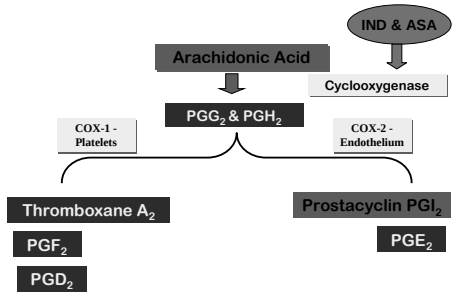
FETAL LUNG
Vasoactive Mediators

- **Vasodilators**
  - Nitric Oxide
  - Prostacyclin
  - Estrogen
  - Adenosine
- **Vasoconstrictors**
  - Endothelin-1
  - Platelet-activating factor
  - Leukotrienes
  - Thromboxane

Nitric Oxide – Mechanisms of Action



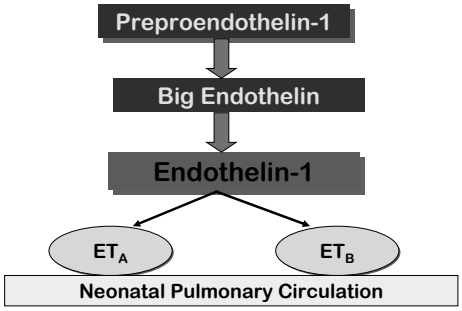
Eicosanoids - Prostaglandins



The Endothelin Family

- Endothelial derived vasoconstrictor peptides
- 3 Isoforms of this 21- amino acid peptide
  - ***Endothelin-1***
  - *Endothelin-2*
  - *Endothelin-3*

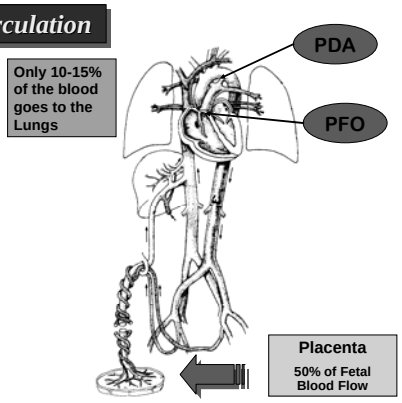
The Endothelin Family



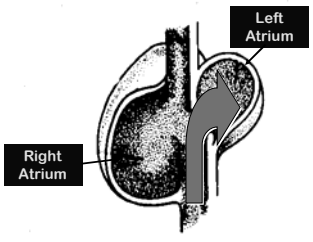
Endothelin – Fetal Lung

- Hypoxia stimulates the production of ET-1
- ET-1 levels increase during gestation, then decrease rapidly in the postnatal period
- Nitric oxide suppresses ET-1 synthesis
  - Low Nitric Oxide production in fetal life may allow the high level of ET-1

Fetal Circulation



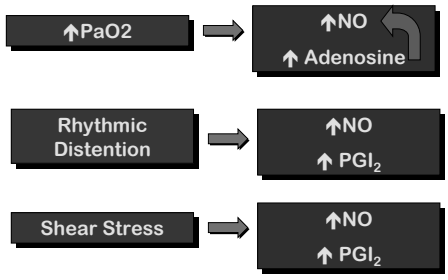
Fetal Circulation – Blood Flow Return to the Heart



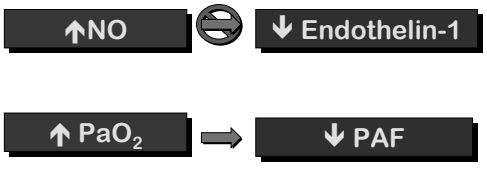
The Fetal Circulation

- ***The Transition to Birth***
  - Endothelium acts as a paracrine modulator of vascular resistance, release of vasoactive products including *Nitric Oxide & Arachidonic Acid Metabolites (PGI_2)*
  - *Oxygen, ventilation, & shear stress* are an important stimuli for endothelial NO & PGI_2 production during transition

Normal Transition



Normal Transition

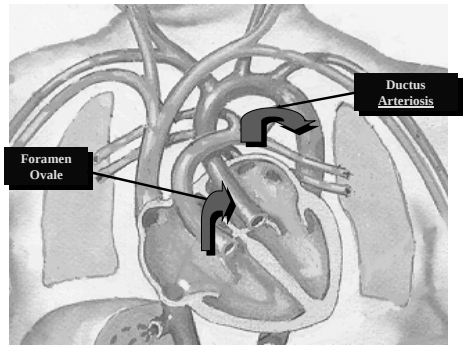


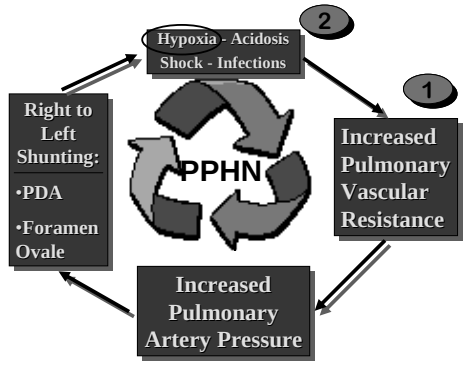
The Fetal Circulation

- ***The Transition to Birth***
  - **Redirecting of blood flow from the placenta – *marked changes in shear stress & oxygen levels***
  - **8-10 x increase in pulmonary blood flow**
  - ***Ductus* closes secondary to high oxygen content**
  - ***Foramen ovale* closes with increased left atrial pressure changes when pulmonary blood flow increases**

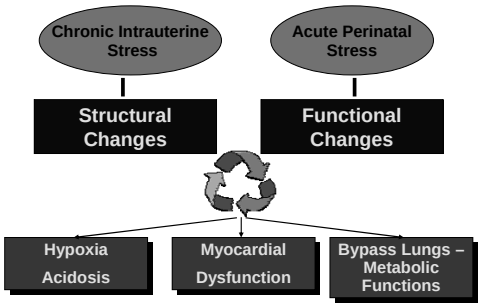
Abnormal Transition –

Persistent Pulmonary Hypertension

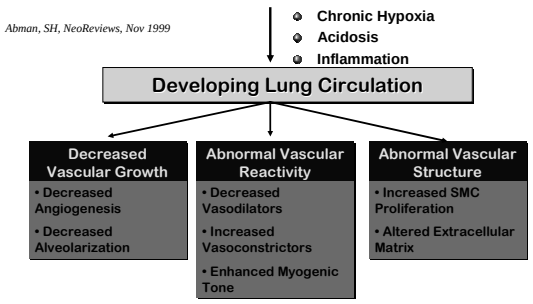




PPHN – Two Pathologic Types



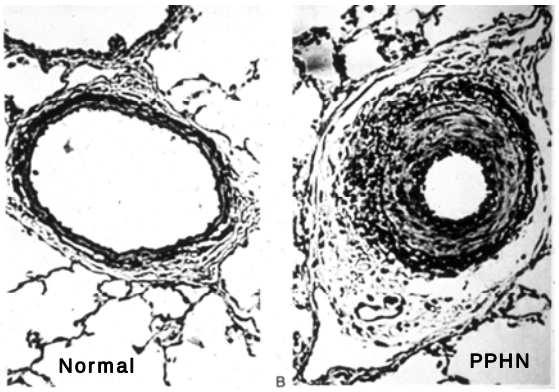
Alteration of Normal Transition – In Utero Causes



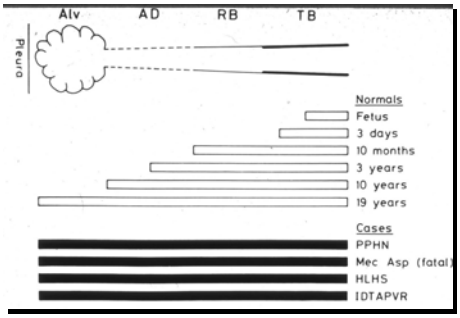
PPHN – *Vascular Changes*

Vascular Changes

- Structurally abnormal vascular bed
  - Increase in pulmonary artery medial smooth muscle
  - Extension of medial smooth muscles into the nonmuscular PAs
  - Increase in collagen formation
- Causes:
  - Altered intrauterine environment, chronic hypoxia, chronic infections
  - Unknown

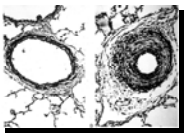


PPHN – Abnormal Vasculature

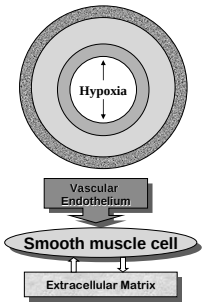


Vascular Development

- Regulation of vascular growth
  - Growth factors
  - Mechanical factors
  - Extracellular matrix
  - Intracellular interaction



Hypoxia & Pulmonary Vasculature Development



Durmowicz & Stenmark, NeoReviews, Nov 1999

Smooth Muscle Cell Proliferation

Matrix Protein:

- ↑ *Elastin*
- ↑ *Collagen*
- ↑ *Fibronectin*

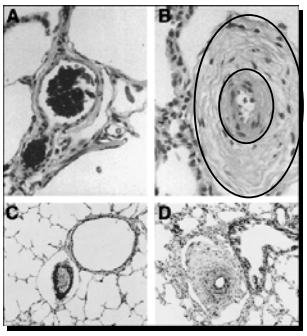
Growth Factors:

- ↑ IGF-1
- ↑ SMEF

Receptors:

- ↓ β-receptors
- ↓ Adenylyl cyclase

From Durmowicz and Stenmark; NeoReviews, e91-e102, Nov 1999



A. Small PA in an infant without PPHN

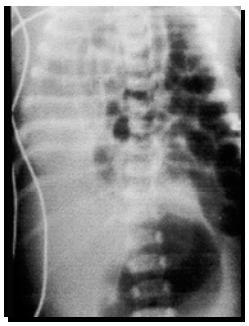
B. Small PA in an Infant with PPHN

C. Small PA from Calf, not exposed to hypoxia

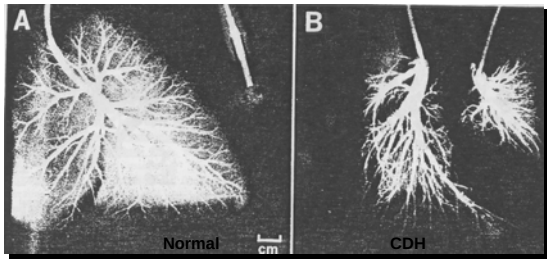
D. Small PA from Calf, exposed to chronic hypoxia

Congenital Diaphragmatic Hernia - PPHN

- **Abnormal number of branching vessels, i.e., hypoplastic lungs**
- **Increased Pulmonary Medial Artery Smooth Muscle**



Congenital Diaphragmatic Hernia - PPHN

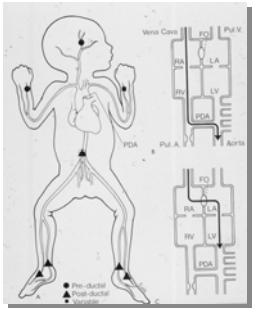


PPHN - Diagnosis

- **Diagnostic Test – Clinical Presentation**
  - **"Flip-Flop" phenomenon – PaO_2 flipping from high to low with only small changes in clinical state**
  - **Chest X-ray – no help**
  - **Hyperoxia test may be negative**
  - **Hyperoxia-hyperventilation test may be positive**
  - **Differential pO_2s or Stats in the Pre & Post Ductal area – seen in PDA shunting infants**
  - **Cardiac ECHO, definitive study**

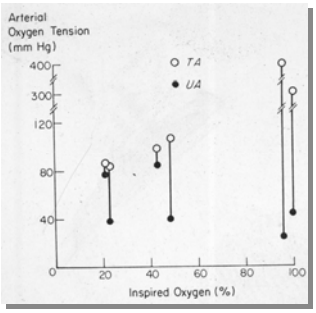
PPHN - Diagnosis

- **Pre-ductal PaO_2 >15 torr higher than Post-ductal PaO_2 , then ductal shunt, indicating PPHN**
- **If shunting primarily at the PFO level, then no oxygen level difference**

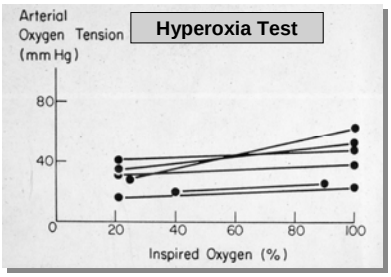


PPHN - Diagnosis

o Preductal
• Postductal



PPHN - Diagnosis



PPHN - Diagnosis

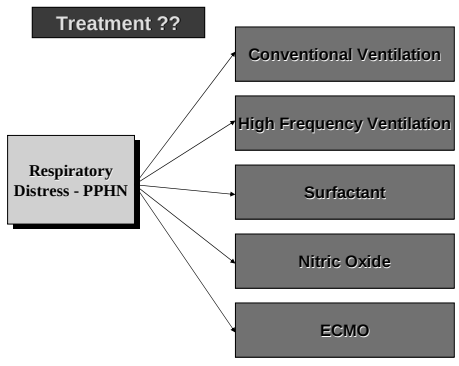
Test	FIO2	Ventilator Status	$PaCO_2$ Goal	pO_2 in PPHN	pO_2 in Parenchymal Disease	pO_2 in CHD
Room Air	21%	Spontaneous Respirations	40 torr	40 torr	40 torr	40 torr
Hyperoxia Test	100%	Spontaneous Resp. or mechanical ventilation	40 torr	40 torr	>100 torr	40 torr
Pre-Post Ductal Shunting Evaluation	100%	Spontaneous Resp. or mechanical ventilation	40 torr	Δ >15 torr	Δ <5 torr	Δ <5 torr
Hyperoxia-Hyperventilation Test	100%	Hyperventilation	20-25 torr	>100 torr	>150 torr	40 Torr

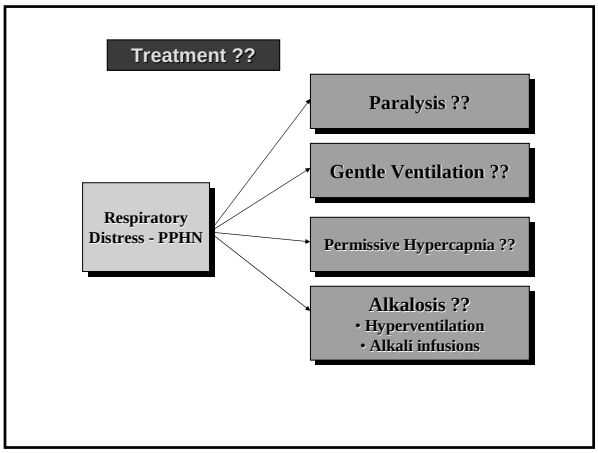
Term Infant – PPHN: Treatment Strategies

- **Lung Protection**
  - Must understand the underlying lung disease
  - Must understand the causes of lung injury
    - *Oxygen toxicity*
    - *Over distension* of lung units (lung volume or stretch, not pressure)
    - *Lung inflammation* makes the lung more susceptible to volutrauma & oxidant lung injury
    - *Surfactant deficiency* – atelectrauma, related to distension

PPHN – Treatment Strategies

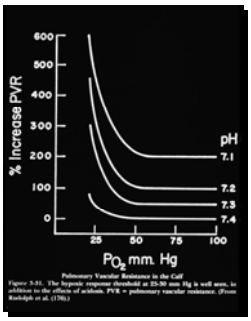
- **Reduce Agitation – sedation & pain management**
  - Morphine/fentanyl & Valium/versed
  - Paralysis if sedation does not work
- **Ventilation techniques**
  - Conventional ventilation
  - HFOV
- **Alkalinization**
  - Respiratory, pH 7.50, $PaCO_2$ 25-35 torr
  - Alkalinizing drip: $NaHCO_3$ or THAM
- **Maintain systemic blood pressure normal or slightly higher than normal**
- **iNO**
- **ECMO**





PPHN - Treatment

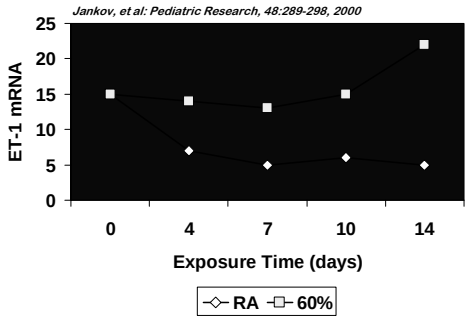
Relationship of PVR to PaO_2 & pH



PPHN - Treatment

- Should we keep the PaO_2 higher than 100 torr ?
  - At what expense ?
  - Hyperoxia, through oxygen radical formation upregulates ET-1
    - ET-1 causes vasoconstriction
    - ET-1 may cause SMC hypertrophy

Endothelin-1 Expression in Hyperoxic States



Hyperventilation: PPHN Treatment

- Two major papers
  - Peckham GJ & Fox, WW, J of Pediatrics, Vol. 93(6): 1005-1010, 1978
  - Drummond WH, Gregroy GA, Heymann MA, & Phibbs, RA; J of Pediatrics, Vol. 98, 603-611, 1981
- Total patients = 14 term infant
  - All had PA lines in place
  - Marked reduction in PA pressure & improvement in oxygenation

Very small numbers. Results only showed immediate response, did not measure long-term outcome

Hyperventilation: CON

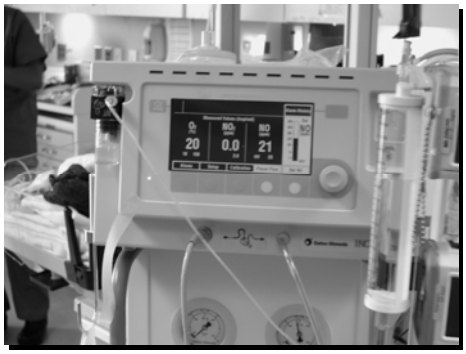
- No controlled trial to show efficacy
- To achieve low pCO2, you must increase ventilator support to a level that you're causing lung injury – small studies have shown improvement with "gentle ventilation approach"
- Severe alkalosis may be related to hearing loss noted in the PPHN population

PPHN - Treatment

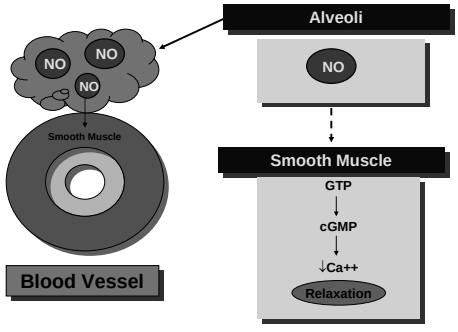
- Vasodilators tried in the past
  - **Acetylcholine**
  - **Isoproterenol**
  - **PGE_1**
  - **PGE_2**
  - **PGI_2**

  } **Systemic side effects**
  - **Tolazoline - Priscoline**

iNO – Selective Vasodilator



Nitric Oxide – *Mechanisms of Action*



Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study

Dennis Davidson, MD*§; Elaine S. Barefield, MD*‡; John Kattwinkel, MD*¶; Golde Dudell, MD*†; Michael Damask, MD#; Richard Straube, MD#; Jared Rhines, BA#; Cheng-Tao Chang, PhD#; and the I-NO/PPHN Study Group

Pediatrics, 101(8):325-334, 1998

Funded by INO Therapeutics (Ohmeda Medical)

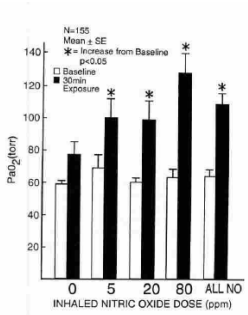


Fig 2. Acute change in Pao_2 during the first half hour of treatment gas administration (control= NO at 0 ppm) to term infants with PPHN. During this period, there were no changes in the Fio_2 or conventional ventilator settings.

Pediatrics, 101(8):325-334, 1998

Davidson, et al: Pediatrics, 101(8):325-334, 1998

TABLE 3. Duration of Treatment*

Treatment Gas	Control Group (n = 43)	Nitric Oxide Groups (n = 114)	P Value‖
Treatment gas (h)			
All patients	68 ± 74	58 ± 58	0.99
Until success: weaning criteria†	107 ± 69	81 ± 59	0.13
Until failure: cardiopulmonary instability‡	10 ± 11	10 ± 13	0.38
Time to ECMO (h)	22 ± 15	42 ± 44	0.24
Duration of ECMO (h)	103 ± 32	129 ± 63	0.26
Mechanical ventilation (h)	199 ± 111	220 ± 177	0.94
Supplemental oxygen (h)			
All patients	155 ± 164	129 ± 136	0.47
Success: weaning criteria†	69 ± 60	97 ± 71	0.13
Failure: cardiopulmonary instability‡	260 ± 224	154 ± 163	0.08
Hospitalization (h)§	628 ± 482	535 ± 267	0.45

Values are mean ± SD.
* Time (hours) starts at initiation of treatment gas.
† Pao_2 ≥60 Torr when Fio_2 <0.6, mean airway pressure <10 cm H_2O.
‡ Study definitions of hypoxemia, hypotension, need for other rescue.
§ Until 8 AM day of discharge.
‖ Wilcoxon rank sum test.

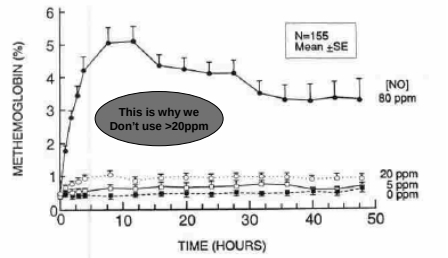


Fig 4. Methemoglobin levels at baseline and during the administration of treatment gases (control = 0 ppm of I-NO) for up to 2 days in term infants with PPHN. All study sites used the same co-oximetry equipment for measuring methemoglobin. If the methemoglobin levels increased above 7%, investigators were permitted to reduce the treatment gas by specific decrements.

Davidson, et al: Pediatrics, 101(8):325-334, 1998

Davidson, et al: Pediatrics, 101(8):325-334, 1998

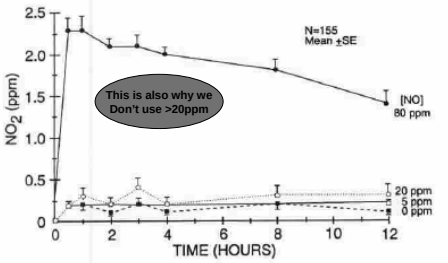


Fig 5. Inspired NO_2 levels at baseline and during the administration of treatment gases (control = 0 ppm of I-NO, NO = 5, 20, or 80 ppm) for up to 12 hours in term infants with PPHN. For one third of the patients in the 80 ppm group, reductions in the treatment gas concentration was mandated by protocol because of methemoglobinemia at a median of 8 hours.

LOW-DOSE NITRIC OXIDE THERAPY FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Reese H. Clark, M.D., Thomas J. Kueser, M.D., Marshall W. Walker, M.D., W. Michael Southgate, M.D., Jeryl L. Huckaby, R.R.T., Jose A. Perez, M.D., Beverly J. Roy, M.D., Martin Keszler, M.D., and John P. Kinsella, M.D., for the Clinical Inhaled Nitric Oxide Research Group*

Table 3. Outcome Analysis.*

Outcome	Control Group (N=122)	Nitric Oxide Group (N=126)	p Value
Received extracorporeal membrane oxygenation			
Intention-to-treat analysis — no./total no. (%)	78/122 (64)	48/126 (38)	0.001
Neonates with no protocol violations — no./total no. (%)	74/116 (64)	43/111 (39)	0.001
Died before 30 days of age — no. (%)	10 (8)	9 (7)	0.40
Died before discharge — no. (%)	13 (11)	10 (8)	0.82
Died before discharge or received extracorporeal membrane oxygenation — no. (%)	80 (66)	50 (40)	0.001
Length of stay in the hospital for survivors			
Neonates assessed — no. (%)	104 (85)	113 (90)	0.09
Mean no. of days	29±23	25±15	
Duration of assisted ventilation for survivors			
Neonates assessed — no. (%)	109 (89)	116 (92)	0.40
Mean no. of days	12±10	11±7	

NEJM, 342:469-474, 2000

Clark, et al: NEJM, 342:469-474, 2000

TABLE 4. RELATIVE RISK OF EXTRACORPOREAL MEMBRANE OXYGENATION ACCORDING TO DIAGNOSIS.

DIAGNOSIS	EXTRACORPOREAL MEMBRANE OXYGENATION		RELATIVE RISK (95% CI)*
	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	
	no./total no. (%)		
Meconium aspiration syndrome	26/42 (62)	15/43 (35)	0.6 (0.3–0.9)
Pneumonia	18/26 (69)	9/26 (35)	0.5 (0.3–0.9)
Idiopathic pulmonary hypertension	9/25 (36)	9/32 (28)	0.8 (0.3–1.9)
Respiratory distress syndrome	9/11 (82)	3/11 (27)	0.3 (0.1–0.9)
Congenital diaphragmatic hernia	16/18 (89)	12/13 (92)	1.0 (0.8–1.2)
Pulmonary hypoplasia	0	0/1	

*The relative risk is expressed as the risk of a need for extracorporeal membrane oxygenation in the group of neonates treated with nitric oxide as compared with the control group. CI denotes confidence interval.

The New England
Journal of Medicine

VOLUME 336 FEBRUARY 27, 1997 NUMBER 9

INHALED NITRIC OXIDE IN FULL-TERM AND NEARLY FULL-TERM INFANTS WITH HYPOXIC RESPIRATORY FAILURE

THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP*

New England J Medicine 336(9): 597-604, 1997

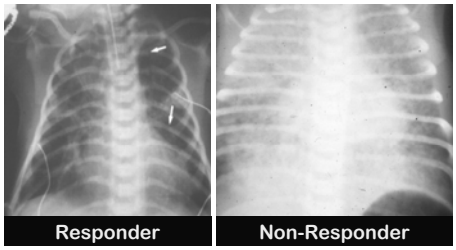
NINOS Trial

OUTCOME	CONTROL GROUP (N=121)	NITRIC OXIDE GROUP (N=114)	P VALUE
Death by day 120 or ECMO — no. (%)	77 (63.6)	52 (45.6)	0.006
Death — no. (%)	20 (16.5)	16 (14.0)	0.60
ECMO	54.5%	38.6%	0.014
Change in PaO_2 — mm Hg	9.7±51.7	58.2±85.2	<0.001
Change in oxygenation index	0.8±21.1	−14.1±21.1	<0.001
Change in alveolar–arterial oxygen gradient — mm Hg	−6.7±57.5	−60.0±85.1	<0.001
Length of Stay	29.5	36.4	0.17
Duration of assisted ventilation — days	11.7±13.0	11.6±7.0	0.97
Air leak after randomization — no. (%)	5 (5.1)	5 (5.2)	0.96
Bronchopulmonary dysplasia — no. (%)†	12 (11.9)	15 (15.3)	0.48

*Plus–minus values are means ±SD. ECMO denotes extracorporeal membrane oxygenation, and PaO_2 partial pressure of arterial oxygen.

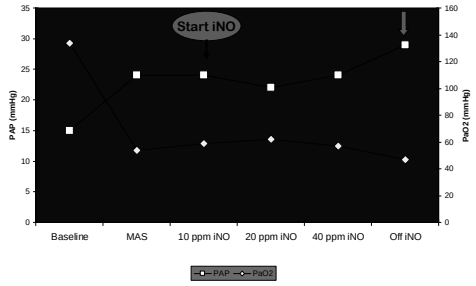
†This condition was considered to be present when there was dependence on oxygen at the age of 28 days accompanied by abnormal results on chest radiography.

Nitric Oxide – Non-Responders



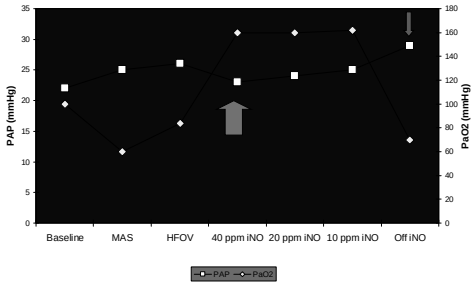
Use of iNO in MAS: lack of response

Fernandez-Martorell, Scand J Clin Lab Invest: 1998;58:177-182

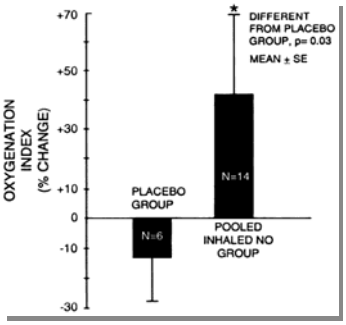


Effect of NO & HFOV in MAS

Rais-Bahrami, et al: Pediatr CCM, 2000; 1:166-169



Rebound - iNO Therapy

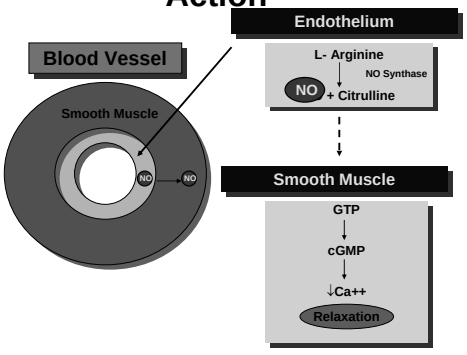


Davidson, et al: Pediatrics, 104:231-236, 1999

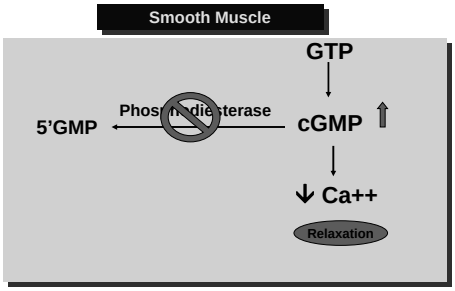
Rebound - iNO Therapy

- Negative feedback loop, i.e., iNO turns off endogenous production of NO
- iNO exposure for 24hrs caused 2-fold increase in serum concentrations of ET-1 (*Kelly,et al, J of Pediatrics, 2002)*

Nitric Oxide – Mechanisms of Action



Nitric Oxide – Mechanisms of Action

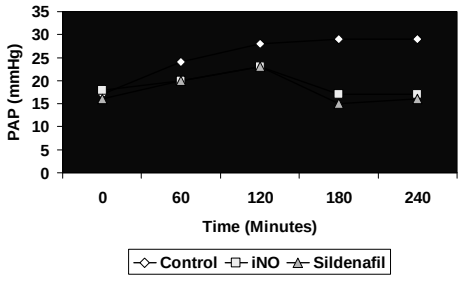


Phosphodiesterase Inhibitors

- Zaprinast, PDE-5
- Dipyridamole, PDE-5
- Sildenafil (Viagra), PDE-5

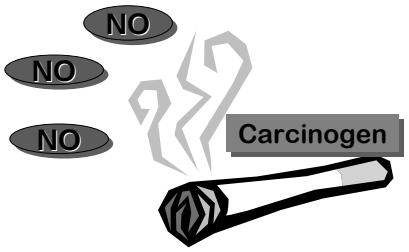
Hypotension

MAS Piglet Model – IV Sildenafil Therapy



Shekerdemian, et al: Am J Respir Crit Care Med, 165:2002

iNO – the Bad



iNO – the Bad

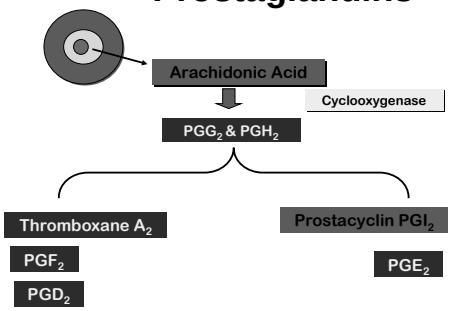
- **NO + O_2 = Peroxynitrite**
  - **Induce lung injury**
  - **Increased apoptosis in cells exposed to 4hrs of NO**
  - **NO produces superoxide in high flow states, maybe responsible for SMC hypertrophy & remodeling of vascular bed in this population**

How Do We Safely Use iNO?

Clark, Pediatrics, 104(2):296-297, 1999

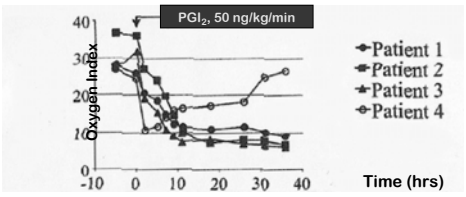
- iNO studies establish that iNO improves oxygenation & reduces the use of ECMO – this does not translate to improved health
  - Length of stay > iNO patients than controls in NINOS Trial, 36 vs 30 days
  - Higher mortality in iNO treated patients, 8% vs 2%
  - Does iNO delay the initiation of ECMO? Is this delay associated with risk for morbidity ?

Eicosanoids - Prostaglandins



PPHN Therapy – PGI_2

- IV form, severe hypotension
- Aerosolized form as potent



Kelly, et al, J of Peds, 2002

Endothelin-A receptor Blockade in Porcine Pulmonary Hypertension

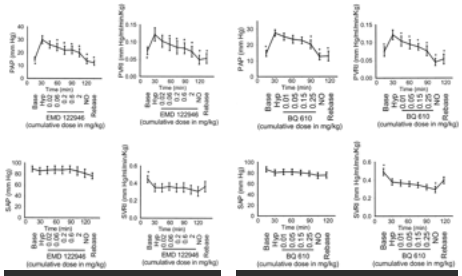
Ambalavavav N., et. al: Pediatric Res Vol 52 (6):913-921, 2002

Compared the physiologic effects of two Endothelin-A receptor blockers, EMD 122946 & BQ 610 on two pathologic conditions with PH

- Hypoxic Induced PH
- GBS induced PH

Endothelin-A receptor Blockade in Porcine Pulmonary Hypertension

Ambalavavav N., et. al: Pediatric Res Vol 52 (6):913-921, 2002



EMB 122946 - Hypoxia | BQ-610 - Hypoxia

Tezosentan: E_A & E_B Blockage in MAS Piglet Model

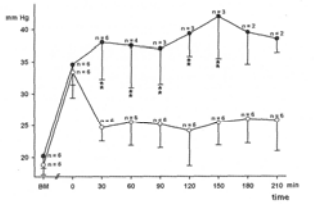


Figure 1. Mean pulmonary artery pressure in animals treated with tezosentan (*open circles*) and controls (*solid circles*). Bars represent SD. Four out of six animals in the control group died during the observation period, whereas all animals receiving tezosentan survived. *BM*, before meconium. Intergroup significance of $^{**}p < 0.01$ and $^{*}p < 0.05$.

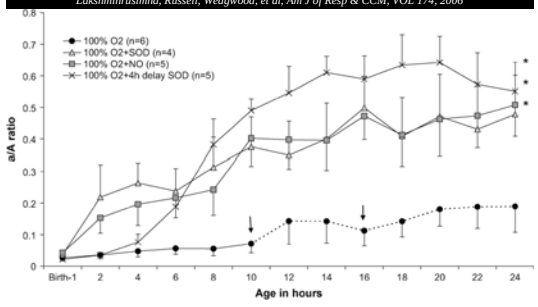
Results:

- 100% survival in Tez animals
- 33% survival in control animals
- Slight drop in systemic pressures noted

Geiger R, et al: Ped Res; 59(1): 147-150, 2006

Superoxide Dismutase Improves Oxygenation and Reduces Oxidation in Neonatal Pulmonary Hypertension:

Lakshminrusimha, Russell, Wedgwood, et al, Am J of Resp & CCM, VOL 174, 2006



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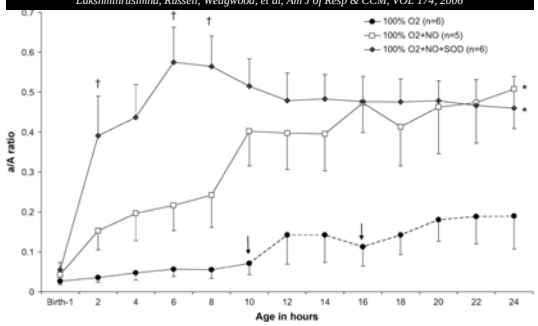


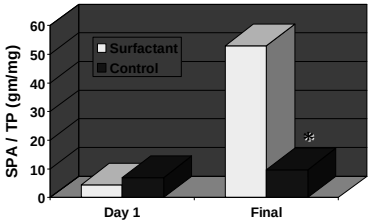
Surfactant Deficiency in Term Infants

- ***Primary lung injury*:** MEC, sepsis, hyperoxia - injury of type II pneumocyte with decreased surfactant production
- ***MEC & protein*** - inhibit surfactant activity
- ***Sepsis*** - leakage of fluid into the alveolar space with destruction of surfactant
- ***Mechanical ventilation*** - may damage the alveolar capillary barrier with cell injury & protein leak

Surfactant Therapy in ECMO Patients

Lotze, et al, J Pediatr 1993;122:261-268

SP-A / TP Concentrations vs Group



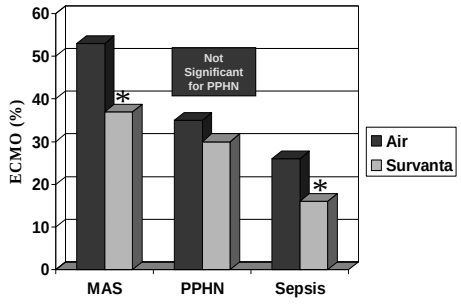
Surfactant Therapy in ECMO Patients

Lotze, et al, J Pediatr 1993;122:261-268

	Surfactant	Control
	n = 20	n = 20
Duration of ECMO (hr)	107 ± 33 *	139 ± 53
Time to extubation (hr)	28 ± 14	58 ± 84
Duration of O_2 (hr)	185 ± 154	351 ± 524
Age at discharge (days)	20 (12-36)	25 (11-129)

Multicenter Study of Surfactant Use in Term Infants With Severe Respiratory Failure

Lotze, et al. J of Pediatrics 1321:40-45, 1998



Multicenter Study of Surfactant Use in Term Infants With Severe Respiratory Failure

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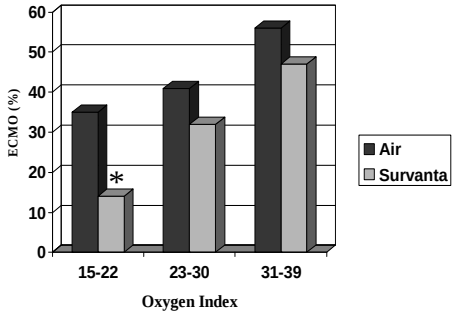
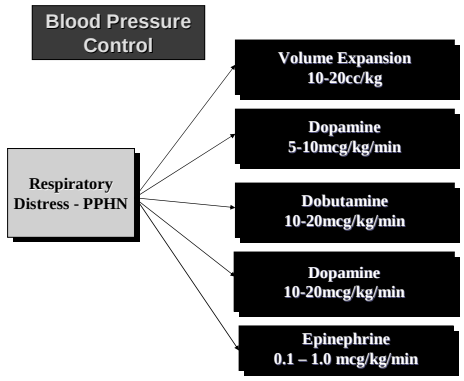


PPHN – Treatment Strategies

- **Maintain systemic blood pressure normal or slightly higher than normal**
  - ***Dopamine*, pulmonary effects if >8ug/kg/min dose (alpha, beta)**
  - ***Dobutamine*, primarily inotropic effect with peripheral vasodilation, maximum dose, 20ug/kg/min (beta)**
  - ***Isoproterenol*, chronotropic effect (increased HR) limits use in newborns (beta)**
  - ***Volume expansion* as needed – NS, 5% Albumin**



Ventilator & Oxygen Management

- Make small changes on the ventilator – large changes may cause the patient to flip back into PH or vasoconstrict and worsen
- Make only one change at a time, e.g., only the FIO_2, not FIO_2 and PIP

PPHN – Normal Course

- By 5 days of age, most infants have resolved their pulmonary hypertension, although some may persist beyond this time period
- After 5 days of age, consider normalizing all blood gas parameters for the patient, e.g., keep $PaCO_2$ 40-60 range; PaO_2 60-80 mmHg