Persistent Pulmonary Hypertension in Newborn

Recent Advances in Management

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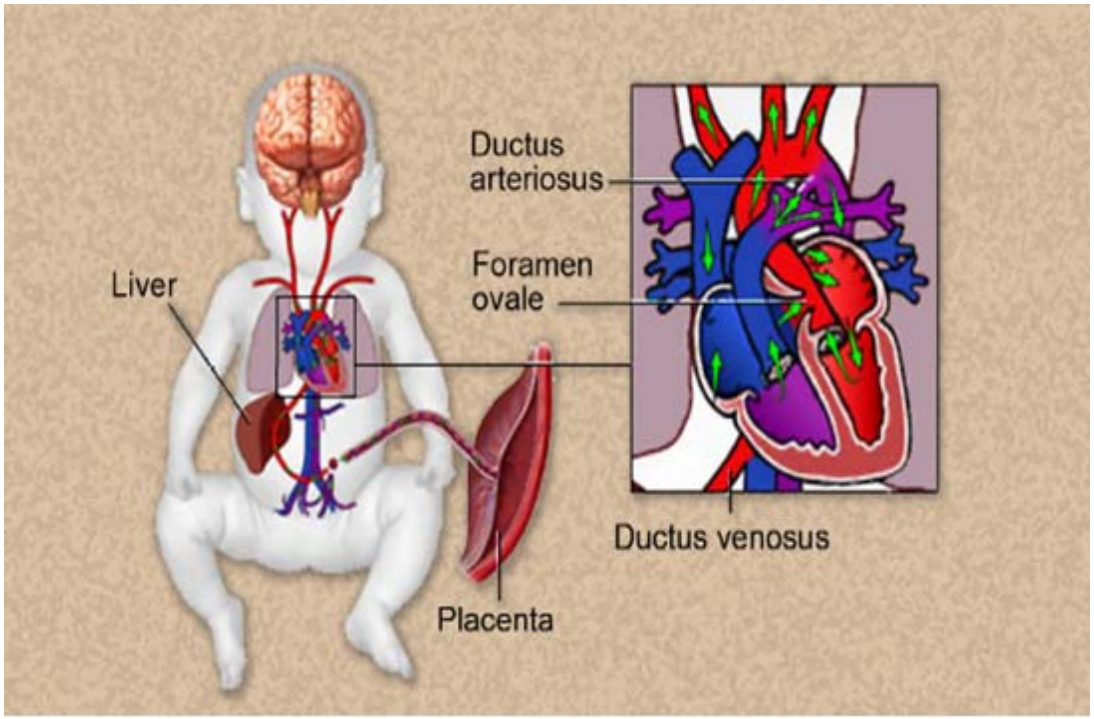
PPHN



PPHN is defined as the failure of normal circulatory transition,that occurs after birth.It is a syndrome characterised by marked pulmonary hypertension that causes hypoxemia and right to left shunting of blood.The clinical clue is the labile hypoxemia out of proportion to the disease process.

PPHN

- Moderate/Severe PHHN
  - 2-6/1000 Live births
  - 10% of all infants admitted to NICU

Mortality	10-35%
Adverse neurological sequelae	19-46%
Re-hospitalization rates	22%

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DIAGNOSIS OF PPHN

PATHOGENESIS

MANAGEMENT POST INO ERA

Persistent Pulmonary Hypertension

- Clinical syndrome of persistent or refractory hypoxemia
- Increased PVR → extrapulmonary right-to-left shunting across the foramen ovale and/or patent ductus arteriosus.
- Prevalence: 2 per 1,000 live births (occurs principally in term & late preterm infants)
- ~ 10% of infants with respiratory failure
- Mortality (ECMO & Nitric oxide ~ 15%)

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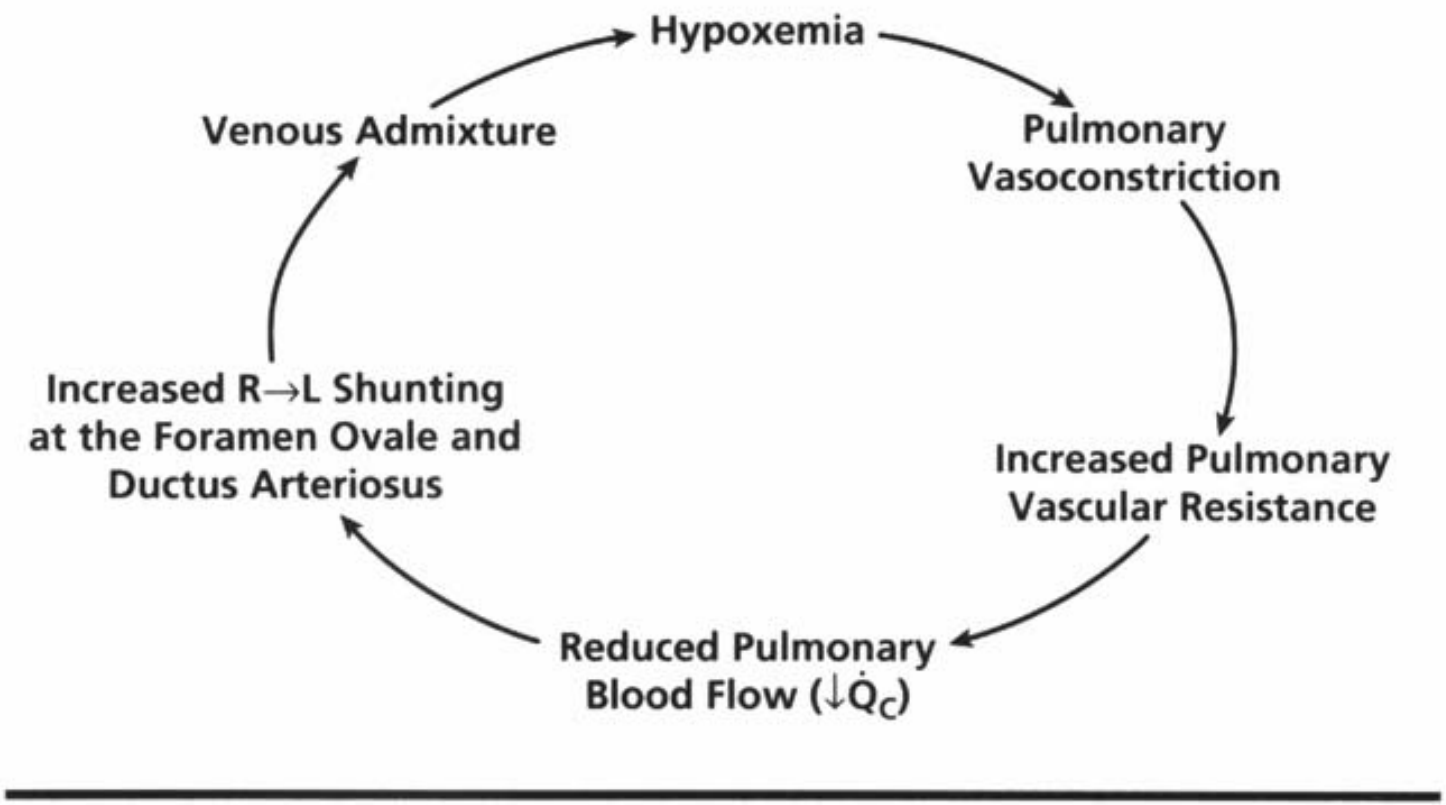
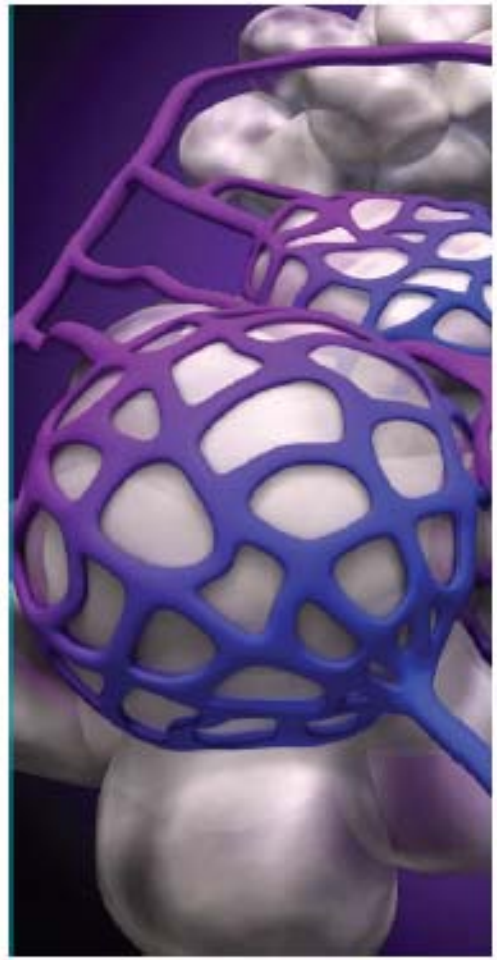
Basics Final common pathway of both hypoventilation and hypoperfusion.

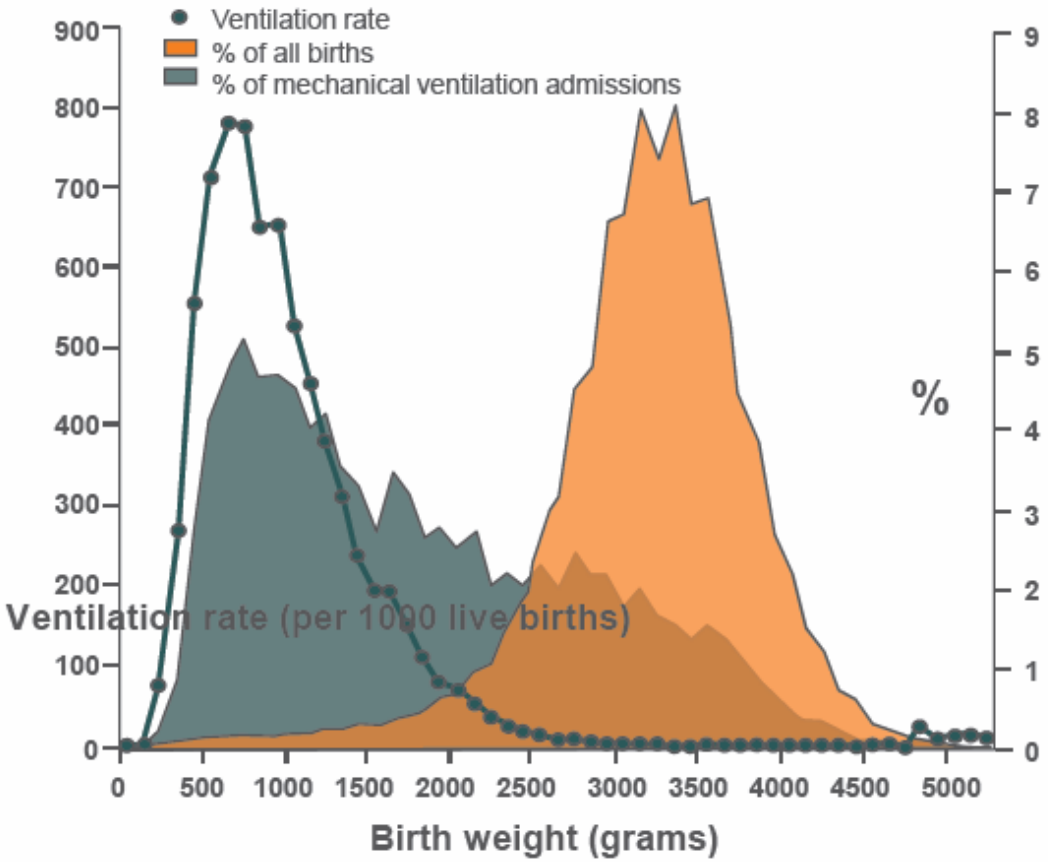


Pulmonary Hypertension Outline

- Epidemiology
- Pathophysiology
- Diagnostic Aspects
- Treatment
- New Therapeutic Options



Neonatal Respiratory Failure



Observational (n = 15,006)

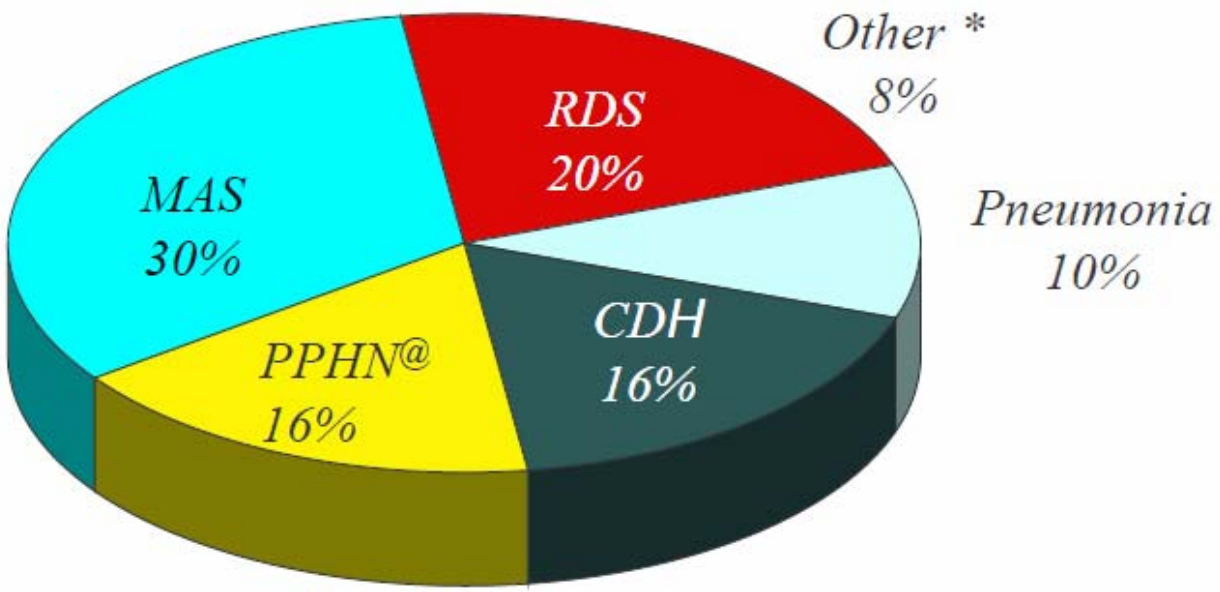
Approximately 2% of all live births will require ventilator support (18/1000 live births)

Highest rate in 700-800gm groups

~1/3 of ventilated babies are term or late preterm

Angus et al AJRCCM 164: 1154, 2001

PPHN: A Clinical Syndrome

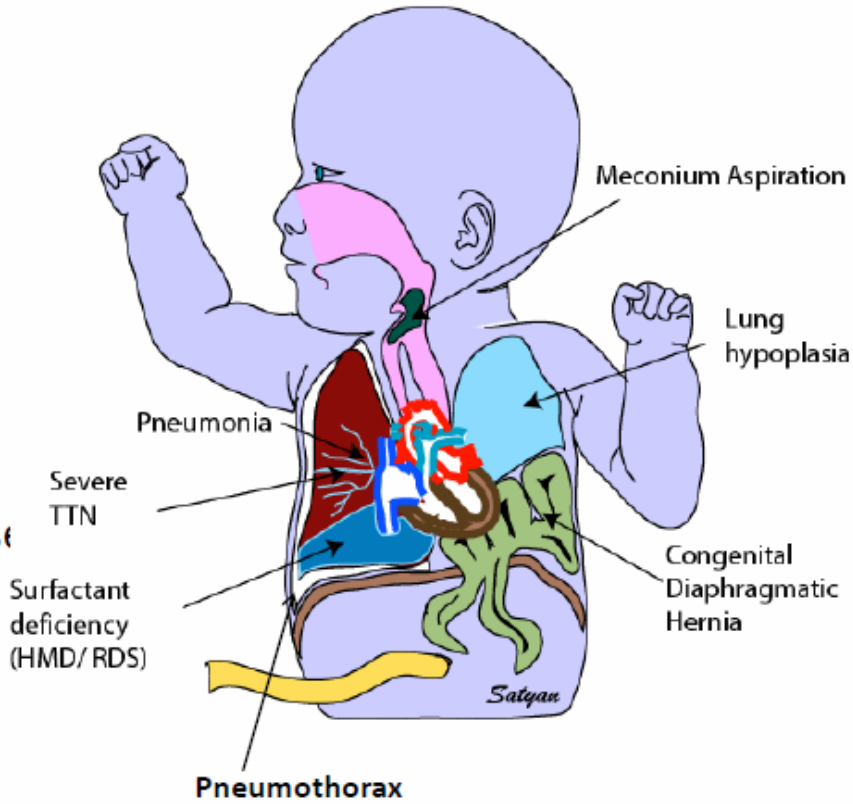


@ = idiopathic

* Other = CHD, Congenital lung anomalies, BPD

Etiology of HRF

- **T**ransient tachypnea of newborn (TTN)
- **A**spiration syndromes - meconium or blood
- **C**ongenital Diaphragmatic Hernia (CDH)
- **HY**aline membrane disease (RDS)
- **PNE**umonia / Sepsis
- **A**ir leaks



Not Enough Oxygen In

- Apnea
  - neurologic and pharmacologic causes
- Diffusion barrier
  - RDS, aspiration, pneumonia
- Obstruction
  - pneumothorax, head position

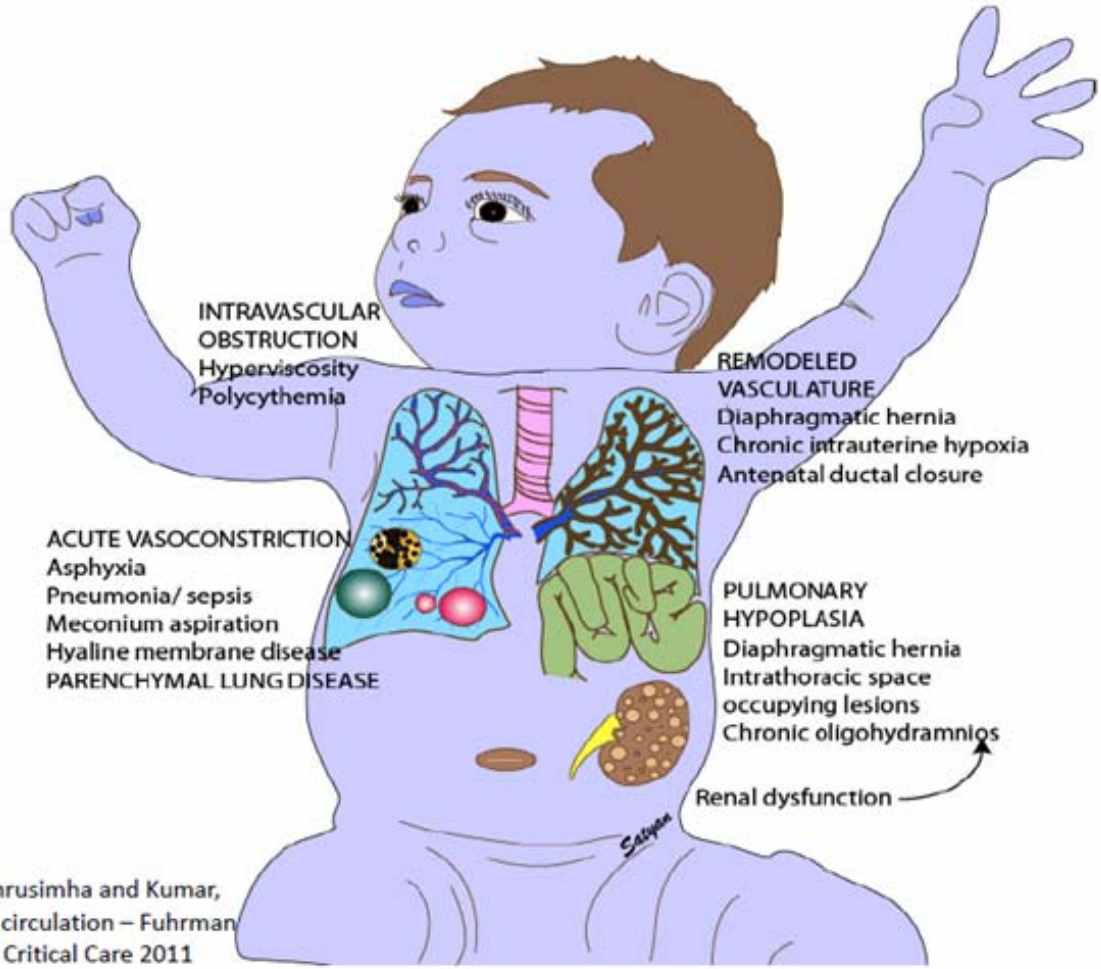
Oxygen “mal-absorption”

- Shunting lesions
  - cardiac
  - non-cardiac (like PPHN)
- Hematologic
  - methemoglobinemia
  - carboxyhemoglobinemia

Too Much Oxygen Out

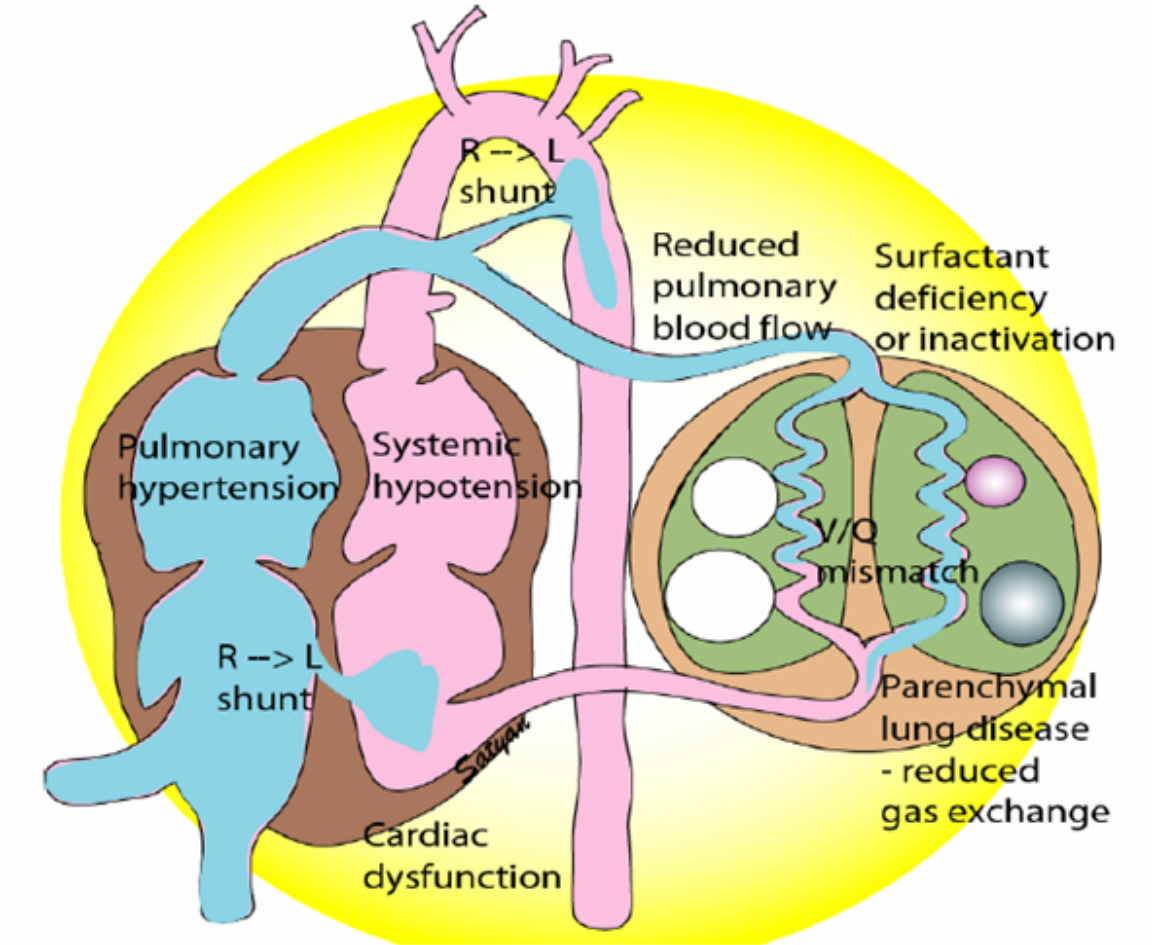
- High oxygen consumption
  - Sepsis
  - Low flow, high extraction
    - acrocyanosis
    - hyperviscosity/polycythemia
    - extravasated (ie bruising)

Vascular Pathogenesis of HRF



Modified from Lakshminrusimha and Kumar,
Disorders of pulmonary circulation – Fuhrman
& Zimmerman Pediatric Critical Care 2011

Hemodynamic Changes in HRF



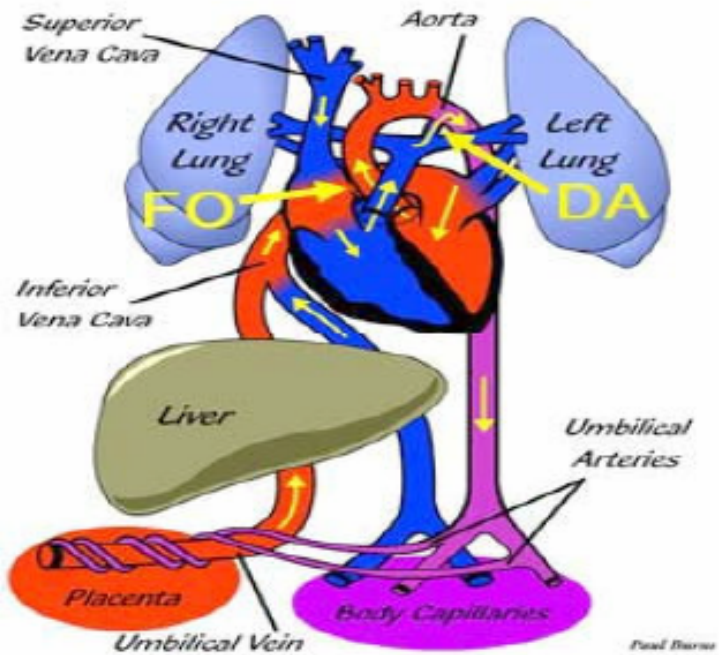
Common Associations with PPHN

- Perinatal association: *gestational age* (late preterm or post-dates gestation), *ethnicity* (black or Asian ethnicity), *maternal conditions* (higher pre-pregnancy weight and diabetes, smoking and maternal asthma)
- Maternal use of *NSAIDS* and Selective Serotonin Uptake Inhibitors (*SSRI*s)
- Sepsis/Pneumonia
- Meconium Aspiration Syndrome
- Perinatal Hypoxia-Ischemia

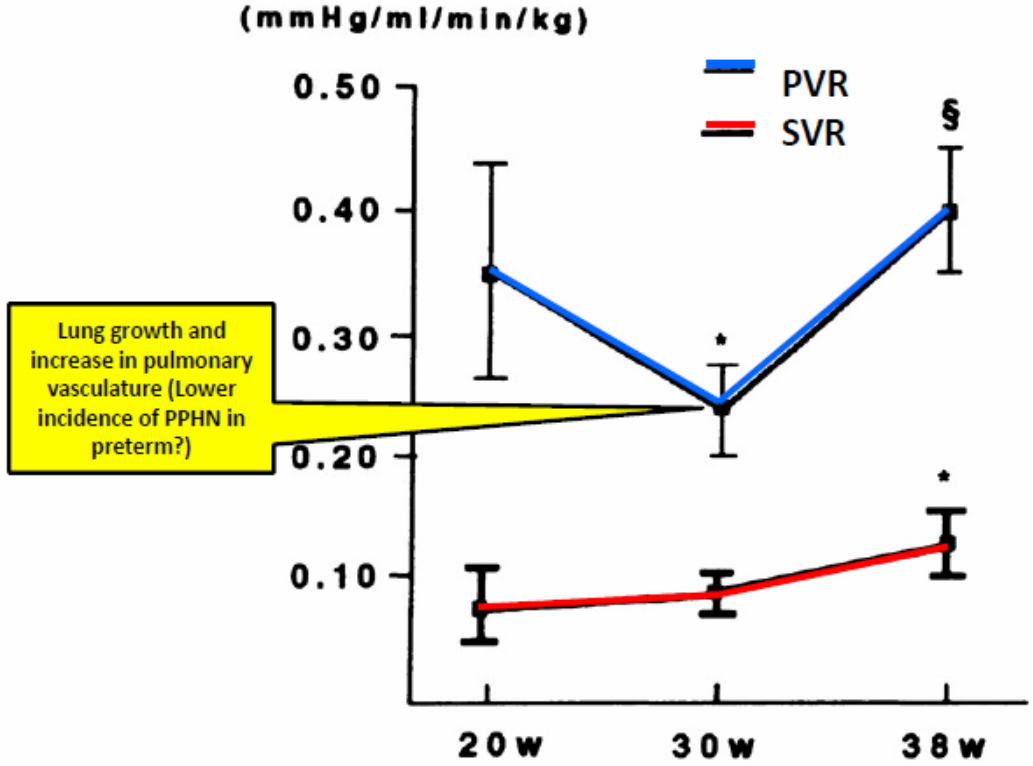
Hernandez-Diaz et al Pediatric 120: e272, 2007

Pulmonary Vascular Resistance is Increased in Fetal Life

- Most of the venous return is shunted across the foramen ovale or dutcus arteriosus, because of the increased pulmonary vascular resistance.
- Lung receives 3-8% of the cardiac output



Variations in PVR and SVR During Gestation Human Fetus

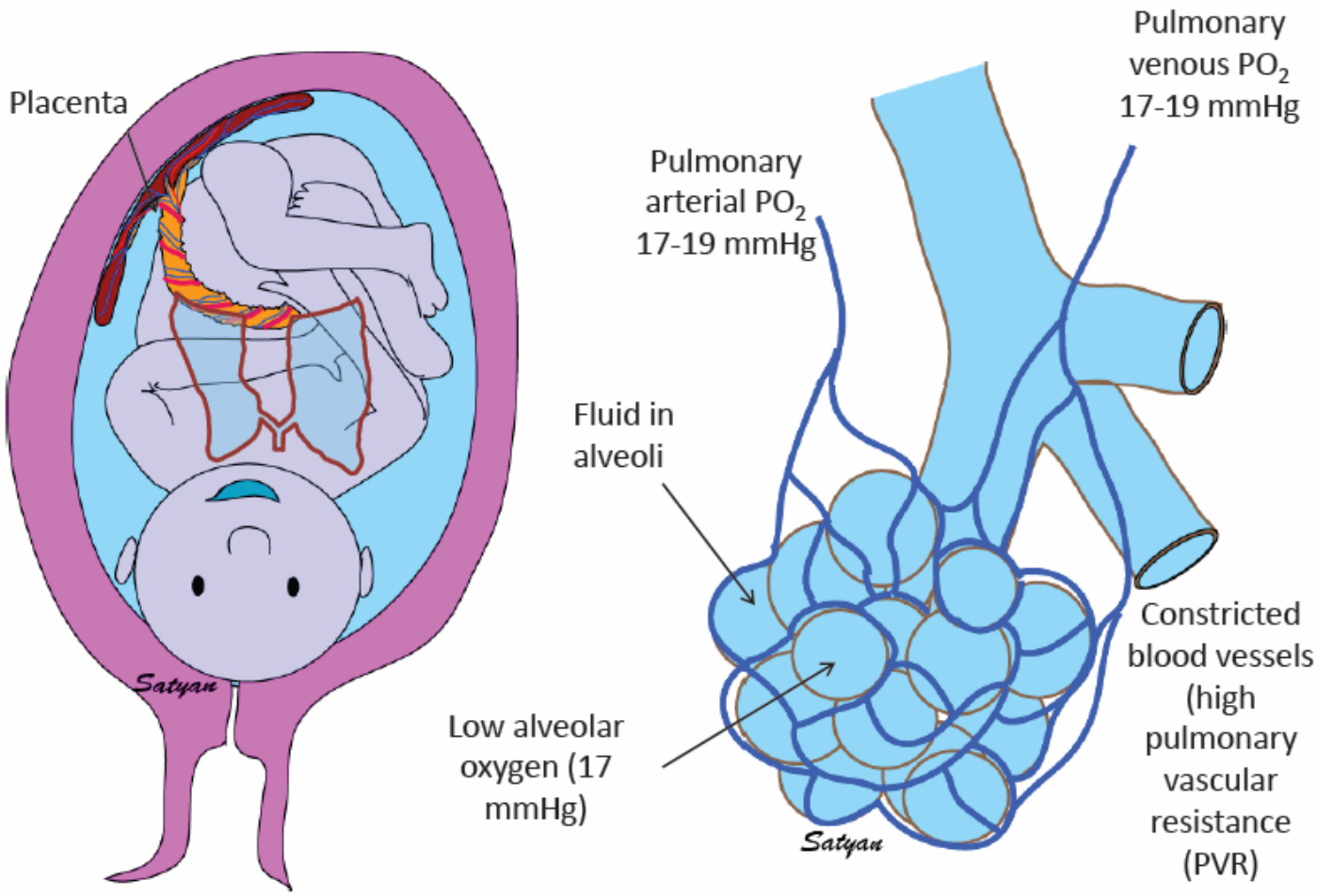


Rasanen, J. et al. Circulation 1996;94:1068-1073

Circulation

American Heart Association
Learn and Live

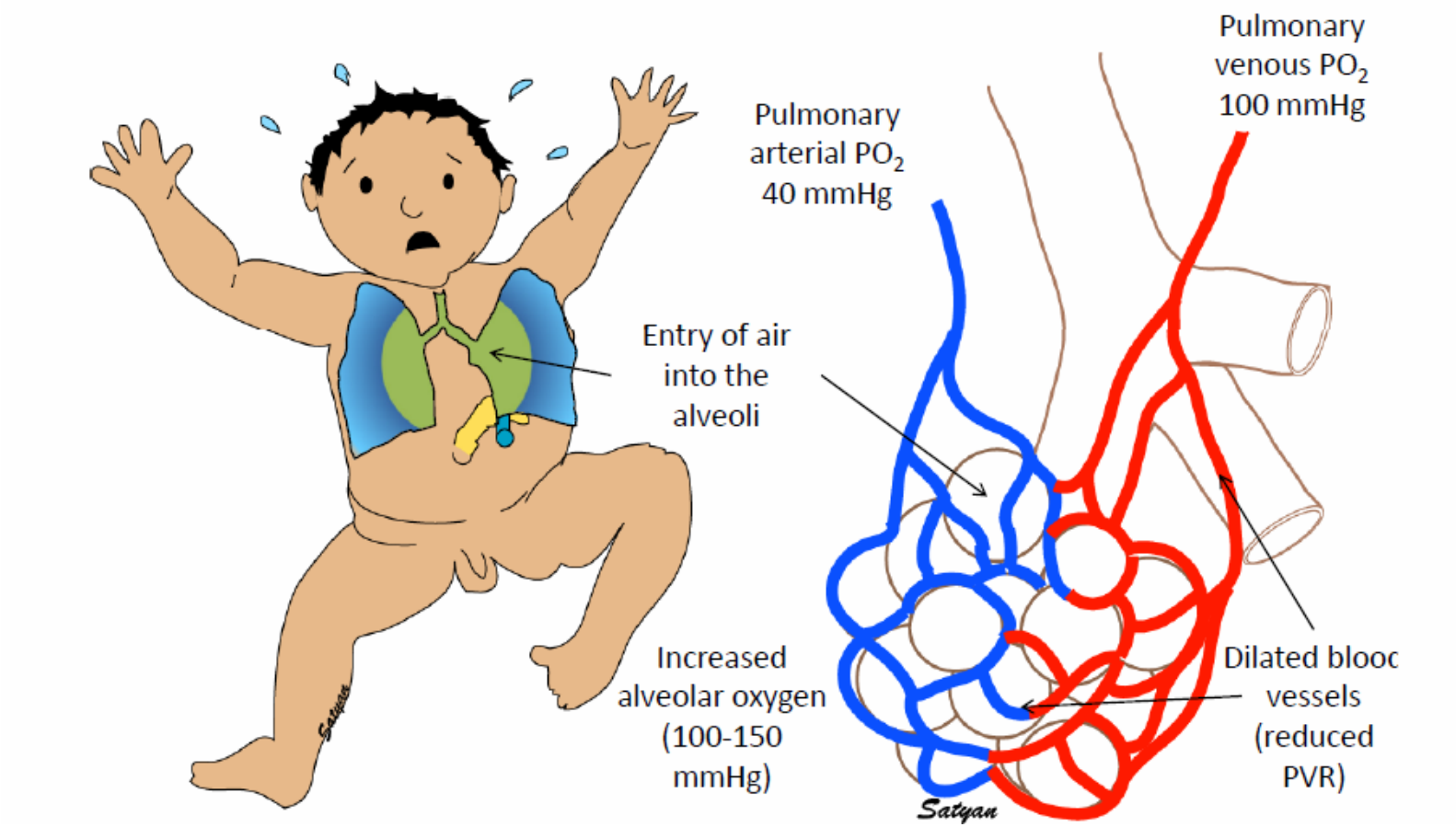
Normal Fetus



Mechanisms of Increased Pulmonary Vascular Resistance in Fetal Life

- Low oxygen tension in fetal life.
- Altered smooth muscle reactivity (enhanced myogenic tone) and increased muscle mass.
- Alveolar fluid pressure (and lack of rhythmic distention of the lung)
- Low basal production of vasodilator products (e.g., PGI_2 and nitric oxide)
- Vasoconstricting effects of leukotrienes (and endothelin-1 *mild*).

Dilation of Pulmonary Blood Vessels at Birth



Pulmonary Vascular Resistance Falls at the Time of Birth

- Lungs are inflated with air (reabsorption of fluid)
- PaO_2 increases, pH increases and $PaCO_2$ falls
- Activity of *vasoconstrictors decreases*.
- Increased pulmonary blood flow increases *sheer stress* and distends the vasculature → *flattening of the endothelium*, thinning of the smooth muscle cells and matrix)
- *Endogenous dilators* (bradykinin, nitric oxide (NO), prostacyclin PGI_2, PGD_2 and histamine) *are released* secondary to sheer stress and hyperoxia

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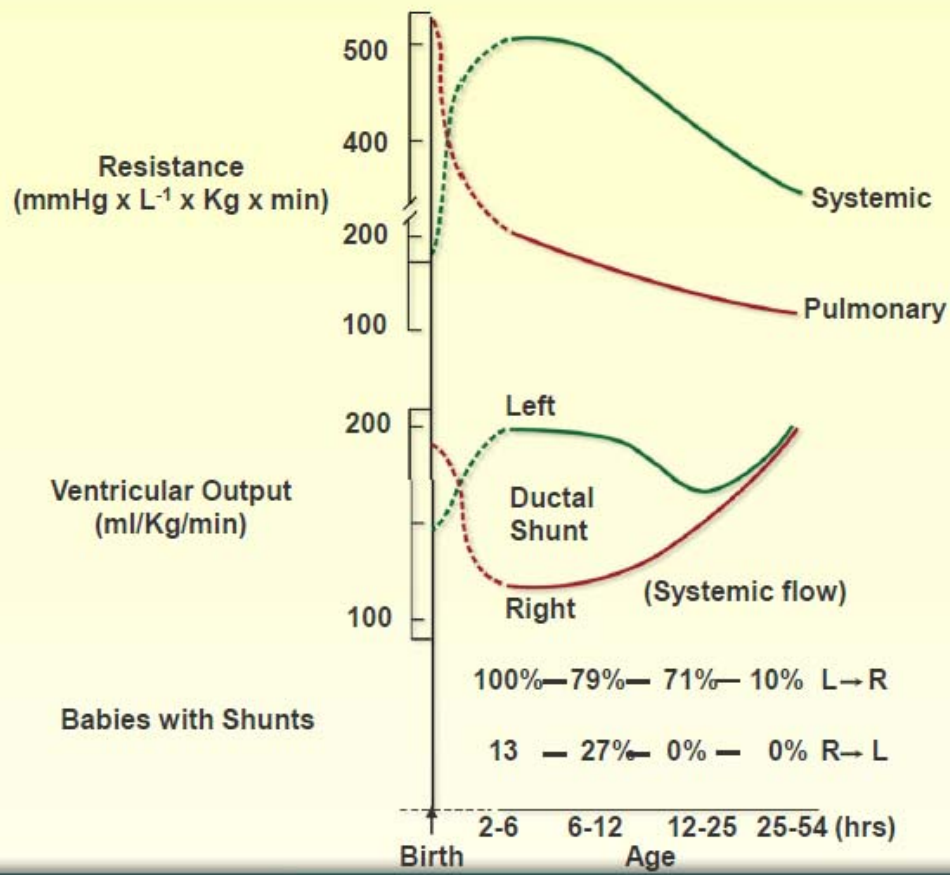


NewYork-Presbyterian
The University Hospital of Columbia and Cornell

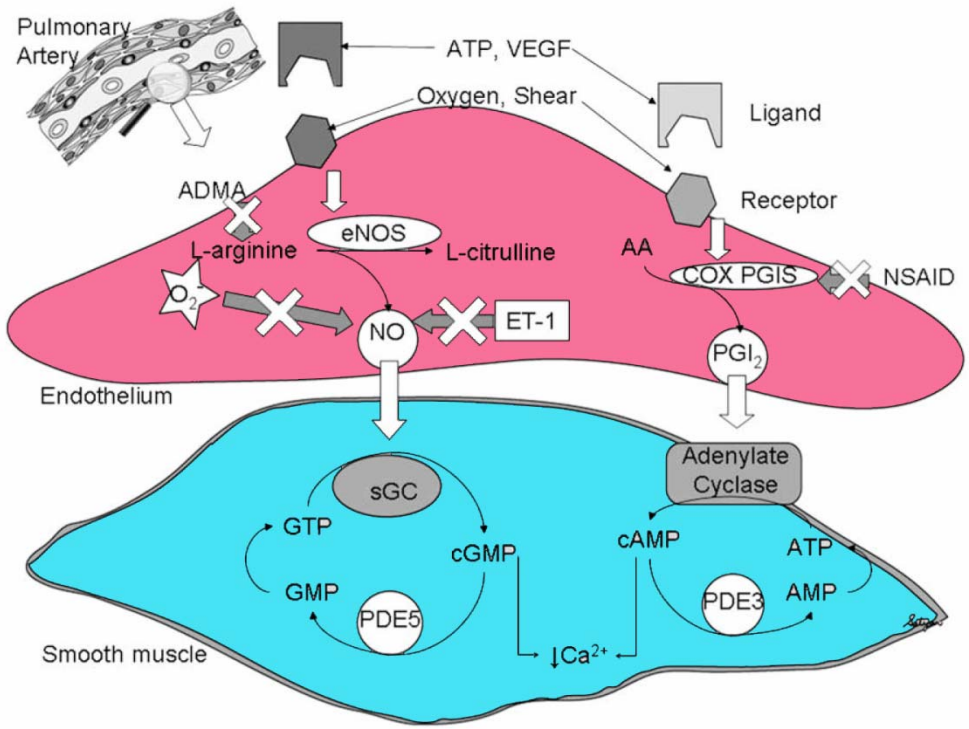
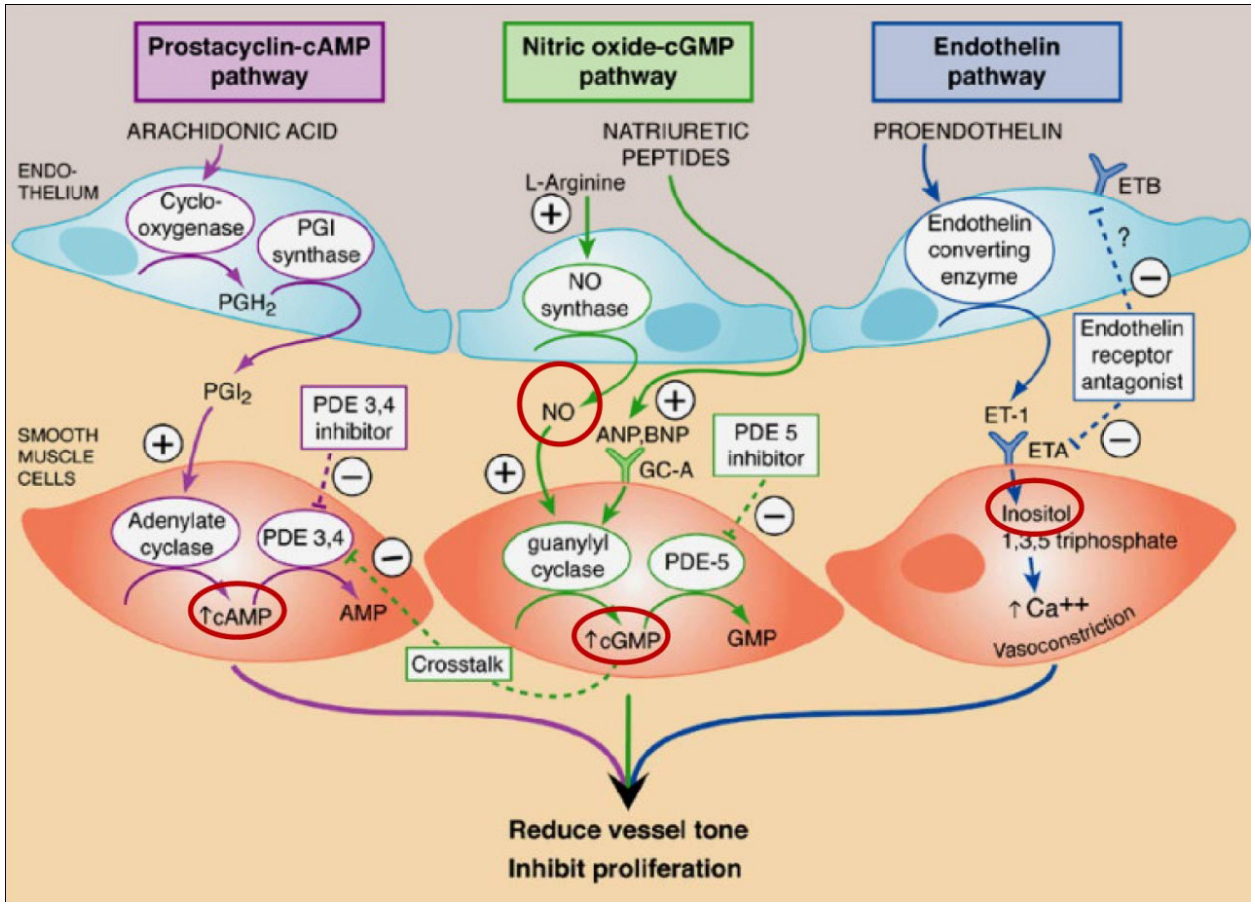
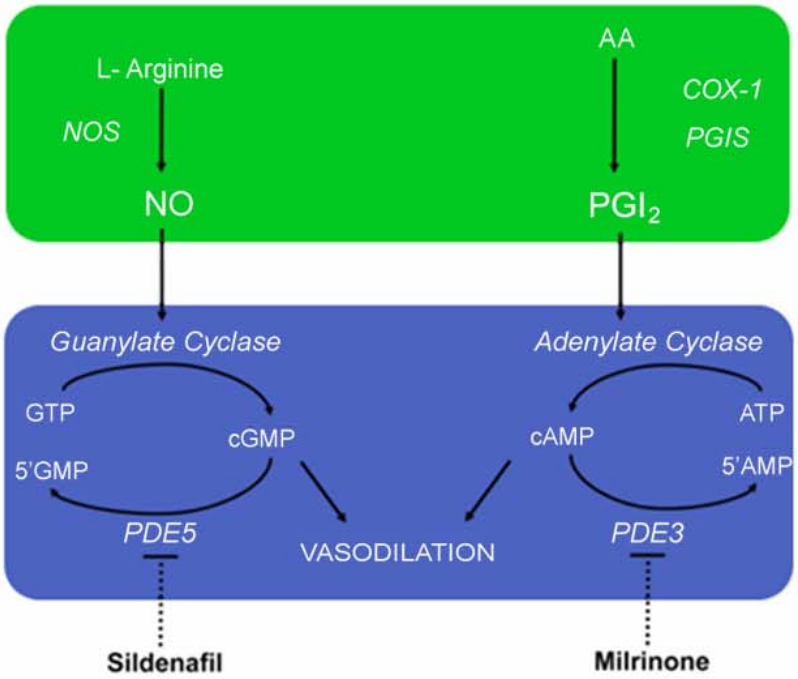


Fig. 1. Mechanism of endothelium-dependent pulmonary vasodilation at birth. NO and prostacyclin (PGI_2) are released in response to birth-related stimuli. NO and PGI_2 increase the cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) levels in the smooth muscle cell. Type 5 and type 3 phosphodiesterases (PDEs) degrade these cyclic nucleotides. A decrease in intracellular Ca^{2+} levels leads to relaxation of vascular smooth muscle. NO levels are decreased by asymmetric dimethyl arginine (ADMA), superoxide (O_2^-), and endothelin (ET-1). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX). AA, arachidonic acid; eNOS, endothelial nitric oxide synthase; GMP, guanosine monophosphate; GTP, guanosine triphosphate; PGIS, PGI_2 synthase; sGC, soluble guanylate cyclase; VEGF, vascular endothelial growth factor. (*Adapted from* Berger S, Konduri GG. Pulmonary hypertension in children. Pediatr Clin North Am 2006;53:966; with permission).

Regulation of Pulmonary Vascular Tone



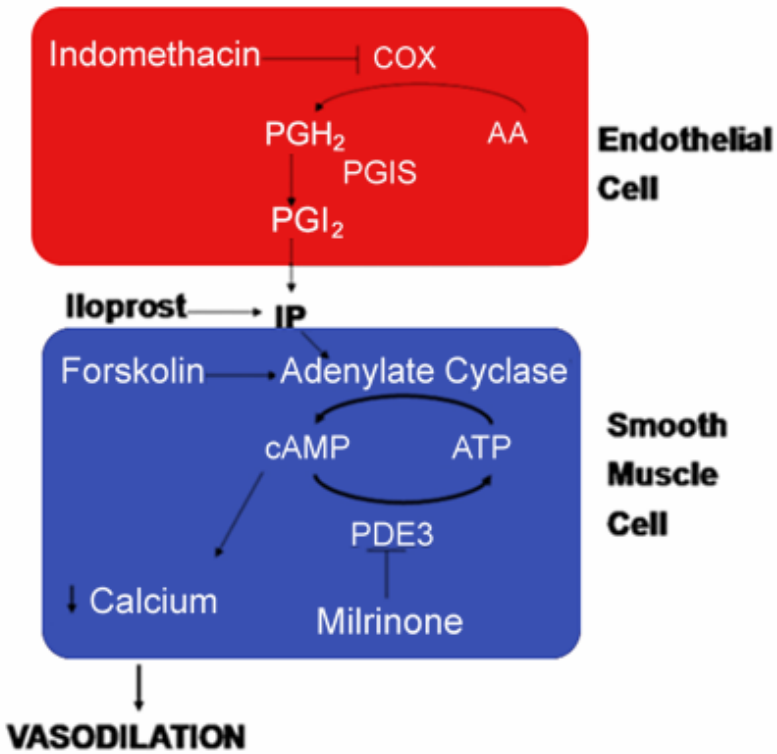
PPHN new modalities of treatment



Nitric oxide (NO) and prostacyclin (PGI_2) signaling pathways in the regulation of pulmonary vascular tone. NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen of L-arginine. NO stimulates soluble guanylate cyclase (sGC) to increase intracellular cGMP. PGI_2 is an arachidonic acid (AA) metabolite formed by cyclooxygenase (COX-1) and prostacyclin synthase (PGIS) in the vascular endothelium. PGI_2 stimulates adenylate cyclase in vascular smooth muscle cells, which increases intracellular cAMP. Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. Specific phosphodiesterases hydrolyze cGMP and cAMP, thus regulating the intensity and duration of their vascular effects. Inhibition of these phosphodiesterases with agents such as sildenafil and milrinone may enhance pulmonary vasodilation.

Steinhorn *Pediatr Crit Care Med.* 2011 March 1.

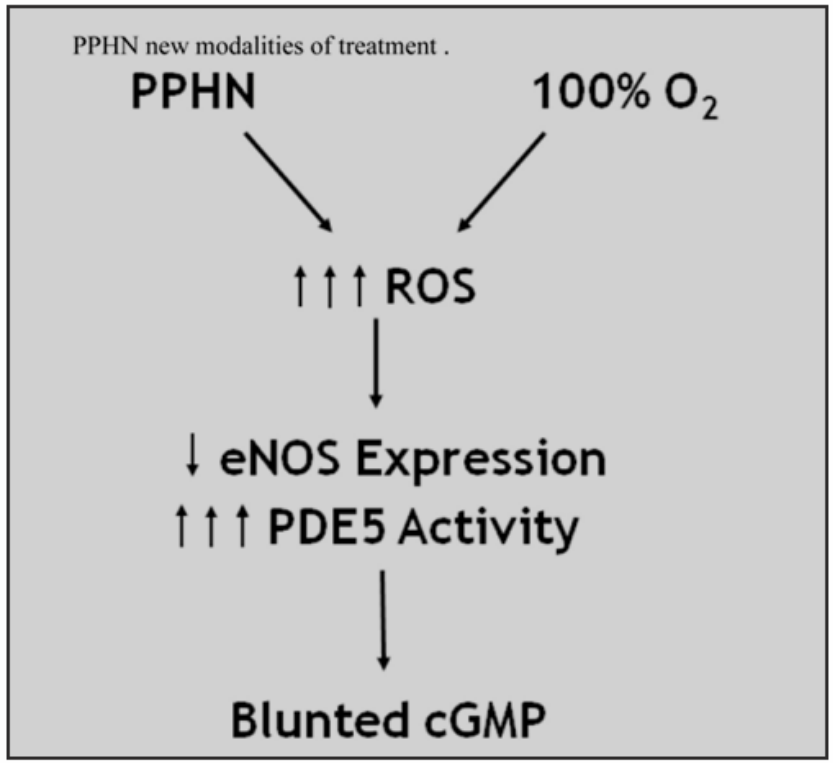
PPHN new modalities of treatment



Schematic showing the pathway for synthesis and mode of action of prostacyclin (PGI_2). Various agents used in this study are also shown in the figure. *COX*, cyclo-oxygenase; *AA*, arachidonic acid; PGH_2, prostaglandin H_2; *PGIS*, prostacyclin synthase; *IP*, prostacyclin receptor; *PDE3*, phosphodiesterase 3.

Lakshminrusimha et al. *Pediatr Crit Care Med.* 2009 September 10.

PPHN new modalities of treatment



Increased reactive oxygen species (ROS) such as superoxide and hydrogen peroxide are produced in the vascular wall of pulmonary vessels affected by persistent pulmonary hypertension of the newborn (PPHN). In addition, even brief exposures to hyperoxia elevate cellular levels of ROS in the neonatal pulmonary vasculature. Increased ROS diminish nitric oxide synthase (NOS) activity and increase type 5 phosphodiesterase (PDE5) activity, both of which blunt the normal production of cGMP.

Steinhorn *Pediatr Crit Care Med.* 2011 March 1.

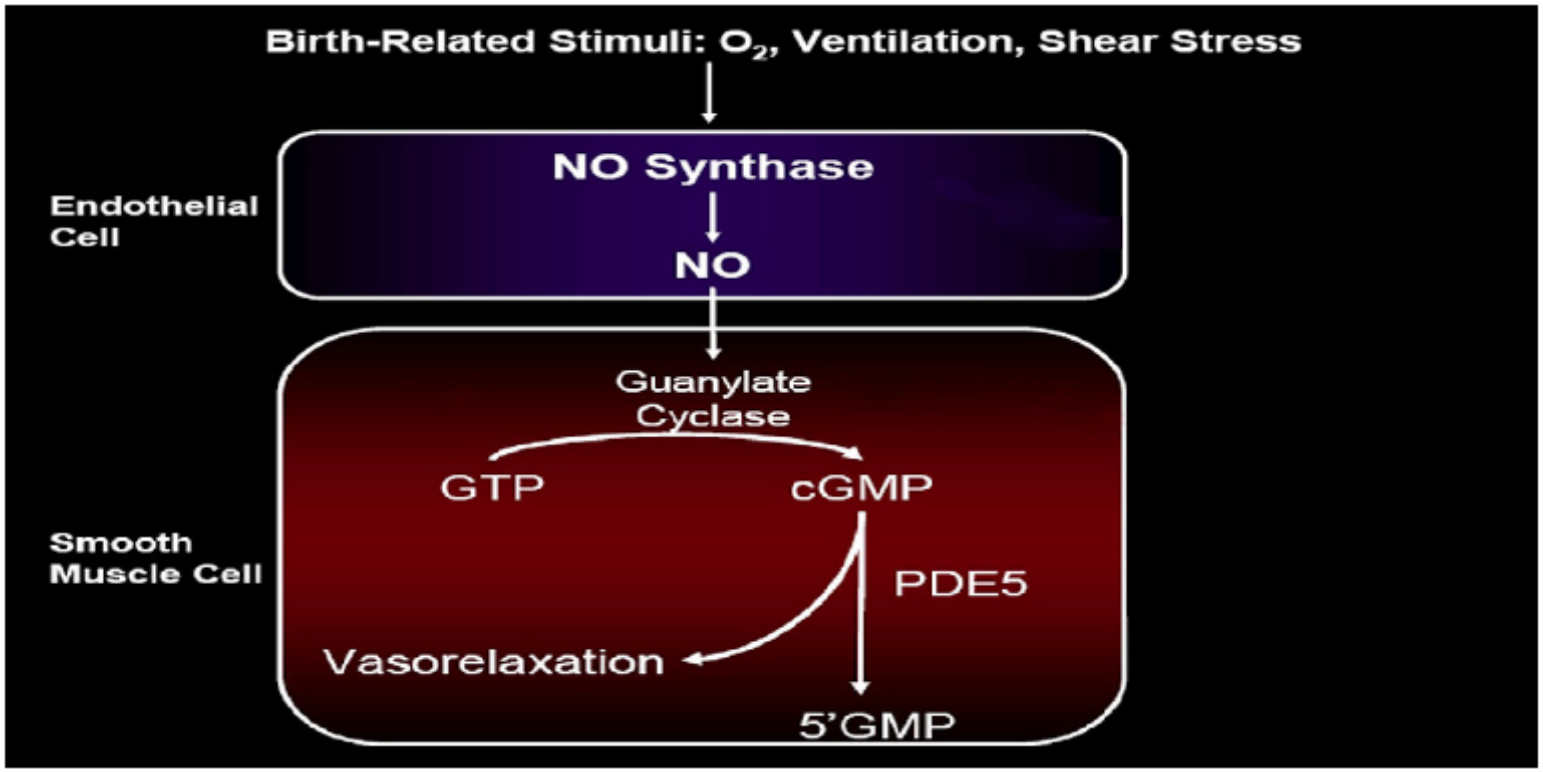
Nitric oxide

- *NO* is not essential for the initial vasodilatation at birth.
- *NO* mediates: 1) basal vascular tone in the fetal pulmonary vasculature (by opposing myogenic tone) and 2) physiologic response to pharmacologic and physiologic stimuli.
- Disturbances in the *NO-cGMP system* are important in the pathogenesis of PPHN
- *NO* enhances lung and vascular growth

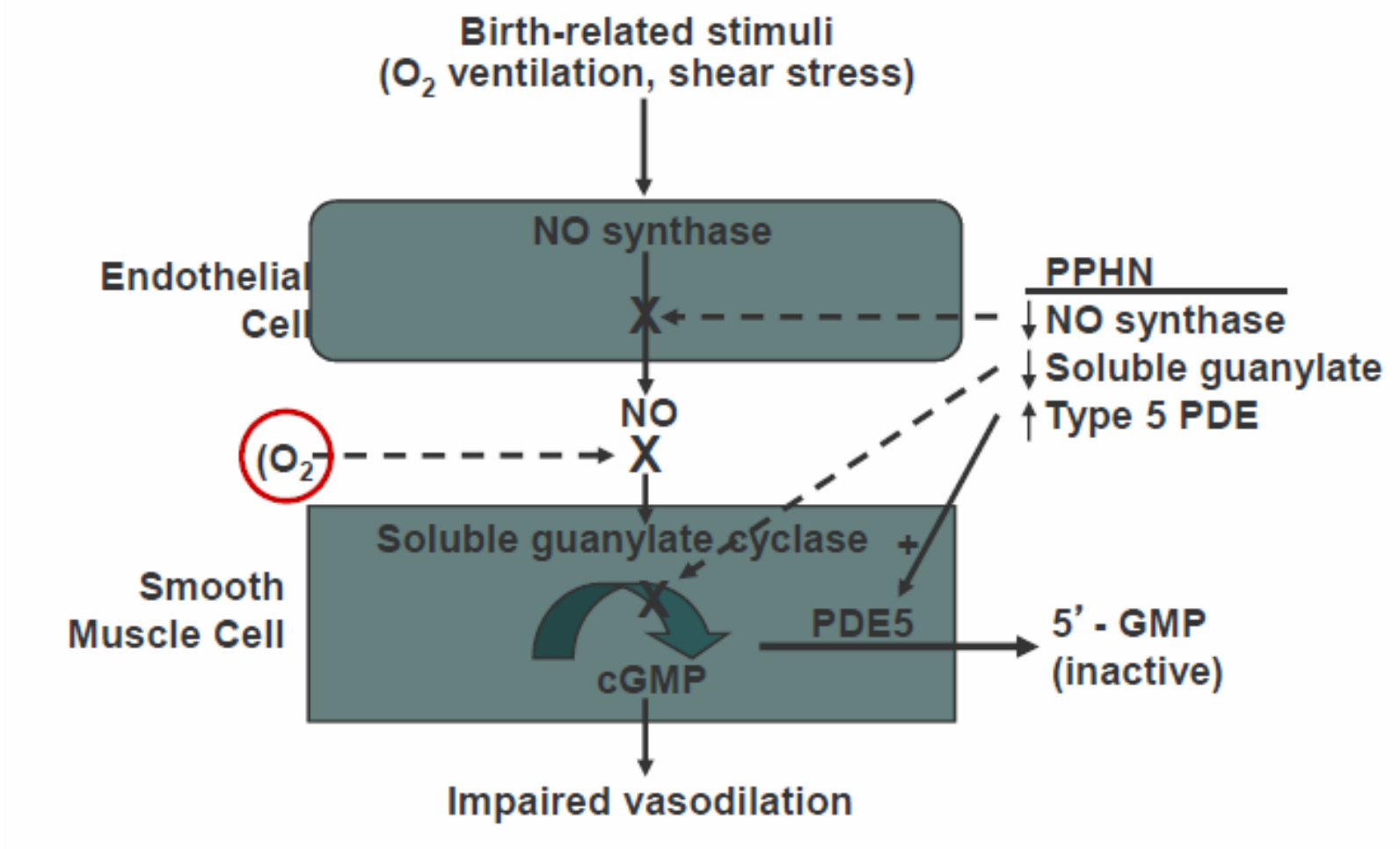
Maturation of the NO-c GMP System

- Lung eNOS (nitric oxide synthase) mRNA and protein are *present in the early fetus* and increase with advancing gestational age and in the postnatal period.
- eNOS expression and activity are affected by *oxygen tension, hemodynamic forces* (sheer stress), *hormonal stimuli* (estradiol. vascular endothelial growth factor (VEGF) and *superoxide production* (which inactivates NO).

Nitric Oxide is a Byproduct of the Conversion of Arginine to Citrulline



Pathogenesis of PPHN



eNOS: A Double Edged Sword

NO and vasodilation

Free Radicals and Vasoconstriction

eNOS, Heat Shock Protein 90 & Superoxide radical(O2-)

- In the generation of NO, eNOS must interact with *heat shock protein 90 (Hsp90)* (a chaperone protein).
- L arginine and a metabolite of folic acid (tetrahydrobiotpterin- *BH4* promote the coupling of eNOS with HSp90.
- Decreased interaction of eNOS with Hsp90 leads to formation of superoxide radical.

(L-arginine + BH4) + [Hsp90 + eNOS] → *Nitric oxide*

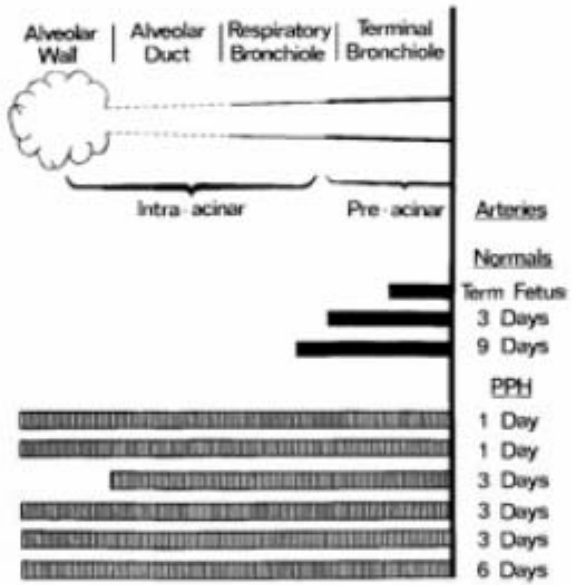
L-arginine + BH4 + eNOS → *Superoxide radical* —(+NO)→ *ONOO-* → *constriction & hypertrophy of muscle*

Pathology of PPHN

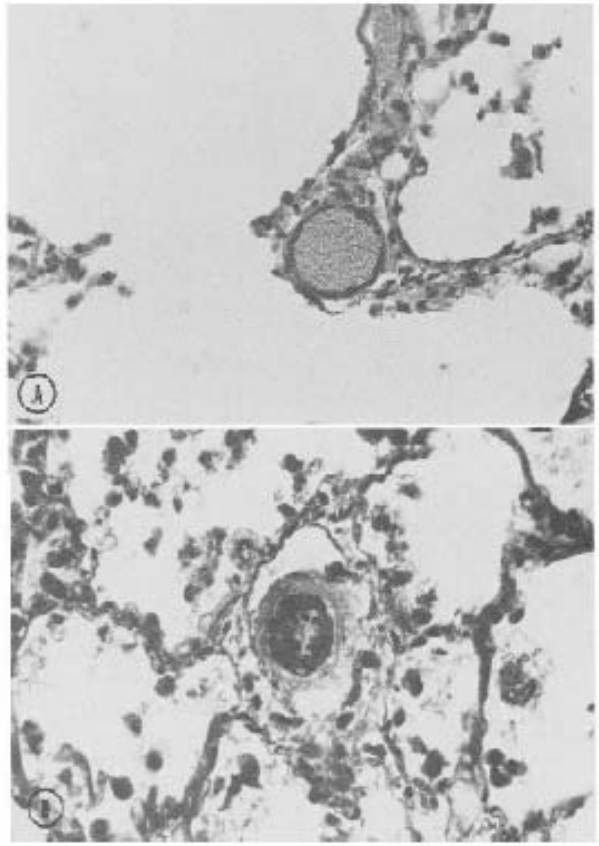
- Malapdatation (vasoconstriction of a normal vessel)*
- The abnormally remodeled vessel (increased musculature)

** Largest category of infants with PPHN; associated with asphyxia, sepsis, MAS or acidosis*

PPHN & Distribution of Muscle



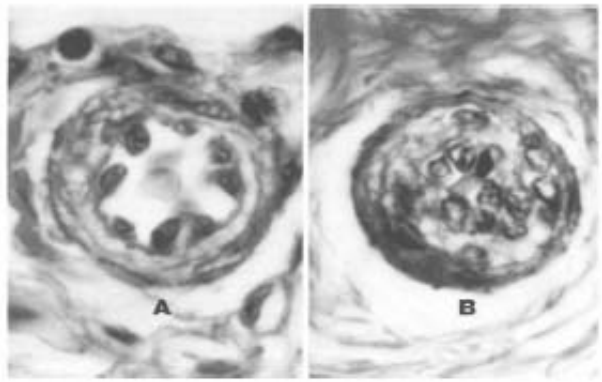
Distribution of muscle



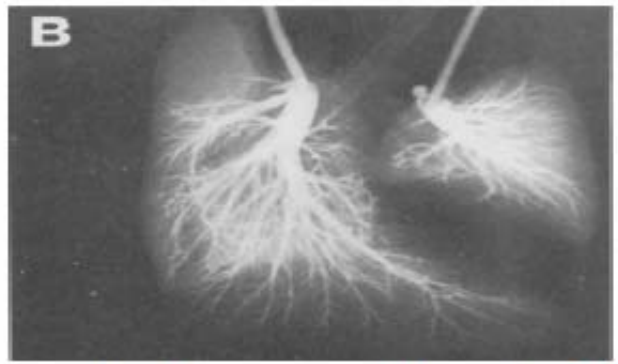
May be secondary to chronic intrauterine hypoxemia

Pathophysiology of Pulmonary Hypertension

- Hypoplastic vasculature, altered vascular reactivity & increased muscle mass in CDH
- Postnatal remodeling (secondary to injury)



Increased muscle mass in CDH



Hypoplastic vasculature in CDH

Diagnosis of PPHN

- Suspected with hypoxemia out of proportion to the severity of parenchymal disease.
- Pre and post ductal saturation monitoring (a difference > 20 mm Hg is significant)- a negative test does not exclude PPHN
- Alveolar-Arterial Oxygen Differences ($AaDO_2$) and Oxygenation Index ($OI = 100 \times MAP / PaO_2 \times FiO_2$)

Cyanosis

- Cyanosis require more than 3g/dL of deoxyhemoglobin
- Low flow areas (tips of extremities) with increased oxygen extraction have more deoxyhemoglobin
- High flow areas with less extraction should not have enough deoxyhemaglobin to appear cyanotic
- Hyperoxia test used to distinguish PPHN from cyanotic congenital heart disease (but is not perfect)

Hyperoxia Test

- Infant on Room Air, get ABG
- Infant on 100% oxygen, get ABG
- PaO_2 unchanged = fixed shunt = CCHD
- Max PaO_2 <100 = CCHD
- Max PaO_2 >200 = No CCHD

Hyperoxia Test

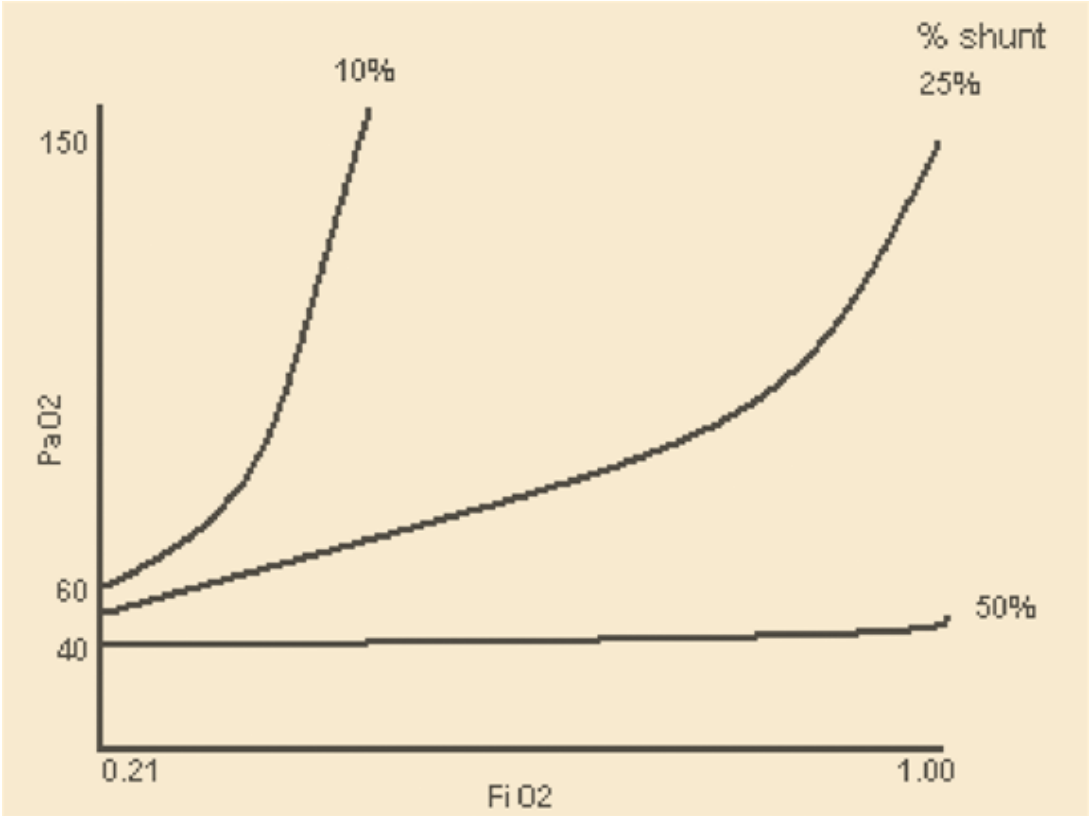
- Jones: 1976
  - 8/109 with CCHD had PaO_2 > 100mmHg
  - 7/23 without CCHD (bad RDS etc) had PaO_2 < 150mmHg
- Hypoplastic Left Heart Syndrome > 300mmHg
- TGA, TAPVR > 200mmHg
- Don’t be fooled by early high PaO_2s

Hyperoxia Test

- Don’t do the room air part
  - Looking for minimal PaO_2 change from 21% to 100% fiO_2
  - Hyperoxia test developed pre pulse-ox
  - With pulse-ox you can tell when PaO_2s are not changing despite big changes in fiO_2 (for sats that are between 70 and 95%)
  - Probably the norm to have some degree of lung disease at the time of the test anyway

Shunt Curves

- Hyperoxia Proper
- Hyperoxia CPAP
- Hyperoxia hyper-ventilation



Thumb Rule to Assess Shunt / PPHN

- Fio 2(%) x 4 optimum pao2
- Fio2(%) x 3 acceptable pao2 with shunt
- Any value of pao2 exceeding 15 to 20 % of this value is a significant shunt

Information Needed

- Clinical appearance
  - "comfortably tachypneic and blue"
- Pulses/perfusion
  - differential, delayed
- Pulse-Ox/ABG
  - pre and post ductal, max PaO_2
- Auscultation
  - S2, Murmur

Information Needed

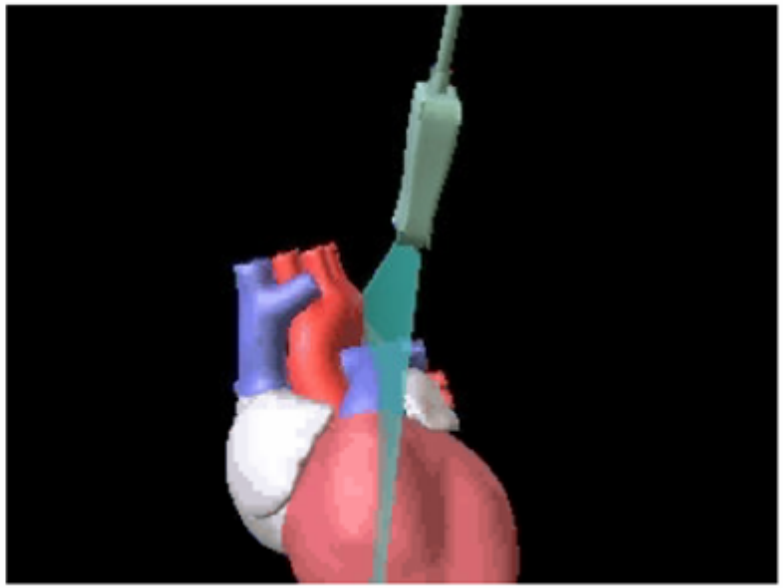
- CXR
  - heart shapes
    - snowman = $TAPVR_1$
    - boot = pulm atresia, TOF, tricuspid atresia
    - egg on string = TGA

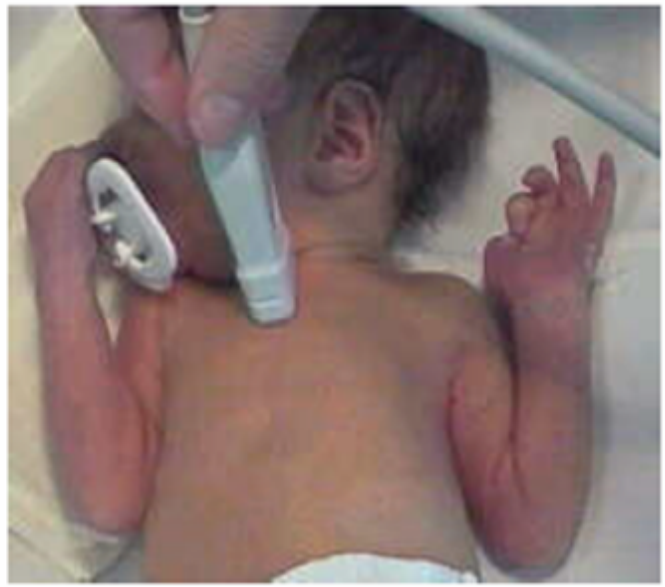
    + /- pulmonary vascularity

- EKG
  - axis
  - increased or decreased forces

- ECHO
  - the most important test in PPHN

Echocardiographic Diagnosis of PPHN





- Pulsed color Doppler: (qualitative and quantitative - velocity of the regurgitant jet at the tricuspid or pulmonary valve, bowing of the atrial septum)

Images from CDROM "Practical Echocardiography for the Neonatologist"
Dr Nick Evans & Dr Girvan Malcolm See: www.cs.nsw.gov.au/rpa/neonatal

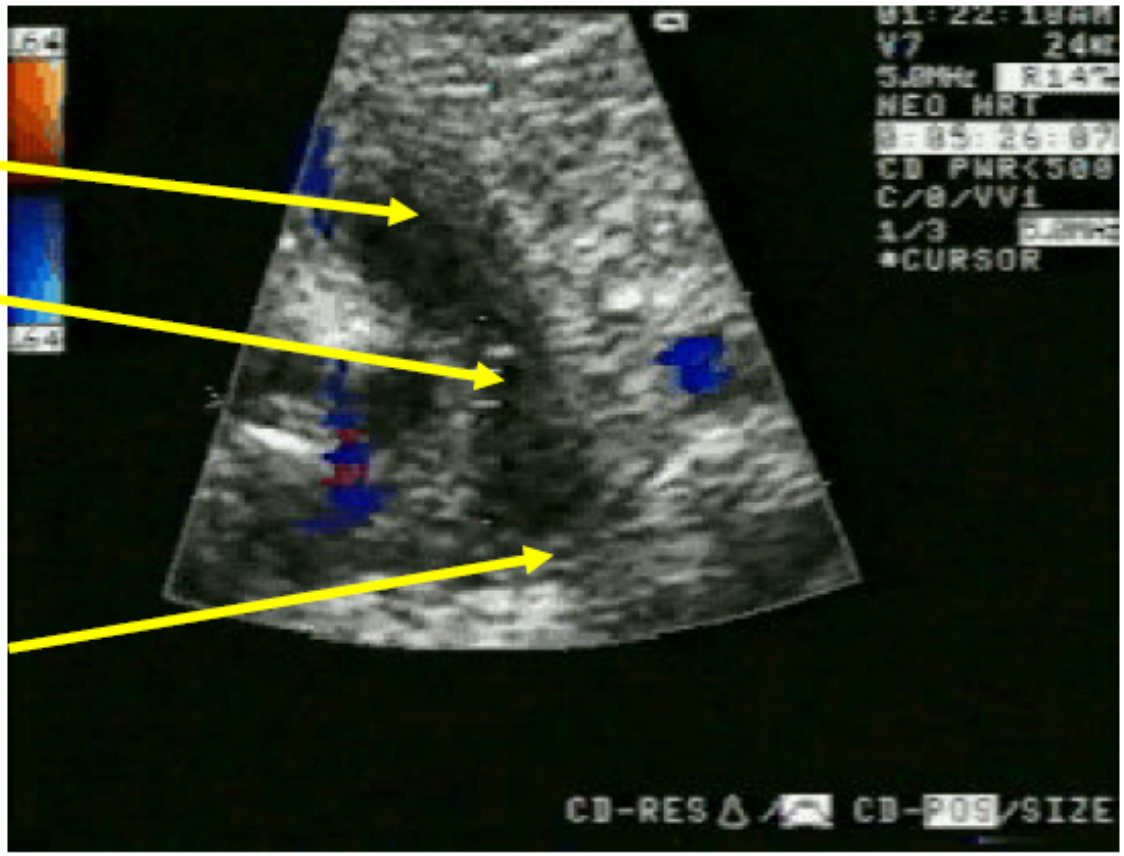
PDA with Right to Left Shunt

Suprasternal notch - transducer

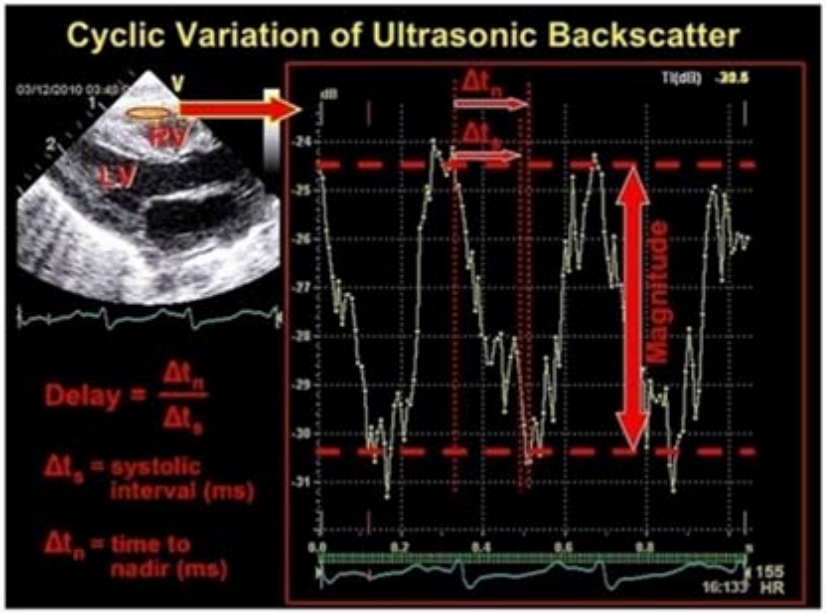
Main Pulmonary Artery

PDA (R to L) with Doppler probe

Descending Aorta



Novel Methods for Assessment of Right heart Structure and Function in Pulmonary Hypertension

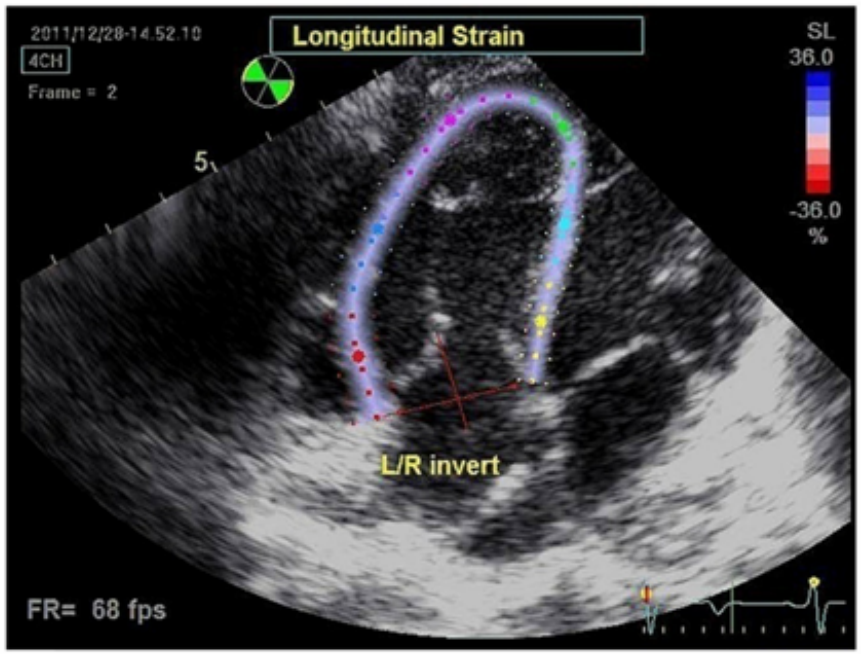


- Conventional methods of assessment of RV structure and function are often qualitative and do not provide sensitive markers of RV remodeling for prognostic information.
- Advances in cardiac imaging of the RV, including ultrasonic tissue characterization by integrated backscatter imaging, tissue Doppler imaging, speckle tracking echocardiography, and flow dynamics, have provided the capability to obtain quantitative information that often precedes the qualitative information provided by conventional methods.

Fig. 1. Cyclic variation of ultrasonic backscatter expressed in magnitude and normalized time delay of the backscatter energy. The magnitude of cyclic variation is defined as the difference in backscatter between the average peak and average nadir values. The normalized time delay of cyclic variation is expressed in terms of a dimensionless ratio, obtained by dividing the time interval from end-diastole to the nadir of the mean backscatter trace (Δt_n) by the systolic interval (Δt_s).

Gautam K. Singh, MD[a,*], Philip T. Levy, MD[a], Mark R. Holland, PhD[b], Aaron Hamvas, MD[a]
Clin Perinatol 39 (2012) 685–701

Novel Methods for Assessment of Right heart Structure and Function in Pulmonary Hypertension



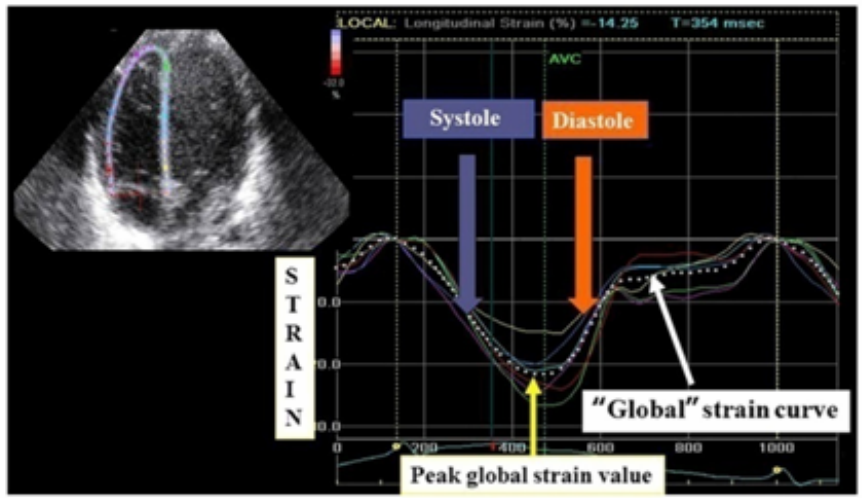


Fig. 2. Strain imaging of the RV in an extremely low gestational age neonate with bronchopulmonary dysplasia and increased pulmonary pressure using speckle tracking echocardiography (*A*). The segmental strain is graphically presented by different color codes and curves and global longitudinal strain by dotted curve with its peak as peak systolic longitudinal strain (*B*). The segmental strains are not synchronous and peak global longitudinal strain is decreased (−21%, normal >−23%). AVC, aortic valve closure; FR, frame rate.

Novel Methods for Assessment of Right heart Structure and Function in Pulmonary Hypertension

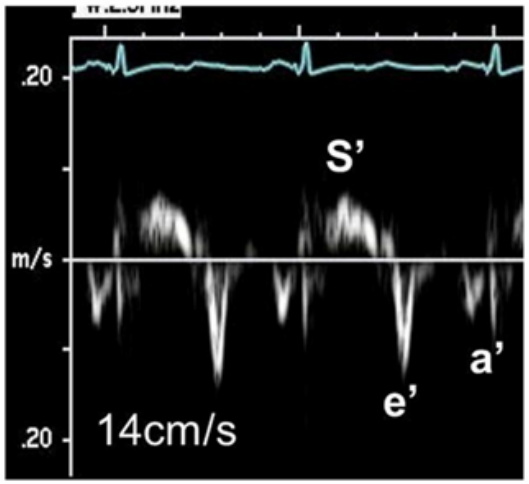


Fig. 4. TDI of myocardial velocity at the tricuspid level of the right ventricular free wall in a normal neonate.

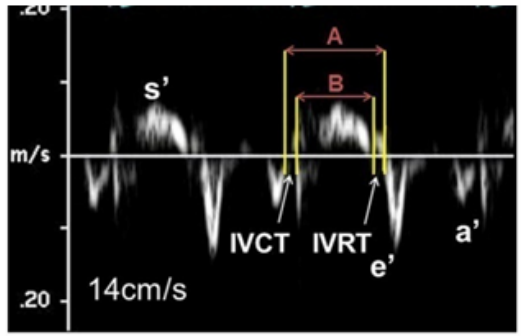


Fig. 5. TDI of myocardial performance index (MPI) using time interval of different phases of the cardiac cycle. Myocardial velocities were measured at the tricuspid level of the right ventricular free wall in a normal neonate. ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time. MPI is the ratio (IVCT + IVRT)/ET. A, time interval includes sum of IVCT, IVRT, and ET; B, ejection time.

Accuracy of clinical diagnosis and decision to commence intravenous prostaglandin E1 in neonates presenting with hypoxemia in a transport setting

Use of intravenous PGE1 in neonates presenting with hypoxemia

Clinical characteristics of neonates with suspected CHD (group 1), suspected PPHN (group 2), or suspected CHD and/or persistent pulmonary hypertension (group 3)

Characteristic	Group 1 (n = 76)	Group 2 (n = 22)	Group 3 (n = 17)	*P*
Gestation at birth (wk)	37.9 ± 2.5	39.1 ± 1.5	38.0 ± 3.0	NS
Birth weight (g)	3081 ± 667	3342 ± 675	3390 ± 877	NS
Age at admission (d)	2.5 ± 3.7	1.7 ± 1.0	1.8 ± 0.9	NS
Stabilization time (min)	208 ± 113	225 ± 89	248 ± 109	NS
Apgar <5 at 5 min	5 (6.6)	1 (4.5)	2 (11.7)	NS
Active resuscitation	19 (25)	9 (41)	7 (41.2)	NS
Hypotension requiring fluid bolus	29 (38)	12 (55)	9 (53)	NS
Hypotension requiring inotropes	18 (24)	16 (73)**	7 (41)	.001
Murmur	32 (42)	4 (18)	3 (18)	.03
Upper-lower SBP gradient of ≥10 mm Hg	14 (18)	0 (0)	3 (18)	.09
Preductal-postductal Spo_2 difference >10 mm Hg	10 (13)	0 (0)	1 (6)	NS
Pao_2 <50 mm Hg (hyperoxia test)	22 [38] (58)	5 [19] (26)**	5 [10] (50)	.07
Arterial pH <7.25 and base deficit >−5	6 [52] (12)	3 [16] (19)	0 [8]	NS
Cardiomegaly/abnormal heart shape on CXR	45 [73] (62)	4 [20] (20)*	9 [16] (56)	.004
Abnormal lung parenchyma on CXR	16 [73] (21)	10 [20] (50)**	3 [16] (19)	.03

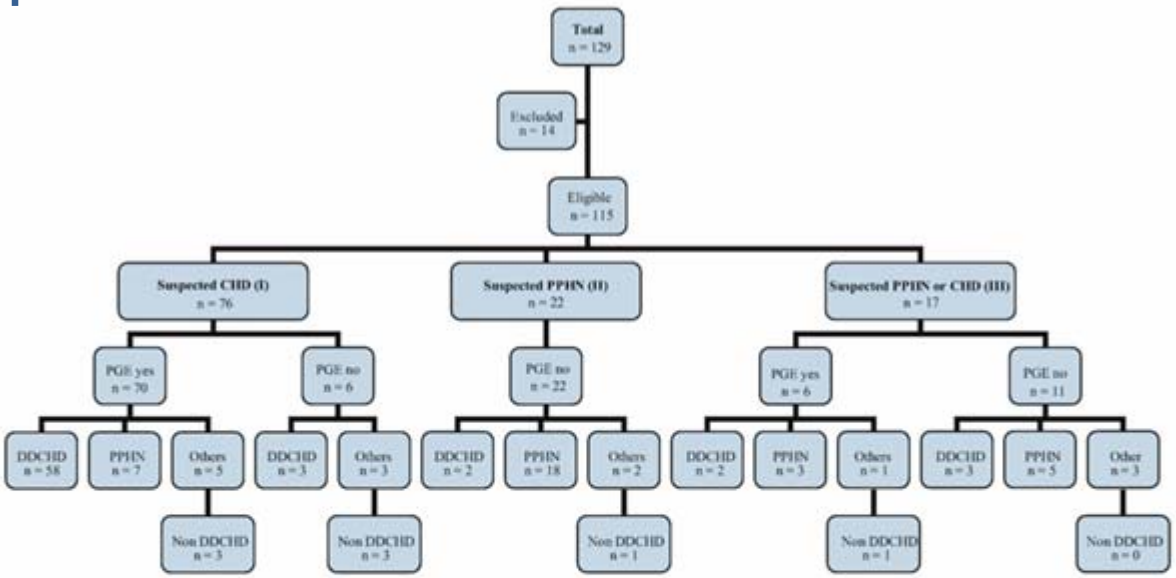
Data are presented as mean ± SD or frequency (%) where relevant. Figures in brackets indicate number of neonates in which the data were available. SBP indicates systolic blood pressure; CXR, chest radiograph; NS, nonsignificant.

* $P < .05$ vs group 1.

** $P < .01$ vs group 1.

Shivananda et al Journal of Critical Care (2010) **25**, 174.e1–174.e9

Use of Intravenous PGE 1 in Neonates Presenting with Hypoxemia



Algorithm showing the proportion of neonates in each group with a diagnosis of CHD or PPHN treated with intravenous PGE_1 or not. DDCHD indicates duct-dependent CHD; other, non-DDCHD or normal anatomical 2-dimensional echocardiography.

The accuracy of a provisional diagnosis of CHD by transport team was 87.7% and the positive predictive value was 88.1%. Sixty neonates (88%) received PGE_1 appropriately. Eight neonates (12%) with duct-dependent CHD (n = 68) did not receive PGE_1 and were considered as missed opportunities. Ventilated neonates in groups 1 and 3 were identified as the groups that can potentially benefit from more liberal use of PGE_1 and without any adverse effects.

Journal of Critical Care (2010) **25**, 174.e1–174.e9

Management of Infants with Pulmonary Hypertension

Control of Blood Pressure

Feel posterior tibial pulsation well

DOPAMINE 10
DOBUTAMINE 10
MILRINONE

Control of FRC

CPAP / PEEP

XRAY aim for about 8.5 to 9 ribs expansion clearance of haziness

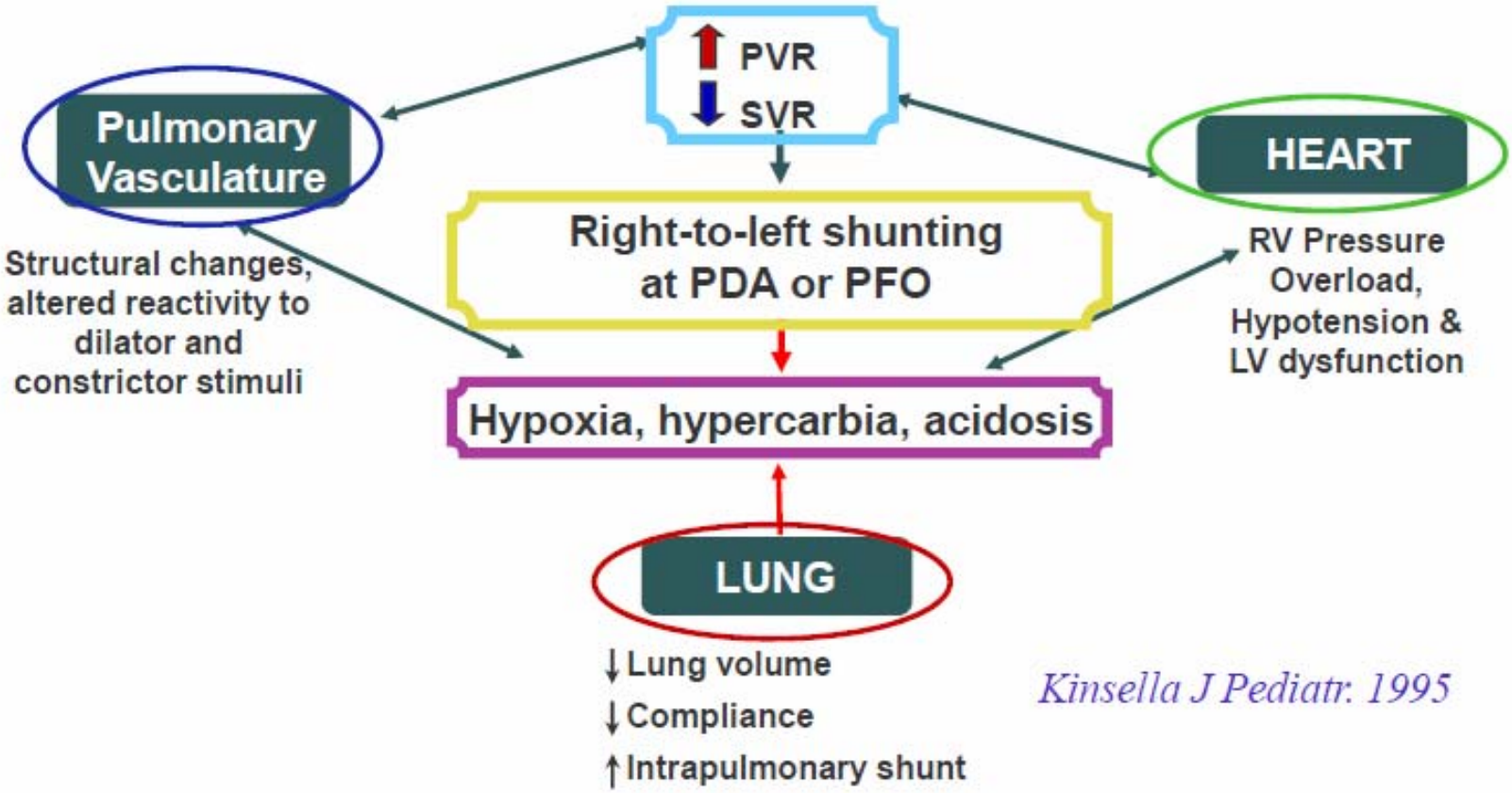
DONT BASH THE LUNG

Ph . > 7.25
Co2 < 60 mmhg
O2 50 - 70 mmhg

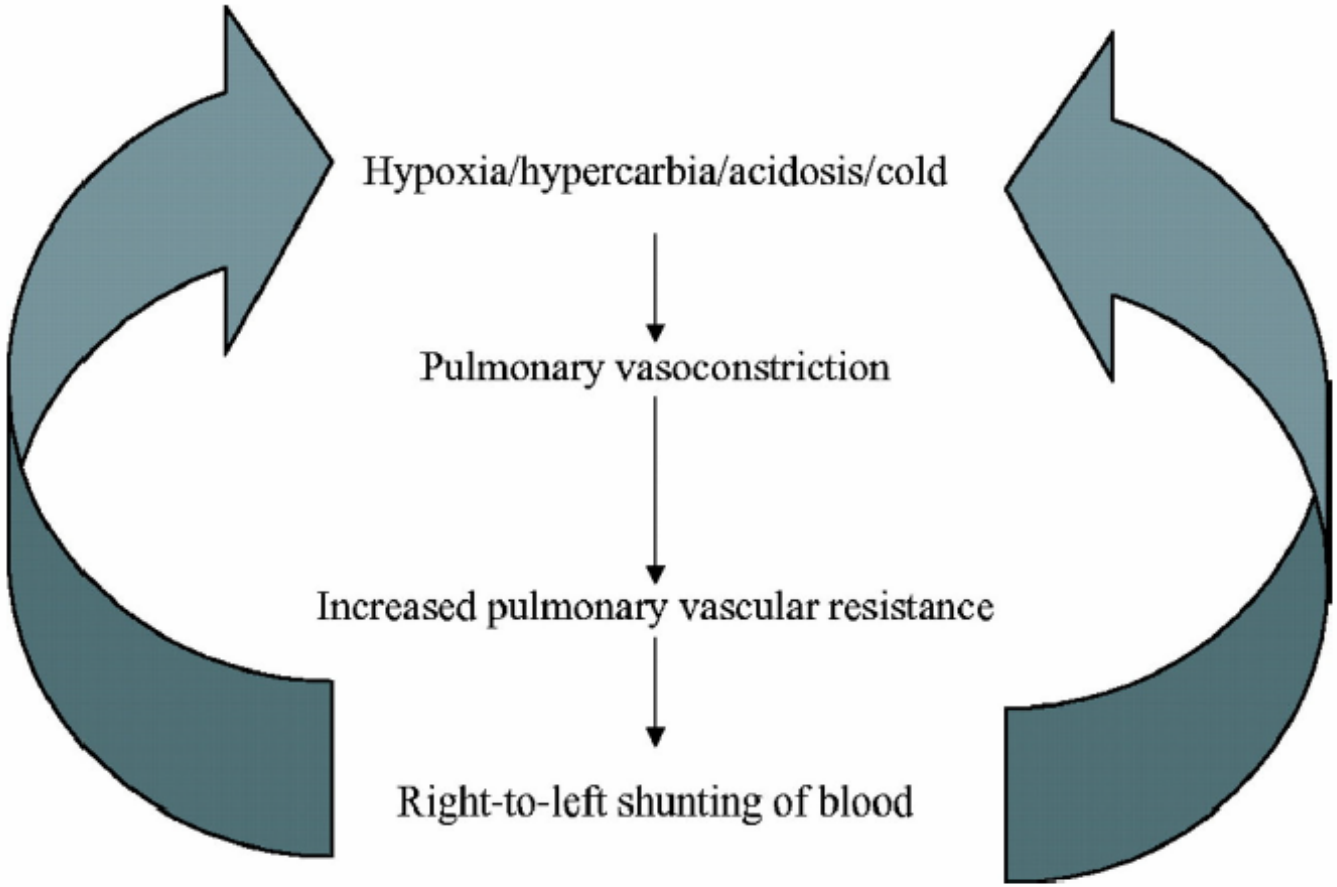
Pediatrics oct 1985 76 (4) 488 -94 Wung JT

DO SO ONLY IF THE END EXPIRATORY PRESSURE OR CPAP IS RIGHT

Cardiopulmonary Interactions in PPHN



The Vicious Cycle of PPHN



Murphy, P. J. Contin Educ Anaesth Crit Care Pain 2005 5:107-112; doi:10.1093/bjaceaccp/mki030

Unproven Therapeutic Strategies in PPHN

- Hyperventilation
- Gentle ventilation
- Alkali infusions
- Intravenous vasodilators (tolazoline)
- Sedation and paralysis

Proven Therapeutic Strategies in PPHN

- Oxygen
- Nitric oxide
- ECMO
- Aggressive management of hemodynamics to enhance cardiac output and oxygen delivery (and decrease right to left shunting.
- Management of the underlying pulmonary disease ventilation and surfactant)

Use of Surfactant in PPHN

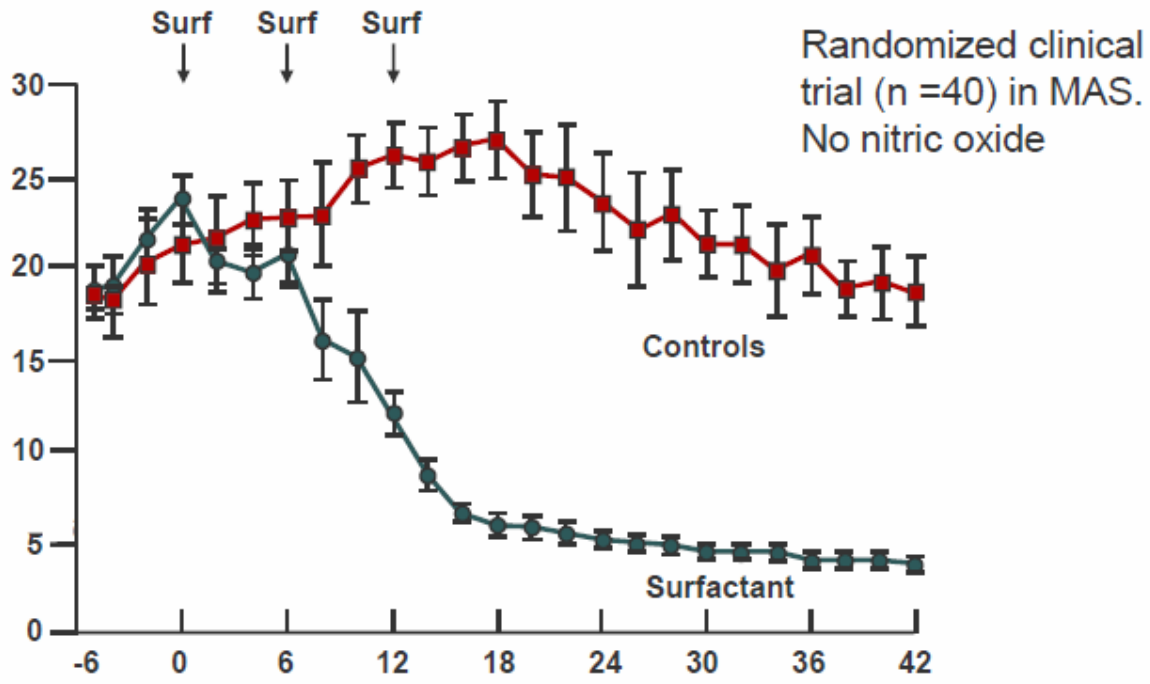
- No benefit for CDH
- Surfactant use in MAS decreased the severity of pulmonary morbidity, air leaks and length of hospital stay (*Pediatrics 97: 48. 1996*)
- Surfactant use is associated with a significant decrease in mortality in infants with respiratory failure (*J Pediatr:122: 261, 1993 & J Pediatr. 148: 595, 2006*).

Surfactant and Meconium Aspiration Syndrome: Mechanisms of Action

- Replaces deficient or inactivated surfactant caused by protein leak into alveolar spaces
- Decreases barotrauma and oxygen toxicity via a reduced need for mechanical ventilation and oxygen
- Modulates the proinflammatory response by down regulating IL-1, IL-6, IL-8, TNF-α and NF$\kappa\beta$

Use of Surfactant in PPHN

Oxygenation Index



Findlay et al Pediatrics 97: 48. 1996

Surfactant Replacement in the Term Newborn

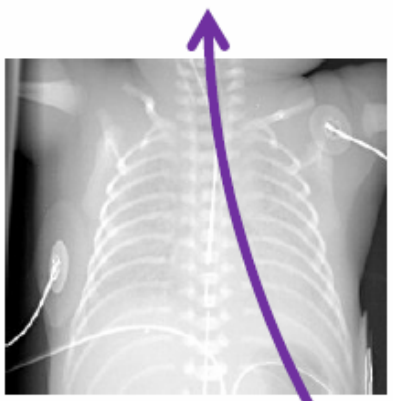
- …Surfactant treatment improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with meconium aspiration syndrome and sepsis/pneumonia. Surfactant treatment may also reduce morbidity and mortality for infants with pulmonary hemorrhage… Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency.

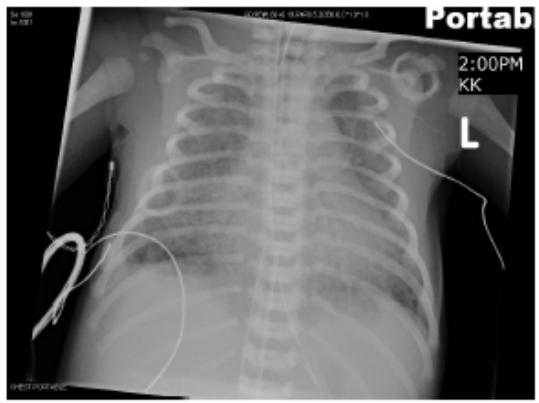
Engel et al Fetus and Newborn Committee 2008

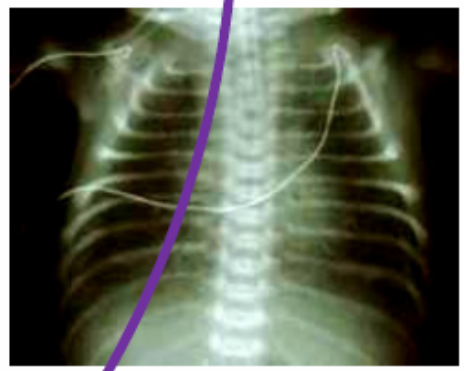
Guidelines for Mechanical Ventilation in PPHN

- Most infants with pulmonary hypertension do not need nitric oxide or ECMO; PPHN physiology will resolve with treatment of the underlying disease process.
- When using NO in infants with underlying parenchymal disease, adequate lung inflation is important with; some infants do better with HFOV.
- Overinflation may increase PVR and worsen pulmonary hypertension

Effect of Ventilation – Pulmonary Vascular Resistance (PVR) is Minimal at FRC







Low lung volume

Optimal lung volume at FRC

High lung volume

Simmons DH et al, Circ. Res. 1961: 9, 465-471

Keszler & Abubakar – Physiologic principles in Goldsmith & Karotkin – Assisted ventilation of the neonate

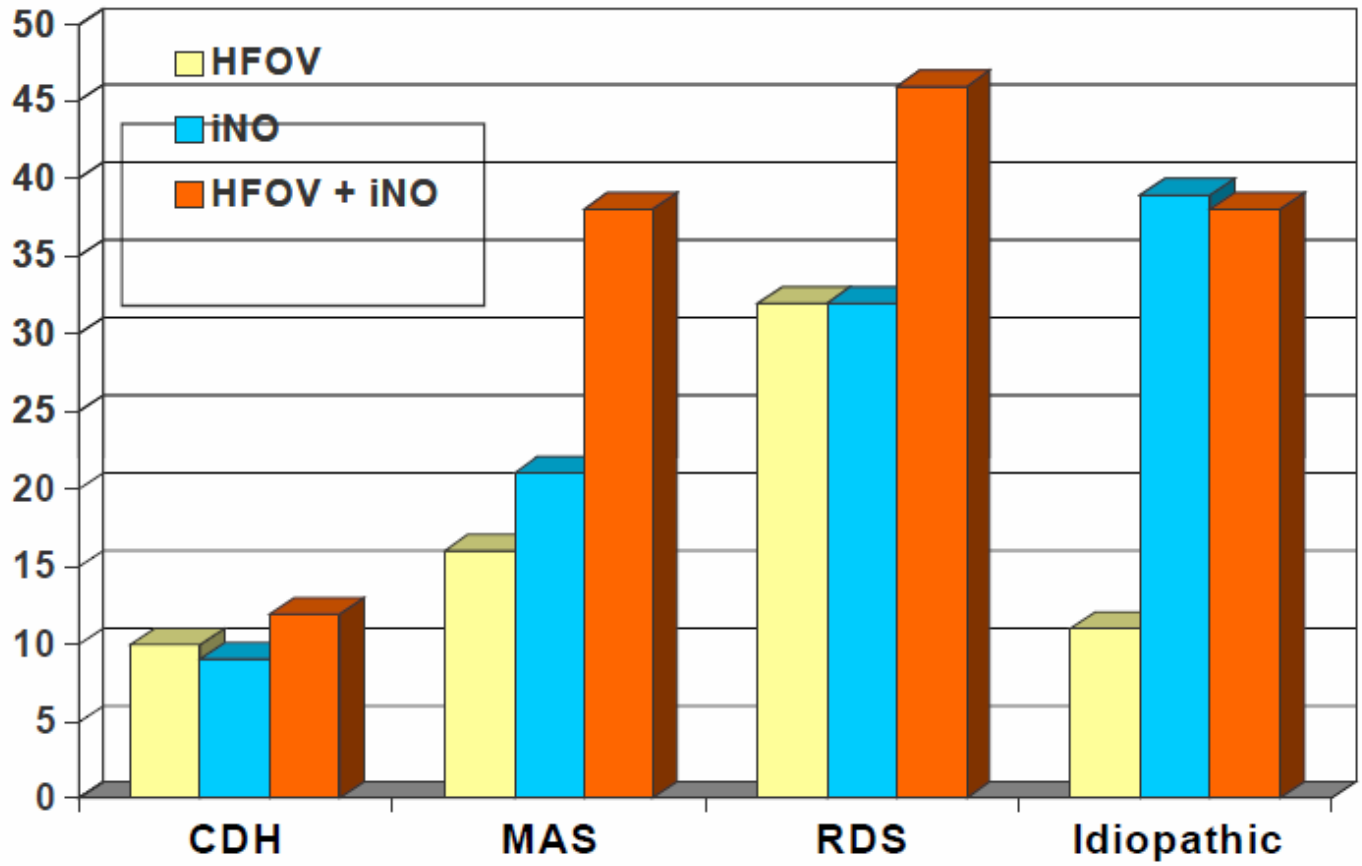
The million dollar question of optimisation of PEEP

Randomized Multicenter Trial of Inhaled NO and High Frequency Oscillatory Ventilation in Severe PPHN

- 205 infants with severe hypoxemia and echocardiographic evidence of PPHN randomized to HFOV or NO (20 ppm).
- Four groups of infants studied: 1) infants with diffuse lung disease (RDS or pneumonia), 2) meconium aspiration syndrome, 3) idiopathic PPHN and 4) congenital diaphragmatic hernia
- Infants failing HFOV crossed over to inhaled NO and if they still remained hypoxemic they received both NO and HFOV
- Infants failing inhaled nitric oxide crossed over to HFOV and if they still remained hypoxemic they received both NO and HFOV

Kinsella JP et al J Pediatr. 131: 55, 1997

Randomized Multicenter Trial of Inhaled No and High Frequency Oscillatory Ventilation in Severe PPHN

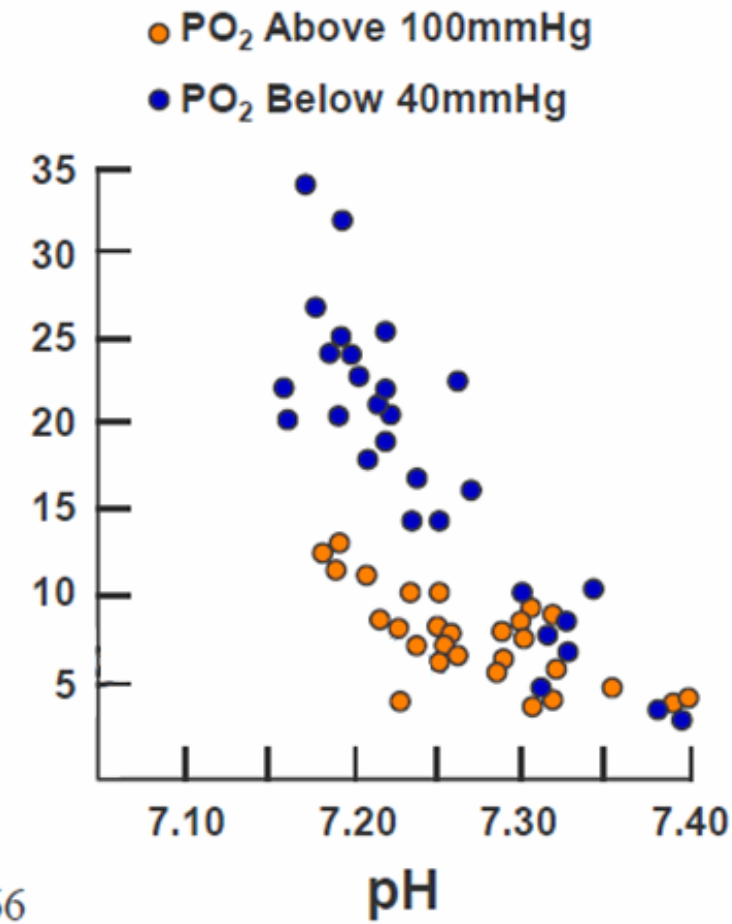


Guidelines for Arterial Blood Gases in PPHN

- Maintain arterial:

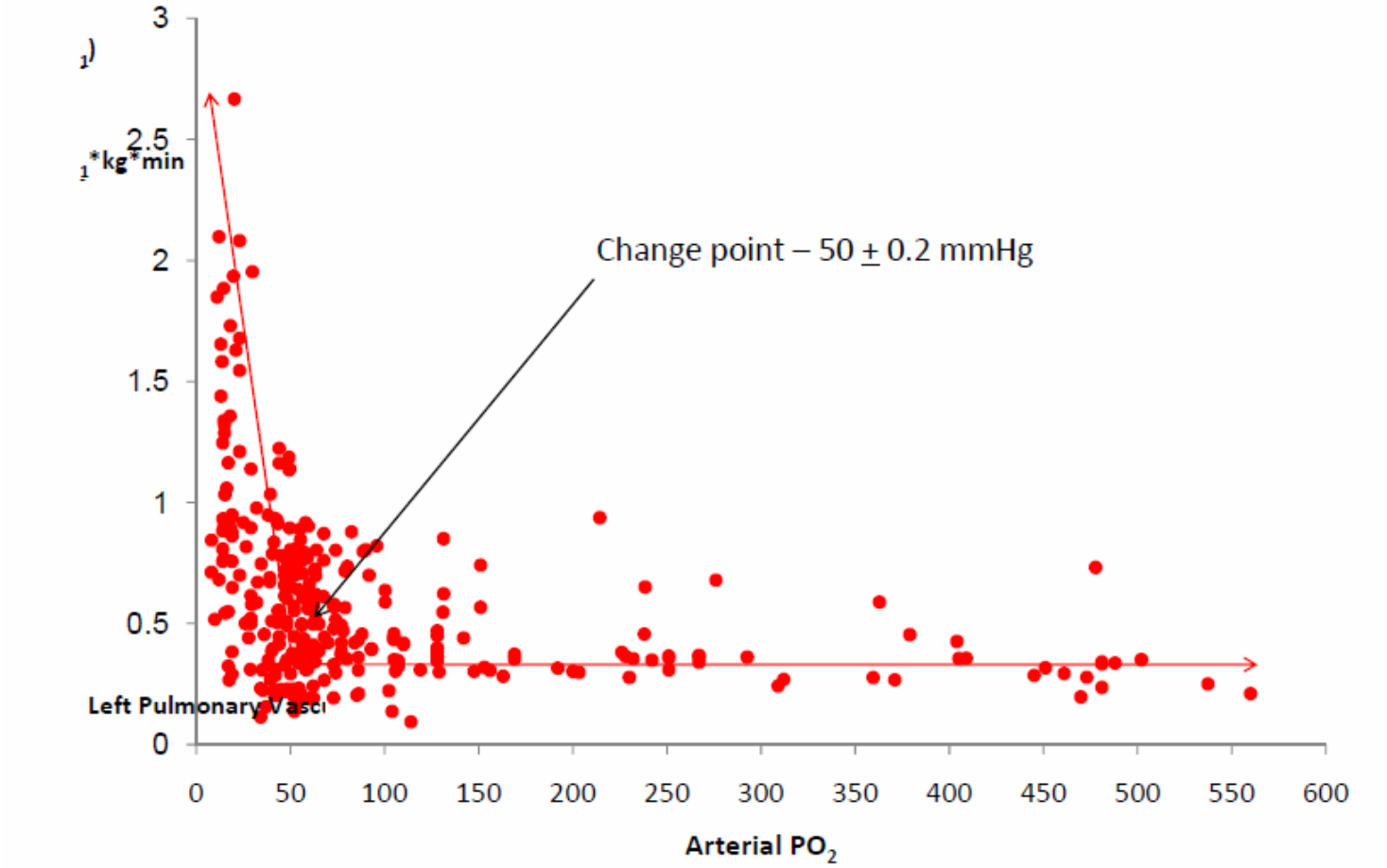
  pH $\geq$ 7.30, $PaCO_2$ 40-45 mm Hg & PaO_2 50-80 mm Hg

Pulmonary Vascular Resistance & pH



Rudolph and Yuan JCI 1966

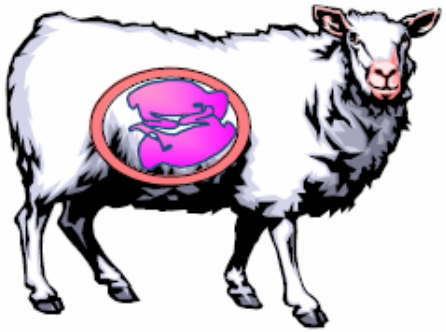
Neonatal Lambs



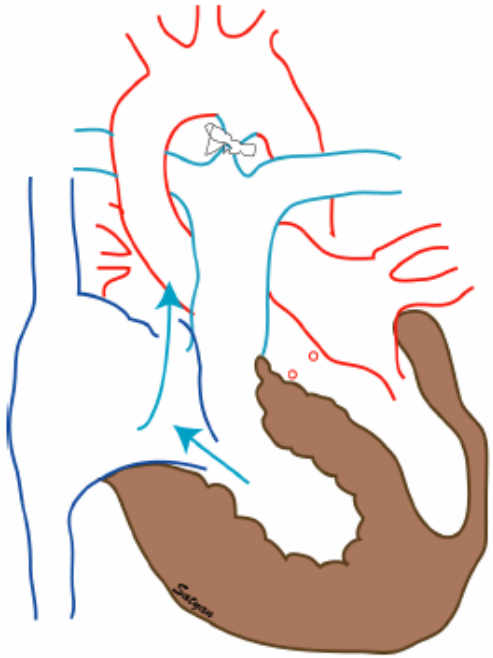
Lakshminrusimha et al, Pediatric Research 2009

Model – PPHN with Remodeled Pulmonary Vasculature

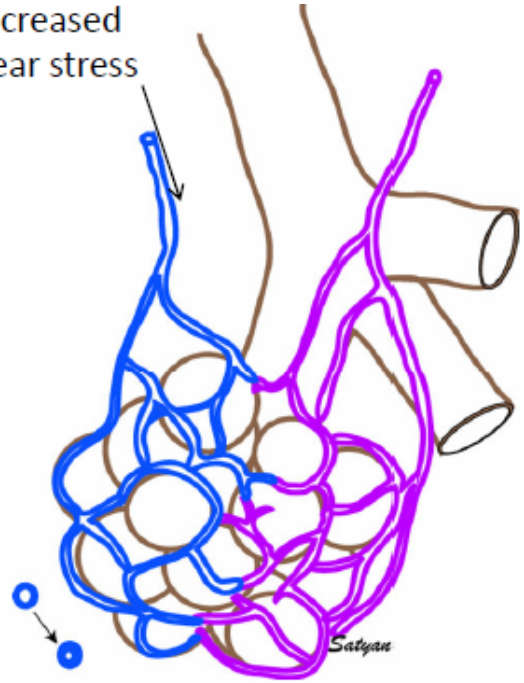
Hysterotomy and fetal ductal ligation at 126 d gestation



Delivery 9 days later by C-section



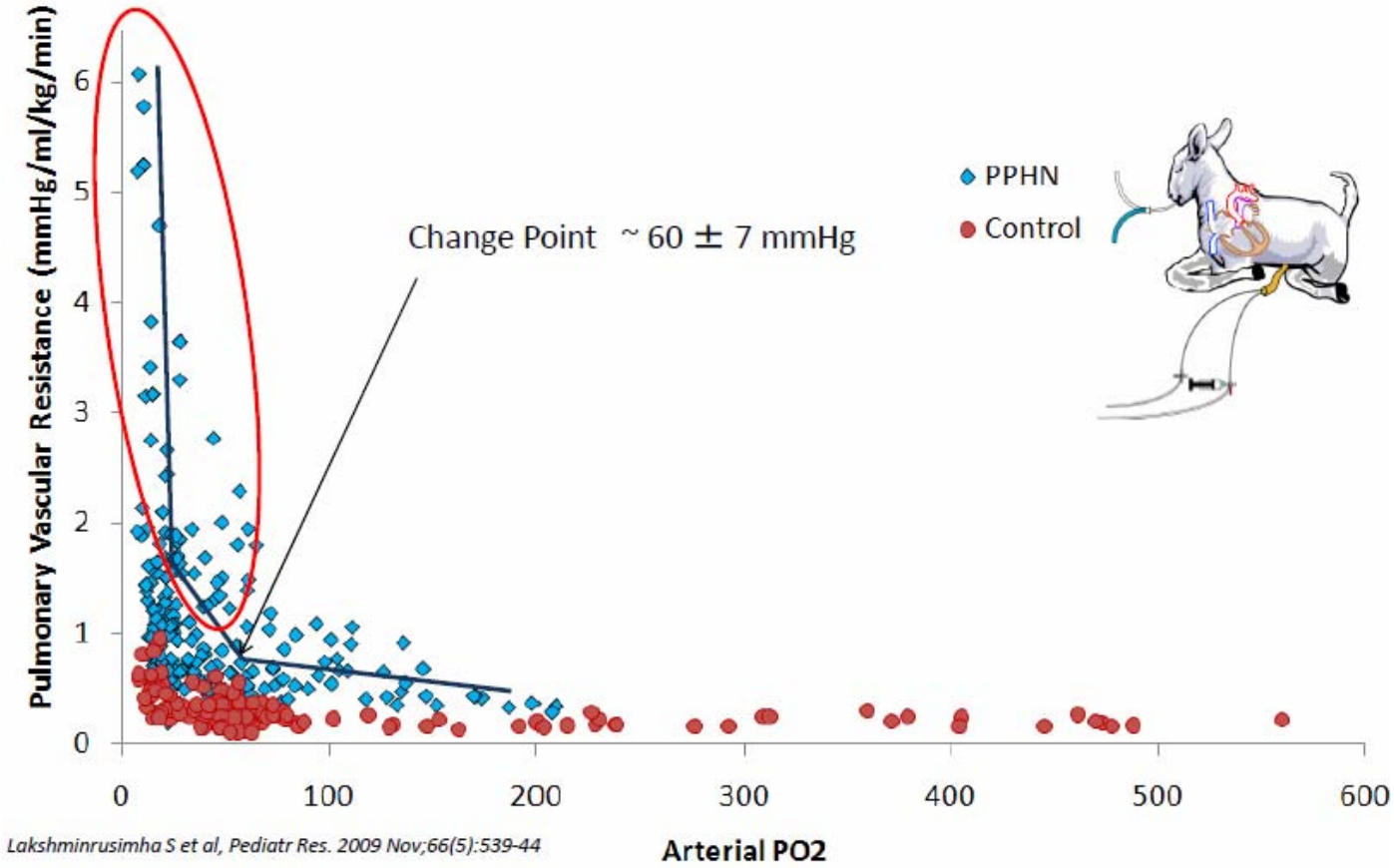
Increased shear stress



Vascular remodeling with smooth muscle hypertrophy

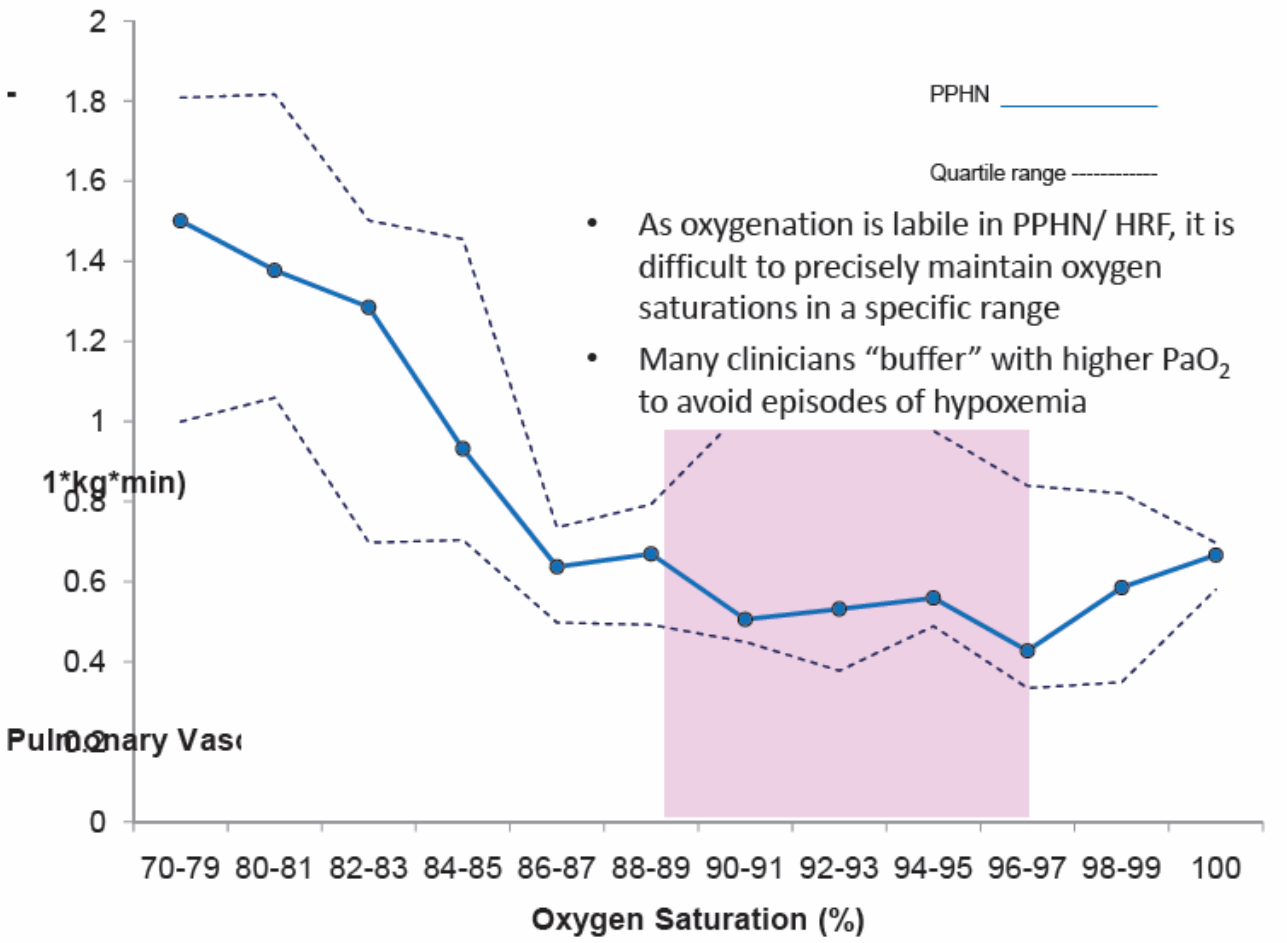
Term ~ 145 days

Severe Hypoxic Pulmonary Vasoconstriction in Lambs with PPHN; Change Point – Similar to Control Lambs



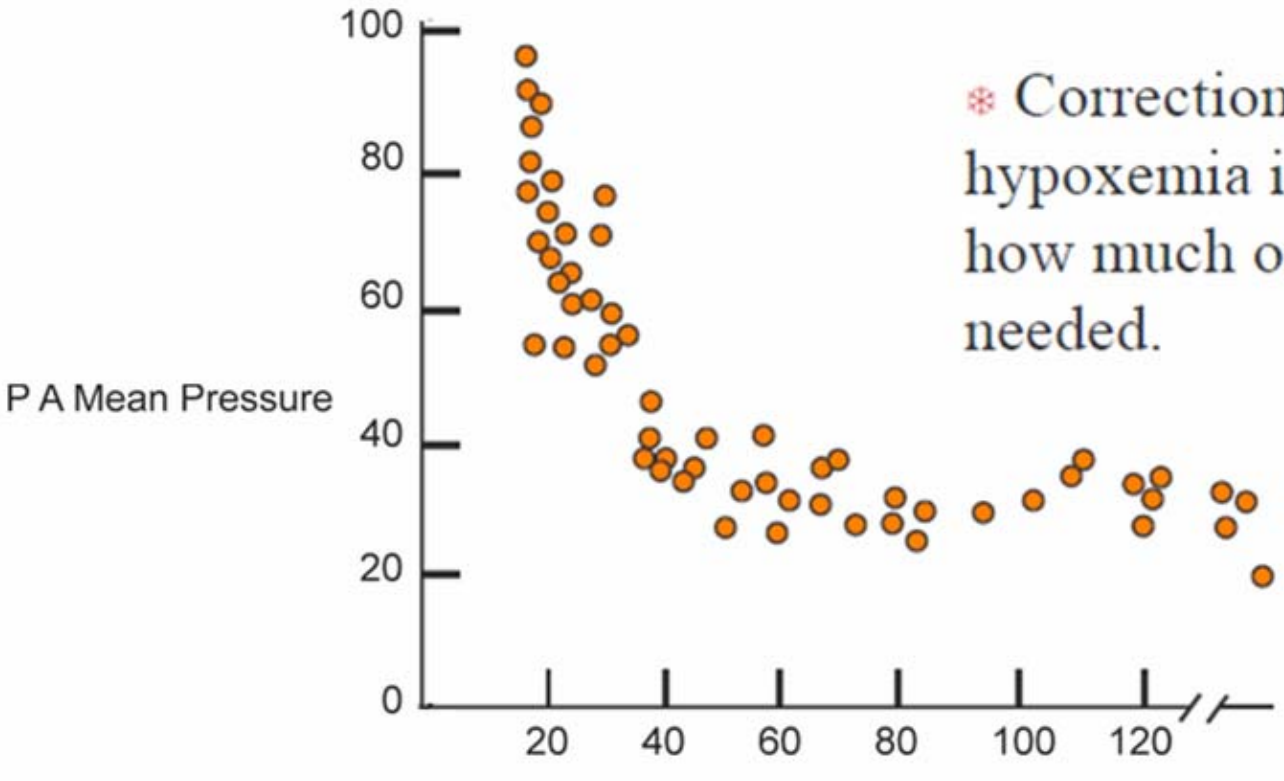
Lakshminrusimha S et al, Pediatr Res. 2009 Nov;66(5):539-44

Oxygen Saturation and PVR



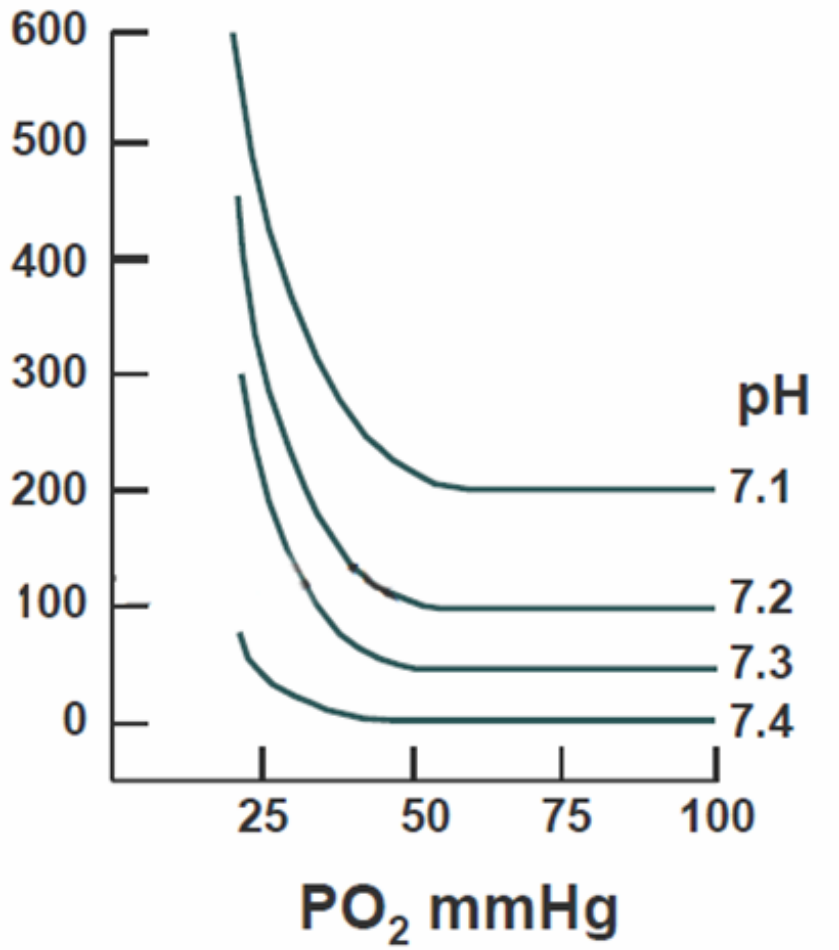
Lakshminrusimha S et al, Pediatr Res. 2009 Nov;66(5):539-44

Use of Supplemental Oxygen in PPHN

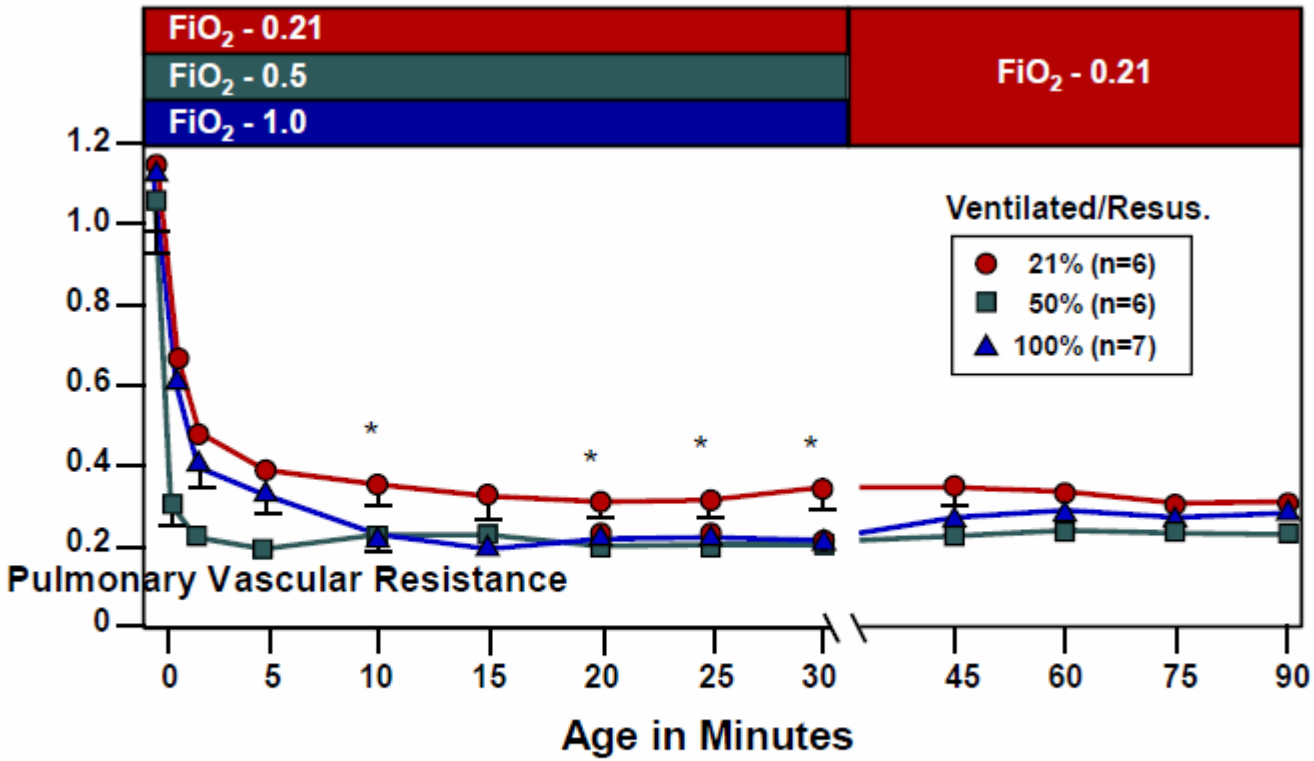


- Correction of severe hypoxemia is important, but how much oxygen is needed.

Pulmonary Vascular Resistance

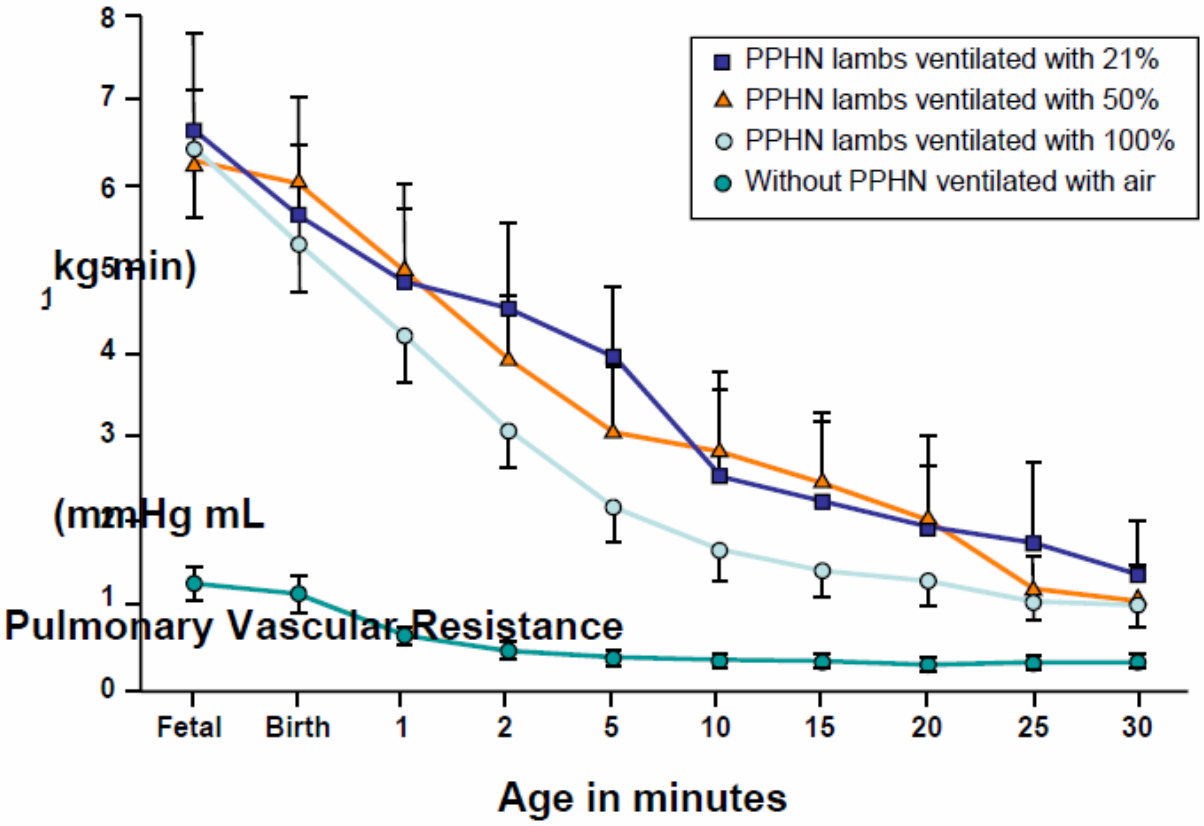


Changes in Pulmonary Vascular Resistance in Lambs Ventilated with 21% or 100% O_2



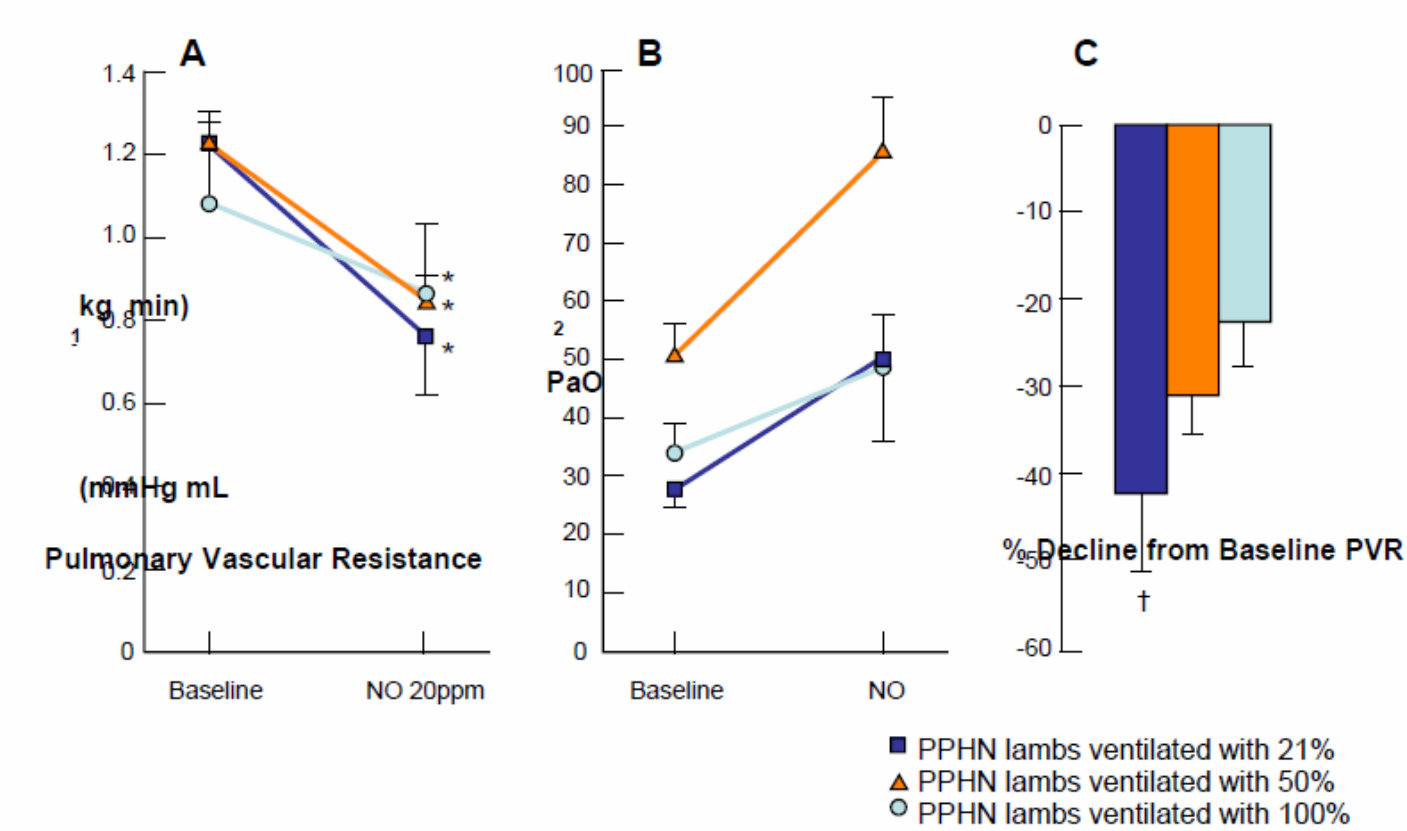
Lakshminrusimha et al. Pediatr. Res. 62: 313-318, 2007

Changes in Pulmonary Vascular Resistance in Lambs PPHN Ventilated with 21%, 50% or 100% O_2



Lakshminrusimha et al. Pediatr. Res. 66: 539-544, 2009

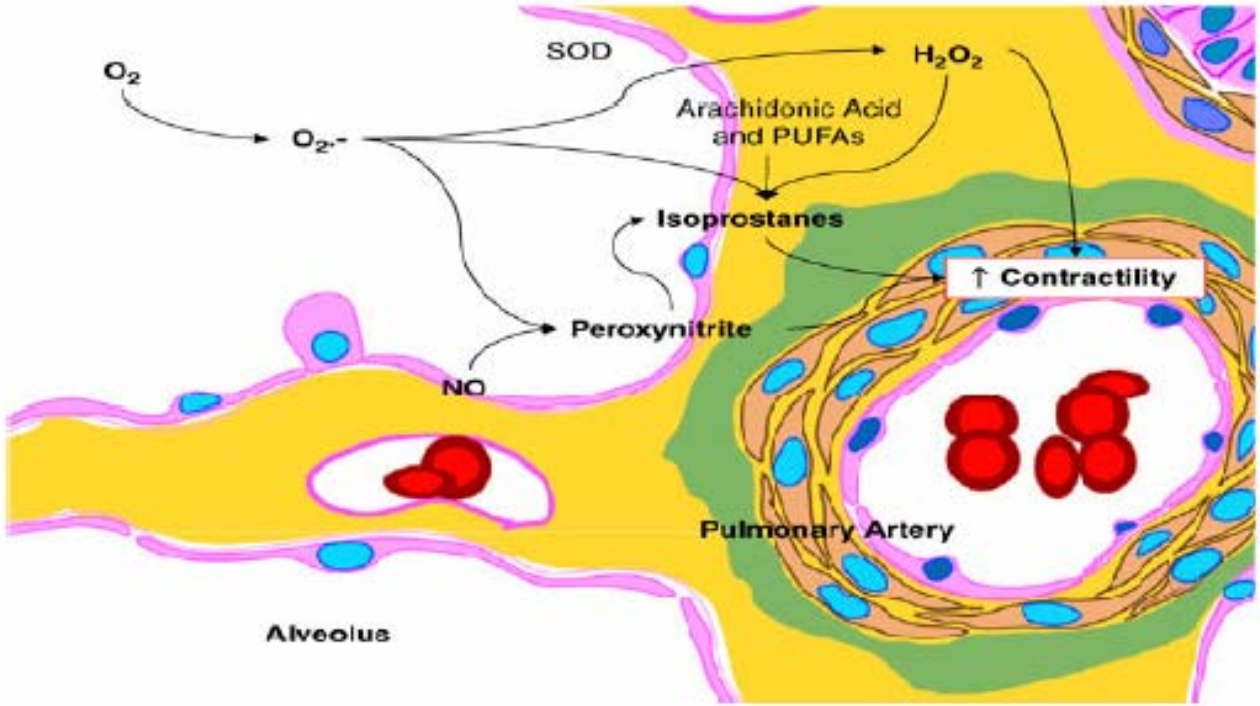
Changes in Pulmonary Vascular Resistance in Lambs PPHN Ventilated with 21%, 50% or 100% O_2



Lakshminrusimha et al. Pediatr. Res. 66: 539-544, 2009

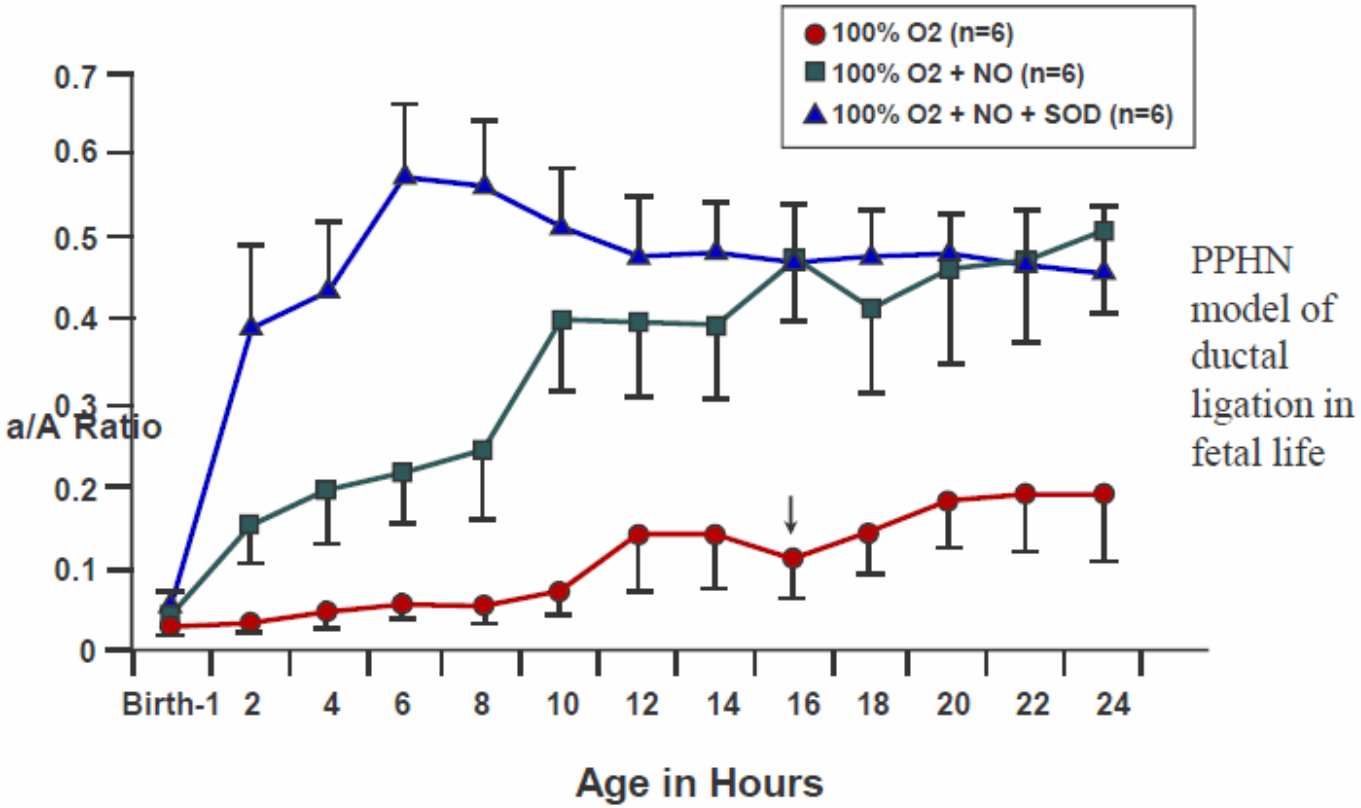
Nitric Oxide and Superoxide Radical

Superoxide radical is produced by NADPH oxidase, xanthine oxidase, *eNOS* or mitochondria



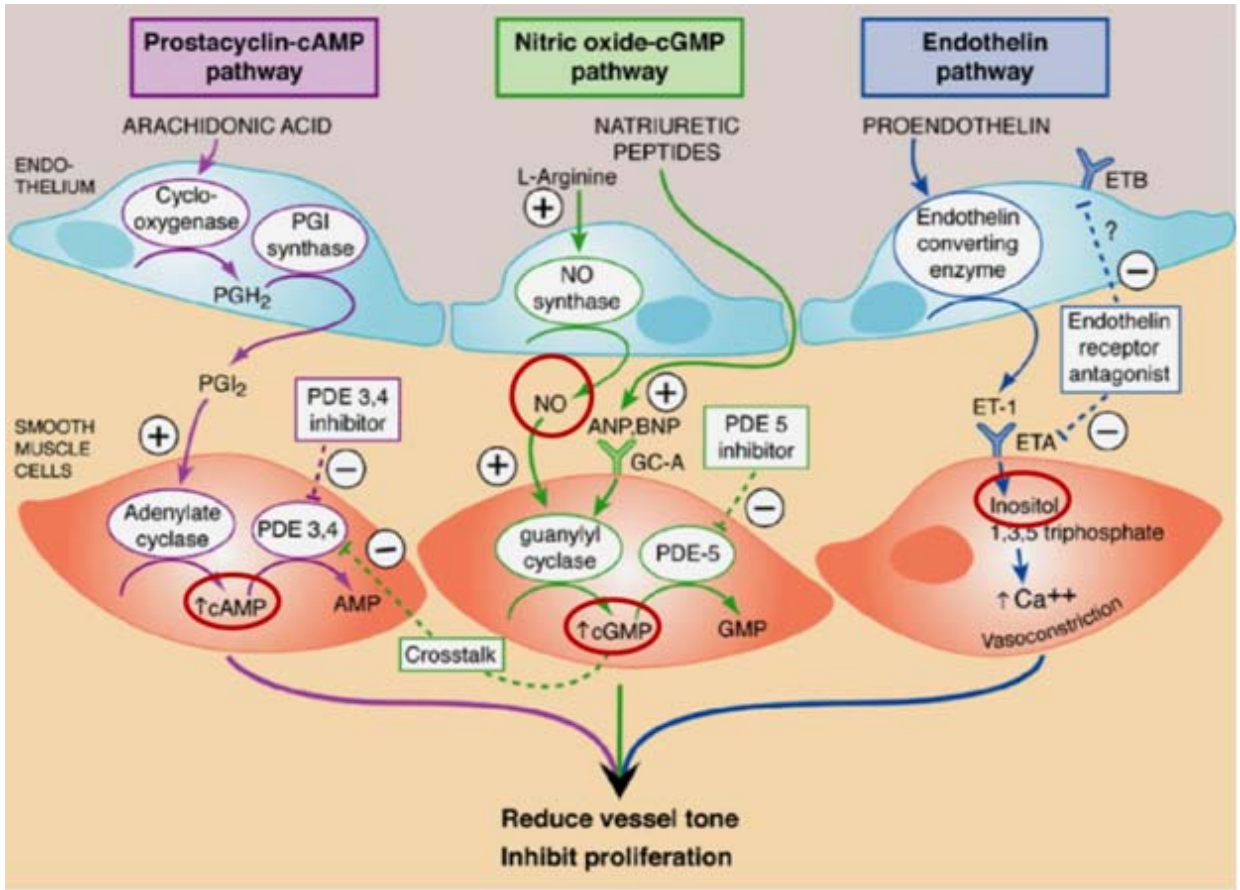
Steinhorn R J Perinatology 28: S67, 2008

Combinational effects of SOD and NO in lambs with PPHN



Lakshminrusimha S et al. Am J. Resp. Crit Care Med. 174: 1370-1377, 2006

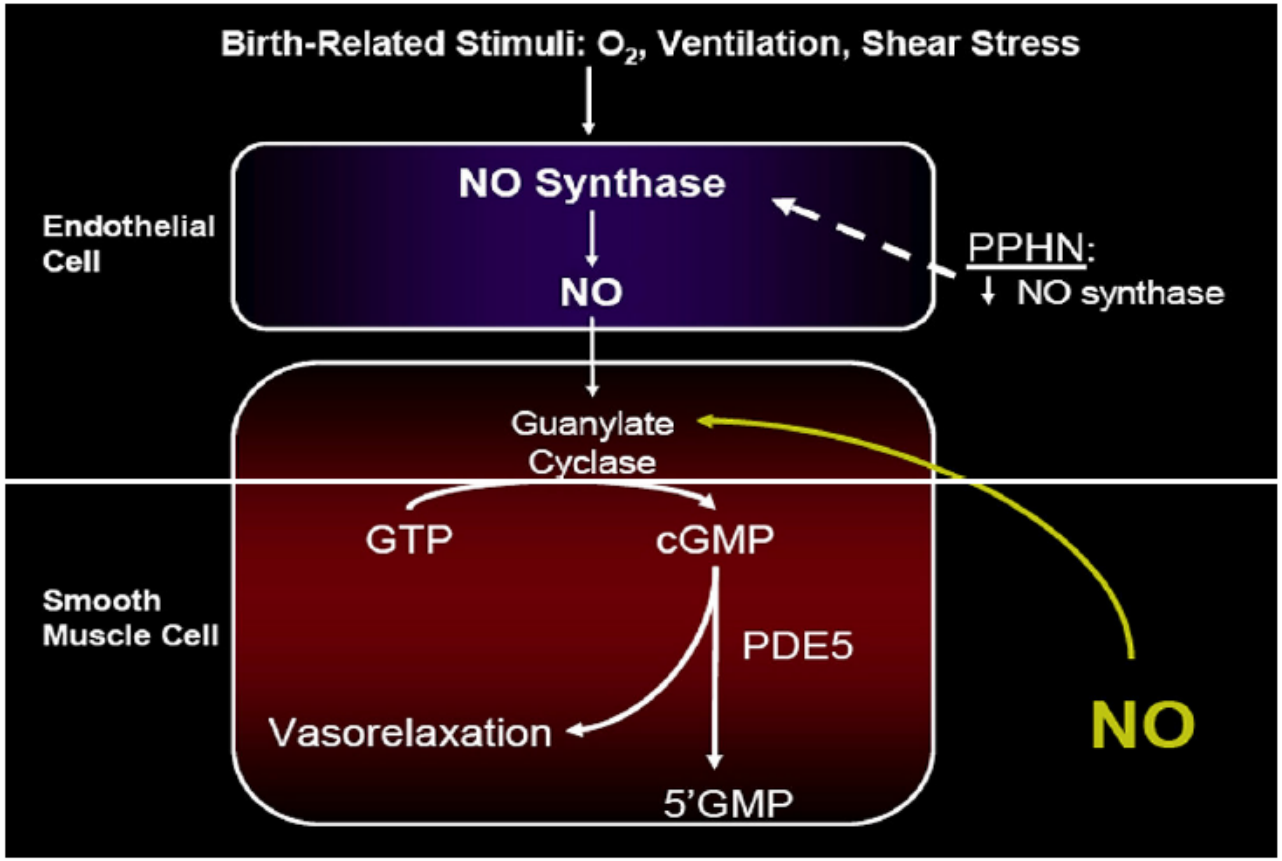
Regulation of Pulmonary Vascular Tone



Nitric Oxide

Persistent Pulmonary Hypertension in Newborn

Recent Advances in Management

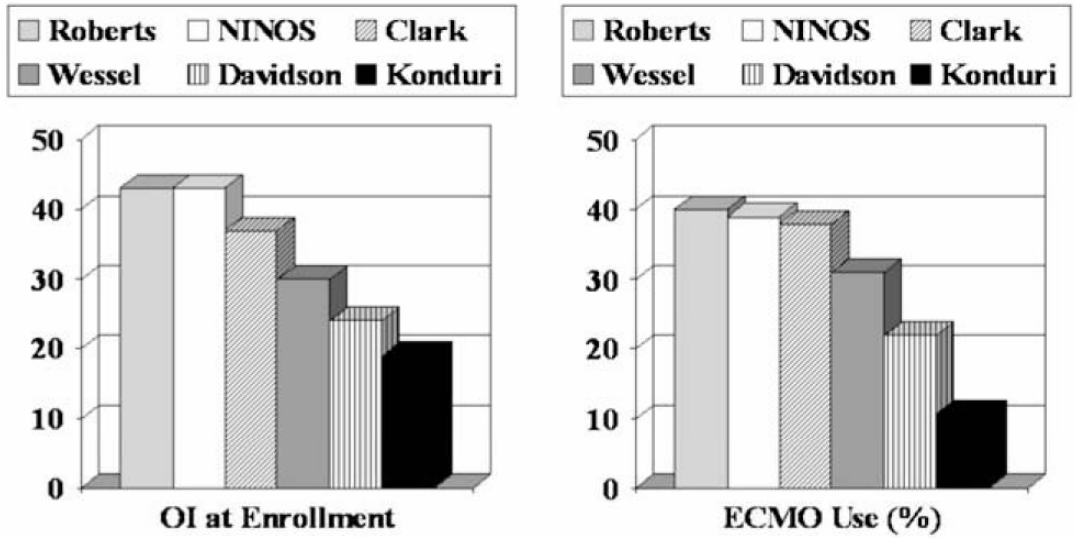


Guidelines for Using NO

- Current recommended starting dose is 20 ppm.
- Higher doses carry an increased risk of methemoglobinemia and are not more effective.
- Lower doses (e.g., 5 ppm) may be effective in many infants.
- Strategies that improve alveolar ventilation enhance the response to NO
- Avoidance of atelectasis is important; therefore use of NO (OI 20) before severe respiratory failure ensues is important

(RCTs suggest the the need for ECMO may be reduced with earlier use)

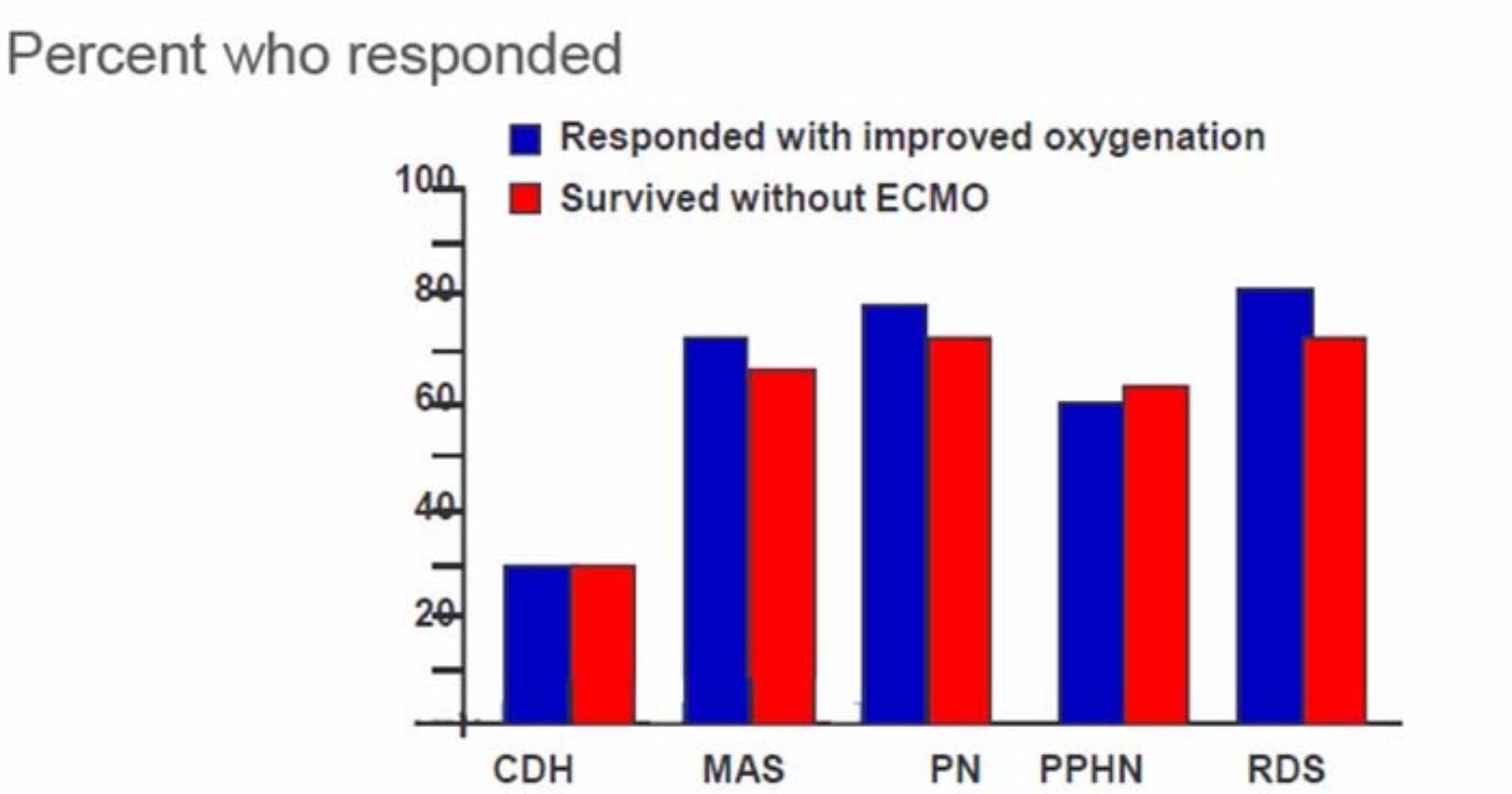
Initiation of INO and ECMO



Relationship of the severity of respiratory failure, defined by the OI at the time of initiation of iNO therapy, to the ECMO rates observed in these neonates. Data are from six randomized trials in term or near-term neonates for babies assigned to the iNO arm in these trials.[6,67,84,86,87,89] The trials are labeled by the name of the first investigator and are shown in the order of highest to lowest OI. NINOS, Neonatal Inhaled Nitric Oxide Study Group. The ECMO rate correlates with the severity of respiratory failure at the time of iNO initiation.

G.G. Konduri. Pediatr Clin N Am 56 (2009) 579–600

Response Rate by Diagnoses



Mechanisms for Poor NO Response

- Poor lung inflation
- Anatomic lung disease
- Anatomic heart disease
- Right or left ventricular failure

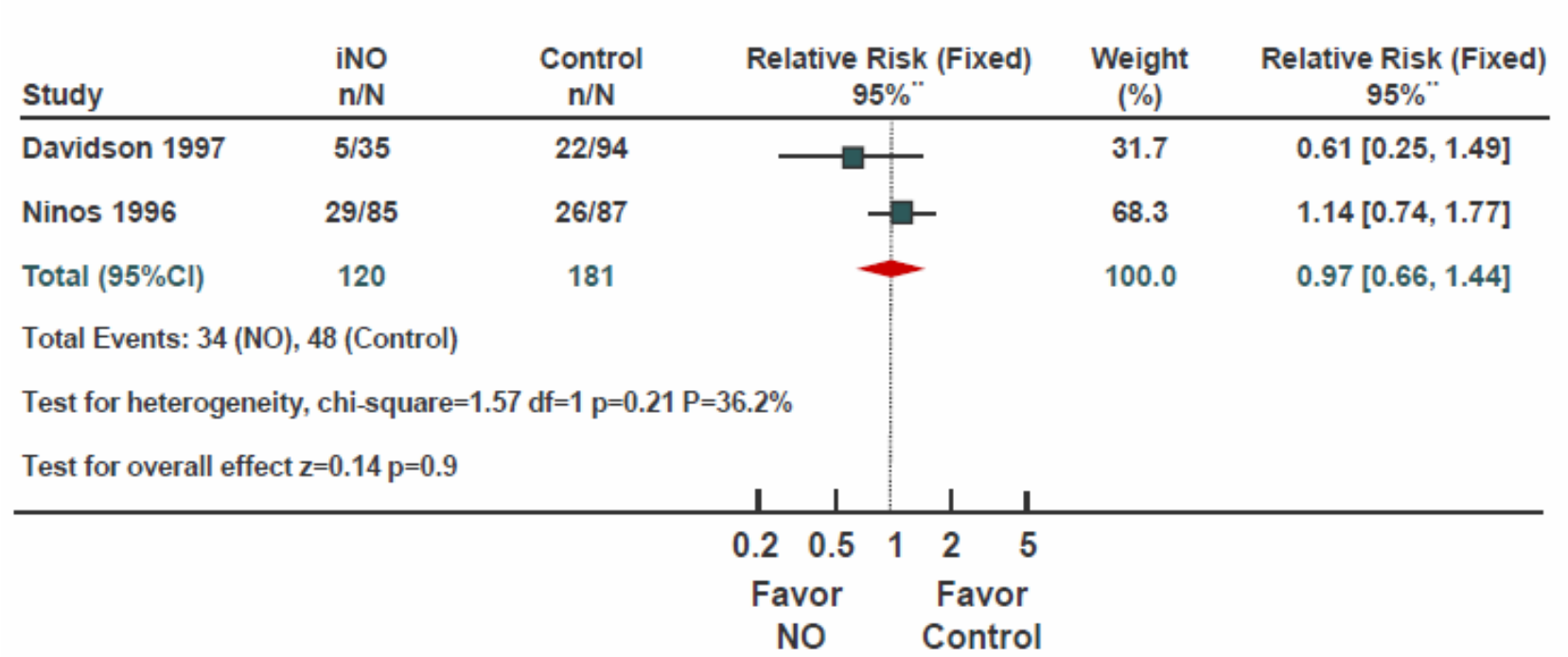
Inhaled NO vs Control: Outcome Requirement for ECMO

Study	iNO n/N	Control n/N	Relative Risk (Fixed) 95%··	Weight (%)	Relative Risk (Fixed) 95%··
01 Requirement for ECMO, studies which did not allow backup use of iNO in controls					
Christou 2000	3/21	11/20		5.6	0.26 [0.00,0.80]
Clark 2000	36/113	62/104		32.3	0.53 [0.39, 0.73]
Davidson 1997	25/114	14/41		10.3	0.64 [0.37, 1.11]
Ninos 1996	44/114	66/121		32.0	0.71 [0.53, 0.94]
Roberts 1996	12/30	20/28		10.3	0.56 [0.34, 0.92]
Wessell 1996	8/26	8/23		4.2	0.88 [0.40, 1.98]
Subtotal (95%CI)	418	337		94.8	0.61 [0.51, 0.72]

Comparison Inhaled NO vs Control, Outcome Death

Study	iNO n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Death, studies which did not allow backup use of iNO in controls					
Christou 2000	2/21	1/20		2.3	1.90 [0.19, 19.40]
Clark 2000	4/113	7/104		16.5	0.53 [0.16, 1.74]
Davidson 1997	9/114	1/41		3.3	3.27 [0.43, 24.98]
Ninos 1996	16/114	20/121		44.0	0.85 [0.46, 1.56]
Roberts 1996	2/30	2/28		4.7	0.93 [0.14, 6.18]
Wessell 1996	2/26	2/23		4.8	0.88 [0.14, 5.79]
Subtotal (95%CI)	417	337		75.7	0.92 [0.58, 1.48]

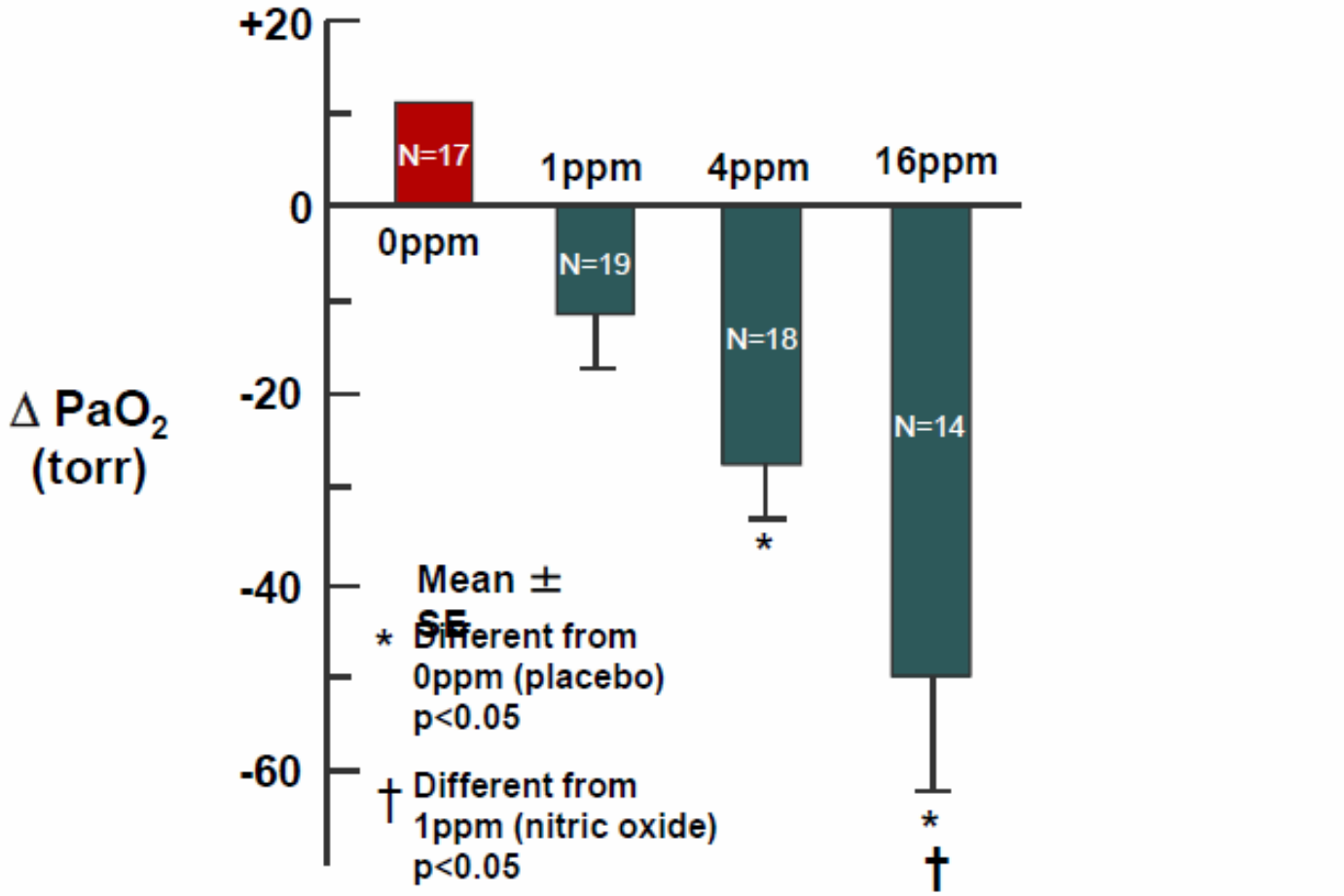
Inhaled NO vs Control: Outcome Neurodevelopmental Disability at 18 to 24 Months Aamong survivors



Discontinuing Nitric Oxide

- Dramatic increases in pulmonary vascular resistance can occur with abrupt withdrawal of nitric oxide.
- Mechanisms: 1) down regulation of endogenous NO production, 2) decreased vascular sensitivity to NO (due to decreased guanylate cyclase or increased PDE5)
- Most of the infants respond to an increase in FiO_2
- Infants with higher pulmonary artery pressure at the time of iNO withdrawal are are greatest risk of "rebound".
  - NO ought to be weaned gradually at doses $\leq$ 5 ppm

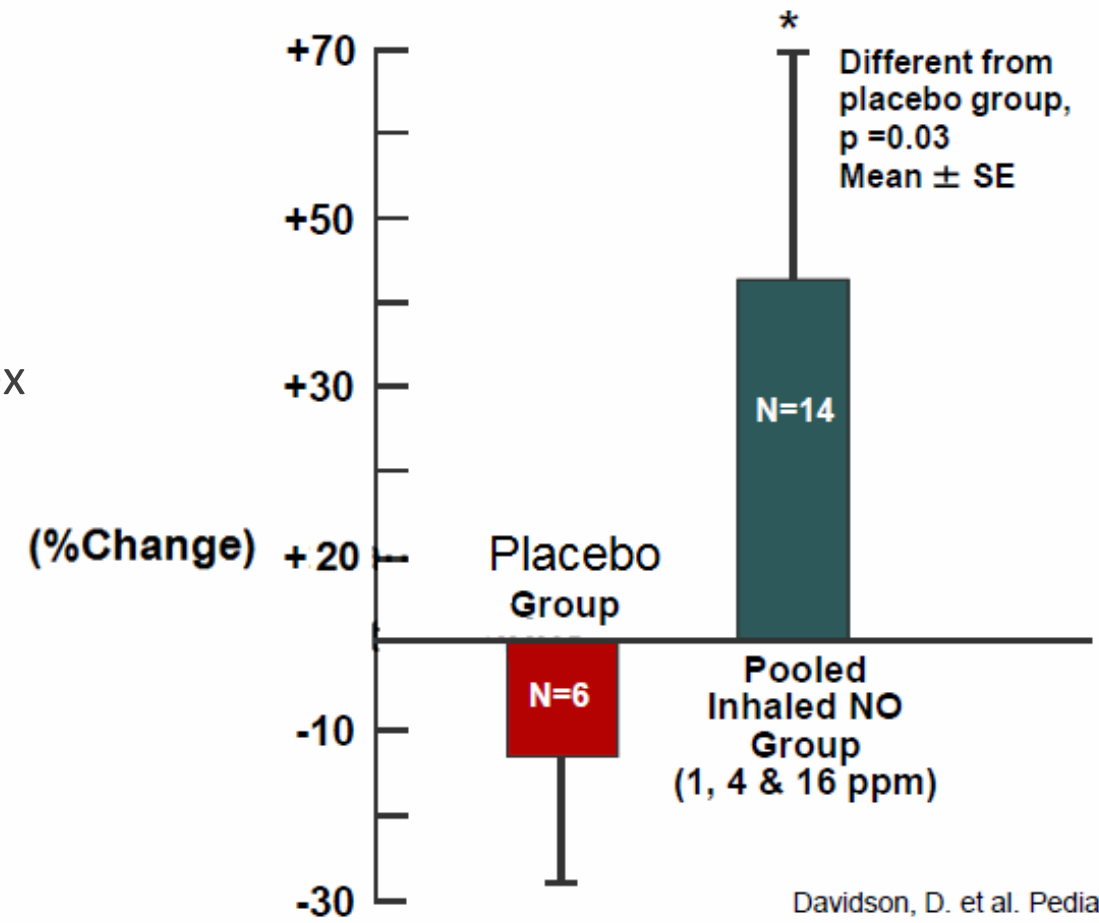
No Levels Before Stopping Treatment



Davidson, D. et al. Pediatrics 1999;104:231-236

Oxygenation Index

Oxygenation Index



Davidson, D. et al. Pediatrics 1999;104:231-236

Post Nitric Oxide Era

Post – INO Era

- Questionnaire to 220 neonatologists in Canada, Australia, New Zealand
- High Likelihood of using other treatments for PPHN

Practice	Response, *n* (%)
Other treatments for pulmonary hypertension	
Sildenafil oral (206)	166 (81)
Milrinone intravenous (204)	121 (59)
Prostacyclin intravenous (200)	110 (55)
Magnesium sulfate (195)	63 (32)
Sodium nitroprusside (190)	45 (24)
Vasopressin (195)	25 (13)
Prostacyclin inhaled (190)	25 (13)
Tolazoline (196)	27 (14)
Adenosine (191)	14 (7)
Levosimendan (191)	7 (4)

Shivananda, 2012

Use of Sildenafil in PPHN

- Sildenafil is a potent (highly specific) PDE5 inhibitor approved for treatment of pulmonary hypertension in adults.
- Effective in animal models of PPHN and may attenuate rebound pulmonary hypertension after withdrawal of NO.
- An intravenous form has recently become available and a phase 1 study has been completed.

Viagra used first time in the world successfully in severe PPHN Dr Rajiv and team June 2002

Viagra used to save lives of 2 new-born kids in AIMS

EXPRESS NEWS SERVICE

Kochi, June 22: In a major medical breakthrough, Viagra, currently used to treat erectile dysfunction, has been successfully used to save the lives of two new-born babies at Amrita Institute of Medical Sciences and Research Centre (AIMS), here.

After all methods to improve the blood levels of oxygen to acceptable levels failed, the team of doctors headed by Dr P K Rajiv, Head, Department of Newborn Intensive Care, AIMS, decided to use small doses of Viagra, also known by the name 'Sildenafil Citrate', along with nitric oxide to treat the babies.

Addressing a Press conference here along with A P S Krishnan, vice-president, AIMS, Dr Rajiv said there has been similar usage of viagra, coincidentally at the same time in Canada, as an alternative to nitric oxide to treat pulmonary hypertension, which results in extreme narrowing of the blood vessels supplying the lung causing severe breathing difficulty.

The babies showed a remarkable improvement after giving 0.3 to 0.5 mg/kg viagra dozage on them every eight hours.

"They could leave the hospital in five days," Dr Rajiv said adding that the viagra had helped in improving the blood levels of oxygen.

In the first case, a newborn baby girl Sunitha from Mavelikkara was brought to AIMS with severe breathing difficulties due to pneumonia and pulmonary hypertension.

As is the practice, the baby was put on conventional ventilation, which did not bring up the blood level of oxygen to a viable range compatible with life. By midnight, the baby was put on high frequency ventilation, which also did not improve the level of oxygenation significantly.

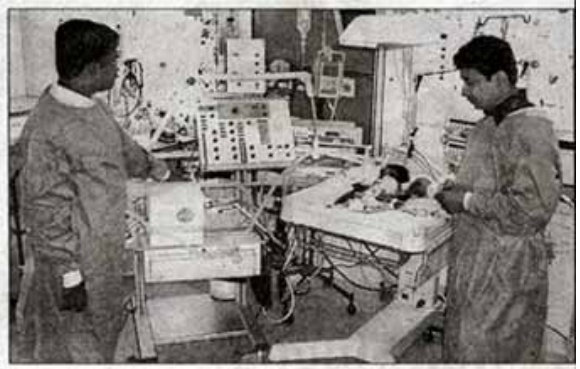
Dr Rajiv said the baby showed signs of severe respiratory failure and nitric oxide was infused through the ventilator. However, this also did not produce the desired results.

Finally, using the information received through the internet that Viagra had been successfully tried in the West on adults, the AIMS doctor gave the child small dosage of viagra, which produced dramatic results and the baby was discharged from the hospitals after five days of treatment.

In the second case, another baby girl Dhanya was cured of a severe pulmonary hypertension with Viagra alone, as against the first case where nitric oxide was also given.

In this case, the baby was also administered small doses of Viagra orally along with nitric oxide. "However, the nitric oxide therapy had to be stopped due to equipment problem.

Two to three doses of Viagra were given to the baby and her condition improved," Dr Rajiv explained adding that this showed that the discontinuation of nitric oxide did not lead to any deterioration in the baby's oxygenation.

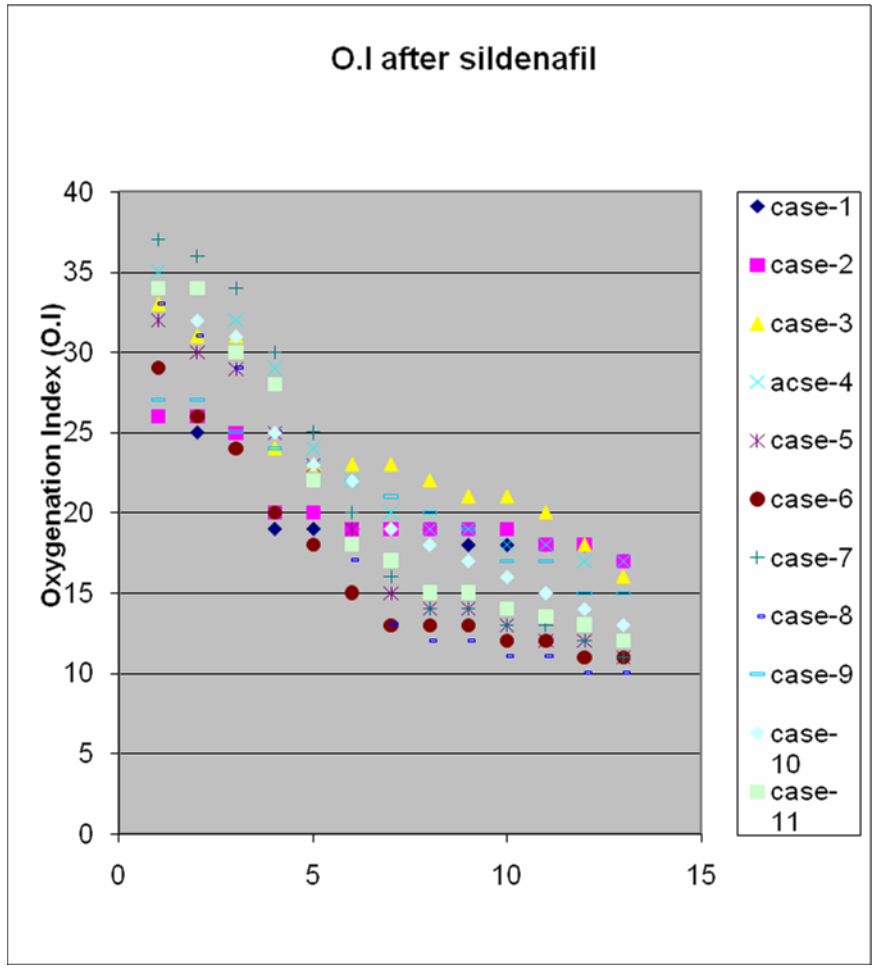


Dr Rajiv (right), head of the department of Newborn Intensive Care, AIMS, Kochi, and a colleague monitor a baby who was successfully treated for severe pulmonary hypertension using small dosage of viagra, at the intensive care unit.

Dr Rajiv said there has been similar usage of viagra, coincidentally at the same time in Canada, as an alternative to nitric oxide, to treat pulmonary hypertension, which results in narrowing of the blood vessels supplying the lung

Viagra on Pulmonary Hypertension

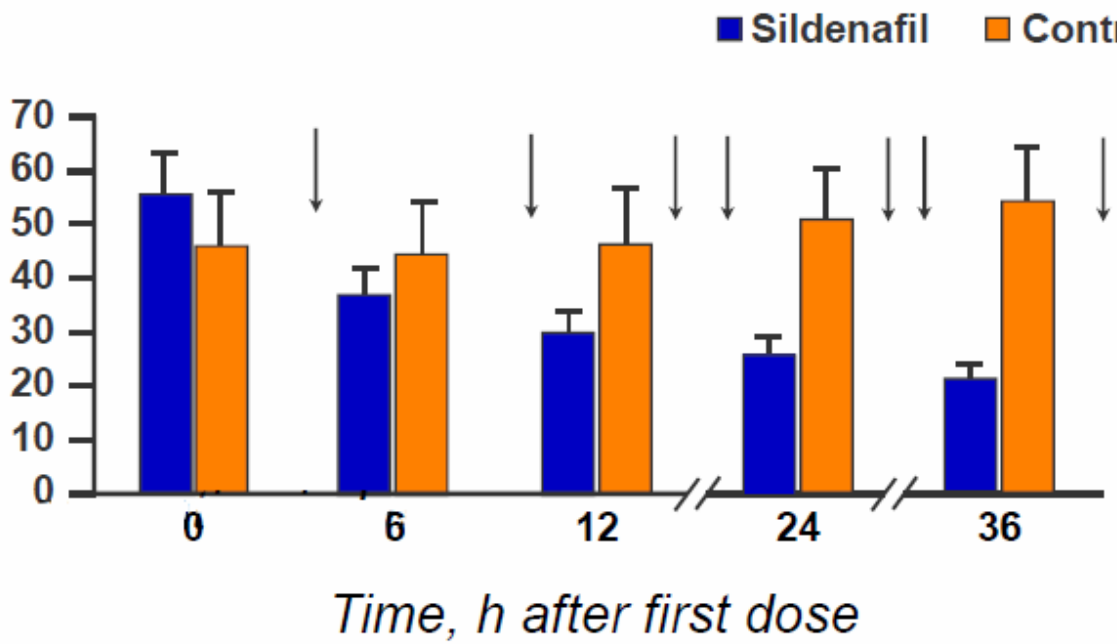
Hour of age after sildenafil	0hr	6hr	12 hr	18hr
case-1	29	25	24	19
case-2	26	26	25	20
case-3	33	31	31	24
acse-4	35	34	32	29
case-5	32	30	29	25
case-6	29	26	24	20
case-7	37	36	34	30
case-8	33	31	29	25
case-9	27	27	25	24
case-10	34	32	31	25
case-11	34	34	30	28



Rajiv et al BMJ. june 2002

Oral Sildenafil Produced Significant Changes in OI

Oxygenation Index



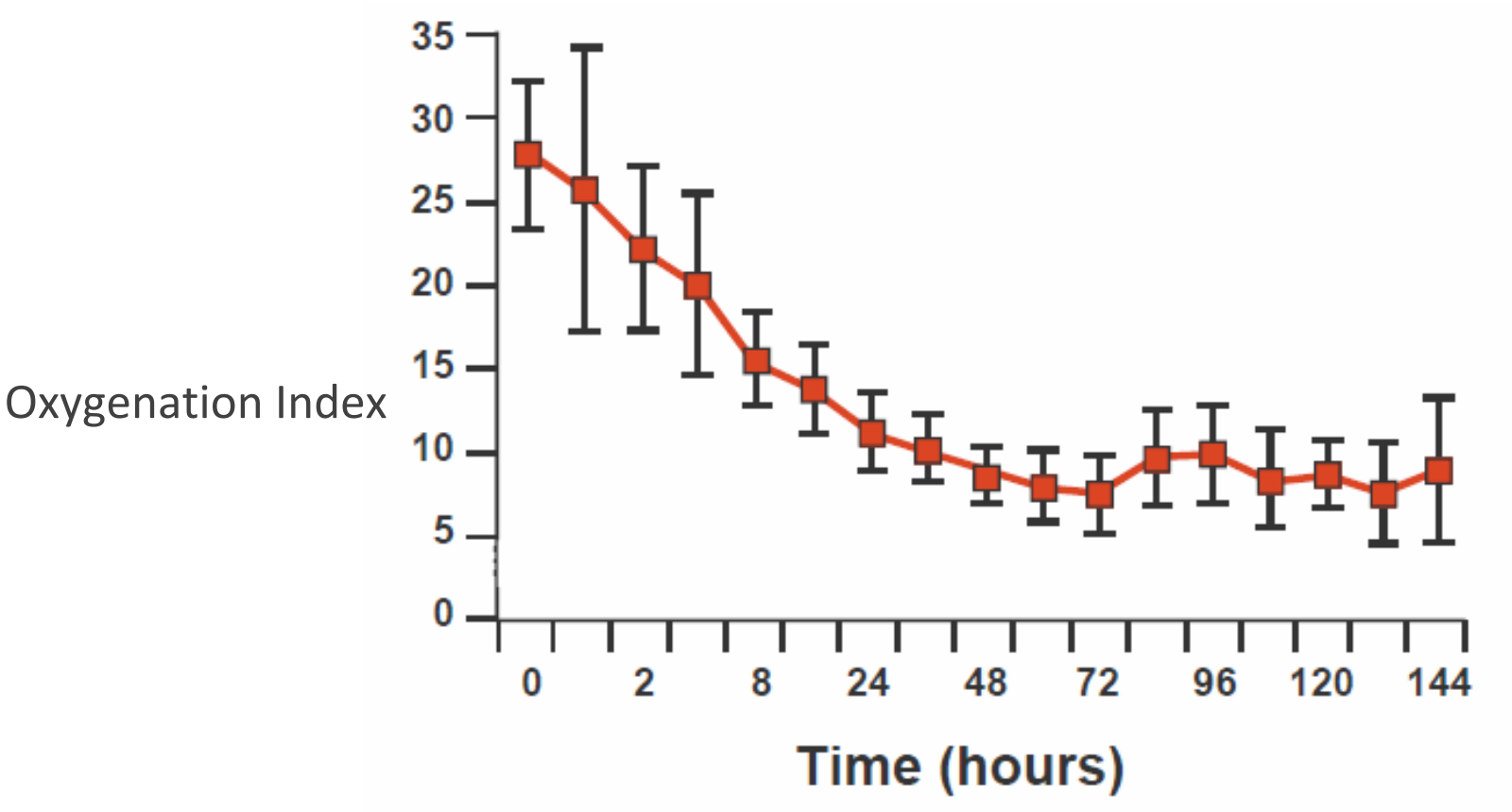
Randomized blinded trial in infants > 35.5 weeks with severe PPHN

Baquero, H. et al. Pediatrics 2006;117:1077-1083

Intravenous Sildenafil in PPHN

- Five centers enrolled 36 neonates with PPHN or hypoxemic respiratory failure in eight "step-up" treatment groups.
- Mean gestational age 39 ± 2 weeks, mean weight 3.44 ± .51 kg and age of enrollment 34 ± 17 hours
- 29/36 infants were already receiving NO

Oxygenation Index Over Time with Intravenous Sildenafil



Intravenous Sildenafil

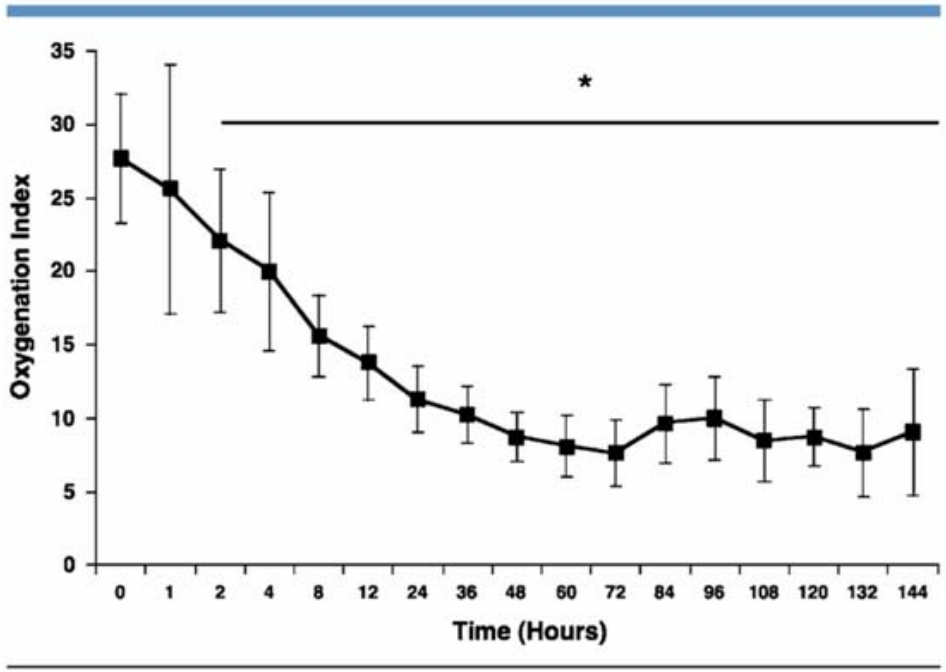


Figure 1. OI over time. For the entire group of infants (n = 36), mean OI before the initiation of sildenafil was 27.7 ± 4.2. OI improved significantly over the initial 24 hours of sildenafil infusion (11.3 ± 2.3; $P < .0001$, based on 34 remaining observations at 24 hours), and improvements were sustained over the course of therapy. By 144 hours, only 5 infants were still receiving sildenafil.

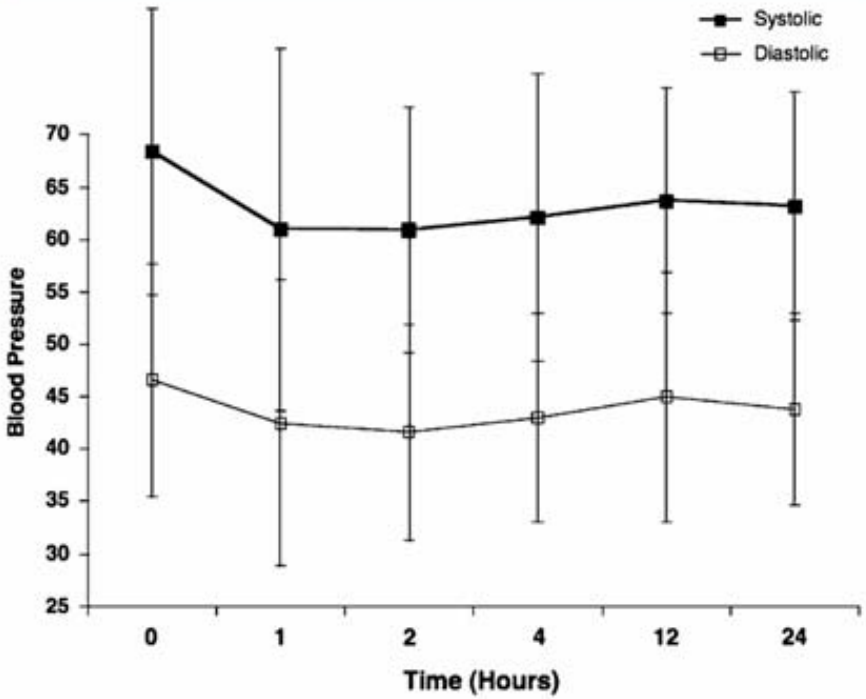


Figure 2. Blood pressure over time. For the entire group of infants (n = 36), systolic blood pressure before the initiation of sildenafil was 68.4 ± 13.7 mm Hg, and diastolic blood pressure was 46.6 ± 11.2 mm Hg. Two infants were excluded from analysis due to discontinuation of sildenafil and cannulation for ECMO. No significant change in systolic or diastolic blood pressure was observed in the remaining infants after initiation of sildenafil.

Intravenous Sildenafil in PPHN

Table II. Sildenafil treatment groups and levels after the loading infusion and 24hours of maintenance infusion

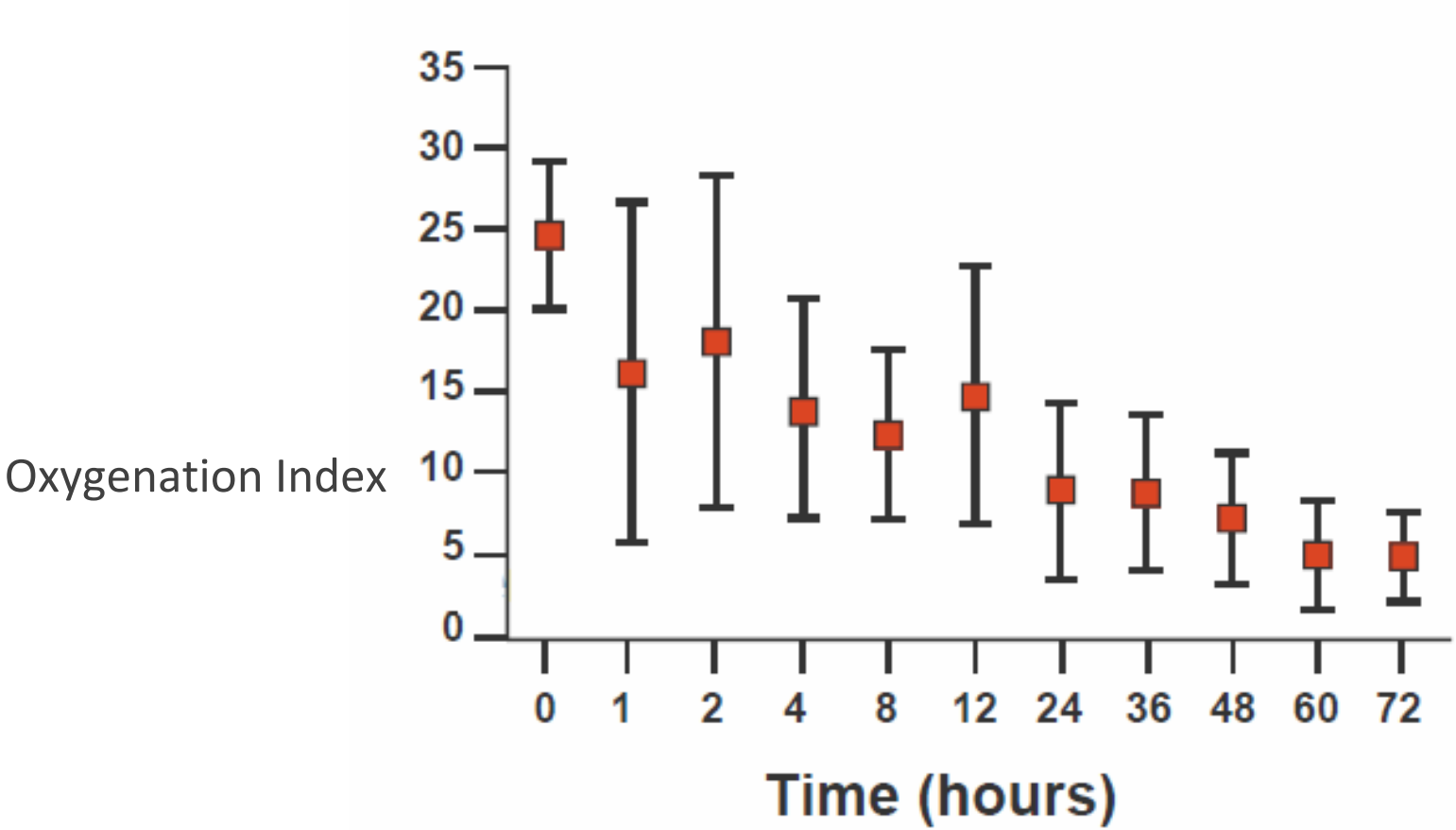
	Loading dose			Maintenance dose		
Treatment group	**mg/kg**	**Duration, hours**	**Blood level, ng/mL**	**mg/hour**	**mg/kg/day**	**Blood level, ng/mL**
1 (n = 2)	0.008 ± 0.005	0.03-0.08	2.28 ± 0.92	0.01	0.07	15.2
2 (n = 4)	0.011 ± 0.0005	0.5	2.99 ± 4.82	0.01	0.08 ± 0.003	6.95 ± 2.56
3 (n = 4)	0.027 ± 0.0029	0.5	4.15 ± 5.70	0.025	0.18 ± 0.017	22.69 ± 12.43
4 (n = 6)	0.056 ± 0.006	0.5	13.44 ± 7.51	0.06	0.36 ± 0.034	33.68 ± 23.24
5 (n = 5)	0.117 ± 0.014	0.5	47.36 ± 23.09	0.12	0.75 ± 0.079	73.45 ± 35.31
6 (n = 6)	0.243 ± 0.03	0.5-1	86.95 ± 25.47	0.22	1.59 ± 0.302	161.15 ± 49.8
7 (n = 5)	NA	NA	76.68 ± 38.5*	0.22	1.64 ± 0.230	101.4 ± 44.62
8 (n = 4)	0.427 ± 0.046	3	107.78 ± 37.03	0.22	1.64 ± 0.17	246.28 ± 177

NA indicates not applicable.
*Group 7 had no loading infusion; thus, the first level was obtained at 6 hours after the start of the maintenance infusion.

Steinhorn *(J Pediatr 2009;155:841-7)*.

Blood pressure did not drop abruptly if loading dose was given over 3 hours

Response to Sildenafil Infusion without iNO

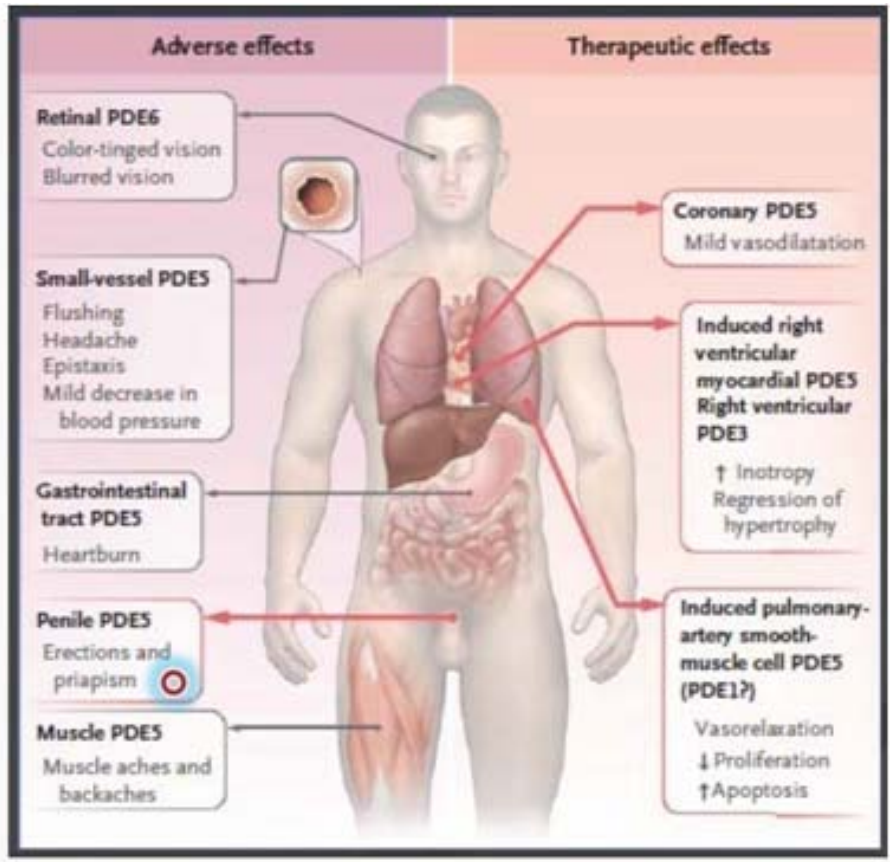


PDE 5 Inhibitor - Sildenafil

- In PPHN, sildenafil may:
  - facilitate weaning from INO
  - Decreases duration of mechanical ventilation, hospital stay
- Sildenafil in combination with:
  - INO did not result in significant ↓ in systemic BP & actually improved oxygenation
  - Milrinone (n=10) was not associated with hypotension or other adverse events

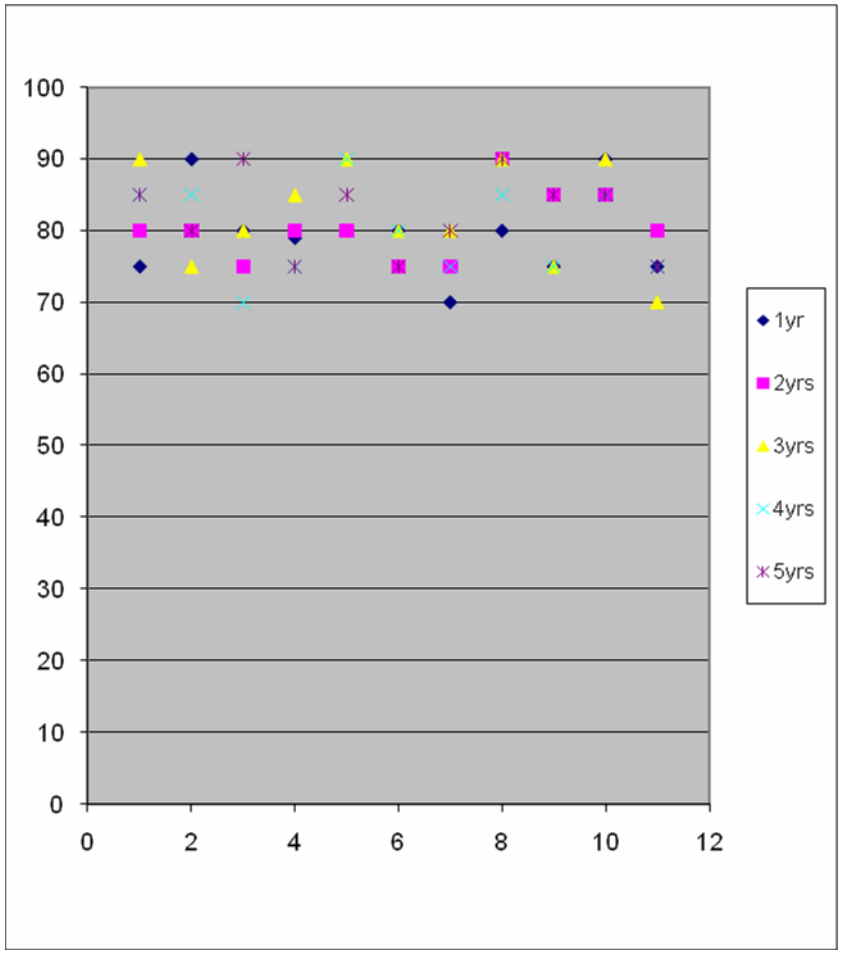
PDE – 5 Inhibitor - Sildenafil

- Potential AEs
  - delayed gastric emptying
  - hypotension
  - PDE6 inhibition - retinal damage
  - Severe ROP - one PT infant
  - Adults- CNS effects – emotional, psychological disturbances, amnesia, loss of consciousness, aggressive behavior, ICH



Viagra and HIE Follow up

Age in yrs	1yr	2yrs	3yrs	4yrs	5yrs
case-1	75	80	90	85	85
case-2	90	80	75	85	80
case-3	80	75	80	70	90
acse-4	79	80	85	75	75
case-5	80	80	90	90	85
case-6	80	75	80	80	75
case-7	70	75	80	75	80
case-8	80	90	90	85	90
case-9	75	85	75	75	85
case-10	90	85	90	85	85
case-11	75	80	70	75	75



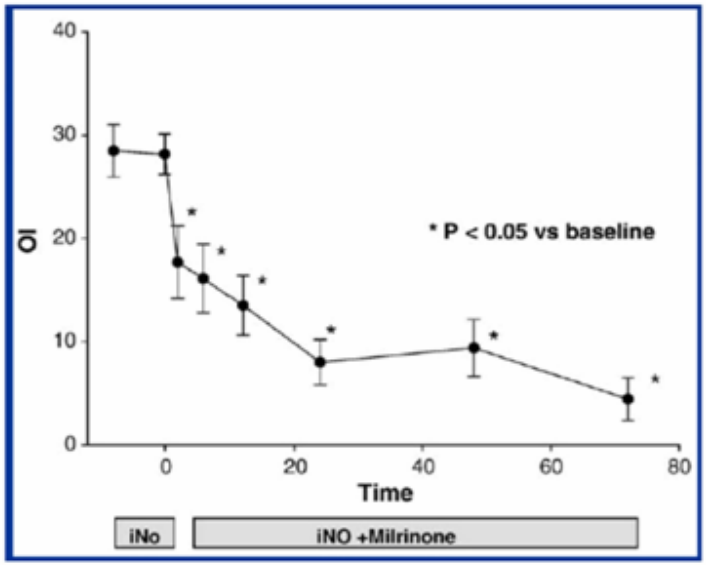
AWAITING PUBLICATION 2012

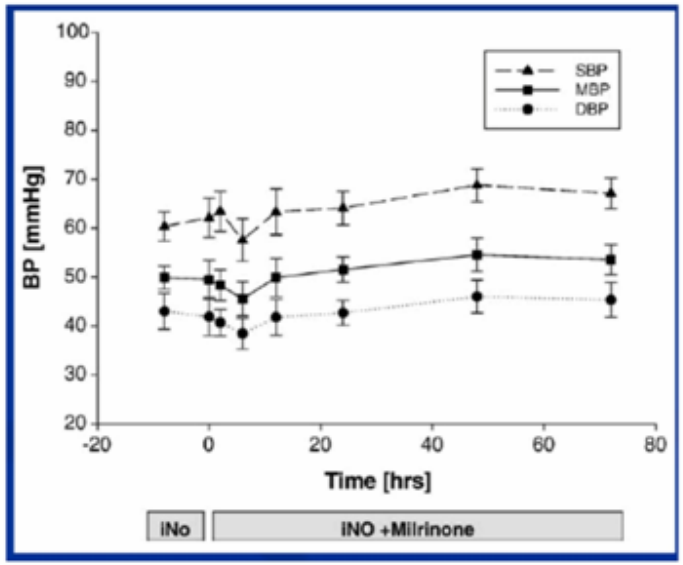
PDE – 3 Inhibitor - Milrinone

- Primary physiological disturbance in PPHN →↑ RV afterload
- Traditionally, physicians reluctant to treat PPHN with afterload-reducing agents because of concerns of systemic hypotension & desire to maintain supranormal systemic BP
  - very high-dose vasopressors
  - dopamine or epinephrine may exacerbate PPHN
  - tachycardia, ↑ increasing myocardial O2 demand,

McNamara, 2006, J Crit Care

Milrinone Improves Oxygenation in Severe PPHN



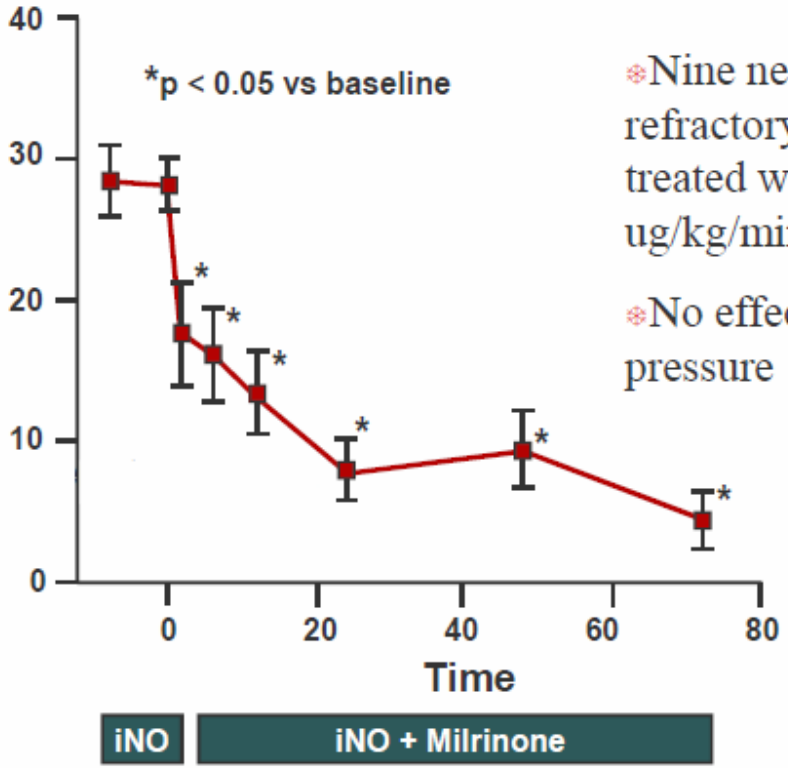


- Routes of administration reported - IV, inhalation
- Potential AEs:
  - Hypotension, thrombocytopenia, intra-cranial bleed

McNamara, 2006, J Crit Care

Milrinone Improves Oxygenation in newborns with Severe PPHN treated with Nitric Oxide

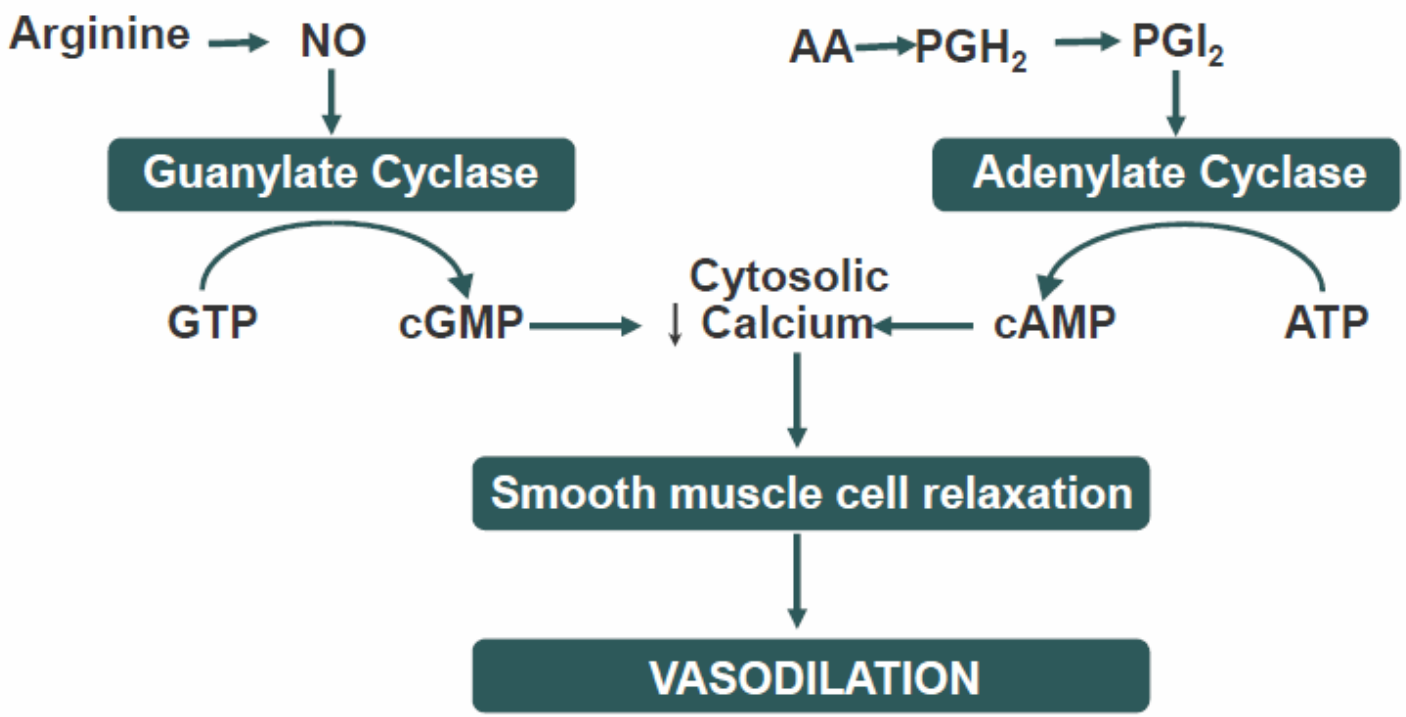
Oxygenation Index



- Nine neonates with PPHN refractory to NO were treated with Milrinone (0.33 ug/kg/min.
- No effect on blood pressure

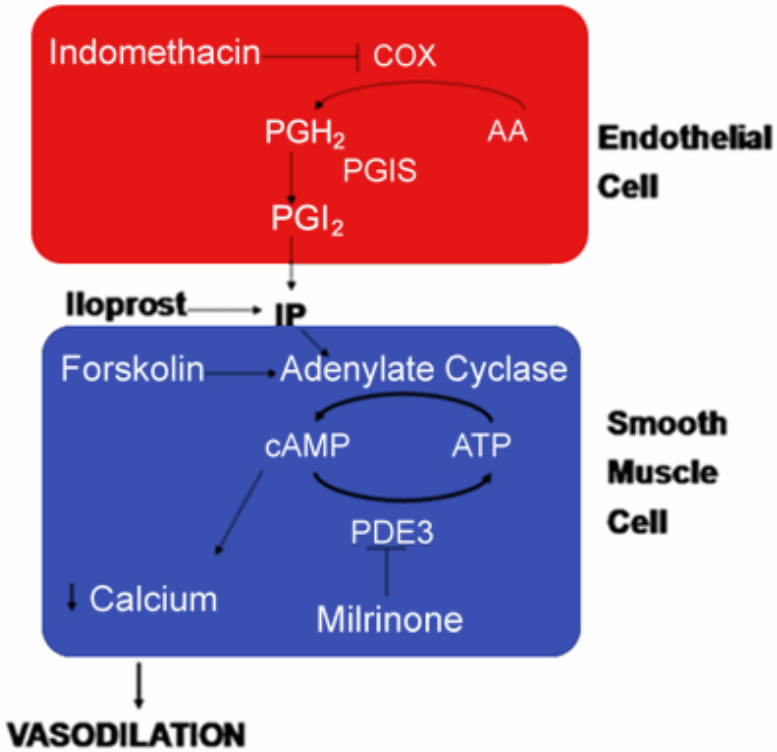
- *McNamara PJ et al Journal of Critical Care 21: 217-223, 2006*

Prostacyclin: Mechanism of Action



Steinhorn, R. H et al. Neoreviews 2007;8:e14-e21

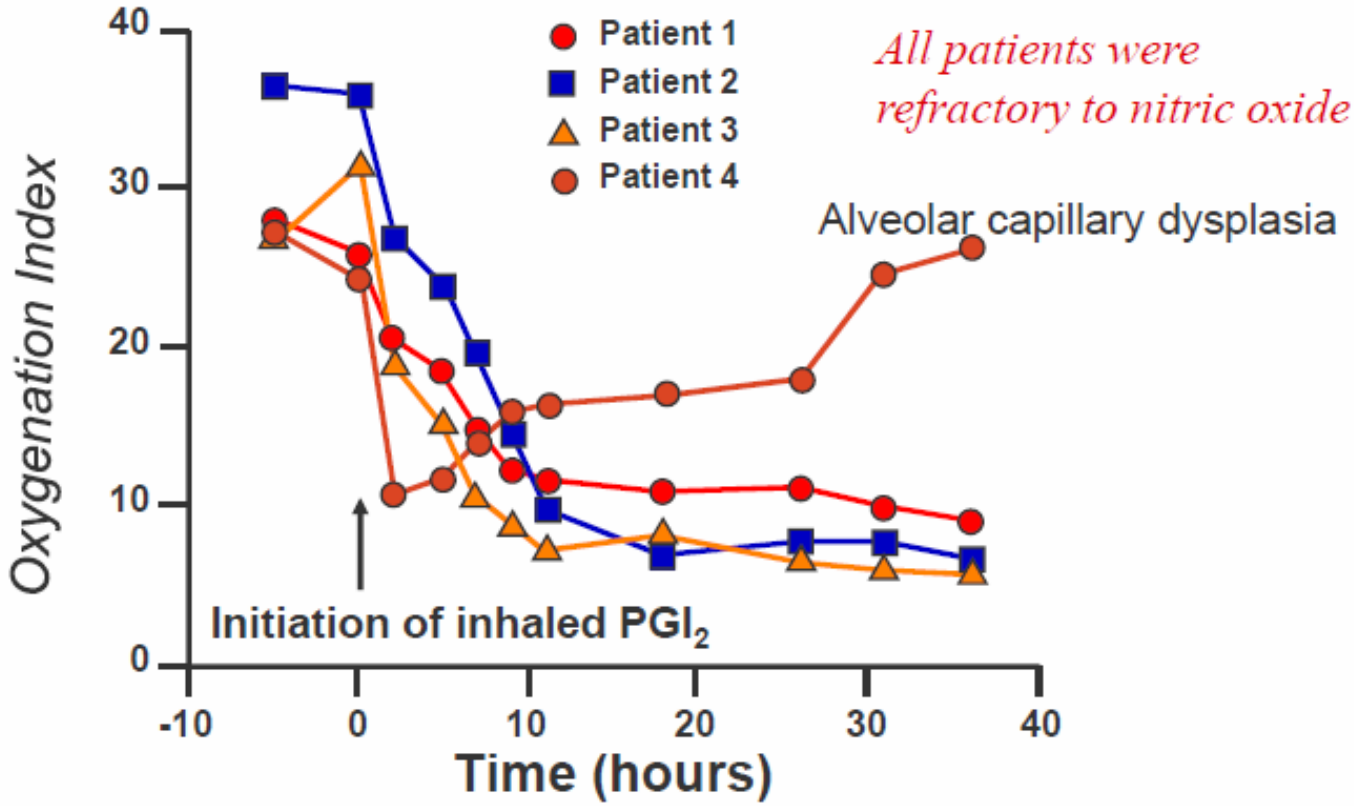
PPHN new modalities of treatment



Schematic showing the pathway for synthesis and mode of action of prostacyclin (PGI_2). Various agents used in this study are also shown in the figure. *COX*, cyclo-oxygenase; *AA*, arachidonic acid; PGH_2, prostaglandin H_2; *PGIS*, prostacyclin synthase; *IP*, prostacyclin receptor; *PDE3*, phosphodiesterase 3.

Lakshminrusimha et al. *Pediatr Crit Care Med*. 2009 September 10.

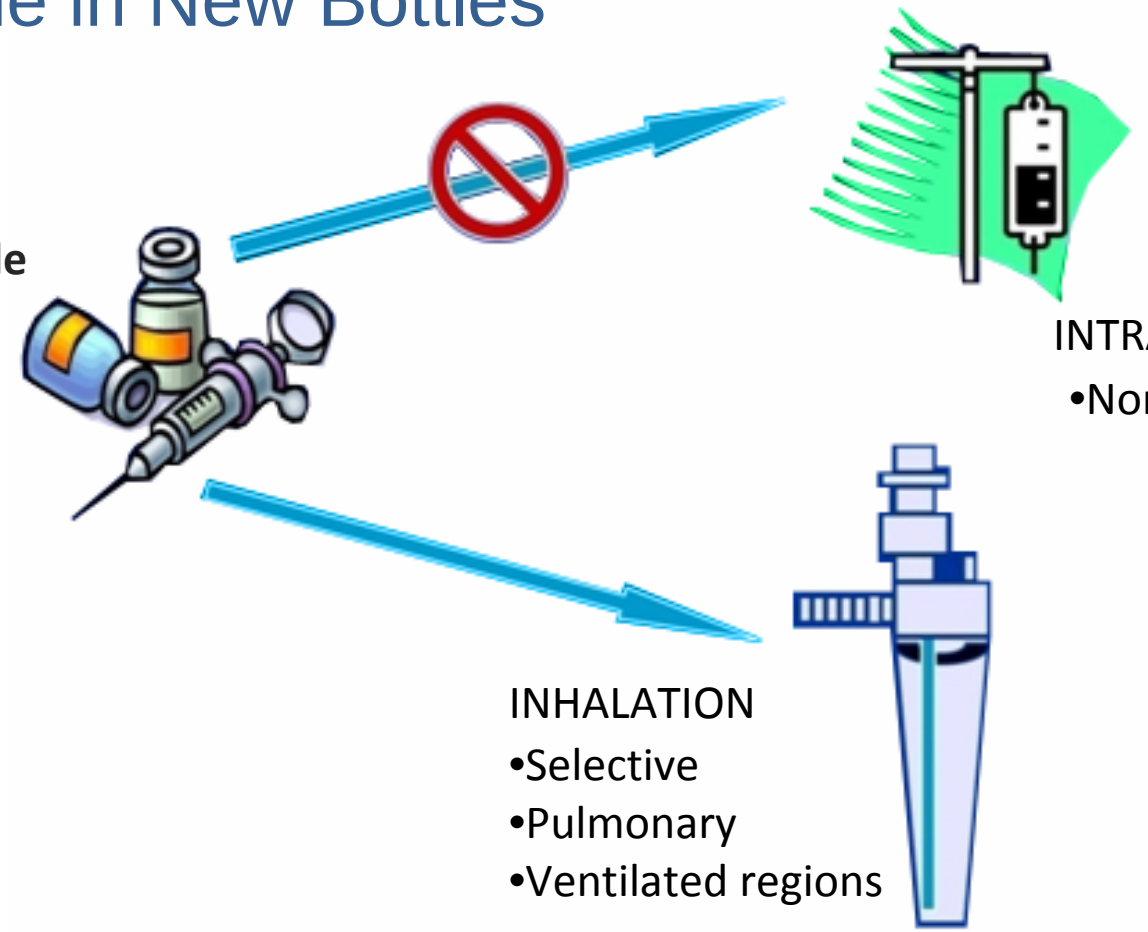
Use of Prostacyclin in PPHN



Kelly LK et al J Pediatr. 141: 830, 2002

Old Wine in New Bottles

PGE1
PGI2
Nitroprusside
Tolazoline
Sildenafil



INTRAVENOUS AGENTS
•Non selective

INHALATION
•Selective
•Pulmonary
•Ventilated regions

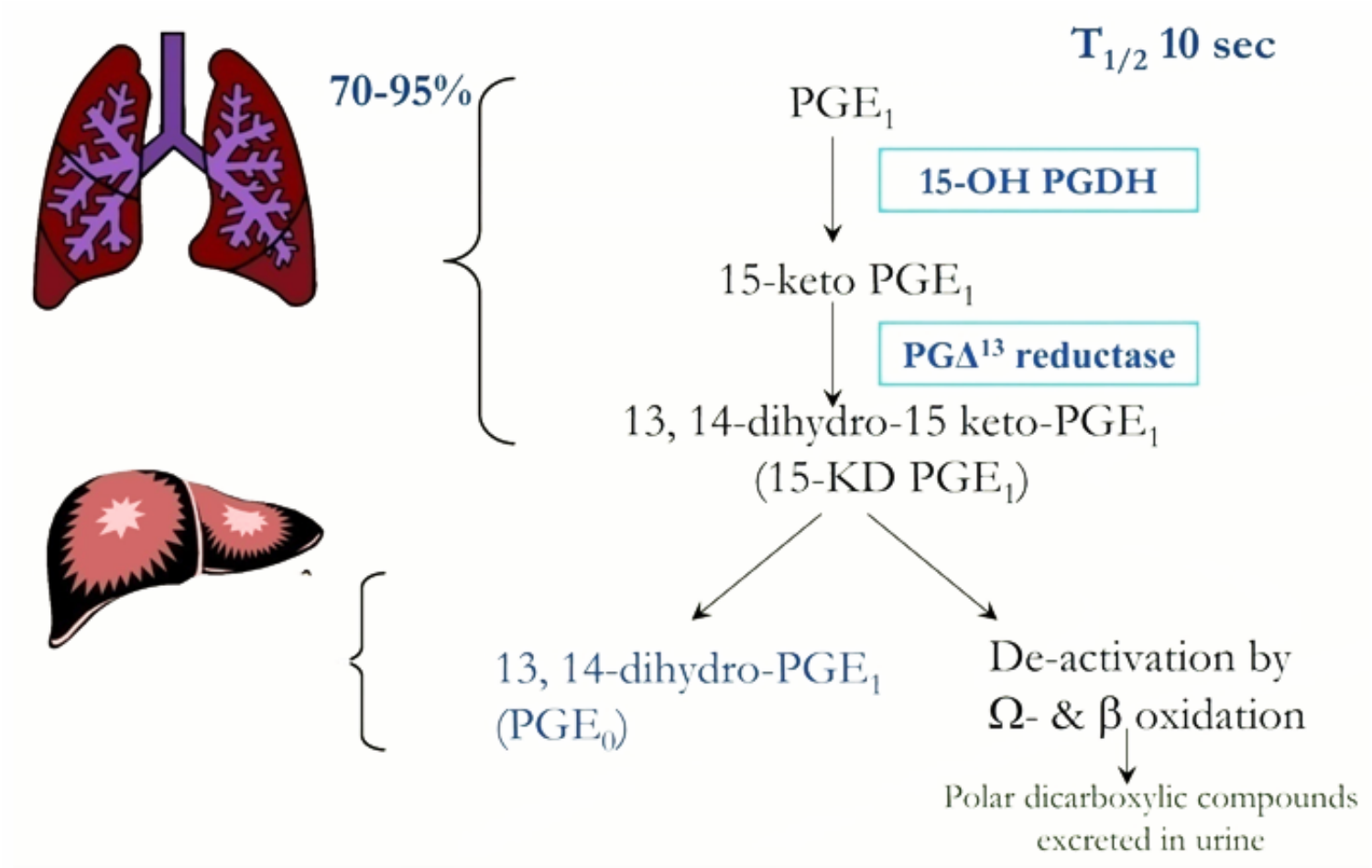
Adapted from Sood et al 2010

SPV – Inhaled Vasodilators

	INO	$IPGE_1$	$IPGI_2$
Inactivation	Pulmonary	Pulmonary	Hepatic
Half-life	seconds	<30 sec	2-3 min
Physical form	Gas	Aerosol	Aerosol
Buffer	--	Ethanol	Glycine
pKa	--	6.5	10.5
Other effects			
Platelet aggregation	Inhibitor	Inhibitor	Inhibitor
Bronchi	Dilator	Dilator	Constrictor ??
Inflammation	Anti	Anti	--
Proliferation	--	Anti	--
Cytotoxicity	✓	×	×

Adapted from Sood et al 2010

PGE 1 - Metabolism

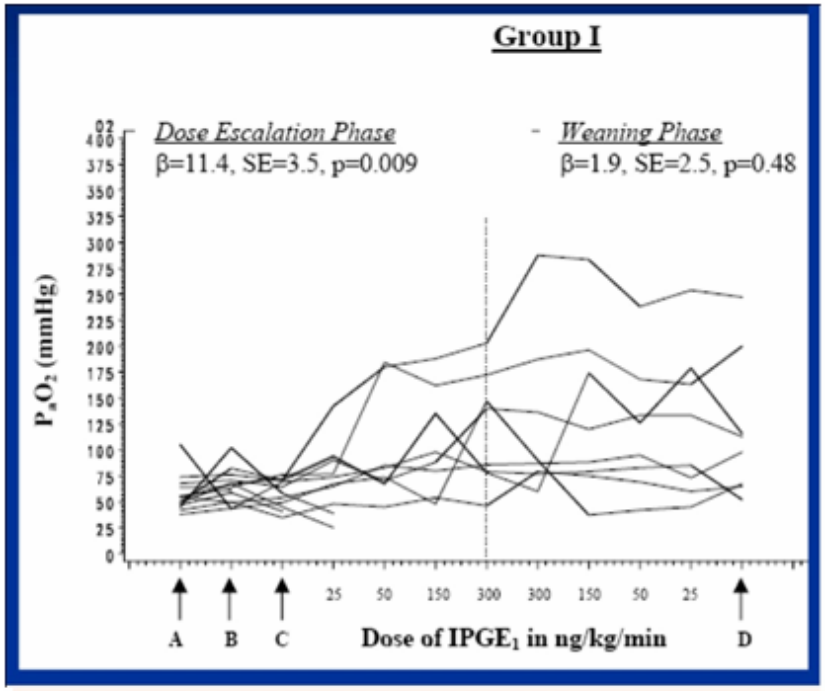


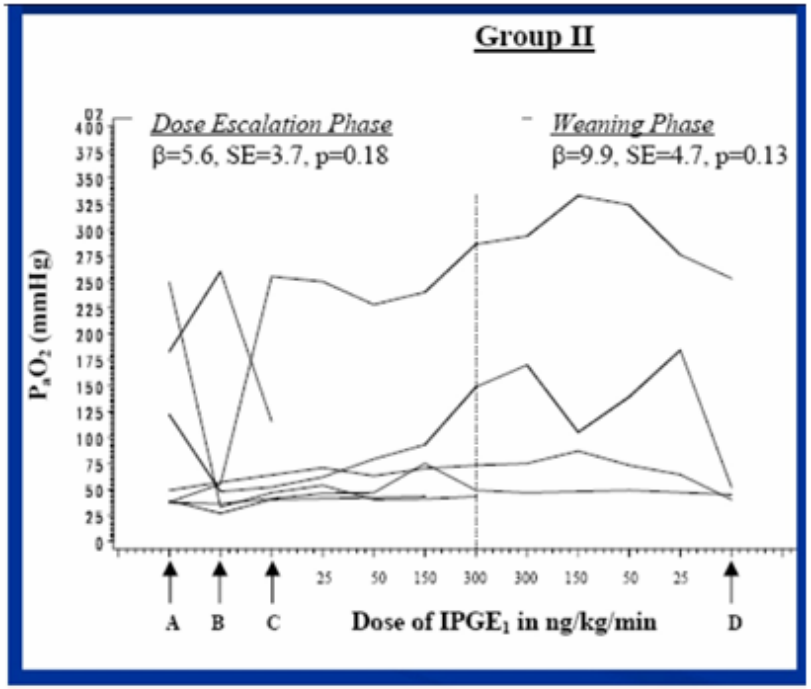
Phase I Clinical Trial of IPGE1 in NHRF

- $IPGE_1$ doses used
  - 25 ng/kg/min (Dose 1)
  - 50 ng/kg/min (Dose 2)
  - 150 ng/kg/min (Dose 3)
  - 300 ng/kg/min (Dose 4)
- Escalation phase (30 min each); Weaning phase (15 min each)
- Total duration – max 3 hours
- Two Groups of patients defined based on disease severity
  - Group I OI ≥ 20, pre-INO n=13
  - Group II refractory to INO n=7

Sood et al, *Ped Res*, 2004

Phase I Trial: Change in Pa O_2





Δ P_aO_2	64.4±71.6	0.038
Δ OI	-14.6±10.0	0.004

Δ P_aO_2	43.5±51.8	NS
OI	-9.0±11.9	NS

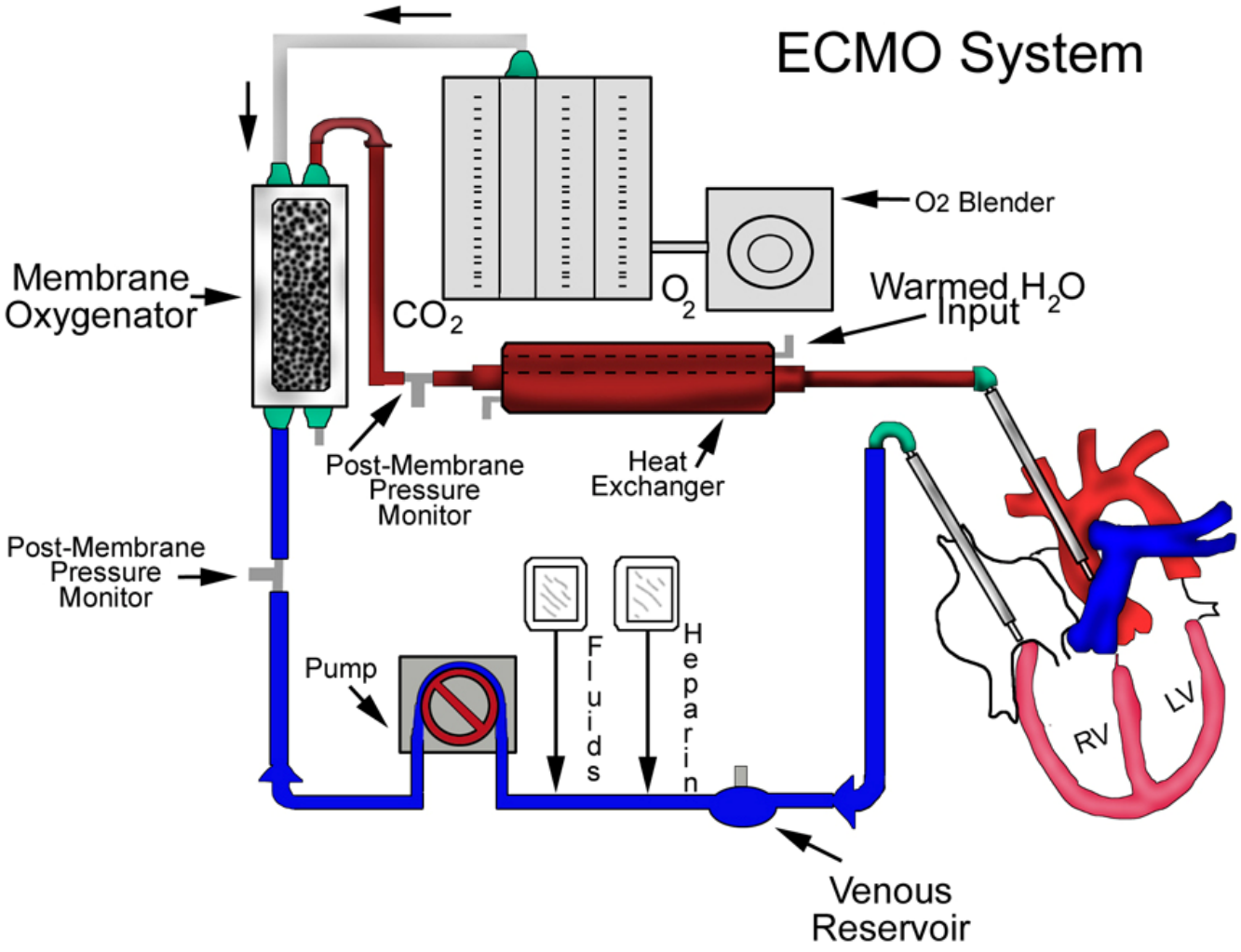
Sood et al, *Ped Res,* 2004

Phase I Trial: Dose Response

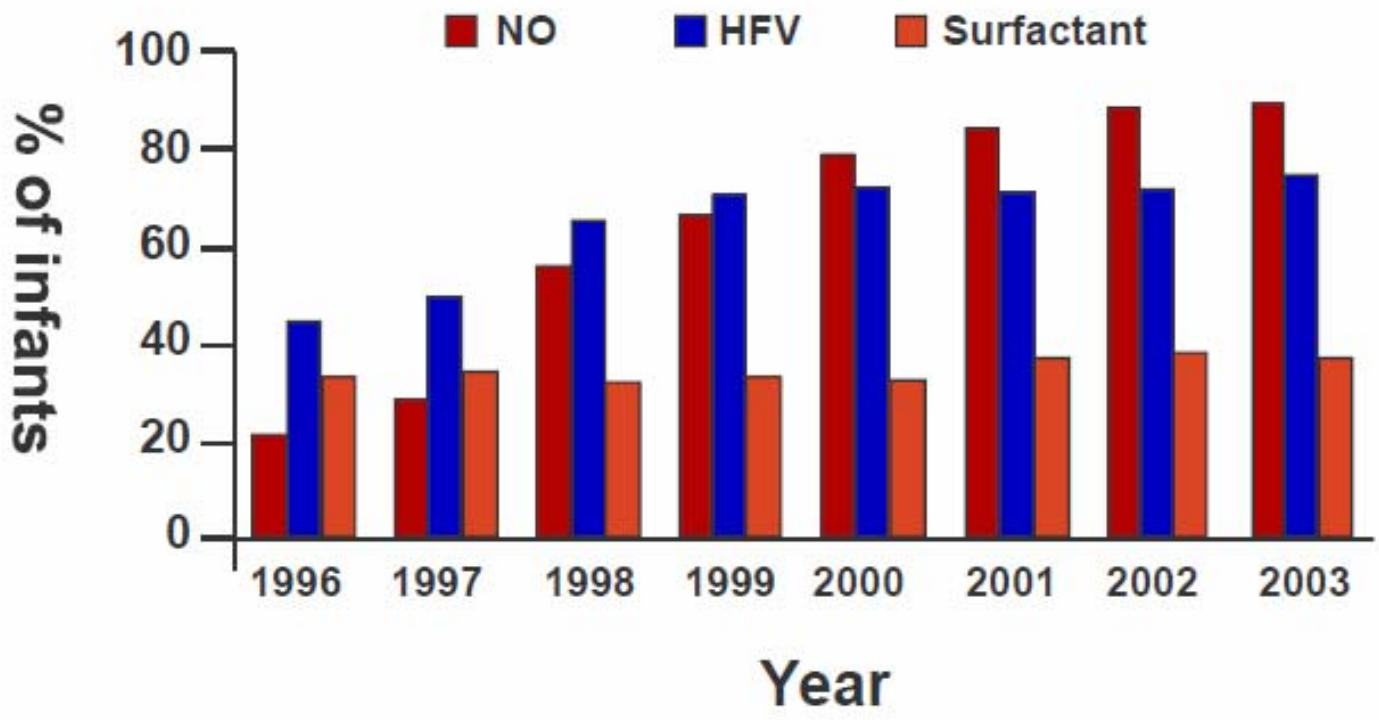
Dose ng/kg/min	Full Response (%)	
	Group I n=8	Group II n=4
25		
50	50	25
150	87.5	50
300	87.5	75
Weaning	100	75

The findings of this small unblinded study need to be validated in large-scale prospective randomized controlled trials

Sood et al, *Ped Res*, 2004

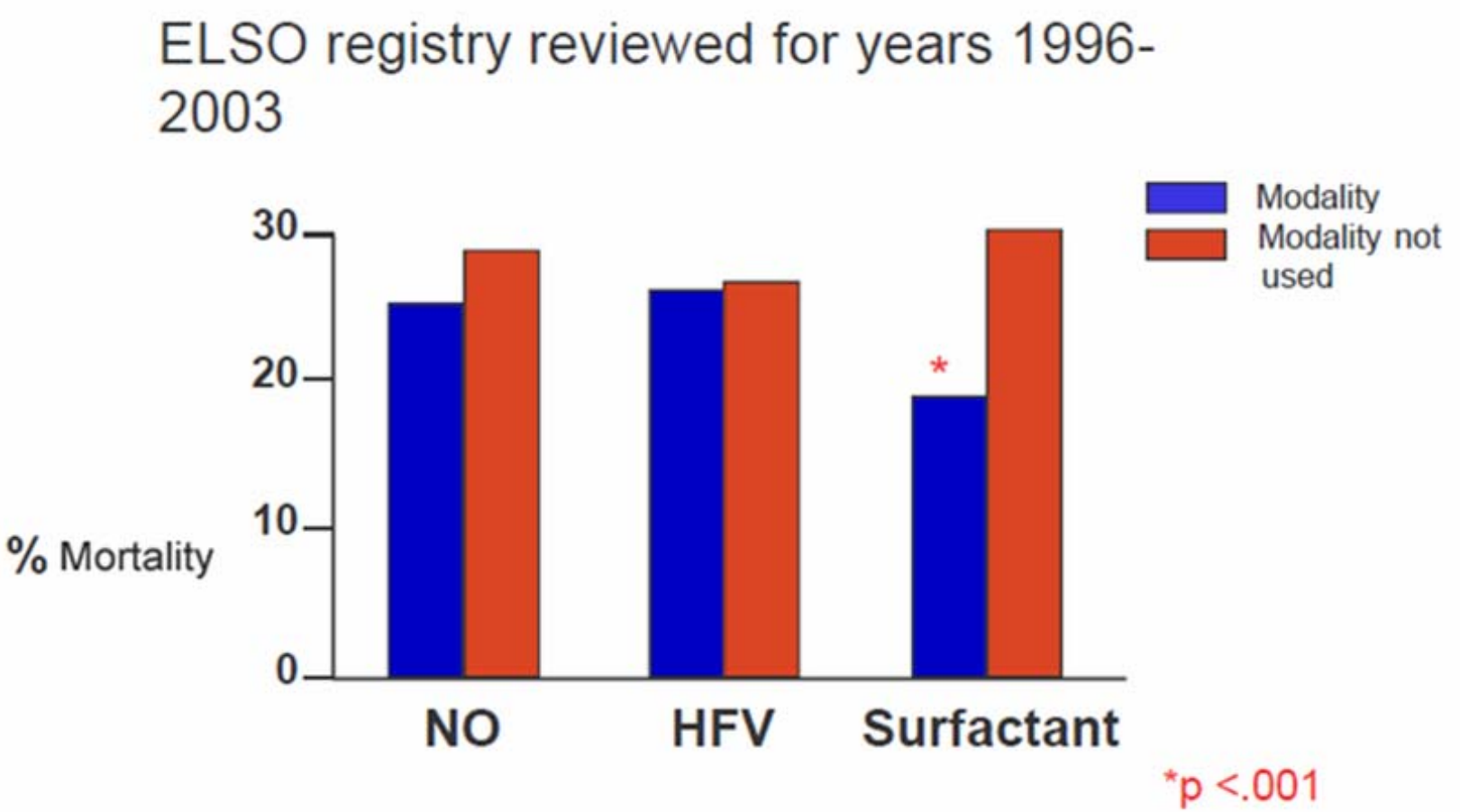

ECMO System
O2 Blender
Membrane Oxygenator
CO_2
O_2
Warmed H_2O Input
Post-Membrane Pressure Monitor
Heat Exchanger
Post-Membrane Pressure Monitor
Pump
Fluids
Heparin
RV
LV
Venous Reservoir

Therapies Prior to ECMO

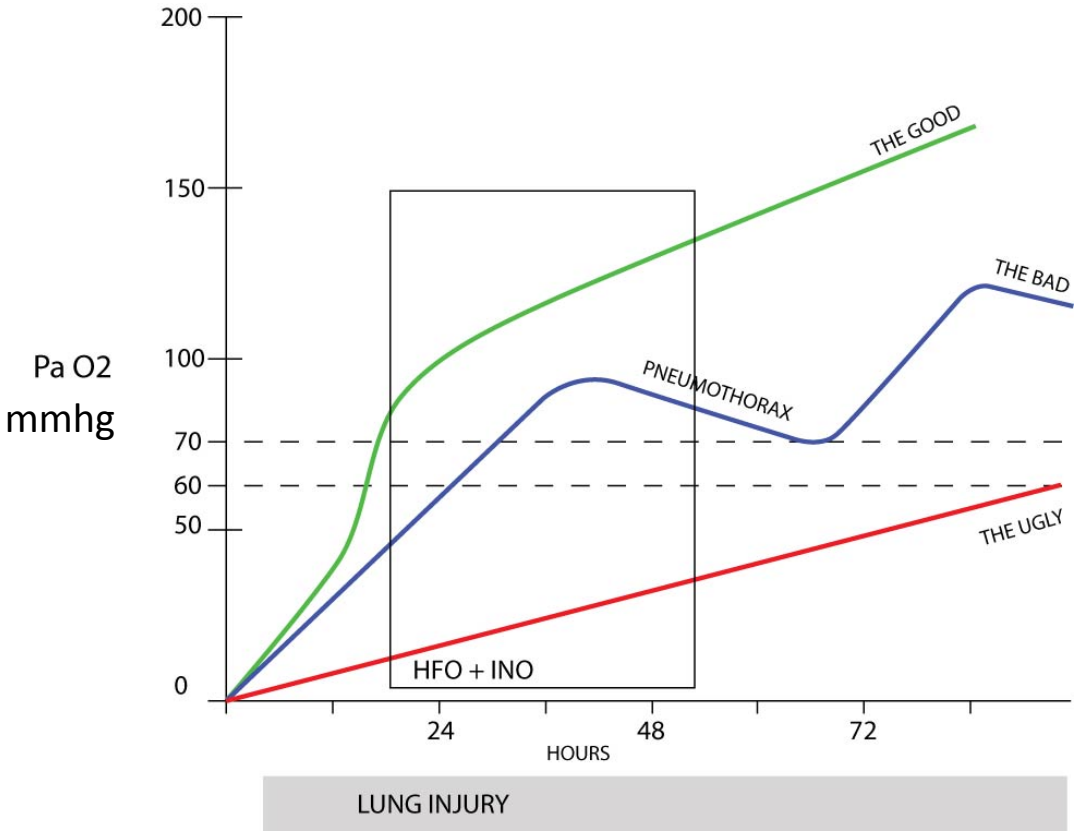


Fliman et al. *J Pediatr*. 2006

Effect of Therapy on ECMO Mortality

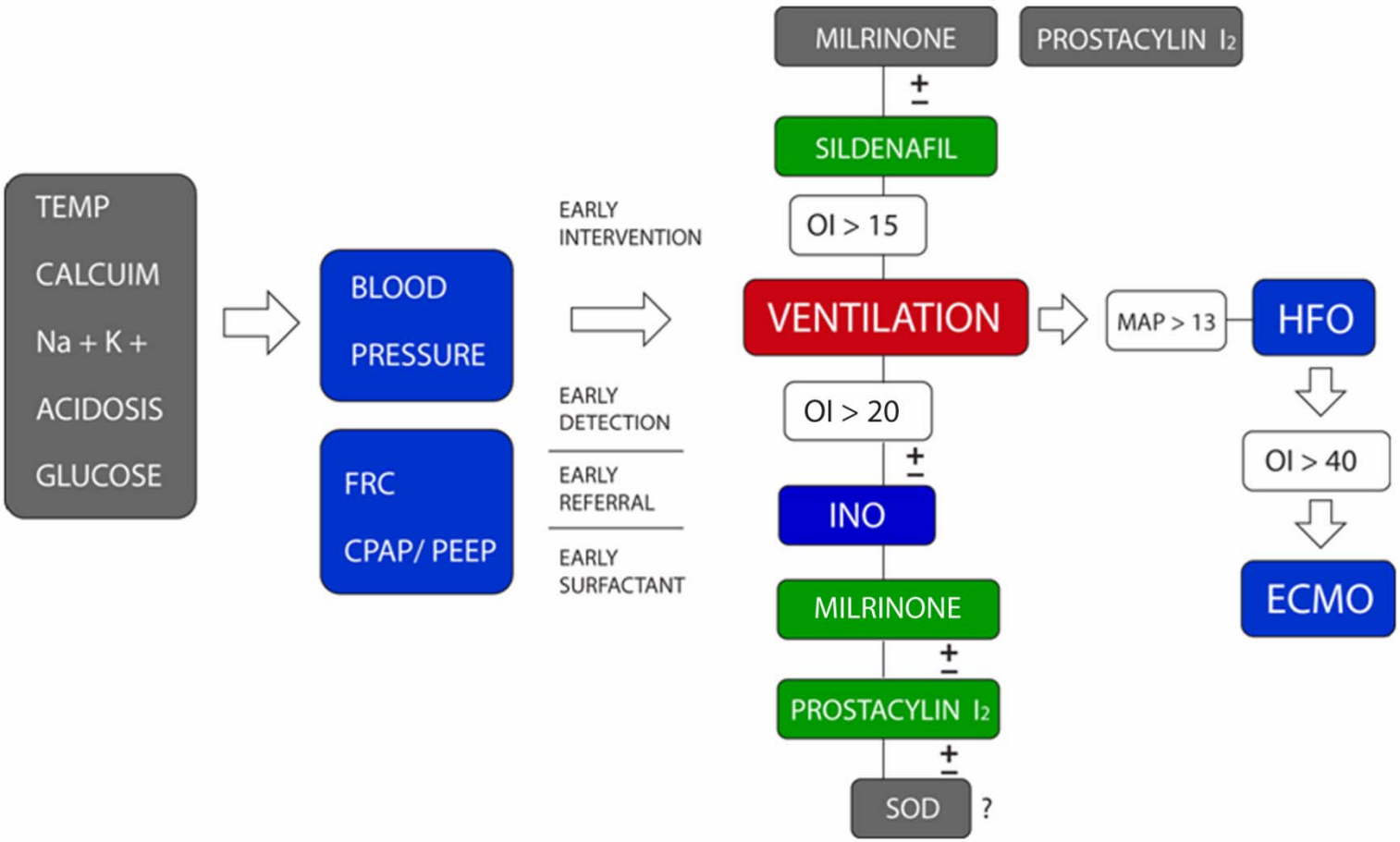


What did you do Rajiv



DON'T USE REMOTE CONTROL
DON'T CHANGE PEEP INADVERTENTLY
AVOID PEEP PHOBIA
Keep Ph > 7.25
KEEP PaO2 > 50 – 70 mmhg
Keep Paco2 < 55 mmhg target paco2 40 -45 mmhg
Tidal volume 4 -5 ml / kg
Reduce Fio2 at earliest signs of pao2 stability
Use pulmonary mechanics judiciously.

Alogarithmic Approach to PPHN



PPHN new modalities of treatment

Recommendations for Treatment of Neonatal Pulmonary Hypertension

Pulmonary Vasodilators:

Inhaled Nitric Oxide:

Inhaled Nitric Oxide should be initiated at 20 ppm for neonates with PPHN or hypoxemic respiratory failure when the oxygenation index exceeds 25. (Class I, Level A)

Sildenafil:

Limited evidence suggests that sildenafil may produce selective vasodilation in infants with PPHN. (Class IIb, Level B)

Other Supportive Modalities

Extracorporeal Life Support (ECLS or ECMO):

Cannulation for ECMO support should be considered for term and near-term neonates with pulmonary hypertension and/or hypoxemia that remains refractory to iNO after optimization of respiratory and cardiac function. (Class I, Level A)

High Frequency Ventilation:

In neonates with parenchymal lung disease (eg, meconium aspiration syndrome, respiratory distress syndrome, pneumonia), high frequency ventilation is often useful to promote lung expansion and enhance the effect of inhaled nitric oxide in infants. (Class IIa, Level B)

Surfactant:

Administration of surfactant may promote lung expansion and reverse surfactant inactivation associated with parenchymal lung disease. (Class IIa, Level A).

Alkalosis:

Alkalosis induced by hypocarbia or infusions of alkali may result in transient improved oxygenation. However, this practice is not recommended because of the lack of demonstrated benefit, and the potential for lung and cerebral injury. (Class III, Level B).

Steinhorn *Pediatr Crit Care Med.* 2011 March 1.

Emerging Therapies for Treatment of PPHN

Emerging Therapies for Treatment of PPHN

Enhancers of NOS Activity
Direct soluble guanylate cyclase activators
Phosphodiesterase inhibitors
Prostacyclin analogues
Rho-kinase inhibitors
Antioxidants

Steinhorn *Pediatr Crit Care Med*. 2011 March 1.

Conclusions

- PPHN is a abnormal physiologic response to diverse causes; treatment of the underlying disorder and correction of hemodynamic derangements are critical.
- Nitric oxide is effective in many infants, but ought to be reserved for infants with extreme lability or an inability to oxygenate ($PaO_2 \geq 50$ mmHg) or an OI (oxygenation index) ≥ 25.
- In infants with parenchymal disease, atelectasis should be corrected (with HFOV) if necessary. (overdistention should be avoided)
- NO should we weaned gradually when the inhaled concentration is < 5 ppm.

Anticipation Balance Strategy Skill God