Persistent Pulmonary Hypertension in Newborn
Recent Advances in Management

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

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

- Hypoxemia
  - Venous Admixture
  - Increased R→L Shunting at the Foramen Ovale and Ductus Arteriosus
  - Reduced Pulmonary Blood Flow ($\downarrow Q_c$)
- Pulmonary Vasoconstriction
  - Increased Pulmonary Vascular Resistance

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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
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PPHN: A Clinical Syndrome

- MAS 30%
- PPHN@ 16%
- RDS 20%
- CDH 16%
- Pneumonia 10%
- Other * 8%

@ = 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)
- **H**yaline 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 (SSRIs)
- 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 ductus 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

Lung growth and increase in pulmonary vasculature (lower incidence of PPHN in preterm?)

Normal Fetus

- Placenta
- Pulmonary venous $\text{PO}_2$
  - 17-19 mmHg
- Pulmonary arterial $\text{PO}_2$
  - 17-19 mmHg
- Fluid in alveoli
- Low alveolar oxygen (17 mmHg)
- Constricted blood vessels
  - (high pulmonary vascular resistance (PVR))

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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

- Entry of air into the alveoli
- Increased alveolar oxygen (100-150 mmHg)
- Pulmonary arterial PO₂ 40 mmHg
- Pulmonary venous PO₂ 100 mmHg
- Dilated blood vessels (reduced PVR)

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Pulmonary Vascular Resistance Falls at the Time of Birth

- Lungs are inflated with air (reabsorption of fluid)
- \( \text{PaO}_2 \) increases, pH increases and \( \text{PaCO}_2 \) falls
- Activity of vasoconstrictors decreases.

- Increased pulmonary blood flow increases \textit{sheer stress} and distends the vasculature → \textit{flattening of the endothelium}, thinning of the smooth muscle cells and matrix

- \textit{Endogenous dilators} (bradykinin, nitric oxide (NO), prostacyclin \( \text{PGI}_2 \), \( \text{PGD}_2 \) and histamine) \textit{are released} secondary to sheer stress and hyperoxia
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Resistance (mmHg x L⁻¹ x Kg x min)
- Systemic
- Pulmonary

Ventricular Output (ml/Kg/min)
- Left
- Ductal Shunt
- Right (Systemic flow)

Babies with Shunts
100% - 79% - 71% - 10% L → R
13% - 27% - 0% - 0% R → L

Age
- Birth
- 2-6
- 6-12
- 12-25
- 25-54 (hrs)

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

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Fig. 1. Mechanism of endothelium-dependent pulmonary vasodilation at birth. NO and prostacyclin (PGI₂) are released in response to birth-related stimuli. NO and PGI₂ 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 Ca²⁺ levels leads to relaxation of vascular smooth muscle. NO levels are decreased by asymmetric dimethyl arginine (ADMA), superoxide (O₂⁻), 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; PGI₂, PGI₂ 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
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PPHN new modalities of treatment

Nitric oxide (NO) and prostacyclin (PGI₂) 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. PGI₂ is an arachidonic acid (AA) metabolite formed by cyclooxygenase (COX-1) and prostacyclin synthase (PGIS) in the vascular endothelium. PGI₂ 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.


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PPHN new modalities of treatment

Schematic showing the pathway for synthesis and mode of action of prostacyclin (PGI₂). Various agents used in this study are also shown in the figure. COX, cyclo-oxygenase; AA, arachidonic acid; PGH₂, prostaglandin H₂; PGIS, prostacyclin synthase; IP, prostacyclin receptor; PDE3, phosphodiesterase 3.

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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.

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

Birth-related stimuli
\((O_2\) ventilation, shear stress)\n
Endothelial Cell

NO synthase

PPHN
\(-\) NO synthase
Soluble guanylate cyclase

Type 5 PDE

(\(O_2\))

Soluble guanylate cyclase

Impaired vasodilation

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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 (tetrahydrobiopterin- **BH4**) promote the coupling of eNOS with HSp90.
- Decreased interaction of eNOS with Hsp90 leads to formation of superoxide radical.

\[
\text{Nitric oxide} \quad \rightarrow \quad (\text{L-arginine + BH4}) + [\text{Hsp90 + eNOS}]
\]

\[
\text{Superoxide radical} \quad \rightarrow \quad \text{ONOO-} \quad \rightarrow \quad \text{constriction & hypertrophy of muscle}
\]
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
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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)
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 (AaDO₂) and Oxygenation Index (OI = 100 x MAP / PaO₂ x FiO₂)
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 deoxyhemoglobin 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
- $\text{PaO}_2$ unchanged = fixed shunt = CCHD
- Max $\text{PaO}_2 < 100 = \text{CCHD}$
- Max $\text{PaO}_2 > 200 = \text{No CCHD}$
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$_2$s
Hyperoxia Test

- Don’t do the room air part
  - Looking for minimal PaO₂ change from 21% to 100% fiO₂
  - Hyperoxia test developed pre pulse-ox
  - With pulse-ox you can tell when PaO₂s are not changing despite big changes in fiO₂ (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

- $\text{Fio}_2(\%) \times 4$ optimum $\text{pao}_{2}$

- $\text{Fio}_2(\%) \times 3$ acceptable $\text{pao}_{2}$ with shunt

- Any value of $\text{pao}_{2}$ 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 PaO₂

• Auscultation
  – S2, Murmur
Information Needed

- **CXR**
  - heart shapes
    - snowman = TAPVR₁
    - 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”

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 ($\Delta t_n$) by the systolic interval ($\Delta t_s$).

Gautam K. Singh, MD, Philip T. Levy, MD, Mark R. Holland, PhD, Aaron Harnas, MD
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 broncho-pulmonary 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

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

* P < .05 vs group 1.
** P < .01 vs group 1.

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.

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 PGE₁. The accuracy of a provisional diagnosis of CHD by transport team was 87.7% and the positive predictive value was 88.1%. Sixty neonates (58%) received PGE₁ appropriately. Eight neonates (12%) with duct-dependent CHD (n = 68) did not receive PGE₁ 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 PGE₁ and without any adverse effects.


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Management of Infants with Pulmonary Hypertension

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Control of Blood Pressure

Feel posterior tibial pulsation well

DOPAMINE 10
DOBUTAMINE 10
MILRINONE
Control of FRC

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

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Pulmonary Vasculature
- Structural changes, altered reactivity to dilator and constrictor stimuli

PVR & SVR
- Right-to-left shunting at PDA or PFO

HEART
- RV Pressure Overload, Hypotension & LV dysfunction

Hypoxia, hypercarbia, acidosis

LUNG
- ↓ Lung volume
- ↓ Compliance
- ↑ Intrapulmonary shunt

Kinsella J Pediatr. 1995
The Vicious Cycle of PPHN

Hypoxia/hypercarbia/acidosis/cold

Pulmonary vasoconstriction

Increased pulmonary vascular resistance

Right-to-left shunting of blood

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 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 NFκβ
Use of Surfactant in PPHN

Randomized clinical trial (n = 40) in MAS.
No nitric oxide

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


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

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The million dollar question of optimisation of PEEP
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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

Randomized Multicenter Trial of Inhaled No and High Frequency Oscillatory Ventilation in Severe PPHN
Guidelines for Arterial Blood Gases in PPHN

* Maintain arterial:

\[ \text{pH} \geq 7.30, \text{PaCO}_2 \, 40-45 \, \text{mm Hg} \, \& \, \text{PaO}_2 \, 50-80 \, \text{mm Hg} \]
Pulmonary Vascular Resistance & pH

Rudolph and Yuan JCI 1966
Neonatal Lambs

Change point – 50 ± 0.2 mmHg

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

Change Point $\sim 60 \pm 7$ mmHg

Oxygen Saturation and PVR

- As oxygenation is labile in PPHN/HRE, it is difficult to precisely maintain oxygen saturations in a specific range.
- Many clinicians “buffer” with higher PaO₂ to avoid episodes of hypoxemia.

Use of Supplemental Oxygen in PPHN

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

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Pulmonary Vascular Resistance

% Increase PVR

[Graph showing the relationship between PO$_2$ (mmHg) and pH on the y-axis and x-axis, respectively, with curves for different pH levels (7.1, 7.2, 7.3, 7.4).]
Changes in Pulmonary Vascular Resistance in Lambs Ventilated with 21% or 100% O₂

Changes in Pulmonary Vascular Resistance in Lambs PPHN Ventilated with 21%, 50% or 100% O₂

Changes in Pulmonary Vascular Resistance in Lambs
PPHN Ventilated with 21%, 50% or 100% O₂

Nitric Oxide and Superoxide Radical

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

Combinational effects of SOD and NO in lambs with PPHN

Regulation of Pulmonary Vascular Tone
Nitric Oxide
Persistent Pulmonary Hypertension in Newborn
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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 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. 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.

Response Rate by Diagnoses

Percent who responded

- **Responded with improved oxygenation**
- **Survived without ECMO**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Responded with improved oxygenation</th>
<th>Survived without ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>MAS</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>PN</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>PPHN</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>RDS</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>
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

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

Recent Advances in Management

## Comparison Inhaled NO vs Control, Outcome Death

<table>
<thead>
<tr>
<th>Study</th>
<th>iNO n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christou 2000</td>
<td>2/21</td>
<td>1/20</td>
<td></td>
<td>2.3</td>
<td>1.90 [0.19, 19.40]</td>
</tr>
<tr>
<td>Clark 2000</td>
<td>4/113</td>
<td>7/104</td>
<td></td>
<td>16.5</td>
<td>0.53 [0.16, 1.74]</td>
</tr>
<tr>
<td>Davidson 1997</td>
<td>9/114</td>
<td>1/41</td>
<td></td>
<td>3.3</td>
<td>3.27 [0.43, 24.98]</td>
</tr>
<tr>
<td>Ninos 1996</td>
<td>16/114</td>
<td>20/121</td>
<td></td>
<td>44.0</td>
<td>0.85 [0.46, 1.56]</td>
</tr>
<tr>
<td>Roberts 1996</td>
<td>2/30</td>
<td>2/28</td>
<td></td>
<td>4.7</td>
<td>0.93 [0.14, 6.18]</td>
</tr>
<tr>
<td>Wessell 1996</td>
<td>2/26</td>
<td>2/23</td>
<td></td>
<td>4.8</td>
<td>0.88 [0.14, 5.79]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>417</td>
<td>337</td>
<td></td>
<td>75.7</td>
<td>0.92 [0.58, 1.48]</td>
</tr>
</tbody>
</table>

Dr. P.K. Rajiv
Inhaled NO vs Control: Outcome Neurodevelopmental Disability at 18 to 24 Months Among survivors

<table>
<thead>
<tr>
<th>Study</th>
<th>iNO n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95%</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davidson 1997</td>
<td>5/35</td>
<td>22/94</td>
<td>0.61 [0.25, 1.49]</td>
<td>31.7</td>
<td></td>
</tr>
<tr>
<td>Ninos 1996</td>
<td>29/85</td>
<td>26/87</td>
<td>1.14 [0.74, 1.77]</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>120</td>
<td>181</td>
<td>0.97 [0.66, 1.44]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Total Events: 34 (NO), 48 (Control)

Test for heterogeneity, chi-square=1.57 df=1 p=0.21 P=36.2%

Test for overall effect z=0.14 p=0.9
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 FiO₂
* 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 ≤ 5 ppm
No Levels Before Stopping Treatment
Oxygenation Index

Different from placebo group, p = 0.03
Mean ± SE

Post Nitric Oxide Era
Post – INO Era

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

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

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 on Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Hour of age after sildenafil</th>
<th>0hr</th>
<th>6hr</th>
<th>12hr</th>
<th>18hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>case-1</td>
<td>29</td>
<td>25</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>case-2</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>case-3</td>
<td>33</td>
<td>31</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>case-4</td>
<td>35</td>
<td>34</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>case-5</td>
<td>32</td>
<td>30</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>case-6</td>
<td>29</td>
<td>26</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>case-7</td>
<td>37</td>
<td>36</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>case-8</td>
<td>33</td>
<td>31</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>case-9</td>
<td>27</td>
<td>27</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>case-10</td>
<td>34</td>
<td>32</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>case-11</td>
<td>34</td>
<td>34</td>
<td>30</td>
<td>28</td>
</tr>
</tbody>
</table>

Rajiv et al. BMJ. June 2002
Oral Sildenafil Produced Significant Changes in Oxygenation Index

*Time, h after first dose*

Randomized blinded trial in infants > 35.5 weeks with severe PPHN

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 $68.4 \pm 13.7$ mm Hg, and diastolic blood pressure was $46.6 \pm 11.2$ 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 24 hours of maintenance infusion

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>Duration, hours</td>
</tr>
<tr>
<td>1 (n = 2)</td>
<td>0.008 ± 0.005</td>
<td>0.03-0.08</td>
</tr>
<tr>
<td>2 (n = 4)</td>
<td>0.011 ± 0.0005</td>
<td>0.5</td>
</tr>
<tr>
<td>3 (n = 4)</td>
<td>0.027 ± 0.0029</td>
<td>0.5</td>
</tr>
<tr>
<td>4 (n = 6)</td>
<td>0.056 ± 0.006</td>
<td>0.5</td>
</tr>
<tr>
<td>5 (n = 5)</td>
<td>0.117 ± 0.014</td>
<td>0.5</td>
</tr>
<tr>
<td>6 (n = 6)</td>
<td>0.243 ± 0.03</td>
<td>0.5-1</td>
</tr>
<tr>
<td>7 (n = 5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8 (n = 4)</td>
<td><strong>0.427 ± 0.046</strong></td>
<td>3</td>
</tr>
</tbody>
</table>

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.


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

Adverse effects
- Retinal PDE6
  - Color-tinged vision
  - Blurred vision
- Small-vessel PDE5
  - flushing
  - Headache
  - Epistaxis
  - Mild decrease in blood pressure
- Gastrointestinal tract PDE5
  - Heartburn
- Penile PDE5
  - Erections and priapism
- Muscle PDE5
  - Muscle aches and backaches

Therapeutic effects
- Coronary PDE5
  - Mild vasodilatation
- Induced right ventricular myocardi al PDE5
- Right ventricular PDE5
  - ↑ Inotropy
  - Regression of hypertrophy
- Induced pulm onary-artery smooth-muscle cell PDE5 (PDE1?)
  - Vasorelaxation
  - ↓ Proliferation
  - ↑ Apoptosis

Dr. P.K. Rajiv
Viagra and HIE Follow up

<table>
<thead>
<tr>
<th>Case</th>
<th>1yr</th>
<th>2yrs</th>
<th>3yrs</th>
<th>4yrs</th>
<th>5yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>75</td>
<td>80</td>
<td>90</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Case 2</td>
<td>90</td>
<td>80</td>
<td>75</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Case 3</td>
<td>80</td>
<td>75</td>
<td>80</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Case 4</td>
<td>79</td>
<td>80</td>
<td>85</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Case 5</td>
<td>80</td>
<td>80</td>
<td>90</td>
<td>90</td>
<td>85</td>
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<tr>
<td>Case 6</td>
<td>80</td>
<td>75</td>
<td>80</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Case 7</td>
<td>70</td>
<td>75</td>
<td>80</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Case 8</td>
<td>80</td>
<td>90</td>
<td>90</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Case 9</td>
<td>75</td>
<td>85</td>
<td>75</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>Case 10</td>
<td>90</td>
<td>85</td>
<td>90</td>
<td>85</td>
<td>85</td>
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<tr>
<td>Case 11</td>
<td>75</td>
<td>80</td>
<td>70</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

AWAITING PUBLICATION 2012
Persistent Pulmonary Hypertension in Newborn
Recent Advances in Management

PDE – 3 Inhibitor - Milrinone

- Primary physiological disturbance in PPHN $\rightarrow$ ↑ 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

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

Prostacyclin: Mechanism of Action

Steinhorn, R. H et al. Neoreviews 2007;8:e14-e21
Persistent Pulmonary Hypertension in Newborn
Recent Advances in Management

PPHN new modalities of treatment

Schematic showing the pathway for synthesis and mode of action of prostacyclin (PGI2). Various agents used in this study are also shown in the figure. COX, cyclo-oxygenase; AA, arachidonic acid; PGH2, prostaglandin H2; PGIS, prostacyclin synthase; IP, prostacyclin receptor; PDE3, phosphodiesterase 3.

Use of Prostacyclin in PPHN

All patients were refractory to nitric oxide

Old Wine in New Bottles

PGE1
PGI2
Nitroprusside
Tolazoline
Sildenafil

INHALATION
• Selective
• Pulmonary
• Ventilated regions

INTRAVENTOUS AGENTS
• Non selective

Adapted from Sood et al 2010
## SPV – Inhaled Vasodilators

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>IPGE₁</th>
<th>IPGI₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivation</td>
<td>Pulmonary</td>
<td>Pulmonary</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>seconds</td>
<td>&lt;30 sec</td>
<td>2-3 min</td>
</tr>
<tr>
<td>Half-life</td>
<td>Gas</td>
<td>Aerosol</td>
<td>Aerosol</td>
</tr>
<tr>
<td>Physical form</td>
<td>--</td>
<td>Ethanol</td>
<td>Glycine</td>
</tr>
<tr>
<td>Buffer</td>
<td>--</td>
<td>6.5</td>
<td>10.5</td>
</tr>
<tr>
<td>pKa</td>
<td>--</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

Other effects

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>IPGE₁</th>
<th>IPGI₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet aggregation</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Dilator</td>
<td>Dilator</td>
<td>Constrictor</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Anti</td>
<td>Anti</td>
<td>--</td>
</tr>
<tr>
<td>Proliferation</td>
<td>--</td>
<td>Anti</td>
<td>--</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>✓</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Adapted from Sood et al 2010
PGE 1 - Metabolism

- **PGE**₁
  - **15-OH PGDH**
    - 15-keto PGE₁
      - **PGA¹³ reductase**
        - 13, 14-dihydro-15 keto-PGE₁ (15-KD PGE₁)
          - De-activation by \( \Omega^- \) & \( \beta \) oxidation
            - Polar dicarboxylic compounds excreted in urine
  - 13, 14-dihydro-PGE₁ (PGE₀)

\[ T_{1/2} 10 \text{ sec} \]
Phase I Clinical Trial of IPGE1 in NHRF

- IPGE1 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 O₂

**Group I**

Dose Escalation Phase: $\beta=11.4$, SE=3.5, $p=0.009$

Weaning Phase: $\beta=1.9$, SE=2.5, $p=0.48$

**Group II**

Dose Escalation Phase: $\beta=5.6$, SE=3.7, $p=0.18$

Weaning Phase: $\beta=9.9$, SE=4.7, $p=0.13$

$\Delta P_a O_2$ 64.4±71.6 0.038

$\Delta OI$ -14.6±10.0 0.004

$\Delta P_a O_2$ 43.5±51.8 NS

$OI$ -9.0±11.9 NS

Phase I Trial: Dose Response

<table>
<thead>
<tr>
<th>Dose (ng/kg/min)</th>
<th>Group I (n=8)</th>
<th>Group II (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>150</td>
<td>87.5</td>
<td>50</td>
</tr>
<tr>
<td>300</td>
<td>87.5</td>
<td>75</td>
</tr>
<tr>
<td>Weaning</td>
<td>100</td>
<td>75</td>
</tr>
</tbody>
</table>

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

![Graph showing therapies prior to ECMO](image-url)

Effect of Therapy on ECMO Mortality

ELSO registry reviewed for years 1996-2003

- **NO**
- **HFV**
- **Surfactant**

% Mortality

* *p < .001*
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

Dr. P.K. Rajiv
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 hypoxic 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 (e.g., 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).

Emerging Therapies for Treatment of PPHN

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

Conclusions

- PPHN is an 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 ($\text{PaO}_2 \geq 50 \text{ mmHg}$) or an OI (oxygenation index) $\geq 25$.
- In infants with parenchymal disease, atelectasis should be corrected (with HFOV) if necessary. (overdistention should be avoided)
- NO should we be weaned gradually when the inhaled concentration is $<5 \text{ ppm}$. 
Anticipation Balance Strategy Skill God