Treatment of Pulmonary Hypertension of Neonate (PPHN)

CHENG Shuk-man
Diagnosis

- Infants with PPHN usually present within the first 12 hours after birth with cyanosis.

- An oxygen saturation level pre ductal which is 5%-10% higher (right arm) than post ductal (lower limbs) indicates the presence of a right-to-left shunt at the PDA or PFO.

- Due to hypoxia, the infant may be acidotic and hypotensive and will remain cyanotic even when exposed to a high oxygen concentration.
Diagnosis

Echocardiography is the gold standard investigation

- make an accurate diagnosis and initiate prostaglandins therapy for ductal-dependent CHD
- right-to-left or bidirectional shunts at the level of the PDA or PFO
- estimate the pulmonary artery pressure from Doppler velocity measurement of the tricuspid regurgitation jet
Diagnosis

◆ Estimation of Pulmonary Artery Pressure (PAP) is an important aspect of the diagnosis and treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN).

◆ Monitor the efficacy of specific therapeutic interventions.
Echocardiographic evaluation of neonatal hypoxemia based on ductal (black bar) and atrial (blue bar) shunts. (From Satyan Lakshminrusimha.)
Treatment Goals for PPHN

- Improve arteriolar oxygen saturation and oxygen delivery to the tissues
- Decrease pulmonary vascular resistance
- Maintain adequate systemic blood pressure
- Minimize barotrauma
Management Strategies
Neonates who have PPHN require supportive care tailored to the degree of hypoxemia and physiologic instability. The overall approach should focus on restoring the cardiopulmonary adaptation while avoiding lung injury and adverse effects on systemic perfusion.
Reduce Pulmonary Vascular Resistance

- Optimal Lung Expansion
- High PaO2
- Prevention of acidosis / normal to mildly alkalotic pH
- Sedation and when necessary paralysis
- Treatment of infection
- Nitric Oxide
- Pulmonary vasodilator therapies
Optimal Lung Expansion

- Mechanical ventilation facilitates alveolar recruitment and lung expansion, potentially improving the ventilation/perfusion (VQ) match.

- The ventilator strategy should target recruitment of the atelectatic segments while avoiding overdistention, which leads to lung injury and increased resistance to pulmonary blood flow.

- The application of surfactant therapy facilitates alveolar expansion in parenchymal lung disease such as RDS or MAS.
Optimal Lung Expansion

“Gentle” ventilation strategies with optimal PEEP, relatively low PIP or tidal volume and a degree of permissive hypercapnia are recommended to ensure adequate lung expansion while limiting barotrauma and volutrauma.
Optimal Lung Expansion

- High-frequency oscillation (HFO) may help to optimize lung expansion in neonates who have PPHN secondary to lung disease.
- Low tidal volumes, HFOV offers less barotrauma. It has been used mainly in cases of pulmonary hypoplasia (diaphragmatic hernia, pulmonary hypoplasia and severe MAS).
High PaO2

- Oxygen is a potent and selective pulmonary vasodilator
- Prolonged exposure to 100% oxygen and aggressive ventilation can be avoided by judicious application of newer therapies, such as iNO, surfactant replacement, and inotropic support.
- The traditional practice of targeting a high PO2 (>100mmHg) and low PCO2 to achieve pulmonary vasodilation has not been shown to improve outcome and is potentially harmful to the developing lung and cerebral perfusion.
Hyperventilation & Alkalosis

• Widely used in the management of PPHN before the introduction of iNO

• Hyperventilation was used to produce hypocarbia and respiratory alkalosis thus to improve oxygenation by reducing PAP in past

• Hyperventilation and resultant hypocarbia result in poor respiratory and neurologic outcomes

• Based on animal studies demonstrating exaggerated hypoxic pulmonary vasoconstriction with pH < 7.25 recommend maintaining pH > 7.25, preferably 7.30 to 7.40 during the acute phase of PPHN.
Use of Sedatives and Muscle relaxants

- Used to minimize fluctuations in oxygenation and facilitate ventilation.

- Muscle relaxants is not recommend to use but this may be necessary to gain initial control in very vigorous babies who are not adequately sedated with narcotics and are fighting the ventilator to their detriment.

- Significant adverse effects and commonly induce hypotension, generalized edema, and deterioration of lung function with prolonged use.

- The role of the neonatal nurse is to effectively anticipate, prevent and managed pain in all neonates regardless of their gestational age or severity of illness, having used an appropriate pain assessment tool.
Promote comfort and minimize stimulations

- A ‘minimal handling’ approach should also be used (such as loud noise, unnecessary handling should be avoided, cover the eyes)

- Providing a neutral thermal environment and clustering care is key in decreasing oxygen requirements.

- Strategies to eliminate stress must be individualized to the neonate and appropriate to the level of illness.
Increase Systemic Blood Pressure

◆ Fluid boluses (crystalloid)
◆ Inotropic agent—Dopamine is your first choice
◆ Colloid as appropriate
◆ Prevention of acidosis / normal to mildly alkalotic pH
◆ Treatment of Infection
Management of systemic hypotension in PPHN

- Systemic hypotension is common in infants with PPHN.
- Decreased systemic blood pressure exacerbates right-to-left shunt and worsens hypoxemia in PPHN.
- Myocardial function is frequently poor, despite reasonable blood pressures.
Management of systemic hypotension in PPHN

- Aim to keep the mean arterial pressures above 50mm Hg in term infants

- The cause of systemic hypotension should be addressed first – administration of volume bolus in hypovolemia, decrease in mean arterial pressure in the presence of hyperinflation and antibiotics for sepsis.
Management of systemic hypotension in PPHN

- Use volume (initially normal saline) and dopamine - starting with 5-10 mcg/kg/min and/or dobutamine 5-10 mcg/kg/min if systemic pressure raises and pulmonary pressure stays the same, R-L shunt will diminish.

- Adrenaline infusions may be indicated if there is severe myocardial dysfunction.
Management of systemic hypotension in PPHN

- Increasing systemic pressure to supraphysiologic levels is not recommended.

- Optimal therapy for reduced pulmonary blood flow is selective pulmonary vasodilation.

- Instead, if pulmonary blood is forced by higher systemic pressure (by limiting right-to-left shunts) through a constricted pulmonary circuit leading to endothelial dysfunction is likely to exacerbate PPHN.
Treatment of underlying disease and metabolic abnormality

- Find out the underlying disease and to treat it, for example, adequate antibiotic coverage for pneumonia and sepsis. Pneumonia and sepsis often present with elevated PVR associated with systemic hypotension and decreased SVR.

- Metabolic abnormalities including hypoglycemia, hypocalemia, and hypomagnesemia should be corrected to ensure adequate myocardial function and response to vasopressors.
Pulmonary hypertension in premature infants

- Prolonged rupture of membranes, pulmonary hypoplasia and intra-uterine growth retardation have been identified as risk factors for hypoxemia secondary to PPHN in premature infants.

- A decrease in the number of pulmonary vessels, altered lung architecture and episodes of hypoxemia and hypercarbia together may contribute to development of pulmonary hypertension in CLD.

- Both iNO and sildenafil have been reported to be beneficial in these infants in decreasing the pulmonary artery pressure.
Management of PPHN

- Minimal stimulation (eye covers and ear muffs)
- Sedation and analgesia (avoid routine paralysis)
- 8-9 rib expansion (esp. on HFOV)
- Arterial PaCO₂ 45 to 60 mmHg
- Arterial PaO₂ (preductal) 55-80 mmHg
- Hypotension (mean < 35 mmHg)
- Blood pressure
- Two 10 mL/kg boluses or Lactated Ringers or Normal Saline followed by pressor therapy
- pH > 7.25
- Lactate < 3.0 mM/L
- Urine output > 1 mL/kg/h
- Surfactant for parenchymal lung disease

Conventional ventilation
- PIP < 25 - 28 cmH₂O
- PEEP 4-5 cmH₂O
- Rate-40 to start
- Consider HFOV if PIP > 28 cm H₂O is required to maintain PaCO₂ < 60 mmHg

Initial settings on HFOV
- 13 to 17
- 33% (I:E of 1:2)
- 30 to 40
- 10 Hz

Inhaled NO - clinical (pre - post ductal saturation difference of > 5-10%) or echocardiographic evidence of PPHN (typically OI > 15 to 25)

From Satyan Lakshminrusimha.
Vasodilator therapy for PPHN.
Vasodilators

- Pulmonary vasodilators can be classified into 2 main categories:
  - Those that increase production of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), e.g. nitric oxide and prostacyclin
  - Those that decrease the breakdown of cGMP, e.g. sildenafil and cAMP, e.g. milrinone

- With the exception of iNO, vasodilator therapies for PPHN are limited by their lack of selectivity for the pulmonary circulation.
Inhaled Nitric Oxide Therapy

- The introduction of iNO therapy has been the most significant milestone in the era of vasodilator therapy for PPHN.
- iNO acts as a messenger molecule:
  - iNO → ↑ the activity of soluble guanylate cyclase (sGC)
  - sGC → the formation of cyclic GMP (cGMP)
  - cGMP → causes vascular smooth muscle relaxation acting through the calcium-gated potassium channels
- Vasorelaxation induced with iNO is transient
  - In the presence of oxygen, iNO rapidly degrades (<10 sec) to higher oxides, losing its bioactivity.
Mechanism of selective effects of iNO
Inhaled Nitric Oxide (iNO) Therapy

iNO is an ideal pulmonary vasodilator:

- Is selective pulmonary vasodilator at doses <100 (ppm)
- Confined to the pulmonary vascular bed (*due to the rapid inactivation by hemoglobin in the pulmonary circulation*)
- It causes vasodilation even in the presence of endothelial cell injury or dysfunction
- It has the ability to improve ventilation-perfusion matching (vasodilation occurs in the ventilated segments of the lung)
Effect of iNO on the pulmonary circulation.

- iNO reaches healthy alveoli, and diffuses to the adjacent pulmonary arteries to cause vasodilation. As NO reaches the lumen of the pulmonary artery, it is inactivated by Hb, limiting its effect to the pulmonary circulation.

- NO does not reach the atelectatic alveoli, maintaining constriction of the adjacent pulmonary arteries. Increased perfusion of the ventilated segments of the lung improves the VQ match and oxygenation in parenchymal lung disease.
Effect of iNO on the pulmonary circulation.
Selective and micro-selective action of inhaled nitric oxide (NO)

(From Satyan Lakshminrusimha.)
iNO dosing

◆ The current recommended starting dose in term infants with respiratory failure is 20 ppm (RCTs)

◆ Other studies have shown that doses as low as 5 ppm were effective

◆ Higher Doses:
  ◆ Are NOT more effective.
  ◆ Are associated with a higher incidence of side effects.

◆ Initiation of iNO at lower doses has the advantage of faster weaning and lesser exposure to nitrogen oxides that cause oxidant stress.
Weaning of iNO therapy

- Exposure to iNO even for a brief period can sensitize the pulmonary circulation to rebound vasoconstriction during discontinuation of iNO therapy.

- A significant decrease in PaO2 during withdrawal of iNO can be avoided by weaning the dose gradually in steps from 20 ppm to the lowest dose possible for a period before its discontinuation.

- Even in babies who show no response to iNO, sudden discontinuation can precipitate pulmonary vasoconstriction and rapid deterioration.
iNO does have some limitations

◆ ~ 30% of cases do not respond to iNO. The reasons for this failure include:

  ◆ Severe parenchymal lung disease
  ◆ Myocardial dysfunction
  ◆ Problems with NO-cGMP signalling

◆ An association of prolonged iNO therapy with decreased endogenous NO synthase activity (PPHN rebound)
Risks and complications of iNO therapy

• Methemoglobinemia
  ◆ Nitric oxide has been found to have an affinity for hemoglobin that is 280 times faster than carbon monoxide -> Methemoglobin.
  ◆ This higher affinity thus causes a shift to the left of the oxyhemoglobin dissociation curve with resultant impaired unloading of oxygen to the tissues.
  ◆ High levels of methemoglobin can potentially interfere with tissue oxygen delivery and result in hypoxia.
  ◆ Peak level between 8-40 hour after treatment
  ◆ S/S include shortness of breath, cyanosis, characteristic chocolate-brown color as compared to normal bright red oxygen-containing arterial blood.
Risks and complications of iNO therapy

- **Methemoglobinemia**
  
  - At some hospitals, methemoglobin levels < 3% are considered acceptable. If at any time the level rises above that point then the concentration of inhaled NO should be reduced or discontinued completely.
  
  - Check the ventilator circuit, particularly the delivery and measuring points of iNO to prevent excessive delivery of iNO.
  
  - Treatment included iv methylene blue, and a transfusion of packed red blood cells (10mL/kg), Exchange transfusion.
Risks and complications of iNO therapy

◆ Is a toxic free radical and causes tissue damage. NO is used by macrophages to kill bacteria. It can theoretically damage the lung combined with O2 free radicals to produce peroxynitrates which are toxic to tissue.

◆ Nitric oxide is unstable in air and undergoes spontaneous oxidation to nitrogen dioxide. NO2 is known to be directly toxic to the respiratory tract. At higher doses, the major toxicologic effect of NO2 is pulmonary edema.

◆ NO is an inhibitor of platelet function. Caution when thrombocytopenia or bleeding problem.
Inhaled Nitric Oxide (iNO) Therapy

◆ Most of these undesirable side effects are minimal when NO is administered in appropriate amounts.

◆ Careful monitoring of the gas administration because nitric oxide has a high affinity for haemoglobin.

◆ Nitric oxide and oxygen can react to produce toxic by-products such as nitrogen dioxide, the delivered amount must be closely monitored.

◆ The nurse should be alert to the neonates increased susceptibility to bleeding.
Alternate approaches to iNO

Given that INO does not improve oxygenation in a significant proportion (30–40%) of cases, there is an urgent need to consider other therapeutic options for PPHN.
Alternate approaches to iNO

◆ The alternatives include:
  
  ◆ Vasodilator prostaglandins such as prostacyclin or PGE1
  ◆ NO precursor L-arginine
  ◆ Phosphodiesterase inhibitors such as sildenafil
  ◆ The free radical scavenger SOD.

◆ Other agents that were investigated in pediatric and adult pulmonary hypertension:
  
  ◆ Adenosine and ATP-MgCl2
  ◆ Magnesium sulfate
  ◆ Endothelin receptor antagonist Bosentan.
Phosphodiesterase inhibitors

◆ iNO $\rightarrow$ ↑ guanylate cyclase (sGC) $\rightarrow$ ↑ cyclic GMP (cGMP)

◆ cGMP is hydrolyzed and inactivated by Type 5 phosphodiesterases (PDE5).

◆ The beneficial effects of PDE5 inhibitors may be optimized by using them in combination with iNO.

◆ Pulmonary administration presumably minimizes the potential for undesired systemic effects.

◆ PDE5 inhibitors include: Dipyridamole, Zaprinast, Pentoxifylline and Sildenafil.
Sildenafil

- A selective pulmonary vasodilator (*animal model*)

- As effective as iNO in pulmonary vasodilatation (humans studies)

- When combined with iNO, it is more effective than either therapy alone

- Attenuates the rebound PPHN upon withdrawal of iNO
Sildenafil

• Given its mechanism of action, sildenafil may NOT have a role in rescue therapy following failure of iNO

• Concerns about its use:
  • In situations of hepatic dysfunction
  • In combination with antifungal therapy
  • Possible retinal damage
  • May worsen V/Q mismatching (non specific vasodilation)
Milrinone

• Is a bipyridine compound that selectively inhibits phosphodiesterase III (PDE3) in cardiac myocytes and vascular smooth muscle

• It reduces PVR and pulmonary artery pressure (PAP) in experimental models of pulmonary hypertension, adult humans, and neonates post cardiac surgery.

• Experience with this drug in neonates is limited (Case series*)
Bosentan

- Endothelin 1 is a powerful vasoconstrictor
- Dual Endothelial 1 receptor antagonist, is a well established therapeutic option in adult PAH.
- Mediates pulmonary vasodilation by blocking effects of endothelin.
- Studies have concluded that bosentan is safe and effective for the treatment of PAH in children
- Significant falls in mean pulmonary artery pressure and PVR.
L-Arginine

• The rationale for using L-arginine infusion is twofold:
  • L-arginine is a required substrate for NO synthesis
  • It promotes NOS activity under stress conditions

• Plasma levels of L-arginine are decreased in neonates with PPHN compared with infants requiring ventilation for other causes.

• The vasodilatory effect is lesser compared to iNO

• It may help preserve the endogenous NOS activity and permit a smoother weaning of iNO therapy.
Prostacyclin

- A potent vasodilator
- Increases the cAMP level in vascular smooth muscle.
- A potential synergistic effect on the vascular tone when used combined with iNO.
- Intravenous and aerosol administration
- Aerosolized PGI2 is more selective
## Drugs Used for Management of PPHN

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<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Doses</th>
<th>Side Effects</th>
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</thead>
<tbody>
<tr>
<td>Inhaled NO</td>
<td>Increased cGMP levels via stimulation of sGC activity</td>
<td>5 - 20 ppm through ventilator</td>
<td>Methemoglobinemia, formation of NO2 and peroxinitrite, inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Increased cGMP levels via specific PDE-5 inhibition</td>
<td>PO 0.5 - 2 mg/kg/dose every 6 hours IV 0.4 mg/kg over 3 hr loading f/b infusion 1.6 mg/kg/d</td>
<td>Hypotension especially with NO, impaired retinal vascular growth, thrombocytopenia is a relative contraindication</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Increased cAMP levels via specific PDE-3 inhibition</td>
<td>0.33 - 0.99 µg/kg/min IV infusion</td>
<td>Systemic hypotension, Intraventricular hemorrhage (IVH)</td>
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<tr>
<td>Prostacyclin (PGI2)</td>
<td>Increased cAMP levels via adenylate cyclase enzyme</td>
<td>5 - 40 ng/kg/min IV infusion</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Iloprost (synthetic analogue of prostacyclin PGI2)</td>
<td>Increased cAMP levels via adenylate cyclase enzyme</td>
<td>20 µg/kg/dose every 90 min inhalation</td>
<td>None reported</td>
</tr>
<tr>
<td>Magnesium Sulphate</td>
<td>Modulates vascular contraction by affecting calcium influx thereby inhibits SMC depolarization and promotes vasodilation</td>
<td>IV 200 mg/kg loading over 20 min f/b 20 - 150 mg/kg/h infusion</td>
<td>Bradycardia, hypotension, respiratory depression</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Increased cGMP levels via ET-1 receptor antagonism</td>
<td>PO 1 mg/kg/dose 12 hourly</td>
<td>Systemic hypotension</td>
</tr>
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</table>
Superoxide dismutase (SOD)-Scavengers of ROS

The rationale for SOD use is:

◆ To reverse the impaired vasodilation by reducing the production of O2 free radicals (Reactive oxygen species ROS) and NO3 formation. (Several laboratory studies have suggested that accumulation of ROS occurs in PPHN).

◆ Animal studies suggest
  ◆ $\uparrow$ superoxide formation in PPHN impairs vasorelaxation
  ◆ $\downarrow$ the ability of pulmonary arteries to respond to iNO.

◆ SOD protects the lung from oxidant damage caused by the combination of exogenous NO and high inspired oxygen concentrations
Superoxide dismutase (SOD)

An antioxidant therapeutic approach may have multiple beneficial effects such as increased availability of endogenous and exogenous NO, reduced oxidative stress and reduced lung injury.
Extra-corporeal membrane oxygenation (ECMO)

- Introduced as a rescue therapy to support neonates in severe respiratory failure
- Provides both respiratory and cardiac support to facilitate the postnatal adaptation to occur while allowing the lungs to recover from barotraumas and O2 toxicity.
- Requires cannulation
- The problem is how to maintain oxygenation in an infant who has little or no pulmonary perfusion during transport.
Future Perspectives

◆ Amplification of eNOS activity may become possible, or newer NO-donor drugs, for example, S-nitrosothiols, may emerge as superior vehicles to deliver NO to specific tissue beds.

◆ Another avenue for future research is neuroprotective effects of iNO, especially in preterm infants.
Conclusions

• With the advent of iNO the management of PPHN entered a new era.

• The wider application of iNO therapy and improved ventilation strategies led to a decrease in the need for invasive life-sustaining therapies such as ECMO.

• Further decreases in morbidity and mortality are possible with specific strategies targeted to correct the alterations in NO and prostacyclin biology and strategies to reduce lung injury.
Take Home Message

- Basic principle is to avoid hypoxia and to achieve selective pulmonary vasodilation without affecting systemic vascular resistance (SVR) thus reducing PVR:SVR ratio and intracardiac shunting.

- The introduction of iNO therapy has been the most significant milestone in the era of vasodilator therapy for PPHN. Inhaled NO therapy is the first choice.

- Given that INO does not improve oxygenation in a significant proportion (30–40%) of cases, there is an urgent need to consider other therapeutic options for PPHN.
References


