Pulmonary Vasodilators in Neonatal/Pediatric Patients:
A new therapeutic objective for Respiratory Therapists.

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Therapeutic objectives (TO) answer the ages-old question, “Hey bubba, why are we in this room with this patient?”

- Improve oxygenation (O2)
- Inhaled medication/bronchodilators (IB)
- Lung reexpansion (LR)
- Mobilize secretions (MS)
- Alveolar ventilation (AV)
- Ventilation: perfusion (V/Q)

The views expressed in this presentation are Doug Masini’s, and do not represent the policy or opinions of Armstrong State University, or Mercer University College of Medicine. Product names serve only as an illustration and do not connote a recommendation. Dr. Masini states no conflict of interest in this presentation.
WHO Group 1: Pulmonary arterial hypertension (PAH)
1. Idiopathic PAH (IPAH)
This refers to PAH which occurs at random, without an apparent cause. IPAH can also be referred to as "primary pulmonary hypertension" or PPH, and some older information will still use this term.

1.2 Heritable PAH
The heritable category, formerly called familial, includes two types of PAH:

1.3 Drug-and toxin-induced PAH
Certain drugs and toxins including aminorex, fenfluramine, dexfenfluramine, and toxic rapeseed oil have been associated with the development of PAH.

1.4 PAH associated with other diseases and conditions. This category includes PAH associated with:
- Connective tissue and collagen vascular disease. This section includes diseases such as scleroderma (SSC), lupus crescent syndrome (CSR), and others such as HIV infection, Portal hypertension, and Congenital heart diseases (CHD) or PH from diet drugs like fenfluramine and dexfenfluramine ("Fen-phen").
- Examination (may include):
  - Chest x-ray, EKG, Echo, Cardiac cath with acute vasodilation test, CBC, Lfts, Urinalysis, Liver study, Collagen vascular studies/ANA, Rheum factor, erythrocyte sed rate, complement, Full PFT and DLCO, MRI, CT, Bronchoscopy and consider Biopsy.
  - HIV, Thyroid function, Hypercoagulation evaluation, sleep study.
  - Toxicology brain natriuretic peptide.
Therapy for PH:
Hyperoxia and hypocapnea.
Selective alpha antagonist pulmonary dilating agents.
Inhaled Nitric Oxide.
Selective endothelin receptor antagonists.
Stable prostacyclin analogues:
Oral Beraprost
Inhaled Iloprost

Oral Phosphodiesterase 5 inhibitor.
Calcium channel Blockers.
Nifedipine, Diltiazem
Continuous intravenous infusion.
Epoprostenol
Continuous subcutaneous infusion.
Trepotinil.
Dual Endothelin receptor antagonist.
Bosentan.
New drugs and options

PFC happens not just in the NICU....
Case study:
A 19 year-old male admitted to primary care service (100 bed hospital) status-post motor vehicle accident with multiple trauma. The patient exhibits severe hypoxemia refractory to therapy, and is transferred, committed to aggressive ventilator and fluid resuscitation. History revealed an asymptomatic murmur, but no therapy or ‘problems’ per family Physician. Patient had a patent ductus arteriosus that re-opened after severe hypoxemic episode; ductus surgically closed and patient improved.
A 28-year-old aerobic instructor with no cardiac history came to the outpatient clinic for screening. She had no symptoms and an excellent exercise capacity. On physical examination saw a healthy young lady, heart rate was 60 beats/min and her blood pressure 110/60 mmHg. First and second heart sounds were normal; a continuous murmur 2/6.

A 14-month-old with chronic lung disease, pulmonary outflow tract is prominent. The central markings are accentuated and fluffy, more so on the right, with increased markings and fluffiness around the hilum. These findings are consistent with chronic lung disease, suggestive of pulmonary hypertension.

Old methods to treat Primary Pulmonary Hypertension (PPH).
A principle neonatal therapy in new clothes.

- Hyperoxemia, O₂ dilates pulmonary vessels, decreases pulmonary vascular resistance.
- Hyperventilation was a standard, effective therapy for persistent fetal circulation with high pulmonary vascular resistance.
- Tolazoline (Priscoline, an alpha adrenergic blocker) given IV with fluid, cautiously administered, relieved pulmonary vasoconstriction without hypotension.

See other research and citations at: http://lib.bioinfo.pl/meid:61355
Retrospective case study of tolazoline:
Objective: To determine the efficacy of tolazoline as a rescue treatment for hypoxemia in preterm infants with respiratory distress syndrome.
Methods: Retrospective chart review on case series of infants weighing <750 g at birth who received tolazoline during a severe hypoxemic episode while receiving maximal ventilator support for respiratory distress syndrome. A slow bolus infusion of low dose tolazoline (0.5 mg–2 mg/kg) mixed with plasmanate or normal saline (10 mL/kg) was administered.
Outcome measures evaluated included an increase in PaO2 ≥20 mm Hg from pretreatment value and an increase in oxygen saturation to >90%.
Results: Forty-three infants with a mean gestational age and birth weight of 24 weeks and 581 g, respectively, received tolazoline. All infants were mechanically ventilated and required a fraction of inspired oxygen of 1.0. Oxygenation improved in 72% (31/43) of infants with a tolazoline dose of 0.5 to 1.0 mg/kg. Of those who responded, PaO2 values (mean ± standard deviation) pretolazoline and post-tolazoline were 32 ± 7.5 mm Hg and 156 ± 114.9 mm Hg, respectively. In all responders, oxygen saturation increased to >90% within 30 minutes of tolazoline administration. Improvement in pH, pCO2, oxygenation index, and mean airway pressure was also noted. Among nonresponders, pH decreased and pCO2 increased after tolazoline. Minimal change in blood pressure was noted in both responders and nonresponders. Heart rate decreased by 19 beats per minute among nonresponders compared with an increase of 3 beats per minute in those who responded to tolazoline.
Conclusion: Tolazoline is an effective treatment of severe resistant hypoxemia in preterm infants who are already on vigorous ventilatory support.

Nitric oxide

How it works – physiologic and inhaled nitric oxide (NO)
- Physiologic NO is a gaseous signaling molecule, playing a role in a variety of biological processes.
- Physiologic Nitric oxide is ‘endothelium-derived relaxing factor’, or ‘EDRF’. The endothelium (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow. Inhaled NO stimulates increased production of cyclic guanylate monophosphate (cGMP) in pulmonary smooth muscle cells; the uptake of calcium into the sarcoplasmic reticulum, leads to muscle relaxation, reduced PA pressure and PVR, and increased oxygenation.
- The production of PNO is elevated in populations living at high altitudes, which helps these people avoid hypoxia by vasodilation pulmonary vasculature.
- Physiologic NO serves as an inflammometer in conditions like asthma, there has been increasing interest in the use of exhaled nitric oxide as a breath test in diseases with airway inflammation.
Vasotone modification with NO
Nitric oxide a potent pulmonary vasodilator.
Inhale 10-80 ppm, risks of methemoglobinemia, NO₂ production / toxicity. Treats and decreases pulmonary vasospasm, vasoconstriction, adult pulmonary hypertension (PHTN). Great for treating persistent fetal circulation / pulmonary hypertension (PHN) of sick newborns, also indicated in adult PPH. (Gardenhire’s Res, pp. 322-325).

Endothelin Antagonism ETA

How the endothelin (ET) system works:

Figure 1.
- Biosynthesis and function of the endothelin (ET) system. ET-1 is generated from big ET-1 in endothelial cells (EC).
- Secreted predominantly toward underlying vascular smooth muscle cells (VSMC). The contractile and growth-promoting effects are mediated by binding to ETB receptors on smooth muscle cells. Activation of ETB receptors on endothelial cells leads to release of nitric oxide (NO), which causes smooth muscle vasodilatation.
PPET-1 = preproendothelin-1, PGI₂ = prostaglandin I₂.
Figure 2. Effects of endothelin (ET)-1 on target organs in cardiovascular disease. Expression of the ET system ETAR, and ETBR might be upregulated in response to several factors and cause damage in the heart, kidneys, and vasculature. Source: www.medscape.com/viewarticle/423213_2

Endothelin Receptor Antagonists (ETA)
Endothelin-1 is a potent modulator of vasoconstriction, trigger of smooth-muscle cell division, cell proliferation, and vascular hypertrophy, which plays an important pathogenic role in the development and progression of PAH. Plasma and pulmonary tissue endothelin-1 are elevated in patients with pulmonary hypertension and correlate with disease severity.

Two distinct types of endothelin receptor have been identified in the pulmonary vasculature:

- **Endothelin type A** receptors are found in pulmonary vascular smooth muscle cells.
- **Endothelin type B** receptors are located primarily in pulmonary vascular endothelial cells, and to a lesser extent in pulmonary vascular smooth-muscle cells.

Dual endothelin antagonists
Bosentan (Tracleer, PO tablets) dual endothelin (Type A & B) receptor antagonist can be taken by children (12-18 years of age) PO as a tablet.

Sources:
- [www.drugs.com/cons/bosentan.html](http://www.drugs.com/cons/bosentan.html)
- [http://www.pulmonary-hypertension-treatments.com/cons.html](http://www.pulmonary-hypertension-treatments.com/cons.html)
Selective endothelin antagonist receptor blocker

Ambrisentan is an oral, selective ETA receptor blocker, given orally at a dose of 5 - 10 mg / day. Sitaxsentan (not approved in US; withdrawn from market, 2010; had been approved in Canada and EU as Thelin) and Ambrisentan are both selective endothelin antagonists. Source: http://www.uptodate.com/home/content/abstract.do?topicKey=ven_pulm/11621&refNum=63

*Ambrisentan was approved for sale by the U.S. FDA on June 15, 2007

Endothelin Receptor Antagonists

**bosentan** (TRACLEER®) Acetelion, Ltd. FDA approved 2001 oral 62.5 to 125 mg, 2 times/day Treatment of pulmonary arterial hypertension (WHO Group I) in WHO Class III or IV symptoms to improve exercise ability and decrease rate of clinical worsening

**ambrisentan** (LETAIRIS®) Gilead Sciences, Inc. FDA approved 2007 oral 5-10 mg/day Treatment of pulmonary arterial hypertension (WHO group I) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening

**sitaxsentan sodium** NOT APPROVED IN US Reviewed & Rejected 3 times by the FDA Last: June 2007 APPROVED IN Canada - 2007 THELIN® Treatment of primary pulmonary arterial hypertension (PAH) and pulmonary hypertension secondary to connective tissue disease in patients with WHO functional class II and patients with WHO functional class II who did not respond to conventional therapy

Thelin withdrawn from market, 2011 due to hepatotoxicity however, there is still interest in resuming human trials of endothelin receptor antagonists

Calcium channel blockers
How calcium channel blockers work in PH:

“More Ca++, stronger channel constriction/contraction”

Calcium channel blockers comprise three chemical groups, all of them bind the L-type Ca++ channel, but each class binds to different binding sites of the same channel:

- **Phenylalkylamines**: verapamil is the only drug in this group, it binds to the V binding site.
- **Benzothiazepines**: diltiazem binds to the D binding site in the L-type Ca++ channel. It shows antihypertensive effects similar to those of verapamil (Class IV antiarrythmics, SVT). Potent arteriolar dilators.
- **Dihydropyridines**: the prototype agent in this group is nifedipine, a first generation dihydropyridine that binds to the N binding site. Second generation agents include isradipine, nicardipine, and felodipine. 
  Amlodipine is considered a third generation dihydropyridine. Source: [pharmamotion.com.ar/calcnalculationscomment-page-1](pharmamotion.com.ar/calcnalculationscomment-page-1)

**Ca++ channel blockers**

**BACKGROUND:** This report presents 13 years of experience with vasodilator therapy for primary pulmonary hypertension (PPH) in children. Two eras were involved: between 1982 and 1987, oral calcium channel blockers were the only agents available for long-term therapy; after 1987, prostacyclin (PGI2) has been available for long-term intravenous use.

**METHODS AND RESULTS:** Seventy-four children underwent short-term vasodilator testing with intravenous PGI2. Those who manifested pulmonary vasodilation (“acute responders”) were treated with oral calcium channel blockers. In the 31 responders, calcium channel blockers improved survival compared with the 43 nonresponders (P=0.0002). Survival was also better in 24 PGI2-treated nonresponders compared with 22 nonresponders for whom PGI2 was unavailable (P=0.0005) as well as in all children who failed conventional therapy (n=31; P=0.002).

**CONCLUSIONS:** Long-term vasodilator therapy improves survival in children with PPH. In acute responders, oral calcium channel blockers generally suffice. In both nonresponders to short-term testing and responders who fail to improve on calcium channel blockers, continuous intravenous infusion of PGI2 improves survival.


**Long-term use of calcium channel blockers** (diltiazem and nifedipine) reduced PAP, decreased right-ventricular hypertrophy, and improved survival over a 5-year period, with improvement in symptoms. The use of oral calcium channel blockers is limited by their dose-related systemic vasodilator effects, which can cause hypotension, worsening right-ventricular functioning, increased intrapulmonary shunt, and hypoxemia.

**Aerosolized calcium channel blockers** have been studied for their protective properties against bronchial reactivity, and they did not cause systemic vasodilation. The possible benefit of selective pulmonary vasodilation from inhaled calcium channel blockers in PAH has not been evaluated. Source: Siobal, M. Pulmonary Vasodilators. Respir Care 2007;52(7):885–899.
Phosphodiesterase 5 inhibitors

![Chemical structure of sildenafil]

Improving outcomes in congenital heart disease with sildenafil.

- PH is a disease of "pre-disposed" individuals. Imbalance between vasodilators as well as substances involving control of pulmonary vascular tone is presumed to be responsible for pathobiology. These include increase in thromboxane and endothelin and decrease in prostacycline and nitric oxide.

- Post-mortem studies suggest that pulmonary vasoconstriction, leading to medial hypertrophy, may occur early in course of the disease and may precede development of plexiform lesions and other fixed pulmonary vascular changes in some children. It is possible that the non-responders in our study had irreversible vascular changes.

- The patients with CHD with PH are at increased risk of post-operative pulmonary hypertensive crisis (2), which is characterized by a sudden increase in pulmonary vascular resistance (PVR) that results in low cardiac output from right ventricular failure. Pre and peri-operative inhaled nitric oxide and epoprostenol have been proven to be useful in preventing such complications by releasing cGMP or cAMP respectively. Therefore, pulmonary vascular reactivity is tested pre-operatively by administering inhaled nitric oxide or prostacycline. The responders are most likely to be benefited by surgery.

Source: S. Daga, C. Valvi, S. Janwale & M. Manivachagan: Sildenafil for Pulmonary Hypertension associated with Congenital Heart Defect. Journal of Pediatrics and Neonatology. 2007 Volume 7 Number 2

Sildenafil (Revatio)

New York Heart Association (NYHA) Class II-IV pulmonary arterial hypertension. Sildenafil is an active vasodilator. Sildenafil is currently approved for patient with PAH in the formulation of Revatio. 20 mg three times daily is the current recommendation by the FDA, but severe PAH may often require higher, and more frequent, dosing. Side effects of sildenafil include headache, back pain, and flushing.

Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 667. This solubility allowed Nahata and workers to compound sildenafil elixir for pediatric PH. Several toxicologic studies and cases have reported minimal side effects when accidentally ingested in adult dosages. Dosing: Initial dose of 0.25 to 0.5 mg/kg given orally every 4 to 8 hours is recommended for pediatric patients with pulmonary hypertension. Dose titration should be based on response. Although no maximum dose has been determined, doses above 2 mg/kg every 4 hours may not provide additional benefits.

Sources:
Sildenafil (Revatio) should not be used in children with pulmonary arterial hypertension. A safety alert was issued by the US Food and Drug Administration (FDA) in August 2012 that described revisions to the prescribing information due to an increased risk of death in children with PAH who are treated with high doses of sildenafil. These labeling changes were based on a randomized, double-blind, placebo-controlled clinical trial of 234 patients with PAH, aged 1-17 years with mild-to-moderate symptoms at baseline. A direct dose-related effect on mortality was observed, with the highest dose having the worst outcome. The hazard ratio for high dose compared with the low dose was 3.5 (p=0.015). Deaths were first observed after about 1 year and then occurred at fairly constant rates within each group. The lower doses of sildenafil were not effective in improving exercise ability in children with pulmonary hypertension.

There is theoretical support for the use of combination vasodilator therapy in patients with IPAH.

Phosphodiesterase (PDE5) inhibitors

<table>
<thead>
<tr>
<th>Sildenafil citrate (REVATIO®) Pfizer Labs June 2005</th>
<th>oral 20mg three times/day</th>
<th>Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil (CIALIS®) Eli Lilly FDA approved</td>
<td></td>
<td>No FDA approved indications for PAH or clinical evidence to support use for PAH</td>
</tr>
<tr>
<td>Vardenafil (LEVITRA®) FDA approved</td>
<td></td>
<td>No FDA approved indications for PAH or clinical evidence to support use for PAH</td>
</tr>
</tbody>
</table>

Prostacyclin analogues
**Prostacyclin analogues** enable the vessels in the lungs to expand and allow blood to move through them with less resistance (vasodilation). Prostaglandins & prostacyclins (PGI2) work by cAMP-mediated 2nd messenger smooth muscle relaxation. These drugs may be given by continuous IV infusion, infusion under the skin, or as an inhaled therapy. Researchers exploring other delivery methods for prostanoids, including oral administration (Prostacyclin is related to eicosanoids).


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**Prostaglandin analogues, (prostacyclins or prostanoids)**

- Flolan Epoprostenol (intravenous)
- Iloprost (inhaicable)
- Treprostinil (Remodulin) subcutaneous drip from modulating pump.
- Half-life is 4 minutes, Epoprostenol usually continuous in a PICC or central line, in pulmonary hypertension.

Source: [http://www.consumerhi.com/topic/pphmeds](http://www.consumerhi.com/topic/pphmeds)

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<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>FDA approval date</th>
<th>Route(s) of Administration</th>
<th>Dose range</th>
<th>FDA Approval Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol sodium</td>
<td>Flolan</td>
<td>GlaxoSmithKline</td>
<td>1995</td>
<td>Continuous IV infusion via central venous catheter using an antemaculation infusion pump</td>
<td>1 to 20 ng/kg/min</td>
<td>Long-term treatment of primary pulmonary hypertension and pulmonary hypertension associated with the systemic spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy</td>
</tr>
<tr>
<td>Iloprost sodium</td>
<td>Iloprost (VENTAVIS)</td>
<td>Asteleco, Ltd.</td>
<td>2004</td>
<td>Inhalation via nebulizer/ether of two pulmonary drug delivery devices</td>
<td>2.5 to 5 mcg, 5 to 9 times/day</td>
<td>Treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class II or IV symptoms. Tyrasus and Ventavis low/no history in kids</td>
</tr>
<tr>
<td>Treprostinil sodium</td>
<td>Remodulin</td>
<td>United Therapeutics Corp.</td>
<td>2002</td>
<td>Continuous SC infusion IV infusion</td>
<td>0.625 to 1.25 ng/kg/min</td>
<td>Treatment of PAH in patients with NYHA Class IV symptoms, to diminish symptoms associated with exercise in patients who require transition from Flolan, to reduce the rate of clinical deterioration.</td>
</tr>
</tbody>
</table>

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*Tyrasus and Ventavis low/no history in kids*
Establish medical necessity:

"...continuous intravenous infusion of epoprostenol sodium (Flolan®) or continuous subcutaneous infusion of treprostinil sodium (Remodulin™), for treatment of patients with idiopathic pulmonary arterial hypertension or pulmonary hypertension associated with connective tissue disorders, such as scleroderma or congenital heart defects.

This therapy has been shown to improve cardiopulmonary hemodynamics and increase exercise tolerance and, in the case of epoprostenol, probably survival for patients who have been unresponsive to conventional medical therapy. In 2004, the Food and Drug Administration (FDA) approved intravenous use of treprostinil (Remodulin™) for those who are not able to tolerate a subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II, III, IV symptoms to diminish symptoms associated with exercise.

According to the FDA product information (NDA 21-2722/S-005), subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min. Remodulin is also indicated to diminish the rate of clinical deterioration in patients requiring transition from Flolan; the risks and benefits of each drug should be carefully considered prior to transition.
Other Adjunctive Therapies:
- Anticoagulation
- Correct hypovolemia
- Diuretics
- Digoxin
- Intravenous inotropes: low dose Dobutamine / Dopamine in severe right heart failure with hypoperfusion.
- Transplantation: Lung or heart - lung (PH sec. to complex CHD).
- Atrial Septostomy (investigational)
Available at:

Summation and Discussion:
Studies in children by Barst and colleagues have shown that long-term vasodilator therapy increases the short-term survival rate.\(^1\)
The acute responder group had a trend toward long-term survival when compared with the nonresponder group.
The 5-year survival rate was 86% in the responders compared with 33% in the nonresponder group.
Patients not responding to acute prostacyclin therapy may also be placed on long-term intravenous prostacyclin therapy, although the long-term results are not as favorable.

The rationale for this approach is that some degree of pulmonary vascular remodeling occurred with long-term vasodilator therapy, especially in children. Additionally, this palliative measure may be reasonable while other newer therapeutic approaches are under development.

Finally, this approach may allow extra time before lung transplantation. Because of the long wait for an organ, listing nonresponders for lung transplantation at the time of that determination is reasonable.
In addition, an important aspect of the rationale for vasodilator therapy is that some patients, especially children, may not respond to short-term drug testing but may nevertheless undergo vascular remodeling with long-term vasodilator therapy.
Conclusion: Each patient must have their own prescription customized to their WHO-based diagnosis, severity and response to therapy.

Combinations of prostacyclin analogues, endothelin receptor inhibition, and/or phosphodiesterase-5 inhibition may have a synergistic effect by working on the multiple pathways that may promote vasoconstriction.

References