Inhaled Epoprostenol (Flolan®)
Via Mechanical Ventilator
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Learning Objectives
- Describe what is Epoprostenol (Flolan)
- Review how it works
- Summarize the indications/contraindications
- Review the equipment set-up and how to administer it via a ventilator circuit.
- Examine a few case applications
- Share some additional resources

What is Epoprostenol (Flolan®)?
- Flolan®, or epoprostenol, is a synthetic prostacyclin which relaxes vascular smooth muscle cells.
- Results in vasodilation of the pulmonary & systemic vasculature in a dose-dependent manner.
- Indications:
  - Pulmonary hypertension
  - Acute right heart dysfunction
  - Hypoxemia related to pulmonary vasoconstriction
- In addition, prostaglandin has an inhibitory effect on platelet aggregation.
- Finally, prostaglandin inhibits activation of leukocytes and monocytes during the inflammatory reaction.

What's inhaled Epoprostenol (cont.)
- Welte and his colleagues (1993) reported that inhaled PGI2 resulted in selective PA vasodilation in dogs.
- Causes selective pulmonary vasodilation, while not causing systemic hypotension.
- Analog drugs: Synthetic analogs of prostacyclin (PGI2).
  - Treprostinil (marketed under the trade names Remodulin for infusion and Tyvaso for inhalation).
  - Inhaled iloprost (Ventavis) by Mask and nebulizer.
- It's NOT a medical gas like Nitric Oxide… but rather a nebulized drug!!!
The use of Epoprostenol causes marked pulmonary vasodilatation.
Also does so while maintaining gas exchange and systemic arterial pressure.
There is a significant decrease in mean pulmonary artery pressures (PAPs) without noticeable change in mean arterial pressures.

Primary Pulmonary Hypertension
Utilized in conjunction with a Ventricular Assist Device, (most commonly Right Ventricular Dysfunction).
Post-Op – To reduce and maintain PA pressures allowing for Heart rest, recovery, and healing.
To treat low (EF) Ejection Fraction of < 20%.
Treatment of hypoxemia secondary to:
  - ARDS
  - Acute Lung Injury

Comparable beneficial effects of pulmonary vasodilatation without affecting systemic systems:
  - Reduced pulmonary artery pressure
  - Reduced pulmonary vascular resistance
  - Reduced transpulmonary gradient

Improved oxgenation.
Lack of data showing increased survival for ARDS patients.

The delivery system(s) are relatively simple
The drug is generally available in most hospitals and more available than inhaled Nitric Oxide.
Much less expensive than inhaled Nitric Oxide.
Data tend to support overall effectiveness in a clinical setting for treating:
  - Pulmonary Htn
  - Pul vasoconstriction with ARDS
Cost Differences Between Epoprostenol and Nitric Oxide???

- **Cost**
  - Nitric Oxide ~ $100/hour or $2,400/day
  - Epoprostenol ~ Approx. $220/day

- Epoprostenol lacks the toxic effects/metabolites of nitric oxide and therefore does not need a complicated delivery system.
- Epoprostenol can inhibit platelet aggregation.
- Epoprostenol does not bind with hemoglobin (no increase in methemoglobin)

Potential Hazards and Side Effects

- In general, Epoprostenol has a favorable safety (Risk to benefit) profile.
- Rarely can exacerbate hypotension & bleeding.
  - Not reported in typical dose range
  - Avoid aerosolized PGI2 during active pulmonary hemorrhage
- More common side effects include:
  - Flushing
  - Headache
  - Nausea & vomiting
  - Hypotension
  - Anxiety
  - Chest pain
  - Dizziness

The Research Evidence

- Limited, but growing body of evidence
- Mostly case reports and small studies
  - Some case studies
  - Many studies had a small number of patients/subjects
  - Few experimental designs (control and placebo groups)
  - Not all results may be attributable to Flolan
  - Incomplete data for some variables, such as PVR, wedge pressure, CVP

Research Evidence (cont.)

- Rabinovich, et al. (2011) *Chest* Physician–Review Article: Inhaled Epoprostenol is as effective as iNO for Short-term mgmt of pulmonary hypertension and impaired oxygenation
  - Potentially fewer side effects
  - Lower costs
  - Greater ease of administration
  - Further randomized, controlled studies are needed
Research Evidence (cont.)

- De Wet, et al. (2004) - Prospective interventional study of 126 cardiothoracic surgical patients with pulmonary Hypertension
  - PGI2 decreased mean PA pressures without altering mean arterial pressure
  - There was a significant improvement in the PaO2/FiO2 ratio in patients with refractory hypoxemia
- Haché, et al. (2001) Chart review of 27 patients who received inhaled PGI2 over a one-year period
  - Selective pulmonary vasodilation occurred in 78% of patients
  - Improvement in PaO2/FiO2 ratio in 88%
  - Concluded that inhaled PGI2 can be useful in the treatment of patients with pulmonary hypertension & severe hypoxia

Evidence: Children and Neonates

- Brown AT, et al., (2012): Inhaled Epoprostenol is effective in treating PH in pediatric patients, but may be more so for neonates.
- Dahlen P, et al., (2004): Randomized, controlled trial, suggests that aerosolized prostacyclin improves oxygenation in children with ALI. Further trials are needed

Settings in which Epoprostenol may be used

- Though it may be used on spontaneously breathing patients
- Patients should in an area capable of continuous cardiac monitoring.
  - Post-Open Heart ICU
  - CCU
  - MICU/SICU
  - OR
  - CATH LAB

Continuation in Transit:

- When started for mechanically ventilated patients, it is recommended that there be no break in drug delivery during transport of the patient.
- When transported from area to area there needs to be an oxygen cylinder to nebulize the Flolan and another cylinder to ventilate the patient.
Medication Dosage

- At St. Joseph’s, a dose schedule based on weight:
  - Dose based on patient’s ideal body weight (IBW)
    - Male: \(50 + 2.3\) (height in inches – 60)
    - Female: \(45 + 2.3\) (height in inches – 60)
  - Pharmacy to prepare Epoprostenol (Flolan)
  - 30,000 nanograms / 50 mL in Aerogen respiratory syringe for inhalation therapy.

### Dose Schedule

<table>
<thead>
<tr>
<th>Patient's IBW</th>
<th>Epoprostenol Dose: nanogram/kg/min</th>
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<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>40 kg</td>
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<td>90 kg</td>
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<tr>
<td>100 kg</td>
<td>2</td>
</tr>
<tr>
<td>&gt;100 kg</td>
<td>2</td>
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</tbody>
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- start at 50 nanogram/kg/min, titrate down to 10 nanogram/kg/min as tolerated
- start at 50 nanogram/kg/min, wean as tolerated.
- Do not decrease dose by more than 10ng/kg/min every 30 minutes.

Condition Specific Dosing & Weaning

- **Hypoxic respiratory failure**: start at 50 nanogram/kg/min, titrate down to 10 nanogram/kg/min as tolerated
- **Pulmonary hypertension/right ventricular dysfunction**: start at 50 nanogram/kg/min, wean as tolerated.

Storage:
- Epoprostenol will be received from pharmacy in appropriate dosage in an Aerogen syringe as ordered by the physician.
- It should be stored in the unit medication refrigerator until needed.
- It can be refrigerated up 40 hours after being prepared by pharmacy.
- It is further recommended that that there be an additional new syringe of Epoprostenol available, to avoid any disruption to administration.
**Epoprostenol Equipment Set-up**

- Confirm physician order, proper medication/strength received from pharmacy.
- The mechanical ventilator will be assembled with a heated circuit and humidification device.
- Insert Aerogen nebulizer on the inspiratory limb, just proximal (before) the humidifier reservoir.
- Assemble Medfusion pump, Aerogen controller and tubing.
- Insert aerogen respiratory syringe.
- Connect tubing to the Aerogen nebulizer.
- Activate Aerogen controller and Medfusion pump at desired dose in ML/hr.
- Ensure that 2 hepa filters located on the expiratory limb of the circuit.
  - The first filter is just after the patient wye.
  - The second is at the end of the circuit prior to the collection bottle.
- The Hepa filters should be changed every three hours or if the peak airway pressures reflect an unexpected increase.
- Monitor patient for response to therapy.

**Special Considerations with Ventilator Administration**

- Glycine buffer makes aerosol sticky
- Change expiratory filters at least Q3H or sooner to prevent sticking of expiratory valve and auto PEEP
- Ventilation pressures may vary due to nebulizer flow into circuit and/or drug deposits in filters.
Complete Set-Up

- Full strength 10mcg/ml
- Half strength 5mcg/ml
- Quarter strength 2.5mcg/ml

- Typical initial dose is 10mcg/ml, at 8ml/hr.
- Add 24ml of drug into a Mini Heart Nebulizer.
- Insert nebulizer into the inspiratory limb of the circuit at the wye.
- Cover the nebulizer to protect the contents from light due to a light sensitivity.
- Run nebulizer at a flow rate of 2 lpm.

Alternate Set-up

- Other dosage protocols call for the are 3 recommended dosages:
  - Full strength 10mcg/ml
  - Half strength 5mcg/ml
  - Quarter strength 2.5mcg/ml
- Typical initial dose is 10mcg/ml, at 8ml/hr.
- Add 24ml of drug into a Mini Heart Nebulizer.
- Insert nebulizer into the inspiratory limb of the circuit at the wye.
- Cover the nebulizer to protect the contents from light due to a light sensitivity.
- Run nebulizer at a flow rate of 2 lpm.

The Mini Heart nebulizer must be shielded from light.
An oxygen blender must be used to power the nebulizer to achieve the same FiO2 as the ventilator settings.

Termination of Epoprostenol:
- An order to discontinue the medication must be obtained prior to discontinuation.
- PA pressures and oxygenation should be documented and followed closely for at least 30 minutes following termination.
- Epoprostenol’s effect is completely resolved within 24 minutes of termination.
- In the event of elevated PA pressures or deterioration of oxygenation, resumption should be considered.

Case 1 – Clinical Use – Cardiac
- 69 YO male with a history of cardiomyopathy is intubated and mechanically ventilated due to a severe exacerbation of CHF. He currently has Swan Ganz catheter in place and his cardiac output is 2.9 L and PAP is 52/35 torr. His FiO2 was recently raised to 65% to maintain an SPO2 of 92%.
- Patient was started on Flolan, 10mcg/ml, at 8ml/hr.
  - Within 6 hours: PAP decreased to 35/19 torr, CO 3.6 L, SPO2 95% on FiO2 50%
  - Within 2 days, other clinical indicators (renal function) improved.
  - Patient successfully extubated 5 days later.

Weaning of Epoprostenol:
- Initial protocol calls for titration down to 10 nanogram/kg/min as tolerated.
- Do not decrease dose by more than 10ng/kg/min every 30 minutes.
- Under alternate approach titrate medication, from 10mcg/ml, to 5mcg/ml, and then to 2.5mcg/ml, prior to discontinuation.
- Titration should be reconsidered and physician contacted if a patient demonstrates an increase of PA pressures or decrease in oxygenation within 30 minutes of titration or discontinuation.

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57 Yo intubated/ventilated female post-trauma patient becomes septic and develops ARDS. Her CXR has bilateral obtuse infiltrates (ground-glass appearance), she has refractory hypoxemia (P:F ratio < 150) and A/W pressures have increased to the mid-40s cm H2O.

She was switched to PCV (from volume control) and started on Flolan, 10mcg/ml, at 8ml/hr.
- Within one day, P:F increased to 245, FIO2 successfully weaned to 50% from 75% . ABG’s were within acceptable limits.
- One week later the patient was successfully extubated.

Use of inhaled Epoprostenol is a promising and cost effective therapy for the treatment of pulmonary hypertension & hypoxia of various origins.

Therapy must be based on:
- Suitable patients
- Proper procedures and training
- Continual therapy, until intentionally withdrawn

Further studies are required to determine dose–responsiveness, optimal condition of utilization, and impact on survival.

The pursuit of its use requires the collaborative effort of respiratory therapists, nurses, physicians and pharmacists.

Additional References

- US Food & Drug Administration: [http://www.accessdata.fda.gov/drugsatfda](http://www.accessdata.fda.gov/drugsatfda)
- **epoprostenol** at [Dorland’s Medical Dictionary](http://www.medical-dictionary.net)
- Rabinovich, et al. (2011) *Chest Physician*–Review Article: Inhaled PG1 is as effective as iNO for Short–term mgt of pulmonary hypertension and impaired oxygenation.