

Respiratory Therapeutics For Pulmonary Arterial Hypertension

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<http://www.geocities.com/jonesapjr/index.html>

Objectives

- ^ Describe the etiologies, manifestations and management of pulmonary arterial hypertension.
- ^ Describe the current status of research on the actions, effects, indications and contraindications for agents used to treat pulmonary arterial hypertension.

Pulmonary Arterial Hypertension (PAH)

- ◆ Elevated pulmonary artery pressure
- ◆ Normal = 13 mm Hg (mean)
- ◆ Hypertension = 25 mm Hg (mean) at rest

Link to Cleveland Clinic Pulmonary Hypertension Web Page
<http://www.clevelandclinic.org/health/health-info/docs/0600/0622.asp?index=6530>

Etiologic Classifications (before 1998)

- ◆ Primary- etiology is uncertain
- ◆ Secondary- hypertension secondary to other conditions; e.g., COPD

Etiologic Classifications (WHO Groups 1993)

- ◆ Group I - Pulmonary arterial hypertension (PAH)
 - ^ idiopathic
 - ^ familial
 - ^ persistent pulmonary hypertension of newborns (PPHN)
 - ^ associated
 - f portal
 - f collagen dx
 - f HIV
 - f toxins; e.g., Fen -Phen

Link to Pulmonary Hypertension Association
<http://www.phassociation.org/Learn/What-is-PH/whoclass.asp>

Etiologic Classifications (WHO Groups 1993)

- ◆ Group I - Pulmonary arterial hypertension (PAH)
- ◆ Group II - Pulmonary hypertension associated with left heart disease
- ◆ Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
- ◆ Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- ◆ Group V - Miscellaneous

Acute PAH and Cardiac Interventions

- ◆ reperfusion injury- return of blood flow to ischemic myocardium- 'stunned myocardium'
- ◆ prolonged postischemic dysfunction of viable tissue salvaged by reperfusion.
 - △ sequel to:
 - f coronary thrombolysis
 - f percutaneous coronary interventions
 - f coronary artery bypass
 - f heart transplantation

Link to AHA article on reperfusion injury
<http://circ.ahajournals.org/cgi/reprint/105/20/2332>

Acute PAH and Cardiac Interventions

- ◆ reperfusion injury mediators
 - △ oxygen free radicals
 - △ endothelial dysfunction- endothelin release (potent vasoconstrictor)
 - △ altered calcium handling
 - △ altered cardiac metabolism (anaerobic)
- ◆ may result in myocyte death
- ◆ endothelin release causes pulmonary hypertension- rationale for postoperative pulmonary vasodilators

NYHA Functional Classifications

- ◆ Class I – no limitation of physical activity.
Ordinary physical activity
- ◆ Class II – slight limitation of physical activity.
 - △ comfortable at rest.
 - △ ordinary physical activity- undue dyspnea or fatigue, chest pain, etc.

Link to NYHA Functional Classifications
<http://www.cochranfoundation.com/docs/nyha-class.htm>

NYHA Functional Classifications

- ◆ Class III – marked limitation of physical activity.
 - △ comfortable at rest.
 - △ minimal activity causes dyspnea, fatigue, chest pain
- ◆ Class IV – inability for physical activity without symptoms.
 - △ right heart failure.
 - △ dyspnea and/or fatigue at rest.
 - △ discomfort with any physical activity.

PAH Manifestations

- ◆ severe hypoxemia, esp. in presence of anatomic shunt
- ◆ dyspnea, fatigue
- ◆ syncope
- ◆ chest pressure or pain.
- ◆ edema- pedaledema, ascites
- ◆ tachycardia, palpitations
- ◆ can mimic asthma, especially in young persons

Link to Medscape pulmonary hypertension
http://www.medscape.com/viewarticle/456942_3

PAH Management

PAH Management

⤴ Algorithm for management

Link to page with treatment algorithm for PHA (slide 7 on the page)
<http://www.cardiosource.com/ExpertOpinions/hottopics/article.asp?paperID=54>

PAH General Management

- ◆ Oxygen
- ◆ Anticoagulants
- ◆ Diuretics
- ◆ Potassium
- ◆ Inotropic agents

Calcium channel blockers

- ◆ amlodipine (Norvasc)
- ◆ nifedipine (Procardia)
- ◆ diltiazem (Cardizem)
- ◆ verapamil (Isoptan)

Link to calcium channel blocker information
http://en.wikipedia.org/wiki/Calcium_channel_blocker

Endothelin antagonist

- ◆ bosentan (Tracleer)
- ◆ oral administration

Link to information on endothelin antagonists
http://www.medscape.com/viewarticle/423213_3

Phosphodiesterase inhibitors

- ◆ sildenafil (Viagra)
- ◆ vardenafil (Levitra)
- ◆ tadalafil (Cialis)
- ◆ milrinone (Primacor)

Link to information on phosphodiesterase inhibitors
<http://cvpharmacology.com/vasodilator/PDEI.htm>

Nitric oxide gas

- ◆ selectively dilates pulmonary vessels, because it is rapidly taken up by hemoglobin and neutralized
- ◆ Effects:
 - ⤴ decreased pulmonary vascular resistance
 - ⤴ improved V/Q matching

Link to nitric oxide and PAH
<http://cvpharmacology.com/vasodilator/PDEI.htm>

Nitric oxide gas

- ◆ **Indications:**
 - △ PPHN- FDA- approved
 - △ ARDS- off label use
 - f short-term improvement in oxygenation
 - f no improvement in survival
 - △ Right ventricular failure, for patients with left-ventricular assist devices
 - △ Independent lung ventilation

Link to nitric oxide and ARDS
<http://www.medscape.com/viewarticle/417909>

Link to nitric oxide and postoperative RV failure
<http://meeting.chestjournal.org/cgi/content/abstract/128/4/302S>

Nitric oxide gas delivery- iNOvent

Link to iNOvent delivery system
http://www.gehealthcare.com/us/en/anesthesia/products/anelifesupport_inovent.html

Nitric oxide donors

- ◆ **agents**
 - △ aerosolized nitroprusside (Nipride)
 - △ aerosolized nitroglycerine
- ◆ **require additional studies**

Links to aerosolized nitroprusside
<http://erj.ersjournals.com/cgi/content/abstract/18/1/15>
<http://www.chestjournal.org/cgi/reprint/119/1/128>

Prostacyclins

- ◆ **endogenous, produced in vascular endothelium**
- ◆ **non-acute indications**
 - △ WHO Group I
 - △ NYHA Class III- IV severity
 - △ failure of other medications

Prostacyclins

- ◆ **prostaglandin i2 analog**
- ◆ **iloprost (Ventavis)**
 - f potency \geq nitric oxide
 - f effect duration = 120 min
 - f aerosol 2.5-5.0 mcg 6-9 times daily
 - f unit doses 2.5 or 5.0 mcg
 - f specific nebulizers required
 - f not for acute care setting

Link to information on iloprost
<http://en.wikipedia.org/wiki/Iloprost>

Prodose AAD (TM Respirationics)

- ◆ **compressor-driven**
- ◆ **microchip-controlled dosage delivery**
- ◆ **aerosol during inspiration, only**
- ◆ **adjusts delivery to patient's ventilatory pattern**



Link to Respirationics AAD nebulizers
http://ineb.respirationics.com/aad_products.asp

I-neb AAD (TM Respirationics)

- ◆ most recent development
- ◆ vibrating mesh nebulization
- ◆ microchip-controlled delivery



Epoprostenol (Flolan)

- ◆ Short-acting PGI-2
- ◆ alternative to iNO in acute care setting
- ◆ less expensive than iNO
- ◆ duration of action 3-5 min.
- ◆ delivery
 - ▲ continuous infusion
 - ▲ aerosol

Link to Flolan information
http://www.flolan-center.com/pages/flolan_effective.html

Epoprostenol (Flolan)

- ◆ Delivery by infusion
 - ▲ same indications as Ventavis for non-acute setting
 - ▲ cost > \$100,000/year
 - ▲ home care setting- patient has infusion pumps

Epoprostenol (Flolan)

- ◆ Contraindication- CHF with severe left-ventricular failure
- ◆ Precautions
 - ▲ abrupt withdrawal can result in rebound, death
 - ▲ should be used only by clinicians experienced with PAH
 - ▲ must be reconstituted with specific solution

Flolan Acute Care Aerosol Delivery

- ◆ Indications
 - ▲ severe PAH, refractory to standard therapy
 - f reperfusion injury; e.g., post-cardiopulmonary bypass
 - f portal-pulmonary hypertension
 - f independent or single-lung ventilation

Flolan Acute Care Aerosol Delivery

- ◆ Indications
 - ▲ severe PAH, refractory to standard therapy
 - f ARDS
 - f PPHN
 - f RV failure
 - f Septic shock

Link to information on iNO and prostacyclin in septic shock
<http://www.medscape.com/medline/abstract/8905421?prt=true>

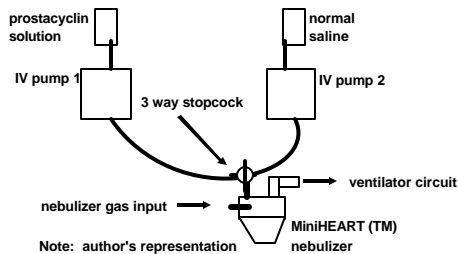
Flolan Acute Care Aerosol Delivery

- ◆ Potential benefits of Flolan
 - ▲ increased splanchnic (gastrointestinal) perfusion
 - ▲ inhibition of platelet aggregation-antithrombotic, anti-inflammatory
 - ▲ stimulation of endogenous NO

Flolan Acute Care Aerosol Delivery

- ◆ Adverse effects
 - ▲ bleeding, due to platelet inhibition
 - ▲ hypotension (spillover to systemic circulation)
 - ▲ flushing
 - ▲ nausea, vomiting
 - ▲ chest pain
 - ▲ rebound PAH, with abrupt withdrawal

Flolan Aerosol Delivery System



Flolan Continuous Aerosol Delivery

- ◆ Flolan reconstituted in pharmacy
- ◆ Flolan and NSS to IV pumps
- ◆ IV pumps to mini-heart nebulizer
- ◆ O₂ flow @ 2 L/min fro output = 8 mL/H
- ◆ pumps adjusted for dosage = 10-50 ng/kg IDBW/min
- ◆ titration charts used to adjust IV pump flows

Aeroneb Pro (TM) Nebulizer

- ◆ currently undergoing trial for Flolan delivery (Siobal, M. personal communication 8/2007)
- ◆ this represents off-label use for this device.



Image courtesy of Aerogen, Inc.
Link to Aeroneb (TM)
<http://www.aerogen.com/aeroneb-pro-micropump-nebulizer-system.html>

Flolan Continuous Aerosol Delivery

- ◆ interruption of delivery can result in rebound, death
- ◆ during transports, nebulizer maintained in vertical position
- ◆ weaning dosages ordered by MD
- ◆ all personnel have well-defined roles and responsibilities.

Flolan Continuous Aerosol Delivery

- ◆ precautions/contraindications
 - △ may cause systemic hypotension
 - △ may cause increased pulmonary shunting
 - △ may cause hemorrhage
 - △ Flolan is photosensitive, so must be shielded from light
 - △ minimize transports, ventilator adjustments, suctioning.

Alternatives to Flolan

- ◆ nebulized iloprost in NSS
 - △ longer duration
 - △ 10 mcg/mL over 20 min.
 - △ administered in OR during CPB

Link to inhaled iloprost following cardiopulmonary bypass
Kassiani T, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. Can J Anesth 2002;49(9):963-967.

Alternatives to Flolan

- ◆ nebulized milrinone (Primacor)- prevents endothelial dysfunction post- CPB
- ◆ nebulized milrinone and Flolan
 - △ additive effects
 - △ separate nebulizers required

Link to nebulized milrinone and Flolan
<http://www.anesthesia-analgesia.org/cgi/content/full/93/6/1439>

Alternatives to Flolan

- ◆ treprostinil (Remodulin)
 - △ formulated for IV or SC injection
 - △ four hour duration of action
 - △ additional study required for aerosol route

Links to treprostinil (Remodulin)
<http://jap.physiology.org/cgi/reprint/99/6/2363>
http://www.rxlist.com/cgi/generic/remodulin_cp.htm

Summary and Review

- ◆ PAH defined- mean PAP >25 mm Hg at rest
- ◆ Etiologic classifications (WHO groups)
- ◆ Functional classifications (NYHA classes)
- ◆ PAH manifestations

Summary and Review

- ◆ PAH management algorithm
- ◆ General management- O₂, etc.
- ◆ Calcium channel blockers
- ◆ Endothelin antagonists
- ◆ Phosphodiesterase inhibitors

Summary and Review

- ◆ Nitric oxide donors- nitroprusside
- ◆ Nitric oxide gas
 - △ Approved for PPHN
 - △ iNOvent required
 - △ costly

Summary and Review

- ◆ Prostacyclins
 - △ Prostacyclin analogs (iloprost)
 - △ Prostacyclin- PGI₂ (Flolan)
 - △ Aerosol delivery systems
 - f Respironics AAD (TM) devices for iloprost
 - f Aeronex Pro (TM) device for Flolan
 - f Precautions for aerosol delivery
- ◆ Alternatives, combination therapeutics
 - △ Milrinone and Flolan
 - △ intravenous, subcutaneous treprostinil

END

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