

Respiratory Therapeutics For Pulmonary Arterial Hypertension

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Learning Objectives

- ^ Explain the etiologies, pathophysiology, manifestations and management of pulmonary arterial hypertension.
- ^ Explain the actions, effects, indications, contraindications and administration techniques for agents used to treat pulmonary arterial hypertension.

Etiologies, Pathophysiology and Classifications

Definition

- ^ Elevated mean pulmonary artery pressure (PAP) > 25 mm Hg (mean) at rest
- ^ Normal = 13 mm Hg (mean)

Click for video on pulmonary hypertension (4 min.)
<https://www.youtube.com/watch?v=SFbCh2wYSxQ>

Pathophysiology

- ^ Vascular analog of asthma
- ^ Increased resistance to pulmonary blood flow, due to:
 - ◆ vasoconstriction
 - ▶ hypoxemia
 - ▶ endothelin
 - ▶ thromboxane
 - ▶ impaired endogenous NO
 - ▶ impaired endogenous prostacyclins

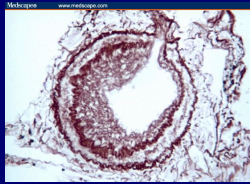
Click to see mediator pathways
<https://err.ersjournals.com/content/errev/19/118/331/F1.large.jpg>

Pathophysiology

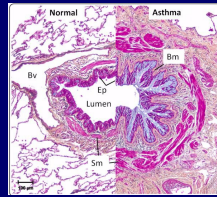
- ^ Increased resistance to pulmonary blood flow, due to:
 - ◆ vascular remodeling
 - ▶ endothelin
 - ▶ coagulation mediators

Pathophysiology

▲ arterial and airway remodeling



arterial



airway

Asthma vs. pulmonary hypertension

Condition	Asthma	PAH
Etiologies	Numerous	Numerous
Pathology	Broncho-constriction Airway remodeling	Vaso- constriction Vascular remodeling
Patho-physiology	Increased WOB	Increased rt. ventricular work
Therapeutics	Bronchodilators Corticosteroids	Vasodilators Endothelin antagonists

Risk factors

- ▲ Genetic predisposition - early age
- ▲ Female gender (female:male = 2:1)
- ▲ Pregnancy
- ▲ Cigarette smoking
- ▲ Congenital heart disease with left-to-right shunt
- ▲ Chronic thrombotic/embolic disease
- ▲ Chronic hypoxemia
 - ◆ pulmonary disease
 - ◆ high altitude residence
- ▲ Peritoneal dialysis

Etiologic Classifications (WHO Groups)

- ▲ Group I - Pulmonary arterial hypertension (PAH)
 - ◆ idiopathic- unknown etiology
 - ◆ familial - inherited
 - ◆ persistent pulmonary hypertension of newborns (PPHN)

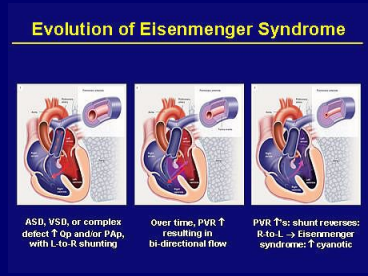
FYI - click to see The Who
<http://www.youtube.com/watch?v=aOUqRZkR8dE>

Etiologic Classifications (WHO Groups)

- ▲ Group I - Pulmonary arterial hypertension (PAH)
 - ◆ associated
 - ▶ portal hypertension
 - ▶ collagen disease
 - ▶ HIV infection
 - ▶ toxins; e.g., Fen-Phen (litigation)
 - ▶ congenital shunts - Eisenmenger's syndrome

Etiologic Classifications (WHO Groups)

▲ Eisenmenger's syndrome



Etiologic Classifications

- ^ Group II - Pulmonary hypertension associated with left heart disease
 - ◆ left-sided atrial or ventricular disease
 - ◆ left-sided valvular disease

◆ Etiologic Classifications

- ^ Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
 - ◆ COPD
 - ◆ interstitial lung disease
 - ◆ sleep-disordered breathing
 - ◆ chronic high-altitude exposure

Etiologic Classifications

- ^ Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- ^ Group V - Miscellaneous
 - ◆ sarcoidosis
 - ◆ histiocytosis
 - ◆ compression of pulmonary vessels (neoplasms)

Acute PAH and Cardiac Interventions

- ^ Reperfusion injury - return of blood flow to ischemic myocardium - 'stunned myocardium'
- ^ Prolonged post-ischemic dysfunction of viable tissue that was salvaged by reperfusion.
- ^ Can affect all organs

Address for excellent article on reperfusion injury
<http://circ.ahajournals.org/cgi/reprint/105/20/2332>

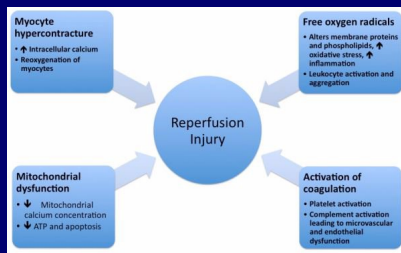
Cardiac reperfusion injury

- ^ Can occur after:
 - ◆ coronary thrombolytic therapy
 - ◆ percutaneous coronary interventions
 - ◆ coronary artery bypass
 - ◆ heart transplantation

Cardiac reperfusion injury

- ^ Reperfusion injury factors
 - ◆ oxygen free radicals
 - ◆ altered calcium handling
 - ◆ cardiac anaerobic metabolism
 - ◆ release of endothelin, causing:
 - ▶ vasoconstriction,
 - ▶ cellular proliferation - remodeling
- ^ May result in myocyte death, AKA apoptosis

Cardiac reperfusion injury



NYHA Functional Classifications

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

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 Diagnosis & Assessment

History

- ▲ Risk factors
 - ◆ gender
 - ◆ family hx
 - ◆ comorbidities; e.g., CHF, COPD
 - ◆ exposure to toxins, altitude
- ▲ Symptoms
 - ◆ progressive exertional dyspnea
 - ◆ dizziness, syncope
 - ◆ chest pain (angina)
 - ◆ peripheral edema

Physical signs

- ▲ Can mimic asthma, especially in young patients
- ▲ Cyanosis - advanced disease
- ▲ Abnormal heart sounds; e.g., pulmonary ejection click
- ▲ Jugular venous distention
- ▲ Hepatic enlargement

Click for video of PAH case (5.2 min)

<http://www.youtube.com/watch?v=hzQVBHWTko8&feature=related>

Diagnostic studies

- △ Electrocardiography - isolate cardiac disease
- △ Chest radiograph
- △ Oximetry, ABGs - hypoxemia
- △ PFTs - spirometry, DLCO
- △ Echocardiography
 - ◆ measure PAP
 - ◆ detect shunt (bubble test)

Click to see echocardiography in PAH (2 min.)
<http://www.youtube.com/watch?v=3yOdNyTH07g&feature=related>

Diagnostic studies

- △ VQ scans - to identify thromboembolism
- △ High resolution CT - identify emphysema, interstitial lung disease
- △ Heart catheterization
 - ◆ definitive diagnosis
 - ◆ assess severity
 - ◆ measure hemodynamic parameters

Diagnostic studies

- △ Pulmonary vasoreactivity test (like bronchial challenge)
 - ◆ NO, prostacyclin or adenosine are administered
 - ◆ to assess benefits of Ca⁺⁺ channel blockers

Evaluation of prognosis

- △ Complications
 - ◆ right heart failure (cor pulmonale)
 - ◆ thromboembolism - PAH caused by clotting and it causes clotting
 - ◆ pulmonary hemorrhage (often fatal)
 - ◆ dysrhythmias; e.g., PSVT

Evaluation of prognosis

- △ Clinical profile
 - ◆ age
 - ◆ comorbidities
 - ◆ etiology
 - ◆ presence of heart failure
 - ◆ speed of progression

Evaluation of prognosis

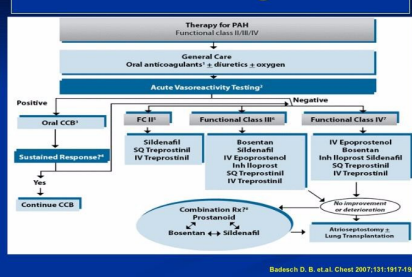
- △ Exercise capacity
 - ◆ Six-minute walk test - simple, inexpensive
 - ◆ Cardiopulmonary exercise testing
 - ▶ method of choice
 - ▶ standardizes exercise
 - ▶ measures parameters; e.g., VO₂MAX

PAH Management

PAH General Management (first line)

- ▲ Oxygen- reverses hypoxemic vasoconstriction
- ▲ Anticoagulants
- ▲ Diuretics
- ▲ Potassium
- ▲ Inotropic agents- increase myocardial contractility

PH treatment algorithm



Click for video on PAH treatment (12 min)
<https://www.youtube.com/watch?v=g6OldQ8NWms>

Calcium channel blockers

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

Endothelin antagonists

- ▲ Oral administration
- ▲ Adverse effects:
 - ◆ birth defects
 - ◆ hepatotoxicity
- ▲ Agents
 - ◆ bosentan (Tracleer)
 - ◆ ambrisentan (Letairis)
 - ◆ sitaxsentan (Thelin)

Endothelin antagonists

- ◆ Sitaxsentan Sodium (Thelin)
 - ▲ FDA approval under consideration
 - ▲ oral administration - once daily
 - ▲ selective endothelin inhibitor
 - ▲ under research for remodeling in asthma

Phosphodiesterase inhibitors

- △ theophylline - not for PAH
- △ sildenafil (Viagra)
- △ vardenafil (Levitra)
- △ tadalafil (Cialis)
- △ milrinone (Primacor) - nebulized for PAH from reperfusion injury
 - ◆ pulmonary vasodilator
 - ◆ positive inotrope

Nitric oxide (NO) gas

- △ Selectively dilates pulmonary vessels, because it is rapidly taken up by hemoglobin and neutralized
- △ Effects:
 - ◆ decreases pulmonary vascular resistance
 - ◆ improves V/Q matching by increasing blood flow to ventilated alveoli

Nitric oxide gas

- △ Indications:
 - ◆ Persistent pulmonary hypertension in newborns (PPHN)- FDA- approved
 - ◆ ARDS- off label use
 - ▶ short-term oxygenation improvement
 - ▶ no improvement in mortality
 - ◆ Right ventricular failure, for patients with left-ventricular assist devices
 - ◆ Independent lung ventilation- increases blood flow to 'good' lung

Nitric oxide gas delivery

- △ Disadvantages of NO
 - ◆ FDA-approved only for PPHN
 - ◆ additional equipment- iNOvent, monitors
 - ◆ additional training required for all
 - ◆ potential toxicity to caregivers
 - ◆ rebound PAH with cessation of delivery
 - ◆ bottom line- very costly

Nitric oxide donors

- △ Agents
 - ◆ aerosolized nitroprusside (Nipride)
 - ◆ aerosolized nitroglycerine
- △ Additional studies needed

Prostacyclins, prostanoids

- △ endogenous, produced in vascular endothelium
- △ prostaglandin i2 analogs (synthetic)
- △ non-acute indications
 - ◆ WHO Group I
 - ◆ NYHA Class III- IV severity
 - ◆ failure of other medications
- △ evidence favors effects on mortality

Prostacyclins

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

Prodose AAD (Respironics)

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



Image courtesy of Respironics

I-neb AAD (Respironics)

- ▲ vibrating mesh nebulization- similar to ultrasonic nebulizer
- ▲ microchip-controlled delivery



Image courtesy of Respironics

Epoprostenol (Flolan)

- ▲ Short-acting PGI-2
- ▲ Duration of action 3-5 min.
- ▲ Equally effective and less expensive than iNO
- ▲ Administration:
 - ◆ continuous infusion- acute or non-acute care
 - ◆ continuous aerosol- acute care alternative to nitric oxide

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 by pharmacist with specific solution

Flolan Acute Care Aerosol Delivery

- ▲ Indication - severe PAH, refractory to standard therapy
 - ◆ reperfusion injury; e.g., post-cardiopulmonary bypass
 - ◆ portal-pulmonary hypertension
 - ◆ independent or single-lung ventilation
 - ◆ ARDS
 - ◆ PPHN
 - ◆ RV failure
 - ◆ Septic shock

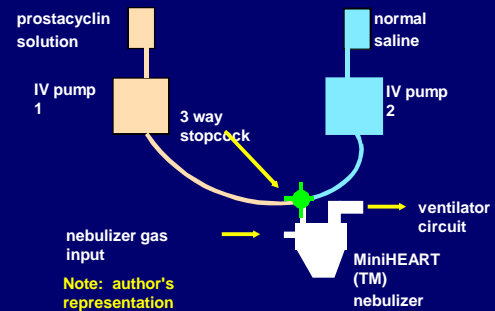
Flolan Acute Care Aerosol Delivery

- ▲ Additional potential benefits of Flolan
 - ◆ increased gastrointestinal perfusion
 - ◆ inhibition of platelet aggregation-antithrombotic, anti-inflammatory
 - ◆ stimulation of endogenous nitric oxide

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

- ▲ O₂ flow @ 2 L/min for output = 8 mL/H
- ▲ Pumps adjusted for dosage = 10-50 ng/kg IDBW/min
- ▲ Titration charts used to adjust IV pump flows

Aerogen Aeroneb Pro Nebulizer

- ▲ Wire mesh technology
- ▲ Does not alter ventilator performance



Image courtesy of Aerogen, Inc.

Flolan Continuous Aerosol Delivery

- ^ precautions
 - ◆ interruption of delivery can result in rebound, death
 - ◆ during transports, nebulizer must be maintained in vertical position
 - ◆ minimize transports, suctioning
 - ◆ medication will clog filters

Flolan Continuous Aerosol Delivery

- ^ precautions
 - ◆ may cause systemic hypotension
 - ◆ may increase pulmonary shunting
 - ◆ may cause hemorrhage
 - ◆ Flolan is photosensitive, so must be shielded from light

Alternatives to Flolan

- ^ nebulized iloprost (Ventavis)
 - ◆ longer duration than Flolan
 - ◆ replaces continuous nebulization
 - ◆ 10 mcg/mL over 20 min.
 - ◆ administered in OR during bypass surgery

Alternatives to Flolan

- ^ nebulized milrinone (Primacor)- prevents endothelial dysfunction post- CPB (5 mL; 1 mg/mL)
- ^ nebulized milrinone and Flolan
 - ◆ additive effects
 - ◆ separate nebulizers required

Alternatives to Flolan

- ^ treprostinil (Remodulin)
 - ◆ intravenous or subcutaneous injection
 - ◆ four hour duration of action
 - ◆ pilot studies of aerosolized treprostinil found sustained vasodilation (>3 H) with dosage delivered in a single breath
 - ◆ metered-dose inhaler under study

Alternatives to Flolan

- ^ Adempas (riociguat)- treats PAH type I and chronic thromboembolic PAH
- ^ Stimulates soluble guanylate cyclase (sGC), the receptor for nitric oxide (NO)
- ^ NO binds to sGC, catalyzes synthesis of cyclic guanosine monophosphate (cGMP).
- ^ Oral administration

Summary and Review

Summary and Review

- ▲ PAH defined- mean PAP >25 mm Hg at rest
- ▲ Pathophysiology - vasoconstriction, vascular remodeling
- ▲ Reperfusion injury - postoperative heart patients
- ▲ Etiologic classifications (WHO groups)
- ▲ Functional classifications (NYHA classes)

Summary and Review

- ▲ PAH diagnosis - echocardiography, heart catheterization, pulmonary vasoreactivity
- ▲ PAH management
 - ◆ General management- O₂, etc.
 - ◆ Calcium channel blockers
 - ◆ Endothelin antagonists; e.g., bosentan, ambrisentan
 - ◆ Phosphodiesterase inhibitors; e.g., Viagra, Primacor

Summary and Review

- ▲ Nitric oxide gas
 - ◆ Approved for PPHN
 - ◆ iNOvent required
 - ◆ costly
- ▲ Nitric oxide donors - nitroprusside, nitroglycerine (experimental)

Summary and Review

- ◆ Prostacyclins
 - ▲ Prostacyclin analogs
 - ▶ iloprost (Ventavis)
 - ▶ treprostinil (Remodulin)- longest acting
 - ▲ Prostacyclin- PGI₂ (Flolan)
 - ▲ Aerosol delivery systems
 - ▶ Respiroics AAD™ devices for iloprost
 - ▶ Aeroneb Pro™ device for Flolan
 - ▶ Precautions for aerosol delivery

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