Respiratory Therapeutics for Pulmonary Arterial Hypertension

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This Presentation is Approved for 1 CRCE Credit Hour

Learning Objectives

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

Etiologies, Pathophysiology, & Classifications

Definition

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

Pathophysiology

- Vascular analog of asthma
- Increased resistance to pulmonary blood flow, due to
  - Vasoconstriction
    - Hypoxemia
    - Endothelin
    - Thromboxane
    - Impaired endogenous NO
    - Impaired endogenous prostacyclins

See links below to view endothelin pathway

Pathophysiology

- Increased resistance to pulmonary blood flow, due to
  - Vascular remodeling
    - Endothelin
    - Coagulation mediators

See links below to view pulmonary artery remodeling & airway remodeling
Asthma vs. Pulmonary Hypertension

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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)

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

Group III - Pulmonary hypertension associated with lung diseases &/or hypoxemia
- COPD
- Interstitial lung disease
- Sleep-disordered breathing
- Chronic high-altitude exposure

Group IV - Pulmonary hypertension due to chronic thrombotic &/or embolic disease

Group V - Miscellaneous
- Sarcoidosis
- Histiocytosis
- Compression of pulmonary vessels (neoplasms)
Acute PAH & 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

FYI see links below for AHA article on reperfusion injury (very good article)

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

See links below to view reperfusion injury flow diagram

NYHA Functional Classifications

- Class I - no limitation of physical activity
  - Comfortable at rest
  - Ordinary physical activity: no undue dyspnea or fatigue, chest pain, etc.
- Class II - slight limitation of physical activity
  - Comfortable at rest
  - Ordinary physical activity: undue dyspnea or fatigue, chest pain, etc.
- Class III - marked limitation of physical activity
  - Comfortable at rest
  - Minimal activity causes dyspnea, fatigue, chest pain
  - Class IV - inability to perform physical activity without symptoms
  - Right heart failure
  - Dyspnea &/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

See links below to view PAH case

**Diagnostic Studies**

- Electrocardiography - isolate cardiac disease
- Chest radiograph
- Oximetry, ABGs - hypoxemia
- PFTs - spirometry, DLco
- Echocardiography
  - Measure PAP
  - Detect shunt (bubble test)

See links below to view echocardiography in PAH

- VQ scans - to identify thrombo-embolism
- High resolution CT - identify emphysema, interstitial lung disease
- Heart catheterization
  - Definitive diagnosis
  - Assess severity
  - Measure hemodynamic parameters

See links below to view PAH diagnostic algorithm
FYI see links below for article on PAH diagnosis

**Diagnostic Studies**

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

FYI see links below for article on pulmonary vasoreactivity testing

**Evaluation of Prognosis**

- **Complications**
  - Right heart failure (cor pulmonale)
  - Thromboembolism - PAH caused by clotting & it causes clotting
  - Pulmonary hemorrhage (often fatal)
  - Dysthymias, e.g. PSVT

- **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. VO2_MAX

FYI see links below for article on PAH & exercise testing

PAH Management

PAH General Management (First Line)

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

See links below to view PAH treatment algorithm

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)

FYI see links below for article on endothelin antagonists for PAH

Phosphodiesterase Inhibitors

- Theophylline - not for PAH
- Sildenafil (Viagra)
- Vardenafil (Levitra)
- Tadalafil (Cialis)
- Milrinone (Primacor) - nebulized for PAH from reperfusion injury
  - Pulmonary vasodilator
  - Positive inotrope

FYI see links below for article on nebulized milrinone
Nitric Oxide (NO) Gas

- Selectively dilates pulmonary vessels, because it is rapidly taken up by hemoglobin & 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

- Prostacyclin 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 ≥ 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....

FYI see links below for info on iloprost
**Prodose AAD (Respironics)**
- Compressor-driven
- Microchip-controlled dosage delivery
- Aerosol during inspiration, only
- Adjusts delivery to patient’s ventilatory pattern

**I-neb AAD (Respironics)**
- Vibrating mesh nebulization: similar to ultrasonic nebulizer
- Microchip-controlled delivery

**Epoprostenol (Flolan)**
- Short-acting PGi-2
- Duration of action 3 - 5 min
- Equally effective & 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**

- O$_2$ flow @ 2 L/min for output = 8 mL/H
- Pumps adjusted for dosage = 1050 ng/kg IDBW/min
- Titration charts used to adjust IV pump flows

**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

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**Aerogen Aeroneb Pro Nebulizer**

- Wire mesh technology
- Does not alter ventilator performance

Image Courtesy of Aerogen, Inc.
FYI see links below to Aerogen
**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

- Nebulized milrinone (Primacor): prevents endothelial dysfunction post-CPB (5 mL; 1 mg/mL)
  - Nebulized milrinone & Flolan
    - Additive effects
    - Separate nebulizers required

FYI see links below for article on nebulized milrinone & prostacyclin

**Summary & 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 & 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 & Review

Nitric oxide gas
- Approved for PPHN
- INOvent required
- Costly

Nitric oxide donors - nitroprusside, nitroglycerine (experimental)

Summary & Review

Prostacyclins
- Prostacyclin analogs
  - Iloprost (Ventavis)
  - Treprostinil (Remodulin): longest acting
- Prostacyclin: PGi₂ (Flolan)
- Aerosol delivery systems
  - Respironics AAD™ devices for iloprost
  - Aeroneb Pro™ device for Flolan
  - Precautions for aerosol delivery

References


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