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)

See links below to view pulmonary hypertension

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

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)

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 complex

See links below to view evolution of Eisenmenger's complex

Etiologic Classifications

- 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

Etiologic Classifications

- 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
- 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 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, DL_{CO}
- Echocardiography
  - Measure PAP
  - Detect shunt (bubble test)

See links below to view echocardiography in PAH

Diagnostic Studies

- 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)
  - Dysrhythmias, 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
- 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 ≥ 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

FYI see links below for Respironics AAD nebulizers

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

FYI see links below to Flolan information center

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

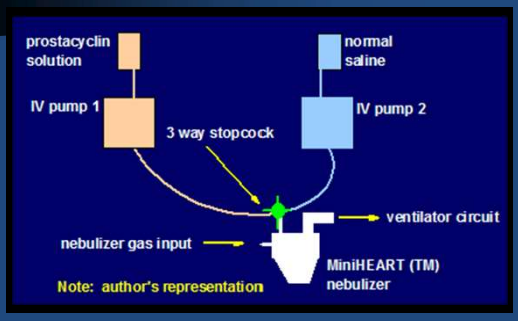
Flolan Acute Care Aerosol Delivery

- 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

- 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

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
  - 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 & Flolan
  - Additive effects
  - Separate nebulizers required

FYI see links below for article on nebulized milrinone & prostacyclin

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

See links below to view treprostinil (Remodulin) pump

Summary & Review

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: O_2, 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

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