Pulmonary Hypertension and Right Heart Failure

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Disclosures

- No conflicts of interest

Pulmonary Hypertension - Definition

- Group of conditions characterized by high blood pressure in lungs, constricted pulmonary arteries
  - Normally this is a low pressure, highly compliant system

- Increase in mean pulmonary arterial pressure (mPAP) of 25 or greater at rest
  - Pre and post-capillary PH based on mPAP, pulmonary arterial wedge pressure (PAWP), and pulmonary vascular resistance (PVR)
Pulmonary Hypertension - Definition

- Pre-capillary - mPAP 25 or greater with PAWP of 15 or less
  - Pulmonary arterial hypertension (PAH)
  - Lung disease
  - Chronic thromboembolic disease
  - Unclear/multifactorial

- Post-capillary - mPAP 25 or greater with PAWP >15
  - Left heart disease
  - Unclear/multifactorial

Pulmonary Hypertension - Classification

- Group 1: PAH
- Group 2: Left heart disease
- Group 3: Lung disease and hypoxia
- Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5: Unclear/multifactorial

Group 1: PAH

- Idiopathic
- Heritable
  - BMPR2 and ALK1 genes in the TGF-beta family
- Drug/Toxins
  - Amphetamines, appetite suppressants
- Connective tissue disease
  - Scleroderma, Sjogrens, etc.
- Congenital heart disease with shunting
  - Eisenmengers, VSD, PDA
- Others
  - HIV, liver disease (portal hypertension; hepatopulmonary syndrome), Sickle cell disease
Group 2: Left heart disease
- LV systolic/diastolic dysfunction
- Valvular disease

Group 3: Lung disease/hypoxia
- COPD
- Interstitial lung disease
- Obstructive sleep apnea
- Obesity hypoventilation syndrome
- Neuromuscular weakness/musculoskeletal disease - leads to alveolar hypoventilation

Group 4: CTEPH
- Chronic thromboembolic disease (CTED)
- Pulmonary embolism
- Mostly blood clots but can also include obstructive PA disease
  - Paroxysmal
Group 5: Unclear/Multifactorial

- Sarcoid
- Hematologic disorders
- Chronic renal failure

Epidemiology

Group 1:
- PAH is increasing and being seen more in older patients than previously (mean of 50-65 years now compared to 36 years in 1981)
- Lowest estimate is 15/1 million (5.9/1 million for idiopathic PAH)

Group 2:
- Prevalence increases as NYHA functional class increases (40-70%)
- Nearly 100% in symptomatic mitral valve disease, up to 61% in symptomatic aortic stenosis

Group 4:
- Incidence after PE 0.5-2%
- Spanish registry: 0.9/1 million cases per year

Epidemiology

- No cure
- Historically, untreated patients with IPAH had median survival of 6 months in patients with WHO functional class IV, 2.5 years for those in class III and 6 years for functional classes I and II
- 15% one year mortality on modern therapy
- Survival has improved
- CCB responders have 95% five year survival rate
- WHO class III-IV treated with epoprostenol have a five year survival rate double that of matched control subjects
- Poor prognosis: family history, male sex, age over 60, evidence of right heart failure
- Better prognosis: BNP<50, DLCO>80, 6MWD>440, NYHA class 1 symptoms at time of diagnosis
- Patients with PAH due to congenital heart disease have the best prognosis
Diagnosis

- Clinical suspicion based on symptoms and physical exam (underlying culprit diseases)
- Symptoms are generic and related to worsening right ventricular disease
  - Shortness of breath, particularly with exertion, Fatigue, Chest pain, Dizziness, Swelling, Syncope
- Physical exam findings
  - Loud P2, murmur (tricuspid regurg or pulmonary regurg), JVD, ascites, edema

Diagnosis - EKG

- Right axis deviation
- P pulmonale
- RV hypertrophy
- RBBB

Diagnosis - Imaging

- Pulmonary venous congestion
- RA/RV enlargement
- Pa-aorta ratio >1
Diagnosis - ECHO
- Estimate RV systolic pressure (a surrogate for pulmonary artery systolic pressure) through the tricuspid regurgitant velocity.
- Determine RV size and function to assess for RV failure.
- Evaluate left heart and valvular disease.
- Bubble study can look for intracardiac shunts.
- Downside: RV overestimated in patients with advanced lung disease, weaker in patients with severe PAH and can be difficult to assess in patients with COPD, underestimates if TR jet poor.

Diagnosis - RHC
- Gold standard for diagnosis.
- Assess hemodynamics (PAP, PCWP, CO).
- Indicated in patients with suspected PAH being considered for PAH-specific therapy and can also be used to assess response to continuous prostanoid or inhaled NO therapies.
- Typically in critically ill decompensated RV failure (WHO Class IV).
- VASOREACTIVITY TESTING—evaluate response to selective pulmonary vasodilators (e.g., inhaled NO, intravenous adenosine, or epoprostenol).
- Positive response defined as both a fall in mean PAP of > 10 mm Hg and subsequent mPAP of < 40 mm Hg with an increased or unchanged cardiac output (must have all 3).
- If positive can start with calcium channel blocker although effectiveness of this therapy tends to wane after a while.

Initial Workup
- Take a good history.
  - Drug use (illegal and prescribed), family history, occupational/exposure
  - Trying to identify underlying etiologies
- Labs: HIV*, connective tissue disease serologies, LFTs, CBC, BNP
- ECHO, EKG
- Sleep study, pulmonary function testing, CXR
- Six minute walk test.
  - Helps identify need for oxygen, get baseline functional status that can then be repeated and monitor for disease progression.
- VQ scan, CT chest*
Pathophysiology

- Angioproliferative and neoplastic disorder
- Vascular changes involve the pulmonary artery and are characterized by vasoconstriction, vascular remodeling with internal and medial proliferation, varying degrees of inflammation, the formation of plexiform lesions, and thrombosis.
- Lead to progressive obstruction of flow, increased pulmonary vascular resistance, right heart failure and death.

- Three pathways are implicated in PAH:
  - Prostacyclin (prostaglandin I2)
  - Nitric oxide (NO)-cyclic guanosine monophosphate-phosphodiesterase 5 (cGMP)
  - Endothelin-1

Pathology

- Increased medial tone
- Intimal hyperplasia
- Adventitial fibrosis
Pathology - Plexiform Lesion

- Complex vascular formations that originate from remodeled pulmonary arteries.
- Consist of vascular channels lined by a continuously proliferating endothelium.
- Hallmark lesion of PAH.
- Development and significance of these lesions not fully understood.

Treatment

- Oxygen and diuretics in all patients as needed.
- Anticoagulation for Group IV and may have benefit in RPLN, anorexigen induced but evidence is poor.
- Treatment of underlying conditions:
  - Infections, CRP, thrombectomy.
- PAH specific therapies based largely on symptoms:
  - Class I - ordinary physical activity without symptoms.
  - Class II - less than ordinary physical activity causes symptoms.
  - Class III - inability to perform any physical activity without symptoms, may have symptoms at rest. Signs of right heart failure present.
  - Class IV - inability to perform any physical activity without symptoms, may have symptoms at rest. Signs of right heart failure present.

Treatment - Prostanoids

- Epoprostenol, Iloprost.
- Cyclic AMP pathway.
- Produced by endothelium.
- Have vasodilatory, antiproliferative effects.
- Reduced in patients with PAH.
- Improve exercise and functional capacity, hemodynamics, survival (Epoprostenol) in Class IV patients.
- Side effects: jaw pain, headaches, anorexia, rebound effect if stopped acutely.
- Recommended for WHO class III and IV.
Treatment - PDE5 Inhibitors

- Sildenafil, Tadalafil
- cGMP pathway
- Pulmonary vascular cGMP levels can be increased by inhibiting phosphodiesterases responsible for cGMP hydrolysis
- Relatively selective pulmonary vasodilation with little systemic hypotension
- Improves functional status, hemodynamics and exercise capacity
- Side effects: abdominal pain, hypotension, headache
- Recommended for WHO Class II and III

Treatment - Soluble Guanylate Cyclase Stimulator

- Riociguat
- cGMP pathway
- Enhance cGMP production
- Improves functional status, hemodynamics and exercise capacity, time to clinical worsening
- Side effects: hypotension, syncope
- Indicated for patients with CTEPH (either after thrombectomy or if patient not a candidate)

Treatment - ERAs

- Bosentan, Ambien, Macentan
- ET-1 produced by endothelial cells
  - vasoconstrictor
- Improve exercise and functional capacity, time to clinical worsening,
  - Bosentan also improves hemodynamics and survival
- Side effects: edema, teratogenic, headache, flushing
- Recommended for WHO class III or IV symptoms
**Treatment - Pathways**

**Treatment - Algorithm**

**Treatment - Combination Therapy**

- Thought is that combination therapy should increase efficacy while decreasing toxicity.
- Likely benefit for WHO 3-4 who fail to improve on initial therapy and for WHO 1 with clinical deterioration.
- Recent meta-analysis showed combination therapy reduced risk of clinical worsening and improved hemodynamics and exercise capacity although no mortality benefit.
- AMBITION trial (combination ERA and PDE5 inhibitor) showed 50% reduction in adverse events (death, hospitalization, disease progression) and improvement in exercise capacity.
- Several studies are looking at other various combinations.
- More severe patients should be on a prostanoid given the survival advantage.
Right Heart Failure

- RV is structurally, developmentally, and functionally different than the LV
  - Prior to birth it is muscular and output is delivered to a high resistance system
  - After birth it becomes more thin but remains efficient, delivering output to a low resistance and high capacitance system
  - RV EF is aided by LV ejection
  - Adapts poorly to sudden increases in RV afterload
  - Gradual increases in afterload allow adaptive hypertrophy
  - RV output is also closely linked to the pulmonary vascular system and any disturbance (increased pressure, reduction in capacity, hypoxia, hypercapnia) can uncouple it
  - Progressive obliteration of the pulmonary vascular bed leads to RV failure once adaptive mechanisms are overwhelmed
  - Acute or decompensated chronic RV failure carries high risk of death

RHF - Normal Anatomy

RHF - Evolution of Disease
Acute RHF – ECHO Findings

A-RHF – Treatment

- Centered on improving RV function
- Preserving coronary blood flow
- Reducing RV/LV asynchrony
- Reducing RV afterload
- Over distended RV reduces LV preload and CO due to decreased RV output but also impairment of LV function
- Increasing inotropy
- Catecholamines can stabilize BP and CO
- Dobutamine can augment cardiac contractility and reduced RV and LV afterload and is the preferred agent for RV failure

Am J Respir Crit Care Med. 2011;184(10):1114-1124
Crit Care Med. 2007;35:2037-2050
A-RHF - Monitoring

- Right heart catheterization
- ECHO
  - Directly visualize RV
  - Measure size and function
- TAPSE - tricuspid annular plane systolic excursion
  - Value less than 1.5cm is marker of negative outcome
- Organ perfusion
  - Urine output
  - Venous oxygen saturation
  - Lactate

Summary

- Pulmonary hypertension is caused by constriction of pulmonary arteries due to a wide range of diseases
- Defined as mPAP of 25 or greater at rest
- Divided into 5 groups
- Only Group 1 (PAH) has specific PH therapies
- Not further defined as elevated PVR (pressure gradient between RA and LA)
- There is no cure, only IV prostanoids improve survival
- Can eventually lead to right heart failure
- Acute or decompensated chronic right heart failure carries high risk of death
- Therapy for right heart failure consists of improving RV function

Questions

- Thank you