Managing Pulmonary Hypertension

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DISCLOSURE

- Dr. Fernandez is a speaker for GlaxoSmithKline on COPD and Asthma
- There are no conflicts of interest associated with this presentation to report
Objectives

- Understand the diagnostic criteria and appropriate diagnostic evaluation for pulmonary hypertension
- Understand the approach to managing the different groups of pulmonary hypertension
- Understand the agents used and mechanism of action for the pharmacologic management of pulmonary hypertension
Pulmonary Hypertension

- Condition with multiple etiologies causing an imbalance in lung biomarkers and development of vascular remodeling leading to increased pulmonary pressures
- Defined as mean pulmonary arterial pressure $> 25$ mmHg
- Right ventricular dysfunction and reduced cardiac output
Symptoms

- Symptoms are vague and nonspecific
  - Inability to adequately increase cardiac output
  - Exertional dyspnea, lethargy and fatigue
  - Exertional syncope
  - Peripheral edema, ascites
  - Right upper quadrant pain
- Delay in diagnosis is common
  - 2.8 years median time to diagnosis
  - 75% of patients are diagnosed in WHO functional class III and IV
Incidence

- Idiopathic Pulmonary Arterial Hypertension 10/1,000,000
- 79% in advanced heart failure ²
- 3.8% following pulmonary embolism ¹
- 6-10% in sickle cell disease ³
- 25%-60% in scleroderma ⁴
- 5-10% of COPD patients have severe PH and 10-30% have mild to moderate disease ¹⁴, ¹⁵
Classification (Evian 1998)

- Group 1: Pulmonary arterial hypertension
- Group 2: Pulmonary venous hypertension
- Group 3: Pulmonary hypertension associated with chronic lung diseases
- Group 4: Pulmonary hypertension associated with chronic thrombotic or embolic disease
- Group 5: Pulmonary hypertension associated with disorders of the vasculature
Classification (Nice 2013)  

WHO Group 1

1. Idiopathic
2. Heritable
   2.1 BMPR2
   2.2 ALK1, SMAD9
3. Drug or toxin induced
4. Associated with
   4.1 Connective tissue disorder
   4.2 HIV
   4.3 Portal hypertension
   4.4 Congenital heart disease
   4.5 Schistosomiasis
Classification (Nice 2013)

WHO Group 2

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular heart disease
- 2.4 Congenital left heart outflow obstruction
Classification (Nice 2013) 5
WHO Group 3

- 3.1 COPD
- 3.2 ILD
- 3.3 Mixed restrictive and obstructive defects
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation
- 3.6 Chronic high altitude exposure
- 3.7 Developmental abnormalities
Classification (Nice 2013)

WHO Group 4

- Chronic thromboembolic pulmonary hypertension
Classification (Nice 2013) 5
WHO Group 5

- 5.1 Hematologic (hemolytic anemia, myeloproliferative disorders)
- 5.2 Systemic disorders (sarcoid, LAM, vasculitis)
- 5.3 Metabolic disorders (glycogen storage diseases, thyroid disease)
- 5.4 Other (fibrosing mediastinitis, chronic renal failure, tumor obstruction)
Define the problem

- **Group 1: Pulmonary arterial hypertension**
- **Group 2: Pulmonary venous hypertension**
- **Group 3: Pulmonary hypertension associated with chronic lung diseases**
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Beginning the Diagnostic Assessment
Physical Examination

- Loud pulmonic valve closure
- Split S2
- Right-sided S4
- Right ventricular heave
- Prominent jugular venous pulses
- Right-sided murmurs or gallops augmented by inspiration
- Systemic signs of right heart failure
Chest X-ray

- Vascular pruning
- Right atrial and ventricular enlargement

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Echocardiogram

- Excellent screening tool
- Assess chamber sizes, systolic and diastolic function, and valve function
- Tricuspid regurgitant jet velocity (TRV)
  - Pulmonary artery systolic pressure (PASP) = \(4 \times [\text{TRV}]^2\) + Right atrial pressure
Echocardiogram predictor

- PH likely if PASP >50 and TRV >3.4
- PH unlikely if PASP <36 and TRV <2.8
- Tricuspid annular plane systolic excursion (TAPSE) is a predictor of mortality
  - TAPSE >1.8 cm, survival at 1 and 2 years was 94% and 88%, respectively
  - TAPSE <1.8 cm, survival at 1 and 2 years was 60% and 50%, respectively
  - TAPSE < 1.8 cm associated with a unadjusted risk of death of 5.7 compared to TAPSE > 1.8 cm
  - For every 1mm decrease in TAPSE, the risk of death increased by 17%
Echocardiogram Pitfalls

- Technical issues (Acoustic windows, Accuracy of measuring the jet)
- Does the estimated PASP correlate with right sided chamber findings?
- Poor correlation with right heart catheterization:
  - 10 mmHg difference in 48% of cases (equal between over and under estimation) 7
  - 52% inaccuracy over 10 mmHg in severe lung disease patients with 48% false positive 10
  - 45% false positive in one study of scleroderma patients
  - 72% false positive in HIV patients (5/18 patients) 8
Pulmonary Studies

- PFTs
  - Help characterize airflow limitation and restrictive defects that may contribute to pulmonary hypertension
  - Diffusion capacity is usually reduced in pulmonary hypertension
- Polysomnography
- Ventilation-Perfusion Lung Scan
  - Improved accuracy in comparison with CT
  - V/Q sensitivity of 96%-97.4% and a specificity of 90%-95%. CT showed a sensitivity of 51% and a specificity of 99%. ¹¹
  - If abnormality is noted, pulmonary angiography is required
Laboratory Studies

- HIV screen
- Liver Function Studies
- Connective Tissue Disease Studies (ANA, RF, Scleroderma)
- Vasculitic serologies
- Hematologic studies
Right Heart Catheterization

- Gold Standard for diagnosis
- Mean Pulmonary Artery Pressure, PCWP, CO and CI
- Important to measure LVEDP
  - 5% of patients with elevated PCWP had normal LVEDP
- Vasodilator reactivity (Nitric Oxide, Adenosine)
  - Positive response is decrease in mean PAP by > 10mmHg and a reduction of the mean PAP to < 40mmHg
- Maintain or improved cardiac output
Waveforms as Catheter is Inserted

- Right ventricle
- Pulmonary artery
- Balloon inflation

Pressure measurements:
- Right atrium
- Right ventricle
- Pulmonary artery
- "Wedge" pressure

Pressure readings:
- 25 mmHg
- 20 mmHg
- 15 mmHg
- 10 mmHg
- 5 mmHg
- 0 mmHg
Treatment Options

- Optimize underlying disease process
  - Especially important in Group 2 and Group 3 Pulmonary Hypertension where advanced pulmonary vasodilators may worsen condition \(^{20, 21, 22}\)
- Volume management with diuretics and fluid/dietary restrictions
- Oxygen therapy
- Anticoagulation
  - Improved survival noted in IPAH \(^{12, 13}\)
- Digoxin therapy
- Calcium channel blockers
Advanced Pharmacologic Therapies for PAH

- **Nitric Oxide Pathway**
  - PDE-5 inhibitors (sildenafil, tadalafil)
  - sGC stimulator (riociguat)

- **Endothelin Receptor Antagonists**
  - Selective inhibitors (ambrisentan)
  - Non-Selective inhibitors (bosentan, macitentan)

- **Prostacycline Analogs**
  - IV (epoprostenol, treprostinil)
  - Subcutaneous (treprostinil)
  - Inhalation (iloprost, treprostinil)
  - Oral (treprostinil)
Surgical Management of CTEPH
Medical Management of CTEPH

- NO/sGC/cGMP pathway
  - L-Arginine → NOS → L-Citrulline

- Riociguat
- PDE-5 inhibitor
- PDE-5

- sGC
  - cGMP
  - GMP

- Vasorelaxation
Ongoing Management

- **Subjective Measurements**
  - Symptoms (dyspnea, chest pain, syncope)
  - WHO/NYHA Functional Class Score

- **Objective Measurements**
  - 6 minute walk tests
  - Echocardiogram
  - CPET
  - Right heart catheterization
REVEAL Prognosis Score 19
REVEAL Prognosis Score

The graph illustrates the predicted 1-year survival percentage based on the Risk score calculator. The survival percentages are categorized into Low, Average, Moderately high, High, and Very high risk levels.
REVEAL Prognosis Score 19
Avoid pregnancy (I-C)
Influenza and pneumococcal immunisation (I-C)
Supervised rehabilitation (IIB-B)
Psycho-social support (IIA-C)
Avoid excessive physical activity (IIIC-C)

General measures and supportive therapy

Expert referral (I-C)

Acute vasoreactivity test (I-C for IPAH)
(IIb-C for APAH)

Vasoreactive

WHO-FC I-III
CCB (I-C)

Sustained response (WHO-FC I-III)

YES
NO

Continue CCB

Nonvasoreactive

Initial therapy

Recommendation-evidence
WHO-FC
II
WHO-FC
III
WHO-FC
IV
I-A
Ambrisentan, bosentan, sildenafil
Ambrisentan, bosentan, sitaxentan, sildenafil, epoprostenol i.v., iloprost i.n.
Epoprostenol i.v.
I-B
Tadalafil
Tadalafil
Troprostilin s.c., inhaled
Ila-C
Sitaxentan
Iloprost i.v., treprostinil i.v.
Ambrisentan, bosentan, sitaxentan, sildenafil, tadalafil, iloprost inhaled, and i.v.
Treprostilin s.c., i.v., inhaled, initial combination therapy
IIb-B
Beraprost

Inadequate clinical response

Sequential combination therapy (Ila-B)*

Prostanoids +
PDE-5 i

BAS (I-C) and/or lung transplantation (I-C)

Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants:
IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
APAH (IIb-C)
Digoxin (IIb-C)


6 Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219


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