Pulmonary Hypertension = abnormally high pressure in the pulmonary arteries
Clinical Classification of Pulmonary Hypertension 2008 Dana Point

- Pulmonary Artery Hypertension
- PH with L heart disease
- PH associated with lung diseases and/or hypoxia
- Chronic Thromboembolic PH (CTEPH)
- Multifactorial / Misc.

Pathogenesis

Risk Factor + Susceptibility → Vascular Injury → Disease Progression

Pulmonary Capillaries

Normal capillaries → Recruitment → Distension → Collapsed capillaries

Pulm. Blood Flow vs Pulm. Artery Pressure

Idiopathic PAH (iPAH)
Rapid Progression and Poor Survival

\[ \text{N}=194. \quad \text{D’Alonzo GE et al. \textit{Ann Intern Med}. 1991;115:343-349.} \]

Survival in Current Era: Comparison with NIH Historical Controls

\[ \text{Therneau T. et al. Chest. 2007;132(4 suppl):487S.} \]

Prevalence of PAH: French National Registry

- Consecutive adult patients
  - \( \geq 18 \) years of age
  - 17 French specialty centers
- Prevalence of PAH: 15.0 cases/million
  - Prevalence of iPAH: 5.9 cases/million

\[ \text{Humbert M et al. \textit{Am J Respir Crit Care Med}. 2006;173:1023-1030.} \]

Prevalence of PAH: French National Registry

- Time interval b/w symptom onset and diagnosis: 27 months
- Mean age \( \sim 50 \) yrs
- Twice as many women as men

\[ \text{Humbert M et al. \textit{Am J Respir Crit Care Med}. 2006;173:1023-1030.} \]

REVEAL: Database Characteristics

- 50-center US database
- Median time from initial symptoms to RHC
  - 14 months
- Median time from to first visit to pulmonary hypertension clinic
  - 15 months
- Average body mass index
  - \( 28.9 \pm 18.4 \) kg/m²


REVEAL: Symptoms at Diagnosis

PAH Associated With Scleroderma

- Prevalence: 10-15%
  - 33% Systemic sclerosis
  - 50% CREST
  - Overestimate: lack of RHC confirmation
- Systemic sclerosis: 75% of PAH associated with CTD
- Rapidly progressive PAH disease course
  - 1-year survival: 45% to 69%


PAH Associated With Connective Tissue Diseases (CTD)

- Prevalence: 10-15%
  - 33% Systemic sclerosis
  - 50% CREST
  - Overestimate: lack of RHC confirmation
- Systemic sclerosis: 75% of PAH associated with CTD
- Rapidly progressive PAH disease course
  - 1-year survival: 45% to 69%


PAH Associated with Congenital Heart Disease (CHD)

- ~1.8 M Americans have congenital heart defect
  - 6 cases/1000 in general population
- 1.6–12.5 cases/million of PAH associated with CHD in adults
- Eisenmenger syndrome more common with large defects
  - Almost all cases of truncus arteriosus
  - 50% with large VSD
  - 10% with large ASD


PAH Associated with HIV

- PAH occurs in 1 in 200 patients with HIV infection
  - PAH a significant mortality factor when present
  - With improved outcomes due to highly active antiretroviral therapy (HAART)
  - Near complete normalization of pressures with vasoconstrictor therapy


Methamphetamine Use as a Risk Factor for PAH*

- Prevalence analysis at single PH center of adults with PH
- Methamphetamine use: PAP = 4.30, PVR = 3.8, CO = 29.8

*Retrospective analysis at single PH center of adults with PH
Chen KM et al. Chest. 2006;130:1577-1583

PAH Progression

- Presymptomatic/Compensated
- Symptomatic/Decompensating
- Declining/Decompensated

CO = cardiac output; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure.
**Diagnostic Approach to PAH**

**Circuit Tests**
- History
- Exam
- CXR
- ECG

**Cardiogram Tests**
- Echocardiography
- V/Q Scan
- PFTs
- EPO
- D-dimer
- ANA
- LFTs
- Paracentesis
- RCH

**Contribute to Assessment of**
- PAH, SCL, SSC, IP, IV, Exclusion
- Echocardiography
- CXR, ECG
- D-dimer
- ANA, LFTs
- Exclusion of PE, Other etiologies

**Severity of Pulmonary Hypertension**

<table>
<thead>
<tr>
<th>Degree of Disease</th>
<th>Mean Pulmonary Artery Pressure (mm Hg) Cath</th>
<th>Systolic Pulmonary Artery Pressure (mm Hg) Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
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**Right Heart Catheterization**
- Required to
  - Confirm diagnosis
  - Calculate PVR
  - Guide therapy for PAH
- Exclude other etiologies for PH
  - Intracardiac or extracardiac shunts
  - Left-heart disease

**Echocardiography**

**Severity of Pulmonary Hypertension**

**The Pulmonary Artery Catheter**

*McGoon M. Chest. 2004;126:14S-34S.*
Right Heart Catheterization

- Measure degree of right-heart dysfunction
  - Right atrial pressure
  - Cardiac output
- Vasodilator testing

Normal Pulmonary Hemodynamic Values

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<tbody>
<tr>
<td>Cardiac Output (liters/min)</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dynes/sec/cm⁻²)</td>
</tr>
</tbody>
</table>

Definition of PAH by Right Heart Catheterization

- Increased mean pulmonary arterial pressure (mPAP): ≥25 mm Hg at rest, or ≥30 mm Hg during exercise
- Normal pulmonary capillary wedge pressure (PCWP): ≤15 mm Hg
- Increased pulmonary vascular resistance (PVR): >3 woods units

Severity of Pulmonary Hypertension

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PAH Diagnostic Workup

- Echocardiography suggests PH
- 6 minute walk & Borg score
- Establish baseline, prognosis and document progression/response to treatment with serial re-assessment
- Functional class
- Right heart catheterization
- Confirm diagnosis PAH
Case Presentation: History

- 52 year old male
  - 7 month h/o progressively worsening dyspnea
- Walking slowly causes immediate severe dyspnea & dizziness (WHO III)
- Symptoms subside at rest

Clinical Problem 1

- Physical exam
  - Temp 37°C
  - BP 105/60
  - Pulse 102 at rest and 120 after walking
  - RR 20/min
  - BMI 32 kg/m².
  - Jugular venous distention +
  - Lungs: Clear to auscultation with no wheezes or crackles
  - Fixed splitting of the S2
  - Increased pulmonic component
  - Grade 1-2/6 holosystolic murmur at left sternal border near the fourth rib that increases with inspiration
  - Lower extremity edema, No cyanosis or clubbing

Diagnostic Data

- CBC (polycythemia vera can lead to PAH) and resting ABG are normal
- ECG rightward QRS axis and large R waves in V1
- Spirometry & plethysmography are normal
- Chest radiograph shows no infiltrates or masses

Clinical Problem 1

- Which of the following is the best next step in the evaluation of this patient?
  A. Bronchoscopy and trans-bronchial lung biopsy
     - Interstitial Lung Disease
  B. Methacholine challenge test
     - Asthma
  C. Right-heart catheterization & pulmonary angiography
     - Pulmonary Hypertension
  D. Trans-thoracic echocardiography
     - Pulmonary Hypertension

Case Presentation: History

- 2 syncopal episodes, both while walking at a brisk pace
- No cough, chest pain, or wheezing
- No other significant medical history
- Takes no medications
Clinical Problem 1

• ANSWER: D
  – Transthoracic echocardiography
• In patients with suspected pulmonary HTN
  – TTE can suggest the presence of pulm HTN
  – Evaluate for cardiac causes of elevated pulm artery pressure

Goals of Management of PAH

• Improve survival
• Prevent worsening
• Improve hemodynamics
• Maintain or improve functional class
• Improve exercise capacity
• Improve daily functioning and quality of life

Considerations for Selecting Initial Therapy for PAH

• Severity of symptoms
• Physical examination (right-heart failure?)
• Rate of progression
• Echocardiogram (RV size and function)
• Right heart catheterization
  – Mean PA pressure and cardiac index

Considerations for Selecting Initial Therapy for PAH

• 6-minute walk distance
• BNP/NT-pro-BNP
• Capability of patient to handle parenteral therapy

Considerations for Selecting Initial Therapy for PAH

• Parenteral therapy is first choice in very advanced patients
• Other issues
  – Drug-drug interactions
  – Adverse events
  – Comorbid conditions (eg, diabetes)
  – Route of administration
  – Dosing intervals
  – Cost

Cost Analysis

• Approximate annual cost
  – Sildenafil $12,761
  – Bosentan $55,890
  – Ambrisentan $56,736
  – Iloprost $92,146
  – Epoprostenol $33,153
  – Treprostinil $97,615

• Based on a 70-kg patient at the lower end of the dosing spectrum
PAH Determinants of Risk

<table>
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<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MW distance</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Very elevated</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiographic findings</td>
<td>Pericardial effusion, significant RV dysfunction</td>
</tr>
<tr>
<td>Normal/near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
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