**Pulmonary Arterial Hypertension - Overview**

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**PAH Overview Outline**

- Background and definition  
- Clinical classification  
- Epidemiology  
- Pathophysiology/Natural history  
- Signs and symptoms/diagnosis  
- Importance of right heart catheterization  
- PAH management trends and outcomes  
- Treatment options

**PAH Background**

- Rare disease (orphan designation) of the pulmonary microvasculature affecting 15 to 50 people per million inhabitants in the Western world\(^1\)  
  - Affects all races  
  - Affects all ages; however, most prevalent in 4th and 5th decades of life  
  - Higher prevalence in females


**PAH Background**

- Global burden of PAH may be underestimated because of:\(^1,2\)  
  - Underdiagnosis (eg, nondescript symptoms)  
  - Misdiagnosis (eg, asthma, left-heart disease)  
  - Increasing risk factors (eg, HIV infection, schistosomiasis)

PAH Defined

• Mean PAP ≥ 25 mm Hg
• PCWP ≤ 15 mm Hg
• PVR > 3 Wood units

• Increased pressure load on RV
• Diagnosis of exclusion

PAH vs. PH

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>PAPm ≥ 25 mmHg, PAWP ≤ 15 mmHg</td>
<td>1. Pulmonary arterial hypertension, 3. PH due to lung diseases, 4. Chronic thromboembolic PH, 5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>PAPm ≥ 25 mmHg, PAWP &gt; 15 mmHg</td>
<td>2. PH due to left heart disease, 5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>Isolated post-capillary PH (i-pc-PH)</td>
<td>DPG &lt; 7 mmHg and/or PVR &lt; 3 WU</td>
<td></td>
</tr>
<tr>
<td>Combined post-capillary and pre-capillary PH (Cpc-PH)</td>
<td>DPG &gt; 7 mmHg and/or PVR &gt; 3 WU</td>
<td></td>
</tr>
</tbody>
</table>

The 2013 Nice Classification of PAH

- Pulmonary Arterial Hypertension (1)
  - Heritable PAH (FPAH)
  - Idiopathic PAH (IPAH)
  - Drug and toxin-induced
  - Associated PAH (APAH)
    - Connective tissue disease (CTD)
    - Human immunodeficiency virus (HIV)
    - Portal hypertension
    - Schistosomiasis
    - Congenital heart disease (CHD)
    - Persistent pulmonary hypertension of the newborn (PPHN)
  - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

- Pulmonary Venous Hypertension (2)
  - Heart failure (normal or low EF)
  - Valvular disease
  - Congenital Heart Disease

- PH due to lung disease / hypoxemia
  - Obstructive sleep apnea
  - Interstitial Lung disease
  - COPD/asthma
  - Mixed restrictive/obstructive
  - High altitude
  - Developmental disorders

- CTEPH (4)

- Multifactorial (5)
  - Metabolic - Thyroid disease
  - Hematological – splenomegaly
  - Systemic – sarcoidosis

WHO Classification: Group 1

Group 1—PAH
Idiopathic PAH
Heritable
BMPR2
ALK-1, endoglin (with or without HHT)
Unknown
Drug and toxin-induced
PAH associated with:
Connective tissue diseases
HIV infection
Portosystemic shunts
Chronic hemolytic anemia
Persistent pulmonary hypertension of newborns
Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

Epidemiology of PAH (WHO Group 1)

• Prevalence of PAH in associated conditions:
  • CTDa: 8%-12%
  • CHD: 15%-30%
  • PoPH: 2%-6%
  • HIV: 0.5%


PATHOPHYSIOLOGY/NATURAL HISTORY

Progression of Pulmonary Vascular Disease

Right Ventricle
Pulmonary Arteries

- The RV wall Healthy endothelium: Normal CO2 diffusion, normoxic arterioles, normal C/O ratio
- Hypertrophy of RV: Abnormal PA arteriopathy: Contractile defect, loss of smooth muscle, resistant to vasodilation
- Dilation of RV: Wall injury, cell proliferation, fibrosis, oxidative stress, inflammation, injury-PAH

Consequences of PAH

- ↑ PVR
- ↑ RV afterload
- ↓ RV ejection (CO) and PBF
- RV hypertrophy and dilation
- Death

Echocardiographic Characteristics of PAH

Parasternal view
Apical 4-chamber view

Echocardiography provides estimated RV systolic pressure and morphologic cardiac abnormalities

Tricuspid Regurgitation

Echocardiography in PAH

Syst PAP = Right Ventricular Systolic Pressure
(in absence of pulmonary outflow obstruction)
RVSP = 4v^2 + RAP*

Schematic Progression of PAH

CO = TPG

PVR

Pre-symptomatic/Compensated
Symptomatic/Decompensating
Declining/Decompensated

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient.

Courtesy of: Valerie V. McLaughlin, MD.
### PAH Determinants of Risk

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Rare</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope†</td>
<td>Repeated syncope‡</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165-440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂&gt;15 mmol/kg (&lt;65% pred.) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11-15 mmol/kg (35–65% pred.) VE/VCO₂ slope 36-44.5</td>
<td>Peak VO₂ &lt;11 mmol/kg (&lt;30% pred.) VE/VCO₂ slope &gt;45</td>
</tr>
<tr>
<td>NT-proBNP (plasma levels)</td>
<td>BNP &lt;50 ng/ml</td>
<td>NT-proBNP &gt;500 ng/ml</td>
<td>BNP 50-300 ng/ml</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm², no pericardial effusion</td>
<td>RA area 18-26 cm², no or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm², pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP = 8 mmHg CI 3.2-5.3 (mean) SVO₂ &lt;65%</td>
<td>RAP 8-14 mmHg CI 2.0-2.4 (mean) SVO₂ 60-65%</td>
<td>RAP &gt;14 mmHg CI &gt;2.0 (mean) SVO₂ &gt;60%</td>
</tr>
</tbody>
</table>

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### Survival by PAH Etiology

**Survival by PAH Etiology**

- CHD
- CVD
- HIV
- PPH
- PoPH

**Survival by PAH Etiology**

- CHD
- CVD
- HIV
- PPH
- PoPH

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**McLaughlin and McGoon. Circulation. 2006;114:1417-1431.**

**McLaughlin et al. Chest. 2004;126:785-928.**
**REVEAL: Most Frequent PAH Presenting Symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea at rest</td>
<td>91.4%</td>
</tr>
<tr>
<td>Cough</td>
<td>95.4%</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td>91.9%</td>
</tr>
<tr>
<td>Palpitations/nervousness</td>
<td>10.3%</td>
</tr>
<tr>
<td>Edema</td>
<td>8.9%</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>5.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.7%</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>54.4%</td>
</tr>
</tbody>
</table>


**NYHA Functional Classification**

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No symptoms with ordinary physical activity</td>
</tr>
<tr>
<td>Class II</td>
<td>Some symptoms with ordinary activity. Slight limitation of activity</td>
</tr>
<tr>
<td>Class III</td>
<td>Symptoms with less than ordinary activity. Marked limitation of activity</td>
</tr>
<tr>
<td>Class IV</td>
<td>Symptoms with any activity or even at rest</td>
</tr>
</tbody>
</table>

**WHO Functional Classification**

<table>
<thead>
<tr>
<th>WHO</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

**Diagnosis of PAH**

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>Evaluate signs and symptoms, family history, associated diseases, ANA</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Assess for RV enlargement, peripheral hypovascularity (pulmonary edema) and prominent pulmonary arteries</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Assess for RV and RA enlargement, RV dysfunction, TR velocity to measure RVSP</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Evaluate for right heart enlargement and strain, cardiac rhythm</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>Evaluate for CHD; measure wedge pressure or LVEDP</td>
</tr>
<tr>
<td>PFTs with DLCO</td>
<td>Assess obstructive and restrictive airway disease</td>
</tr>
<tr>
<td>VQ scan</td>
<td>Rule out thromboembolic disease</td>
</tr>
</tbody>
</table>
# PAH Diagnostic Testing

<table>
<thead>
<tr>
<th>Phased Tests</th>
<th>Contingent Tests</th>
<th>Contribute to Assessment of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>VQ Scan</td>
<td>Value of Blood gases (O2, CO2)</td>
</tr>
<tr>
<td>Exam</td>
<td>Echocardiogram</td>
<td>PH, VHD, CHD, LV failure, PHTN</td>
</tr>
<tr>
<td>CXR</td>
<td>ECG</td>
<td>Left heart disease, RV failure, RV function, Pulmonary HTN</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>PFTs</td>
<td>Ventilatory function, RV function</td>
</tr>
<tr>
<td>PFTs</td>
<td>Over Night Oximetry</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Over Night Oximetry</td>
<td>HIV Infection</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>ANA</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>ANA</td>
<td>LFTs</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>LFTs</td>
<td>Functional Test</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Functional Test</td>
<td>(6MWT, CPET)</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>TEE</td>
<td>TEE</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Exercise Echo</td>
<td>Pulmonary Angiography</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Pulmonary Angiography</td>
<td>Coagulopathy Profile</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Coagulopathy Profile</td>
<td>Polysomnography</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>Vasodilator Test</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Vasodilator Test</td>
<td>Exercise RH Cath</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Exercise RH Cath</td>
<td>Volume Loading</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Volume Loading</td>
<td>Left Heart Cath</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
<tr>
<td>Left Heart Cath</td>
<td>Right Heart Cath</td>
<td>Ventilatory function, O2 Exchange</td>
</tr>
</tbody>
</table>

## Chest X-Ray Consistent With PH

- RA enlargement, prominent PA
- Loss of retrosternal airspace RV enlargement

## CT-Chest: Pulmonary Dilation

- Dilated Pulmonary Artery


## CT-Chest: RA, RV, PA Enlargement

- Enlarged PA, RV, RA, Pleural Effusions
- Lack of Significant Parenchymal Disease
Ventilation Perfusion (V/Q) Scintigraphy in CTEPH

Case Example: Perfusion is intact primarily to the right upper lobe
Hypo-perfused regions representing perfusion defects


Pulmonary Hypertension

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Right Heart Catheterization

- Confirm diagnosis
  - Gold standard
- Evaluate severity of PAH
- Assess congenital heart defects
- Exclude left-sided heart disease
- Assess response to vasodilator challenge
- Assess key hemodynamic parameters
Importance of Right Heart Catheterization

- Vast majority of PH cases are non–WHO group 1
- PAH characterized by
  - ↑ PVR
  - ↑ TPG
  - Normal left-sided filling pressures
- PVH characterized by
  - ↑ PCWP
  - ↑ LVEDP
  - ↑ LAP

PAH Disease Pathways

- Soluble GC Stimulator
  - Enhancing the sensitivity of sGC to nitric oxide NO
  - Direct sGC stimulator that will activate sGC to synthesize cGMP in the absence of NO
- Nitric Oxide Deficiency
  - PDE-5 inhibitors block the activity of PDE-5, restoring vasodilation through an increase in cGMP
- Prostacyclin
  - Supplement the deficiency in PGI2, resulting in vasodilation and inhibition of platelet aggregation.
- Endothelin Receptor Antagonists
  - Block the binding of ET-1 to its receptors, preventing a vasoconstriction effect

TREATMENT OF PULMONARY ARTERIAL HYpertension
**PAH Treatment Goals**

- Improve quality of life and survival
- Improve to FC I or II
- Improve 6MWD to ≥380 m
- Improve hemodynamics
- Alleviate symptoms

**PAH Treatment**

- Endothelin Receptor Antagonists
  - Bosentan
  - Ambrisentan
  - Macitentan
- Phosphodiesterase Inhibitors
  - Sildenafil
  - Tadalafil
- Soluble GC Stimulator
  - Riociguat
- Prostanoids
  - Epoprostenol (IV)
  - Treprostinil (IV, SQ, inhaled, oral)
  - Ilprost (inhaled)
  - Selexipeg (oral)
- Calcium Channel Blockers

**Prostanoids - Infused**

- Epoprostenol
- Treprostinil

**Prostanoids -- Inhaled**

- Iloprost
- Treprostinil
Calcium Channel Blocker Therapy

- Used for patients with IPAH who respond to acute vasodilator testing at the time of cardiac catheterization
  - Response defined by reduction in mPAP ≥10 mm Hg to a mPAP ≤40 mm Hg, with an unchanged or increased CO
- Approximately 13% of patients with IPAH respond to acute vasodilator testing
  - Only 6.8% had a favorable clinical response to chronic CCB therapy at 1 year
- Other PAH treatments should be evaluated if patient does not improve to FC I or II

MORTALITY IN PATIENTS WITH PAH IN THE MODERN ERA: DATA FROM THE QUALITY ENHANCEMENT RESEARCH INITIATIVE (QUERI)

**QuERI Methods**

- Despite advances in PAH therapy, patient mortality remains unacceptably high.
- Although ACCP guidelines have been developed to assist clinicians in managing patients with PAH, the effectiveness of these guidelines is unclear.
- Database was designed to collect information regarding medical management of patients with PAH initiated in 2005. Newly and previously diagnosed patients were enrolled (N=782).
- Patients were enrolled from PAH centers and community centers.
- Study determined whether ACCP guidelines were followed, including RHC for diagnosis.

**QuERI: Patient Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Disease subtype, %</th>
<th>All cases (N=782)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>38</td>
</tr>
<tr>
<td>Familiar</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
<td>30</td>
</tr>
<tr>
<td>Congenital heart diseases</td>
<td>7</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Drug exposure</td>
<td>7</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO functional class, %</th>
<th>All cases (N=782)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>39</td>
</tr>
<tr>
<td>III</td>
<td>48</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
</tr>
</tbody>
</table>

**QuERI: Overall PAH Therapy Use in Enrolled Population**

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5i</td>
<td>28</td>
</tr>
<tr>
<td>ERA</td>
<td>43</td>
</tr>
<tr>
<td>Prostanoid</td>
<td>25</td>
</tr>
<tr>
<td>Combination</td>
<td>22</td>
</tr>
</tbody>
</table>

QuERI: 1-Year Mortality Remains High in FC IV Patients¹,²

FC, functional class; QuERI, Quality Enhancement Research Initiative; WHO, World Health Organization.


QuERI: Current Use of CCB Therapy

• 87% of patients receiving CCB did not respond to acute vasoreactivity testing
• ~10% were receiving PAH therapy without RHC-confirmed diagnosis


Has Survival Meaningfully Improved With Modern Therapies?


Conclusions

• PAH is a rare disease associated with very high mortality if untreated.
• PAH is a diagnosis of exclusion and diagnosis requires a comprehensive cardiopulmonary evaluation as well as a right heart catheterization
• Current guidelines recommend use of upfront combination therapy, if tolerated.
• Patients with advanced PAH and right heart failure, should be treated with parental prostacyclins alone or in combination with other oral specific PAH vasodilators.
• Goals of care: functional capacity class I or II and normal right ventricular function