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
  • 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. Underdiagnosis (eg, nondescript symptoms)
  2. Misdiagnosis (eg, asthma, left-heart disease)
  3. 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

Table 3 Haemodynamic definitions of pulmonary hypertension

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

### The 2013 Nice Classification of PAH

**5th WSPH**

#### 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)
  1. 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

<table>
<thead>
<tr>
<th>Group 1—PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PAH</td>
</tr>
<tr>
<td>Heritable</td>
</tr>
<tr>
<td>BMPR2</td>
</tr>
<tr>
<td>ALK-1, endoglin (with or without HHT)</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Drug and toxin-induced</td>
</tr>
<tr>
<td>PAH associated with:</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Congenital systemic to pulmonary shunts</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of newborn</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis</td>
</tr>
</tbody>
</table>

Epidemiology of PAH (WHO Group 1)

- Prevalence of PAH in associated conditions:
  - CTD\(^a\): 8%-12%\(^2,3\)
  - CHD: 15%-30%\(^4\)
  - PoPH: 2%-6%\(^5,6\)
  - HIV: 0.5%\(^7\)

Progression of Pulmonary Vascular Disease

- **Right Ventricle**
  - Normal
  - Hypertrophied RV
- **Pulmonary Arteries**
  - Normal
  - Hypertrophied PA
  - Dilation RV

- **Right Ventricles**
  - Thin RV wall
  - Healthy PA endothelium
  - Thin-walled relaxed PAs
  - Large capillary network
  - Normal CO, PVR, and perfusion

- **Pulmonary Arteries**
  - Hypertrophied RV
  - Abnormal PA endothelium
  - Constricted stiff PAs
  - Loss of microvessels
  - Normal CO, mild ↑ PVR, moderate ↓ in perfusion

- **Distorted RV**
  - Cell proliferation in PA wall
  - Obstructive PA remodeling
  - Severe ↓ CO and perfusion, with severe ↑ PVR
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 = $4v^2 + \text{RAP}$

Estimation of RAP

<table>
<thead>
<tr>
<th>Findings</th>
<th>Estimated RAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small &amp; collapse</td>
<td>0–5 mmHg</td>
</tr>
<tr>
<td>Normal &amp; normal ↓ size</td>
<td>5–10 mmHg</td>
</tr>
<tr>
<td>Normal &amp; abnormal ↓ size</td>
<td>10–15 mmHg</td>
</tr>
<tr>
<td>Dilated &amp; abnormal ↓ size</td>
<td>15–20 mmHg</td>
</tr>
<tr>
<td>Dilated &amp; no change in size</td>
<td>&gt;20 mmHg</td>
</tr>
</tbody>
</table>

Schematic Progression of PAH

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

Courtesy of: Vallerie V. McLaughlin, MD.
Schematic Progression of PAH

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

Courtesy of: Vallerie V. McLaughlin, MD.
### Determinants of Risk

<table>
<thead>
<tr>
<th>Determinants of prognosis</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>Slow</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 ml/min/kg (&gt;65% pred.) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO₂ slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/l</td>
<td>BNP 50–300 ng/l NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</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 &lt;8 mmHg CI ≥2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>

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### Survival by PAH Etiology

![Survival by PAH Etiology Graph](image)

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SIGNS, SYMPTOMS & DIAGNOSIS

- Dizziness and/or fainting (syncope)
- Shortness of breath (dyspnea)
- Chest pain (angina)
- Rapid, hard, or irregular heartbeats (palpitations)
- Swollen abdomen (ascites)
- Swollen ankles or legs (edema)

Feeling tired or worn out (fatigue)
REVEAL: Most Frequent PAH Presenting Symptoms


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&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Evaluate signs and symptoms, family history, associated diseases, ANA</td>
</tr>
<tr>
<td>Chest x-ray&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Assess for RV enlargement, peripheral hypovascularity (pruning), 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&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Evaluate for CHD; measure wedge pressure or LVEDP; establish severity and prognosis; test vasodilator therapy</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

## Pivotal Tests
- History
- Exam
- CXR
- ECG
- Echocardiogram
- VQ Scan
- PFTs
- Overnight Oximetry
- HIV
- ANA
- LFTs
- Functional Test (6MWT, CPET)
- Right Heart Cath

## Contingent Tests
- TEE
- Exercise Echo
- Pulmonary Angiography
- Chest CT Angiogram
- Coagulopathy Profile
- ABGs
- Polysomnography
- Other CTD Serologies
- Vasodilator Test
- Exercise RH Cath
- Volume Loading
- Left Heart Cath

## Contribute to Assessment of:
- Index of Suspicion of PH
- RVE, RAE, RVSP, RV Function
- Left Heart Disease
- VHD, CHD
- Chronic PE
- Ventilatory Function
- Gas Exchange
- Sleep Disorder
- HIV Infection
- Scleroderma, SLE, RA
- Portal pulmonary Hypertension
- Establish Baseline
- Prognosis
- Confirmation of PH
- Hemodynamic Profile
- Vasodilator Response

## Chest X-Ray Consistent With PH
- RA enlargement, prominent PA
- Loss of retrosternal airspace RV enlargement
CT-Chest: Pulmonary Dilation

Dilated Pulmonary Artery

PA Dilation 3.9cm

PA size and ratio vary by patient size and sex

Sex-specific cutoff values
- Men 29 mm
- Women 27 mm

Normal PA:aortic ratio = 0.9


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
  - \( \uparrow \) PVR
  - \( \uparrow \) TPG
  - Normal left-sided filling pressures
- **PVH** characterized by
  - \( \uparrow \) PCWP
  - \( \uparrow \) LVEDP
  - \( \uparrow \) LAP

PAH Disease Pathways

↓ vasoconstriction
↓ proliferation
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)
  - Iloprost (inhaled)
  - Selexipeg (oral)
- Calcium Channel Blockers
**Prostanoids - Infused**

- **Treprostinil**
  - Crono Five
  - CADD MS-3® (micropump)
  - Subcutaneous or Intravenous infusion

- **Epoprostenol**
  - CADD Legacy®
  - Intravenous infusion

**Prostanoids -- Inhaled**

- **Iloprost**
  - I-neb® AAD®

- **Treprostinil**
  - Tyvaso Inhalation System
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 $\geq 10$ mm Hg to a mPAP $\leq 40$ 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


PAH MANAGEMENT TRENDS & OUTCOMES
Treatment Algorithm for PAH

Treatment naïve patient

PAH confirmed by expert center

Acute vasoreactivity test (IPAH/HPAH/DPAH only)

CCB Therapy (Table 18)

Vasoreactive

Non-vasoreactive

Low or intermediate risk (WHO FC II–III) a

High risk (WHO FC IV) b

Initial monotherapy b (Table 19)

Initial oral Combination b (Table 20)

Initial combination including i.v. PCA c (Table 20)

Double or triple sequential combination (Table 21)

Inadequate clinical response (Table 15)

Consider listing for lung transplantation d (Table 22)

Patient already on treatment

Inadequate clinical response (Table 15)

Vasoreactive

Non-vasoreactive

Low or intermediate risk

High risk

Initial therapy b (Table 19)

Initial oral Combination b (Table 20)

Initial combination including i.v. PCA c (Table 20)

Double or triple sequential combination (Table 21)

Inadequate clinical response (Table 15)

Consider listing for lung transplantation d (Table 22)

General measures (Table 16)

Supportive therapy (Table 17)

Ambition: upfront combination of Tadalafil + Letairis


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>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>38</td>
</tr>
<tr>
<td>Familial</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>%</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**

- PDE-5I: 28 patients (%)
- ERA: 43 patients (%)
- Prostanoid: 25 patients (%)
- Combination: 22 patients (%)

ERA, endothelin receptor antagonist; PDE-5I, phosphodiesterase type 5 inhibitor; QuERI, Quality Enhancement Research Initiative.

QuERI: 1-Year Mortality Remains High in FC IV Patients\textsuperscript{1,2}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{chart1.png}
\caption{WHO FC and 1-Year mortality}
\end{figure}

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

QuERI: Current Use of CCB Therapy

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{chart2.png}
\caption{Patients with positive response to CCB therapy}
\end{figure}

- 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.