PH is an observation of elevated pulmonary pressures.

Encompasses a diverse group of conditions that lead to elevated arterial and/or venous pulmonary pressures.
PH is defined hemodynamically as mean PAP >25 mm Hg at right heart catheterization.

Does not reveal etiology, pathophysiology or clinical significance of this increased pressures.

Diagram courtesy of Teresa De Marco, MD

World Symposium Pulmonary Hypertension (WSPH)

- 1973: Geneva, Switzerland
- 1998: Evian, France
- 2003: Venice, Italy
- 2008: Dana Point, California
- 2013: Nice, France
  - 129 experts from around the world divided into 12 task forces
### 5th World Symposium on PH: Modified Classification of PH 2013

1. **Pulmonary arterial hypertension**
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
     - 1.2.1 BMPR2
     - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
     - 1.2.3 Unknown
   - 1.3 Drug- and toxin-induced
   - 1.4 Associated with
     - 1.4.1 Connective tissue diseases
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease (update)
     - 1.4.5 Schistosomiasis
   - 1.4.6 Chronic hemolytic anemia

2. **Ph due to LHD**
   - 2.1 LV systolic dysfunction
   - 2.2 LV diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow obstruction

3. **PH due to lung diseases and/or hypoxia**
   - 3.1 COPD
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases (update)

4. **CTEPH**

5. **PH with unclear multifactorial mechanisms**
   - 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3 Metabolic disorders:
   - 5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

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### Pulmonary Hypertension (PH)

<table>
<thead>
<tr>
<th>Mean pulmonary artery pressure (mPAP)</th>
<th>≥25 mm Hg</th>
</tr>
</thead>
</table>

### Pulmonary Arterial Hypertension (PAH)

<table>
<thead>
<tr>
<th>Mean pulmonary artery pressure (mPAP)</th>
<th>≥25 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery wedge pressure (PAWP)</td>
<td>≤15 mm Hg</td>
</tr>
</tbody>
</table>

### PH Hemodynamic Definition

| Pulmonary vascular resistance (PVR) | >3 Wood units |

As measured by right-heart catheterization.

PH is common

Pulmonary Hypertension:
Group 2: PH due to LHD

2.1 LV systolic dysfunction
2.2 LV diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/ left heart inflow/outflow obstruction

Epidemiology of PH by Echo

- Single echo lab / Australian community of 165,450
- Etiology of PH noted on echocardiogram

- PAH, 2.7%
- CTEPH, 2.0%
- Lung disease, Sleep-related hypoventilation, 9.3%
- Miscellaneous, 2.7%
- Unknown, 15.4%
- Left heart disease, 67.9%


Pulmonary Hypertension: Group 3: Hypoxemic lung disease

3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

### Clinical Classification of Pulmonary Hypertension

**Group 4 and 5**

**Group 4 – Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**

**Group 5 – Pulmonary Hypertension with Unclear Multifactorial Mechanisms**

- Hematologic disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
- Systemic disorders: Sarcoidosis, pulmonary Langerhans cell histiocytosis, Lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
- Others: Segmental PAH, tumoral obstruction, fibrosing mediastinitis, chronic renal failure


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### PH Classification

**Group 1 Pulmonary Arterial Hypertension**

**Group 2 Pulmonary Venous Hypertension**

**Group 3 PH associated with respiratory diseases or hypoxemia**

**Group 4 PH associated with chronic thromboembolic disease**

**Group 5 Miscellaneous**
PAH is very UN-common!

5th WSPH: Clinical Classification of Pulmonary Hypertension

- Group 1 Pulmonary Arterial Hypertension (PAH)
  - Idiopathic (IPAH)
  - Heritable (HPAH)
    - BMPR2
    - ALK-1, endoglin, SMAD9, CAV1, KCNK3
    - Unknown
  - Drugs and toxins induced
  - Associated with
    - Connective Tissue Diseases
    - HIV Infection
    - Portal Hypertension
    - Congenital Heart Diseases
    - Schistosomiasis
- Group 1’ Pulmonary Veno Occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis (PCH)
- Group 1” Persistent pulmonary hypertension of the newborn (PPHN)

Pulmonary Vascular Histopathology

Normal Pulmonary Artery

IPAH

Postulated Pathogenesis of PAH

Adapted from Gaine S. JAMA. 2000;284:3160-3168.
Progressive increase in mPAP/PVR
\[ \downarrow \]
Pressure overload of right ventricle
\[ \downarrow \]
RV dilation
\[ \downarrow \]
RV FAILURE

**Idiopathic PAH: Survival If Untreated**

- Incidence: 2-6 cases per million in US
- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

Advanced Functional Class at Diagnosis Common and Indicates Delayed Recognition

- Approximate prevalence: 15 cases/million
- More common in women
- Spans broad age range
- Delay in diagnosis persists
- Most patients diagnosed with late symptoms
- Poor prognosis if untreated (median survival <3 yr)

REVEAL Registry (N=1831)  NIH Registry (N=187)  French Registry (N=674)


Diagnostic Algorithm for PAH

History, Symptoms, Signs Suggestive of PAH
Is There a Reason to Suspect PAH?

Risk Factors

- Family history
- Connective tissue disease
- Congenital heart disease
- Portal hypertension—orthotopic liver transplant candidate
- Environmental/drug factors
- HIV

Clinical Presentation

- Symptoms
  - Breathlessness
  - Fatigue
  - Weakness
  - Angina
  - Edema/Ascites
  - Syncope

- Signs
  - Accentuated pulmonary component of second heart sound (P2) at apex
  - Midsystolic ejection murmur
  - Right ventricle S₄ gallop
  - Prominent jugular “a” wave
  - Diastolic murmur: PR
  - Holosystolic murmur: TR
Diagnostic Algorithm for PH

History, Symptoms, Signs Suggestive of PH

Consider Common Causes of PH

Group 2: Left Heart Disease

Group 3: Lung Diseases and/or Hypoxia

Echocardiography:
Morphologic Features of PAH

• ↑RA and RV diameter
• RV hypertrophy
• Thickening of RV moderator band
• RV hypokinesis
• Leftward shift of septum
  – D-shaped left ventricle
• Significant tricuspid insufficiency
• Dilatation of inferior vena cava
• Pericardial effusion
• Shunt

Echocardiogram: Apical Four Chamber

Normal

Severe Right-heart Failure

Chest X-Ray Consistent With PH

Image courtesy of Vallerie McLaughlin, MD
Findings of PAH on PFTs

- Findings suggestive of PAH
  - DLco 40% - 80% of expected
  - Mild to moderate reduction of lung volumes
  - Arterial O₂ tension normal or slightly reduced at rest

- Findings suggestive of alternate PH diagnoses
  - Hypoxic PH due to COPD
    - Irreversible airway obstruction + increased residual volumes + reduced DLCO + normal or increased CO₂ tension
  - Interstitial lung disease
    - Decrease in lung volume + decreased DLCO

Diagnostic Algorithm for PH

Consider Group 2 or 3 PH → Yes

No

Ventilation Perfusion Scan
Diagnostic Algorithm for PH

Group 2 or 3 PH

Yes

No

Perform V/Q Scan

Segmental Perfusion Defects

CTEPH

Yes

V/Q Scan More Sensitive Than Mutidetector CT
Pulmonary Angiography (CTPA)

<table>
<thead>
<tr>
<th></th>
<th>V/Q High-Probability Scans</th>
<th>CTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.2%</td>
<td>51.3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.6%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95.2%</td>
<td>82.8%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>97.9%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>90.3%</td>
<td>97.6%</td>
</tr>
</tbody>
</table>

N=227 undergoing both V/Q and CTPA at single center.

Diagnostic Algorithm for PH

- Consider Group 2 or 3 PH
  - Yes
  - No
  - Perform CTEPH
    - Yes
    - Segmental Perfusion Defects
      - Yes
      - Perform V/Q Scan
        - No
        - No
        - Perform RHC

Cardiac Catheterization

*Required when PAH is suspected*

- Confirm echo findings
- Survey for left heart disease
  - measure wedge pressure or LVEDP
- Measure CO; calculate PVR
- Exclude systemic to pulmonary shunts
- Establish severity and prognosis
- Acute vasodilator challenge
Definition of Vasodilator Responder

"Vasodilator Response"

- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO

- Only acute vasodilator responders should be tried on CCB therapy to treat PAH


Diagnostic Algorithm for PAH: Results of RHC

Perform RHC

- mPAP ≥25 mmHg
- PWP ≤15 mmHg
- PVR >3 WU

Search for other causes

Specific diagnostic tests for PAH causes

Evaluating Causes of PAH

mPAP ≥25 mmHg
PAWP ≤15 mmHg
PVR >3 WU

Specific diagnostic tests for PAH causes:

CTD
HIV
Portopulmonary
PVOD/PCH

No known cause

Drugs/Toxins
Congenital heart disease
Schistosomiasis

Idiopathic or heritable PAH

Long-term Management of PAH: Recommended Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Ea 4 – 6 months</th>
<th>3 – 4 months after therapy initiation or change</th>
<th>@ clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Assessment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>6MWD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CPET</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Echo</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>✓✓</td>
<td></td>
<td></td>
<td>✓✓</td>
</tr>
</tbody>
</table>

### WHO Functional Classification Assessment of PH Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of usual activities</td>
</tr>
</tbody>
</table>
| II    | Mild limitation of usual activities  
No discomfort at rest  
Normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope |
| III   | Marked limitation of physical activity  
No discomfort at rest  
Less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope |
| IV    | Patient unable to perform any physical activity at rest and may have signs of right ventricular failure  
Dyspnea and/or fatigue and/or syncope/near-syncope may be present at rest, and symptoms are increased by almost any physical activity |


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### 5th WSPH: Prognostic Variables Used In Clinical Practice To Set Treatment Goals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Functional class (FC)</td>
<td>I or II</td>
</tr>
<tr>
<td>Echocardiography/CMRI</td>
<td>Normal/near normal RV size and function</td>
</tr>
</tbody>
</table>
| Hemodynamics                                       | Normalization of RV function  
• RAP < 8 mm Hg and  
• CI > 2.5 to 3.0 L/min/m²                                                        |
| Cardiopulmonary exercise testing                  | Peak VO₂ >15 mL/min/kg and EqCO₂ <45 L/min/L/min                                  |
| B-type natriuretic peptide                        | Normal                                                                          |

PAH Treatment Goals

- Improve survival
- Improve quality of life
- Improve exercise capacity
  - 6MWD
  - WHO functional classification
- Improve hemodynamics
- Fewer/less severe symptoms
- Prevent clinical worsening
  - escalation of therapy
  - hospitalization
  - lung transplantation
  - death

Supportive Therapy and General Measures in PAH

- Supervised exercise program rehabilitation
- Avoid pregnancy
- Psychological and social support
- Provide appropriate training and counseling on infection prevention
  - Pneumococcal and flu vaccines

5th WSPH: PAH Supportive Therapy

• Oral anticoagulants (IPAH/HPAH/DT-PAH)
  – Favorable data primarily from retrospective/prospective observational trials

• Diuretics
  – Clinician preference on choice of agents
  – Monitor renal function and blood chemistry
    • Avoid hypokalemia and effects of decreased intravascular volume

• Oxygen
  – Follow guidelines for COPD: Administer if PaO₂ <60 mm Hg for >15 hours/day

• Digoxin
  – Modest increase in cardiac output
  – No data available on long-term management


Role of Calcium Channel Blockers (CCBs) in PAH

• PAH patients should NOT be treated empirically with CCBs

• In PAH patients with right heart failure, CCB therapy may worsen the heart failure

• Patients who do not respond to acute vasodilator challenge should NOT be treated with CCBs

• Responders to acute vasodilator challenge may be treated with high dose CCBs
  – Monitor closely for signs of treatment failure

Mechanisms of Action of Approved Therapies for PAH


PAH-specific Treatment Options for Patients Failing Acute Vasoreactivity Testing

<table>
<thead>
<tr>
<th>Oral Therapy</th>
<th>Inhaled Therapy</th>
<th>Continuous Parenteral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERAs</td>
<td>PDE5 Inhibitors</td>
<td>sGC Stimulator</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Sildenafil</td>
<td>Riociguat</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Tadalafil</td>
<td></td>
</tr>
<tr>
<td>Macitentan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Simplified Treatment Algorithm for Initial PAH

Definite PAH diagnosis including RHC

Overall "Lower Risk" Profile
- Oral therapy

Overall "Higher Risk" Profile
- Consider parenteral therapy
- Consider early combination therapy


Goals of Collaborative Care

Clinical Practice Guidelines
- Local Practitioners
- PH Specialists
- Best Practice

Clinical Trial Evidence
Concluding Remarks

• Differentiating PAH from other types of PAH is difficult but important to effectively treat.

• Evaluation must be methodical and include echocardiography and right heart catheterization.

• Prognosis improves with therapy, but PAH remains a progressive fatal disease.

• Therapies and management strategies continue to evolve.

• Collaborative care with a PH specialist is important.