Pulmonary Hypertension

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No Relevant Disclosures
Definition OF Pulmonary Arterial Hypertension

- Mean Pulmonary artery pressure of 25 mm or greater at rest and 30 or greater with exercise
- Pulmonary capillary wedge pressure (PCWP) <15 mmHg
- Pulmonary vascular resistance (PVR) >120 dynes/sec/cm5
WHO Classification

- **Group 1.** Pulmonary arterial hypertension (PAH)
- **Group 2.** Pulmonary hypertension with left heart disease
- **Group 3.** Pulmonary hypertension associated with lung diseases and/or hypoxemia
- **Group 4.** Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- **Group 5.** Miscellaneous
PAH Is Difficult to Diagnose

- Early symptoms of PAH are subtle and nonspecific
  - Symptoms include dyspnea, fatigue, angina, syncope, among others\(^1,2\)
- Idiopathic pulmonary arterial hypertension (IPAH) is a diagnosis of exclusion
  - Diagnosis typically takes 2 to 3 years\(^3\)

### Clinical Presentation

<table>
<thead>
<tr>
<th>Common Initial Symptoms</th>
<th>Patients</th>
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<tbody>
<tr>
<td>(N =187)</td>
<td>(%)</td>
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<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>13</td>
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<tr>
<td>Chest pain</td>
<td>7</td>
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<tr>
<td>Palpitations</td>
<td>5</td>
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<tr>
<td>Leg edema</td>
<td>3</td>
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</table>
Diagnosis Of Pulmonary Hypertension

- Patients suspected of having PH generally undergo extensive diagnostic testing, which is aimed at confirming its presence and identifying its cause.

- The goal of diagnostic testing is to confirm that PH exists and to identify its underlying cause.
Diagnosis of Pulmonary Hypertension

- **Pulmonary function tests** It is usually severe interstitial lung disease (with lung volumes below 50 percent of predicted) or obstructive lung disease that produces PH. In most circumstances, PH should not be attributed to lung disease if the PFTs are only mildly abnormal since PH itself can cause PFT abnormalities.

- **Chest radiograph** enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, Right ventricular enlargement.

- **Electrocardiography** signs of right ventricular hypertrophy or strain Most ECG signs are not sensitive.
Diagnosis of Pulmonary Hypertension

- **Overnight oximetry** Overnight oximetry can be used to screen patients for Obstructive Sleep Apnea-Hypopnea (OSAH)-related nocturnal oxyhemoglobin desaturation, although it is not an acceptable diagnostic test for OSAH. Polysomnography is the gold standard diagnostic test for OSAH and should be considered when the clinical suspicion for OSAH is high.

- **V/Q scan** Ventilation-perfusion (V/Q) scanning is used to evaluate patients for thromboembolic disease. A normal V/Q scan accurately excludes chronic thromboembolic disease with a sensitivity of 90 to 100 percent and a specificity of 94 to 100 percent.
Echocardiography is performed to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function. In addition, echocardiography can evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts.
Diagnosis of Pulmonary Hypertension

- **Right heart catheterization**
  - Right heart catheterization is necessary to confirm the diagnosis of PH and accurately determine the severity of the hemodynamic derangements
  - The presence and/or severity of a congenital or acquired left-to-right shunt can be confirmed when noninvasive studies are not definitive
  - A vasoreactivity test is necessary for reasons other than the initiation of advanced therapy
Is there a reason to suspect PAH?
Clinical history, Exam, CXR, ECG

Is PAH Likely?
Echocardiogram

Is PAH Likely?  Rationale
Echocardiogram

Measure RVSP, RVE, RAE, RV dysfunction

Is PAH due to LH Disease?
Echo

Dx LV systolic; diastolic dysfunction; valvular dysfunction.
Appropriate treatment and further evaluation if necessary

Is PAH due to CHD?
Echo with contrast

Dx abnormal morphology; shunt surgery; medical treatment of PAH or evaluation for further definition or contributing causes
ACCP Diagnostic Guidelines (cont.)

Is PAH due to CTD, HIV? Serologies
- Yes: Dx scleroderma, SLE, other CTD, HIV. Medical treatment for PAH and further evaluation for contributing causes
- No: Is chronic PE suspected?

Is chronic PE suspected? V/Q scan
- Yes: Is chronic PE confirmed and operable?
  - Yes: Thromboendarterectomy if appropriate or medical treatment
  - No: Is PAH due to lung disease or hypoxemia? PFT's, arterial saturation
- No: Is PAH due to lung disease or hypoxemia? PFT's, arterial saturation
  - Yes: Dx parenchymal lung disease, hypoxemia or sleep disorder. Medical treatment, oxygen, positive pressure breathing, and further evaluation for other contributing causes
  - No: Diagnosis other.

What limitations are caused by the PAH?
- FC, 6 MWT

What are the precise hemodynamics?
- RHC

Document exercise capacity regardless of cause of PH: Establish baseline, prognosis and document progression/response to treatment with serial re-assessment.

Document PA and RA pressures, PCWP (LV or LA pressure if PCWP unobtainable or uncertain), transpulmonary gradient, CO, PVR, SvO2, response to vasodilators: Confirm PAH, or IPAH if no other cause identified. Discuss genetic testing and counseling of IPAH family.
Classification of PAH Group

One (ACCP 2004)

1.1 Idiopathic (iPAH)

1.2 Familial

1.3 Associated with

- Collagen vascular disease
- Congenital systemic to pulmonary shunts
- Portal hypertension
- HIV infection
- Drugs and Toxins
- Other (hemoglobinopathy, glycogen storage diseases etc.)

1.4 Associated with significant venous or capillary involvement

1.5 Persistent pulmonary hypertension of the newborn
## At-Risk Populations for PAH

<table>
<thead>
<tr>
<th>Populations</th>
<th>Prevalence/Incidence</th>
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<tr>
<td><strong>IPAH</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1-2/million</td>
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<tr>
<td><strong>CTD</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Systemic Sclerosis</td>
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<tr>
<td>CREST syndrome</td>
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<tr>
<td>UNCOVER&lt;sup&gt;3&lt;/sup&gt;</td>
<td>30%</td>
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<tr>
<td></td>
<td>50%</td>
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<tr>
<td></td>
<td>27% (11% newly identified)</td>
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<tr>
<td><strong>CHD</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Up to 50% of patients with large VSDs develop</td>
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<td>Eisenmenger syndrome, often associated with PAH</td>
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<td><strong>HIV</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1/200</td>
</tr>
<tr>
<td><strong>SCD</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>20-40%</td>
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<tr>
<td><strong>Drugs/Toxins</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Direct relationship with anorexigens (amphetamines, cocaine); L-tryptophan may also be associated with PAH</td>
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Increased Pulmonary Resistance and Pressure

Pre-Symptomatic  Symptomatic  Severely Symptomatic

High flow, low resistance vessel  Low flow, high resistance vessel

As PAH Progresses Cardiac Output Declines

Pre-symptomatic/Compensated

Symptomatic/Decompensating

Declining/Decompensated

PAP

PVR

CO

Symptom Threshold

Right Heart Dysfunction

Time
IPAH: Rapid Progression and Poor Survival

PAH: Survival Based on Etiology

Survival in PAH

- CHD
- CVD
- HIV
- IPAH
- Portopulm

PAH/SSc Progresses Even More Rapidly

PAH Treatment: Targeting Known Pathophysiological Pathways

Pathways Involved in PAH

- ET-1 binds to $\text{ET}_A$ and $\text{ET}_B$ receptors on smooth muscle and endothelial cells\(^1\)
- NO stimulates the cGMP pathway\(^2\)
- PGI\(_2\) stimulates the cAMP pathway\(^2\)
- Stimuli such as decreased blood flow, hypoxia, or shear stress induce the overproduction of ET-1 and decrease NO production\(^3-5\)
- Chronic imbalance of ET-1, NO, and PGI\(_2\) levels lead to pathophysiological changes\(^3-8\):
  - Vasoconstriction
  - Increased vascular tone
  - Smooth muscle cell proliferation
  - Vascular remodeling
  - Right-heart hypertrophy
Endothelin Is 1 of 3 Main Pathways in PAH

Endothelial Dysfunction Primarily Drives PAH

- Two hallmarks of PAH are vasoconstriction and vascular remodeling\(^1\)
  - Vasoconstriction and cellular proliferation are driven by ET-1\(^2\)
  - Vasodilation is driven by nitric oxide (NO) and prostacyclin (PGI\(_2\)), which are antiproliferative in nature\(^3\)

- Disease severity is associated with excess circulating ET-1 levels\(^4\)

## PAH Treatment: Timeline of Recent Advances\(^1-^3\)

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<tr>
<td><strong>Prostacyclins</strong></td>
<td>Epoprostenol</td>
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<td></td>
<td>Treprostinil</td>
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<td></td>
<td>Iloprost</td>
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<td><strong>Endothelin receptor antagonists</strong></td>
<td>Bosentan</td>
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<td>Sitaxsentan*</td>
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<tr>
<td><strong>PDE-5 inhibitors</strong></td>
<td>Sildenafil</td>
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*Late stage clinical development*

## WHO Functional Class of PAH

<table>
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<tr>
<th>Class</th>
<th>Description</th>
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<tr>
<td><strong>Class I</strong></td>
<td>Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, chest pain, or near syncope.</td>
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<tr>
<td><strong>Class II</strong></td>
<td>Patients with PH 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>
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<tr>
<td><strong>Class III</strong></td>
<td>Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<tr>
<td><strong>Class IV</strong></td>
<td>Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
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</tbody>
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Rubin. *Chest* 2004
PAH: Conventional Therapy

• Includes¹
  - Supplemental oxygen to treat chronic hypoxemia
  - Diuretics
  - Anticoagulants
  - Digoxin

• Some patients benefit from high-dose calcium channel blockers¹
  - Can alleviate pulmonary vasoconstriction and increase survival²
  - Hypotension and edema can result in poor tolerance of required doses³
  - Candidates identified by acute vasodilator challenge¹,²

PAH: Prostacyclin Therapy

- Epoprostenol (Flolan®)
- Indicated for IPAH and for PAH patients associated with scleroderma
  - Class III-IV
- Given by continuous infusion
  - Requires in-dwelling central venous catheter
- Common dose-limiting adverse events: nausea, vomiting, headache, hypotension, and flushing
- Abrupt withdrawal can result in rebound PAH symptoms
- Must keep reconstituted solution between 2° and 8°C

PAH: Prostacyclin Therapy (cont)

- Treprostinil (Remodulin®)\(^1\)
- Indicated for PAH patients
  - Class II-IV
- Given via subcutaneous or intravenous infusion
- Longer half-life than epoprostenol
  - Reduces risk of rebound worsening
- Common adverse events: pain (85%) or reaction (83%) at infusion site
- Stable at room temperature

PAH: Prostacyclin Therapy (cont)

- Inhaled iloprost (Ventavis®)\(^1\)
- Indicated for PAH patients (WHO Group I)
  - Class III-IV
- Given via nebulizer
  - Short duration of action\(^2\)
  - 6 to 9 inhalations per day
- Common adverse events: flushing, cough, headache

PAH: Phosphodiesterase-5 Inhibitor Therapy

- Sildenafil (Revatio™)¹
- Indicated for PAH patients (WHO Group I)
- Oral
  - Recommended dose 20 mg three times per day
- Common adverse events: headache, dyspepsia, flushing

PAH: Endothelin Receptor Antagonist Therapy

- Bosentan (Tracleer®)\(^1\)
- Indicated for PAH patients (WHO Group I)
  - Class III-IV
- Oral
  - Initial dose: 62.5 mg bid x 4 weeks
  - Maintenance dose: 125 mg bid
- Liver enzymes measured prior to initiating treatment and then monthly
- Common adverse events: headache, flushing, abnormal hepatic function, leg edema, anemia
- Pregnancy must be excluded before start of treatment; monthly pregnancy tests required

Significant Change in 6MWD

BREATHE-1

Data are mean ± SEM. Walk distance was somewhat greater with 250 mg BID, but the potential for increased liver injury causes this dose not to be recommended [125 mg BID (n=74) change in walk distance (m): 27 ± 75, 250 mg BID (n=70) change in walk distance (m): 46 ± 62].

FLOLAN® (epoprostenol sodium)
Long-Term Survival

![Graph showing long-term survival for FLOLAN® (epoprostenol sodium) compared to historical controls.](image)

- **Survival, % of patients**
  - Epoprostenol (n = 178)
  - Historical controls (n = 135)

- **Time, months**
  - 0, 12, 24, 36, 48, 60

- **Statistical Significance:** $p < 0.001$

FLOLAN® (epoprosthenol sodium)
Increased Exercise Capacity

6MWD = 6-minute walk distance; NS = Not significant.
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PAH: Class II/III/IV Treatment Algorithm\(^1\)