Screening Diagnosis and Treatment of PAH: An Overview

Kerri Akaya Smith, MD
Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension (PAH): An Overview

New Jersey Association of Osteopathic Physicians & Surgeons
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Faculty Disclosure

- Dr. Smith has received research support/grants from Eiger BioPharmaceuticals, Inc, Gilead Sciences, Inc., Actelion Pharmaceuticals US, Inc, and United Therapeutics Corporation.
- Dr. Smith has also served on an advisory committee for United Therapeutics Corporation.
The Pulmonary Hypertension Association (PHA) is the leading non-profit organization for PH research, public awareness, and services. The organization has over 12,000 members, including patients, family members, and medical professionals.

www.PHAssociation.org

Vascular Pressure in Systemic and Pulmonary Circulations (mm Hg)

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

5th World Symposium on PH: Classification of PH

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 Unknown
   1.3 Drug or alcohol 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
   1.5 Unknown

2. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1. PPHN

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 Other

4. CTEPH

5. PH with unclear multifactorial mechanisms
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: chronic renal failure, segmental PH


5th World Symposium on PH: Hemodynamic Definition of PH/PAH

PH: Mean PAP ≥25 mm Hg at rest during RHC

PAH: Mean PAP ≥25 mm Hg plus PAWP ≤15 mm Hg plus PVR >3 Wood units


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      1.4.4 Congenital heart disease
   1.5 Unknown

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
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Heritable PAH

- Autosomal dominant
- BMPR2 (bone morphogenetic protein receptor type 2) is the major predisposing gene
- Mutation detection rate for known genes is ≈75% in familial PAH
- Major predisposing gene has a highly variable penetrance between families
- Genetic anticipation
- ALK1 (ACVRL1; activin A receptor type-II-like kinase 1) is major gene when PAH is associated with hereditary hemorrhagic telangiectasia (HHT)


PAH Related to Connective Tissue Disease

- Connective tissue diseases
  - limited scleroderma (most common)
  - diffuse scleroderma
  - mixed connective tissue disease
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - Sjogren’s syndrome
- PH is one of the leading causes of death in scleroderma
- Similar to IPAH pathology
- Medical treatment same as for IPAH, but benefits less than for IPAH


Prevalence of PAH in Scleroderma

- Prevalence 7.9% in large prospective study (N=599) with confirmatory catheterizations
  - excluded severe PFT abnormalities
  - all underwent Doppler echocardiography
  - catheterization if VTR >3 m/sec or 2.5–3 m/sec + unexplained dyspnea
- Prevalence of PAH: found in 47 of 599 scleroderma patients
  - 29 had known PAH at study entry
  - 18 patients were newly diagnosed with PAH

Portopulmonary Hypertension

- Prevalence overall: 2-5% by RHC; liver transplant candidate: 4% to 17%
- Dependent on portal HTN, not hepatocellular dysfunction
- Poor prognosis: higher risk of death than IPAH pts
- Liver transplant
  - may improve survival with mild to moderate PAH (28-56%, 5 yr)
  - significant PAH (mPAP >35 mm Hg) predicts unacceptably high perioperative mortality

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   1.2.3 Unknown
   1.3 Resp. and/or stress
   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
      1.4.5 Schistosomiasis

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 Other chronic lung disease
   3.5 Arterial hypoxemia
   3.6 Chronic hypoxemia in high altitudes
   3.7 Developmental lung diseases

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: glycogen storage disease, Gaucher disease
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Most Common Cause of Elevated PAPs by Echo: Left Heart Disease

Symptoms
- paroxysmal nocturnal dyspnea
- orthopnea

History
- diabetes
- hypertension
- obesity
- coronary artery disease
- metabolic syndrome

ECG
- atrial fibrillation
- absence of right axis deviation

Echo
- left atrial enlargement
- left ventricular hypertrophy
- normal RA, RV
- abnormal diastolic filling
- mitral or aortic disease
Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

### Percentage of PAH and PVH Patients With All 4 Metabolic Syndrome Factors

- **PAH**: 40%
- **PVH**: 60%

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>DM</td>
<td>1.4 (1.2-1.6)</td>
</tr>
<tr>
<td>KC</td>
<td>1.1 (0.9-1.3)</td>
</tr>
</tbody>
</table>

*p≤0.005; **p=0.023.


### 5th World Symposium on PH: Classification of PH

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   - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Rho and/or medi- and/or RA
   - 1.4 Associated with
     - 1.4.1 Connective tissue disease
     - 1.4.2 IV drug use
     - 1.4.3 Portal hypertension
   - 1.5 Other

2. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

3. PH due to lung diseases and/or hypoxia
   - 3.1 COPD
   - 3.2 Interstitial lung disease
   - 3.3 Other parenchymal disease with mixed restrictive and obstructive pattern
   - 3.4 Sleep disordered breathing
   - 3.5 Arterial hypoxemia disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. PH with unclear multifactorial mechanisms
   - 4.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 4.2 Systemic disorders: sarcoidosis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 4.3 Metabolic disorders: collagen storage diseases, Gaucher disease, thyroid disorders
   - 4.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

**Simonneau G et al. JACC 2013;62:D34-41.**

### Chronic Obstructive Pulmonary Disease (COPD) and PH

- Retrospective study of 215 COPD patients
- 13.5% had a PA mean >35 mm Hg
- Correlated best (inversely) with PaO2
- A small number had only moderate obstruction: treatable sub-group?

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

5th World Symposium on PH: Classification of PH

- Primary Pulmonary Hypertension
  - 1. Idiopathic PAH
  - 1.1 BMPR2
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  - 1.4 Associated with:
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    - 1.4.3 Congenital heart disease
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- Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- 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
- Pulmonary arterial hypertension with mixed restrictive and obstructive pattern
- Pulmonary arterial hypertension 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: glycogen storage disease, Gaucher disease, thyroid disorders
  - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Incidence of CTEPH

- Approximately 3% to 4% 1-2 yr after acute PE
- USA: 600,000 cases of acute PE each year
- Only 40% to 50% of CTEPH patients have a history of previous episodes of acute PE
- VQ scan identifies old PE better than CTA

Pathology of PAH

WHO Group I: Characterized by progressive growth and vasoconstriction of small pulmonary arteries
PAH: Hemodynamic and Clinical Course

Adapted from Gaine S. JAMA. 2000;284:3160-3168.

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

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Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

**Survival in PAH**

- [Graph showing survival rates for different conditions: Congenital heart disease, Portopulmonary, IPAH, CTD, HIV.]

**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


**French Registry: Kaplan-Meier Survival Estimates in Combined PAH Population vs NIH-predicted**

- [Graph showing observed vs predicted survival.]
Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

**REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata**

![Graph showing survival rates](image)

<table>
<thead>
<tr>
<th>Months from enrollment</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
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<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
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<tr>
<td>7</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

**Key Pathways Implicated in PAH Pathogenesis**

![Diagram showing key pathways](image)

**Case: Jane**

- 37-yr-old woman, previously healthy
- Delivered second child 14 mo previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea while playing with older child; syncope while walking up an incline
Jane: Initial Symptoms

- Currently has dyspnea with mild exertion, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema

Multiple Guidelines, Consistent Message: Comprehensive Diagnostic Evaluation/Robust PH Specialty Center Collaboration Are Necessary

Follow Basic Steps of American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Consensus Algorithm, With Some Updates

- To identify:
  - the presence of PH
  - which group of PH (WHO I-V)

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

[Image of a flowchart and text]

- **History and Physical Exam Findings AreInsensitive Unless Advanced Disease/RV Failure Present**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam (PH)</th>
<th>Exam (RV Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea (86%)</td>
<td>Loud P2 (listen at apex)</td>
<td>JVD; increased A wave, V wave; hepatojugular reflex</td>
</tr>
<tr>
<td>Fatigue (27%)</td>
<td>RV lift (left parasternal – fingertips)</td>
<td>Pulsatile liver</td>
</tr>
<tr>
<td>Chest pain (22%)</td>
<td>RV S3, S4</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Edema (22%)</td>
<td>Systolic murmur (TR; inspiratory augmentation)</td>
<td>Edema</td>
</tr>
<tr>
<td>Syncope (17%)</td>
<td>Early systolic click</td>
<td>Ascites</td>
</tr>
<tr>
<td>Dizziness (15%)</td>
<td>Midsystolic ejection murmur</td>
<td>Low BP, low PP, cool extremities</td>
</tr>
<tr>
<td>Cough (14%)</td>
<td>Diastolic murmur (PR)</td>
<td></td>
</tr>
<tr>
<td>Palpitations (13%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


- **Jane: Physical Exam**

  - HR 90 bpm; BP 130/68 mm Hg; Wt 190 lb; Ht 5’4”
  - JVP ~15 cm, reduced carotid upstrokes
  - Clear lungs
  - Palpable RV heave, RRR, normal S, loud P2, III/VI, TR m
  - 2+ LE edema
Jane: Additional History

- PMH: 2 children, 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- Allergies: contrast dye
- FH: PPH in a paternal aunt, CAD, DM, Htn
- SH: rare ETOH, o/w unremarkable

Chest Radiograph May Show Right Heart and Vascular Abnormalities in Advanced Disease

Healthy

PH

**Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension**

**Electrocardiogram May Show Right Heart Abnormalities in Advanced Disease**

- Right Axis Deviation
- Right Atrial Enlargement
- Right Ventricular Hypertrophy
- Right Ventricular Strain

Image courtesy Christopher F. Barnett, MD, MPH

**ACCF/AHA Diagnostic Algorithm**

- **Pivotal Tests**
  - Echocardiography
  - PFTs
  - Polysomnography
  - V/Q Scan

- **Contingent Tests**
  - HIV
  - ANA
  - LFT's
  - RH Cath
  - TEE
  - Exercise Echo
  - Pulmonary Angiography
  - Chest CT Angiogram
  - Coagulopathy Profile
  - Volume Loading

- **Contribute to Assessment at**
  - Index of Suspicion of PH
  - Right Ventricular, Right Atrial, Right Ventricular Strain, RV Function
  - Left Heart Disease, Left Ventricular Hypertrophy
  - Chronic Thromboembolic PH
  - Ventilatory Function, Gas Exchange
  - Sleep Disorder
  - Left Intercostal
  - Arterial Blood Gas, Arterial Blood Gases
  - Cardiac Catheterization
  - Cardiac Magnetic Resonance
  - Confirmation of PAH Hemodynamic Profile
  - Vasodilator Response


**Checklist for Echocardiographic Assessments When PH Is Suspected**

- Estimate pulmonary artery systolic pressure
- Evaluate severity of TR
- Evaluate right heart size and function
- Exclude left heart valvular disease and systolic dysfunction
- Exclude congenital heart disease
- Differentiate PAH from PH due LHD
- Estimate RA pressure
- Evaluate for pericardial effusion

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

PASP Is Estimated Using Tricuspid Regurgitant Jet Velocity

\[ \text{PASP} = 4(V_{TR})^2 + \text{RAP} \]

PASP = RVSP in the absence of pulmonic outflow obstruction

Modified Bernoulli Equation

Images courtesy Christopher F. Barnett, MD, MPH

TR Jet Signal Quality Affects Reliability of Estimated PASP

Poor signal quality

Good signal quality

Structural Echocardiographic Findings in Patients With PH

• RV enlargement
• RA enlargement
• Septal flattening
• Pericardial effusion

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

Ventilation Perfusion Scan (V/Q): Best Screening Test to Exclude CTEPH

- Should never be missed
- Is potentially curable with pulmonary endarterectomy (PEA)
- 3% to 4% of acute PE will develop CTEPH
- Half of those with CTEPH do not have an apparent history of thromboembolism
- Normal V/Q scan excludes CTEPH
- CTEPH may be diagnosed on CT pulmonary angiogram, however, reported sensitivity varies from 50-95%


Ventilation Perfusion Scan (V/Q) to Exclude CTEPH

Image courtesy Kelly Chin, MD
High-Quality Conventional Pulmonary Angiography: Gold Standard Test for CTEPH Diagnosis


CTEPH: A Surgical Disease
Survival Without Surgery Is Poor

Image courtesy Christopher F. Barnett, MD, MPH

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

ACCF/AHA Diagnostic Algorithm


ACCF/AHA Diagnostic Algorithm

Index of Suspicion of PH
Pivotal Tests
Contingent Tests
Contribute to Assessment of:

Left Heart Cath

Index of Suspicion of PH

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High-Quality Conventional Pulmonary Angiography
CTEPH Diagnosis


CTEPH: A Surgical Disease
Survival Without Surgery Is Poor

Image courtesy Christopher F. Barnett, MD, MPH

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

ACCF/AHA Diagnostic Algorithm

Presence and Severity of Lung Disease Must Be Assessed

- Abnormalities on PFTs may suggest cause of PAH or reveal PH from lung disease (Group III)
- CT scanning useful in identifying parenchymal lung disease

<table>
<thead>
<tr>
<th>IPAH and CTEPH</th>
<th>Systemic Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 20% have isolated reduction in DLCO</td>
<td>- 20% have isolated reduction in DLCO</td>
</tr>
<tr>
<td>- DLCO mildly reduced (60%-80% predicted NIH registry)</td>
<td>- Severely predicts future PAH</td>
</tr>
<tr>
<td>- PVR correlates with reduction in DLCO</td>
<td>- DLCO correlates inversely with PASP</td>
</tr>
</tbody>
</table>

DLCO: diffusing capacity of the lungs for carbon monoxide.

Overnight Pulse Oximetry Is a Useful Screening Test for Sleep Disordered Breathing

- Hypoxia may signal underlying sleep apnea
- In patients with obstructive sleep apnea (OSA), PAPs reported to decrease in response to CPAP therapy
- Untreated—response to other treatment likely to be less effective

Functional Assessment: WHO Functional Class
Modified From NYHA Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity; no discomfort at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity; no discomfort at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without symptoms; signs of right-heart failure; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity</td>
</tr>
</tbody>
</table>

Jane: Laboratory Studies

- **ANA:** negative
- **Echo:** normal LV function, RAE, RVE, RVSP 60 mm Hg, TEE—no shunt found after agitated saline injection
- **VQ:** normal
- **PFTs:** normal volumes and flows, DLCO 81%
- **6MWD:** 222 m, 99-96%
Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

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

Assessment of Pressures as the Catheter Passes Through the Heart

PH: The Importance of Hemodynamics

Pulmonary venous hypertension
*Elevated PCWP, normal PVR*

PAH
PH with respiratory disease
CTEPH
*Normal PCWP, elevated PVR*
Vasodilator Testing Identifies Patients Who Respond Well Long Term to Treatment With Calcium Channel Blockers

- Vasodilator testing
  - Nitric Oxide inh or epoprostenol IV
  - Positive test defined by:
    Drop in mPAP >10 mm Hg to a mPAP≤40 mmHg + normal CO


Jane: Right Heart Cath

<table>
<thead>
<tr>
<th></th>
<th>1/29/07 Baseline</th>
<th>Nitric Oxide 20 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mm Hg)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>93/40, mean 63</td>
<td>93/46, mean 64</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>52.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Femoral artery</td>
<td>91.4</td>
<td>91.7</td>
</tr>
<tr>
<td>Cardiac output / Cardiac index (L/min) Fick</td>
<td>2.5/1.3</td>
<td>2.88/1.52</td>
</tr>
<tr>
<td>PVR (Wood units) Fick</td>
<td>21.2</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Screening and Diagnosis Summary

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Evaluate potential causes/contributing issues
- RHC required prior to initiating PAH therapy
- Baseline functional evaluation
PAH Treatment Goals

• Fewer/less severe symptoms
• Improved exercise capacity
• Improved hemodynamics
• Prevention of clinical worsening
• Improved quality of life
• Improved survival

5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>I or II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function (RAP &lt;8 mm Hg and CI &gt;2.5-3.0 L/min/m²)</td>
</tr>
<tr>
<td>Echocardiography/MRI</td>
<td>Normal/near normal RV size and function</td>
</tr>
<tr>
<td>BNP level</td>
<td>'Normal'</td>
</tr>
<tr>
<td>6MWD</td>
<td>380-440 m, may not be aggressive enough</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO₂ &gt;15 mL/kg/min, VE/VCO₂ @ AT &lt;45</td>
</tr>
</tbody>
</table>


What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

**Chronic Adjuvant Therapies in PAH**

**Digoxin**
- Variable inotropic effect and use
- No long-term data; need to balance unproven benefits with known risks

**Oxygen**
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt

**Diuretics**
- Most need; hypotension not a contraindication (may need BP support)
- Renal function and electrolytes must be monitored closely

**Anticoagulation**
- Recommended in IPAH
- Observational studies only (2 retrospective, 1 prospective); need to balance unproven benefits with known risks
- INR 1.5 – 2.5


**Other Management Issues**

- Encourage exercise and activity within the limits of disease and ability to maintain O₂ levels
- Consider enrollment in a pulmonary rehabilitation program
- Immunizations
- Contraception

**What Is the Optimal Treatment Strategy?**

Survival in IPAH: Long-term CCB Responders

Revised Definition of Vasodilator Responder

PAH Determinants of Risk
What Is the Optimal Treatment Strategy?

<table>
<thead>
<tr>
<th>Oral CCB</th>
<th>Sustained Response</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Vasoreactivity Testing</td>
<td>Positive</td>
<td>LOWER RISK</td>
<td>HIGHER RISK</td>
</tr>
<tr>
<td>No</td>
<td>Determinants of Risk</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual Progression of Symptoms</td>
<td>Rapid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer (&gt;600 m)</td>
<td>Shorter (&lt;300 m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO₂ &gt;10.4 mL/kg/min</td>
<td>Peak VO₂ &lt;10.4 mL/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD ≥300 m</td>
<td>6MWD ≤300 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>CI ≥2.8 L/min/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained Response</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acute Vasoreactivity Testing

Approved Therapeutic Targets

Prostacyclin Analogues: Intravenous, Subcutaneous, Inhaled, or Oral

Prostacyclin Analogues: Pivotal Trials for IV and SC Formulations

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy
Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations

<table>
<thead>
<tr>
<th>Study Name / Drug</th>
<th>N / Etiol</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIR</td>
<td>202 PAH</td>
<td>Double-blind 12-week</td>
<td>• Composite end point EMWD - Symptoms - Hemodynamics</td>
</tr>
<tr>
<td></td>
<td>III/IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIUMPH I</td>
<td>235 PAH</td>
<td>Double-blind 12-week on background oral Rx</td>
<td>• EMWD</td>
</tr>
<tr>
<td></td>
<td>III/IV*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FREEDOM-M</td>
<td>220 PAH</td>
<td>Double-blind placebo-controlled 12-week</td>
<td>• 6MWD</td>
</tr>
<tr>
<td></td>
<td>l-l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRIPHON</td>
<td>1156 PAH</td>
<td>Double-blind, naïve or on background ERA and/or PDE5I, event-driven morbidity/mortality</td>
<td>• Time to first morbid or mortality event</td>
</tr>
<tr>
<td></td>
<td>l-l</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Approved for class III only. **Approved for class III only inhaled and PAH IV in IV-ERA (due to short half-life).

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Rebound PH if interruption of epoprostenol delivery (due to short half-life)
- Delivery site complications (pain, infection, cough, thrombosis, infusion)

Vary according to drug and route of delivery

Approved Therapeutic Targets

Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension

**Endothelin Receptor Antagonists: Pivotal Trials**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>N Etiology Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREATHE-1</td>
<td>Oral bosentan*</td>
<td>PAH II, IV</td>
<td>Double-blind 12-week</td>
<td>6MWD, delay clinical worsening, symptoms</td>
</tr>
<tr>
<td>EARLY</td>
<td>Oral bosentan*</td>
<td>PAH II</td>
<td>Double-blind 6-month</td>
<td>Delay clinical worsening, hemodynamic</td>
</tr>
<tr>
<td>ARIES-1&amp;2</td>
<td>Oral ambrisentan§</td>
<td>PAH II, III</td>
<td>Double-blind 12-week</td>
<td>6MWD, delay clinical worsening</td>
</tr>
<tr>
<td>SERAPHIN</td>
<td>Oral macitentan†</td>
<td>PAH II, III</td>
<td>Event-driven</td>
<td>Delay disease progression, 6MWD, symptoms</td>
</tr>
</tbody>
</table>

*Bosentan = Tracleer®, Approved for FC II–IV, 62.5–125 mg po bid.
§Ambrisentan = Letairis®, Approved for FC II–III, 5–10 mg po qd.
†Macitentan = Opsumit®, Approved for FC II–III, 10 mg po qd.


**Endothelin Receptor Antagonists: Side Effects**

- Nasal congestion
- Abnormal hepatic function* – monthly LFTs required for bosentan
- Anemia – monitor CBC quarterly
- Edema – lower extremity edema may require diuretic adjustment
- Teratogenic – use requires dual contraceptive methods (hormonal plus barrier)

*PHA Scientific Leadership Council recommends LFT testing at onset of all treatments for PAH and periodically thereafter, at prescriber’s discretion.

**Approved Therapeutic Targets**

- Endothelin Pathway
- Nitric Oxide Pathway
- Prostacyclin Pathway

[Diagram showing pathways and targets]
PDE-5 Inhibitor Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>N Etio</th>
<th>Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUPER-1</td>
<td>Oral sildenafil*</td>
<td>278</td>
<td>PAH I-IV</td>
<td>Double-blind 12 week</td>
<td>• 6MWD • Symptoms • Hemodynamics</td>
</tr>
<tr>
<td>PHIRST-1</td>
<td>Oral tadalafil §</td>
<td>405</td>
<td>PAH I-IV</td>
<td>Double-blind 16 week</td>
<td>• 6MWD • Delay clinical worsening • Hemodynamics • HRQoL</td>
</tr>
</tbody>
</table>

*Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.


PDE-5 Side Effects

- Nose bleed
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes

Contraindicated with use of nitrate

sGC Stimulator Pivotal Trials

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug</th>
<th>N Etio</th>
<th>Class</th>
<th>Design</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT-1</td>
<td>Oral riociguat*</td>
<td>443</td>
<td>PAH I-IV</td>
<td>Double-blind 12 week</td>
<td>• 6MWD • Symptoms • Hemodynamics • Delay clinical worsening</td>
</tr>
<tr>
<td>CHEST-1</td>
<td>Oral riociguat</td>
<td>261</td>
<td>CTEPH I-IV</td>
<td>Double-blind 16 week</td>
<td>• 6MWD • Symptoms • Hemodynamics</td>
</tr>
</tbody>
</table>

*Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.

sGC Stimulator Side Effects

- Headache
- Dizziness
- Dyspepsia/gastritis
- Nausea
- Diarrhea

- Hypotension
- Vomiting
- Anemia
- Gastroesophageal reflux
- Constipation

Contraindicated in pregnancy, with use of nitrates or NO donors in any form, or with use of PDE inhibitors

5th World Symposium on PH: 2013 PAH Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS

Sequential Combination Therapy (II-6)
- ERAs
- Prostansids
- PDE-5 I or sGCs

Inadequate Clinical Response on Maximal Therapy (II-6)

Balloon Atrial Septostomy (II-6)

Consider Eligibility for Lung Transplantation

Inadequate Clinical Response

Referral for Lung Transplantation (II-C)

Acute vasoreactivity test (II-C for IPAH; II-C for APAH)

General measures and supportive therapy

Expert Referral (I-C)

NON-VASOREACTIVE

Sustained response (WHO FC I-II)

NO

VASCORACTIVE

WHO FC > II CCB (I-C)


5th World Symposium on PH: 2013 Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS

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Sustained response (WHO FC I-II)

NO

VASCORACTIVE

WHO FC > II CCB (I-C)

INITIAL THERAPY WITH PAH-APPROVED DRUGS

<table>
<thead>
<tr>
<th>Evidence</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A or B</td>
<td>Ambrisentan</td>
<td>Macitentan</td>
<td>Epoprostenol</td>
</tr>
<tr>
<td>C</td>
<td>Iloprost</td>
<td>Macitentan</td>
<td>Treprostinil</td>
</tr>
<tr>
<td>B</td>
<td>Ambrisentan</td>
<td>Macitentan</td>
<td>Treprostinil</td>
</tr>
</tbody>
</table>

Combination Therapy

- **sGC Stimulators**
  - PATENT-1
  - TRUMPH
  - SERAPHIN
  - GRIPHON

- **Prostanoids**
  - Epoprostenol
  - Iloprost
  - Treprostinil

- **Endothelin Receptor Antagonists**
  - Ambrisentan
  - Bosentan
  - Macitentan

- **Phosphodiesterase Inhibitors**
  - Sildenafil
  - Tadalafil

**AMBITION: Effect of Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening**

- Hazard ratio, 0.50 (95% CI, 0.35-0.72)
- P<0.001

Participants with no event (%)

- Combination therapy: 253, 229, 186, 145, 106, 71, 36, 4

*Death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response.

**Screening, Diagnosis, and Treatment of Pulmonary Arterial Hypertension**

**GRIPHON: Effect of Selexipag on Time to First Morbidity or Mortality Event**

- **Selexipag vs placebo:** RR 40%; HR=0.60; \( p<0.0001 \)
- No. at Risk:
  - Placebo: 582, 433, 347, 240, 149, 88, 28
  - Selexipag: 574, 455, 361, 246, 171, 101, 40

**SERAPHIN: Effect of Macitentan on Disease Progression**

- 64% on background therapy: -60% PDE5i -5% Prostanoid
- No. at Risk:
  - Placebo: 250, 198, 146, 158, 122, 64, 23
  - Macitentan 3 mg: 250, 213, 168, 166, 147, 80, 32
  - Macitentan 10 mg: 242, 208, 167, 171, 155, 51, 41

**COMPASS-2: Effect of Sildenafil + Bosentan Versus Sildenafil + Placebo on Time to First Morbidity/Mortality Event**

- All-cause death, hospitalization for worsening PAH or IV prostanoids, lung transplantation or cardiac surgery
- No. at Risk:
  - Sildenafil + Bosentan: 175, 154, 140, 123, 118, 107, 90, 75, 68, 61, 58, 46, 43, 36, 26, 24, 21, 15
  - Sildenafil + Placebo: 159, 144, 128, 114, 105, 97, 88, 82, 68, 57, 50, 42, 32, 24, 21, 15

---


Combination Therapy Caveats

• Experience evolving
• Most data from ‘add-on’ - ? De novo? Order?
• More drugs available
  – more options
  – more ways to get it wrong
• More questions than answers
• Costs/expenditures; third-party hurdles


Jane: Initial Management

• Admitted to hospital following cath
• IV diuresis
• IV epoprostenol initiation

On-therapy Prognostic Indicators

• Functional class I or II
• 6MWD >380 m
  – limiting supporting data; do not use in isolation
• Hemodynamics
  – normal cardiac index (>2.2 L/min/m²)
  – normal RA pressure
• Positive response to CCB
• BNP <180 pg/mL
### Important Prognostic Variables

<table>
<thead>
<tr>
<th>French Registry</th>
<th>REVEAL Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Functional class</td>
<td>- Functional class</td>
</tr>
<tr>
<td>- 6-minute walk</td>
<td>- 6-minute walk</td>
</tr>
<tr>
<td>- RAP</td>
<td>- PVR, RAP</td>
</tr>
<tr>
<td>- CO</td>
<td>- Vitals</td>
</tr>
<tr>
<td>- Age</td>
<td>- BNP</td>
</tr>
<tr>
<td>- Gender</td>
<td>- Pericardial effusion</td>
</tr>
<tr>
<td>- Etiology</td>
<td>- DLCO</td>
</tr>
</tbody>
</table>


### Jane: Return Visits in May & September

- Significantly improved
- No limitations
- Functional class I
- Meds
  - epoprostenol 30 ng/kg/min
  - warfarin
  - furosemide 20 mg
  - KCl 10 mEq qd

### Jane: Follow-up Physical Exam

- HR 80 bpm; BP 103/59 mm Hg; Wt 144.8 lb
- JVP 6, carotid upstrokes normal
- Clear lungs
- Palpable RV heave, normal S, loud P2, II/VI TR murmur
- No LE edema
Jane: 6MWD

- 222 m: 99-96% in January
- 486 m: 99-97% in May
- 556 m: 99-97% in September

Collaborative Care With PH Centers:

- Diagnostic dilemmas
- Diagnostic cath/vasodilator trial
- Fluid management
- Acute issues
- PAH-specific therapies
- Side effects
- Hospitalizations
- Transplant
- Clinical trials

Thank you for your participation!

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