Pulmonary Hypertension

Stephanie M. Levine MD, FCCP
UT Health -San Antonio
South Texas VA Hospital
Conflict of Interest Disclosure

• No Conflicts of Interest
Learning Objectives

At the conclusion of this presentation, you will be able to:

• Describe the WSPH classification of PH and PAH.
• Understand the pathophysiology of PAH
• Provide the approach to diagnosis and assessment of PAH
• Discuss the recommended treatment regimens for PAH
Pulmonary Hypertension (PH) is an observation of elevated pulmonary pressures.

Encompasses a diverse group of conditions that lead to elevated arterial and/or venous pulmonary pressures.
Classification of PH is based on accurate findings on right heart catheterization (RHC).

**Pulmonary Hypertension (PH)**

Mean pulmonary artery pressure (mPAP) \( \geq 25 \text{ mm Hg} \) (\( >20 \text{ mmHg}^* \))

---

*New 2019

As measured by right heart catheterization.
PH: Clinical Classification by Groups

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Classification based on accurate findings on right heart catheterization.

<table>
<thead>
<tr>
<th>Pulmonary Hypertension (PH)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure (mPAP)</td>
<td>≥25 mm Hg*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-Capillary PH (including PAH)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pulmonary artery pressure (mPAP)</td>
<td>≥25 mm Hg*</td>
</tr>
<tr>
<td>and</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery wedge pressure (PAWP)</td>
<td>≤15 mm Hg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PH Hemodynamic Definition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary vascular resistance (PVR)</td>
<td>&gt;3 Wood units</td>
</tr>
</tbody>
</table>

* > 20 mmHg

As measured by right heart catheterization.

PH: Clinical Classification by Groups

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis

1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Histopathology of PAH: Vasculopathy of the small pulmonary arteries

- Pulmonary arteriopathy
  - Medial hypertrophy and intimal thickening
  - Plexiform/dilation lesions and/or arteritis
  - Cellular and/or fibrotic intimal thickening
- Pulmonary occlusive venopathy
- Pulmonary microvasculopathy
- Vasoconstriction

Progression of PAH

Adapted from: Hill NS. Pulmonary Hypertension Therapy. Summit Communications, LLC; 2006:9.
Etiologies of PAH

Overall
- Idiopathic, 46.6%
- Heritable, 2.7%
- PVOD, 0.4%
- Associated, 50.7%

Associated
- Connective Tissue Disorders, 49.9%
- Congenital Heart Disease, 19.9%
- Drugs/Toxins, 10.5%
- Portopulmonary Hypertension, 10.8%
- Other, 5.5%
- HIV, 4.0%

REVEAL: Registry to Evaluate Early and Long-term PAH
N=2,967 patients enrolled from 54 US centers.

Heritable PAH:

- IPAH and HPAH:
  - **BMPR2**: 75% of HPAH and 25% of IPAH
  - Autosomal Dominant with variable penetrance of disease
    - Penetrance: F 42%, M 14%
  - Other mutations: **ALK-1, KCNK3, Endoglin, SMAD9, Caveolin-1**

- Hereditary Hemorrhagic Telangiectasia (HHT) and PAH:
  - **Alk-1, BNPR1B, SMAD9 and Endoglin**

- Group 1’ Heritable PVOD/PCH:
  - **EIF2AK4**

- Consideration should be given for genetic counseling/screening of relatives

# Drugs and Toxins Associated With PAH

<table>
<thead>
<tr>
<th>Definite Risk</th>
<th>Possible Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aminorex</td>
<td>• Cocaine</td>
</tr>
<tr>
<td>• Fenfluramine</td>
<td>• Phenylpropanolamine</td>
</tr>
<tr>
<td>• Dexfenfluramine</td>
<td>• St. John’s wort</td>
</tr>
<tr>
<td>• Toxic rapeseed oil</td>
<td>• Chemotherapeutic agents</td>
</tr>
<tr>
<td>• Benfluorex</td>
<td>• IFN alpha and beta</td>
</tr>
<tr>
<td>• SSRIs (PPTN of the newborn)</td>
<td>• Amphetamine-like drugs</td>
</tr>
<tr>
<td>• Methamphetamines</td>
<td></td>
</tr>
<tr>
<td>• Dasatanib</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Likely Risk</th>
<th>Unlikely Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amphetamines</td>
<td>• Oral contraceptives</td>
</tr>
<tr>
<td>• L-tryptophan</td>
<td>• Estrogen</td>
</tr>
<tr>
<td></td>
<td>• Cigarette smoking</td>
</tr>
</tbody>
</table>

Connective Tissue Disease (CTD) and PAH

Scleroderma (limited) (SSc), SLE, mixed CTD, RA, dermatomyositis, Sjogrens

SSc most common CTD associated with PAH

- May be isolated or associated with ILD
- Can have PVH, PAH, or PVOD/PCH associated disease
- Echocardiogram as a screening test and annual echocardiograph, DLCO and biomarkers. **Need RHC to differentiate what type of PH.**
- Worse outcomes then IPAH or other CTDs
PAH associated with portal hypertension (PoPH)

• Do not confuse with hepatopulmonary syndrome (HPS)
• Associated with portal hypertension
• Echocardiogram screening should be done in all patients with symptoms and in all pre-liver transplant patients.
• Co-existence of portal hypertension and PH does not mean they have PAH (ie: high CO in liver disease).
• RHC required to elucidate PH
• Evaluation and therapy requires center with experience in both liver disease and PH.
HIV

• Pathogenesis of HIV related PAH remains unclear.
• Patients may have other risk factors of PAH: (ie: liver disease, DT-PAH, PVOD)
• Only symptomatic patients need to be screened.
• **PAH is an independent risk factor for death in HIV patients.**
• Treatment with HAART as well as PAH medications
Pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH)

- Classified together as Group 1’
- Overlap pathologically, clinically and genetically.
- Clinical findings:
  - Low DLco, out-of-proportion hypoxemia
  - Male predominance in PVOD
  - Mutation: EIF2AK4
- Associated with CTD, some medications, and other conditions
- Lack of response or development of pulmonary edema with PAH-specific therapy
- Refer to PH specialist or center for careful therapy and monitoring
- Lung transplantation referral (early)
CT Imaging Findings Suggestive of PVOD

Diffuse poorly-defined centrilobular nodular opacities with associated septal line thickening

Enlargement of right heart chambers (star)

Associated mediastinal lymph node enlargement (arrow)

Widespread confluent ground-glass opacification (less common)

Question 1: RHC

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>BP (mmHg)</th>
<th>SpO₂ (%)</th>
<th>RAP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PCW (mmHg)</th>
<th>CO (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>154/90</td>
<td>92</td>
<td>12</td>
<td>58/24</td>
<td>35</td>
<td>27</td>
<td>4.6</td>
</tr>
</tbody>
</table>

PVR = \frac{mPAP - PCW}{CO} = 1.74 WU

What is the diagnosis?

A. Group 1  
B. Group 2  
C. Group 3  
D. Group 4
Question 1: RHC

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>BP (mmHg)</th>
<th>SpO₂ (%)</th>
<th>RAP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PCW (mmHg)</th>
<th>CO (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>154/90</td>
<td>92</td>
<td>12</td>
<td>58/24</td>
<td>35</td>
<td>27</td>
<td>4.6</td>
</tr>
</tbody>
</table>

PVR = \frac{mPAP-PCW}{CO} = 1.74 \text{ WU}

What is the diagnosis?

A. Group 1
B. Group 2 PH: Left Heart Disease
C. Group 3
D. Group 4
1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Group 2 PH

- PH-LHD can complicate any left heart disorder, most common is HFpEF.

- PCWP > 15 mmHg

- Most frequent type of PH (Group 2).

- Analysis with pulmonary vascular resistance (PVR), transpulmonary gradient (TPG) help to differentiate Group 1 and Group 2 PH.

- Classic calculations:
  \[ \text{TPG} = (\text{mean PAP} - \text{mean PCWP}) \]
  \[ \text{PVR} = \frac{\text{TPG}}{\text{CO}} \]
PH: Clinical Classification by Groups

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Group 3 PH

- COPD, ILD and **CPFE** are the *most common* lung diseases associated with PH.
- Severity of PH poorly associated with severity of lung disease
- Disproportionate DLCO and low pCO2
- Referral to expert center recommended
- Optimize therapy for underlying lung disease
- The use of PAH medications not recommended in patients with lung disease
- If severe PH, other potential causes (LHD or CTEPH) should be excluded.
PH: Clinical Classification by Groups

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Chronic Thromboembolic Pulmonary Hypertension (CTEPH): Group 4 PH

- PH arising from single or recurrent pulmonary emboli.
- Incomplete resolution of emboli obstructs or narrows pulmonary arteries.
- Progressive distal small vessel vasculopathy develops over time.
- Potentially curable with thromboendarterectomy (PEA).
- One half of those with CTEPH do not have an apparent history of acute PE.
- Residual PH is not uncommon following PTE

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH (IPAH)
   1.2. Heritable
      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 diseases
      1.4.5. Schistosomiasis
   1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   1” Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia
   3.1. Chronic obstructive pulmonary disease
   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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis
   5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Diagnostic Approach to Pulmonary Hypertension

- Symptoms, signs, history suggestive of PH
- Echocardiography compatible with PH?
  - YES: Consider most common causes of PH (i.e., left heart disease, lung disease)
  - NO: PH unlikely
- History, signs, risk factors, ECG, X-ray, PFT incl. DLCO, consider BGA, HR-CT
- Diagnosis of heart disease or lung disease confirmed?
  - YES: Signs of severe PH/RV dysfunction
  - NO: Consider other causes or recheck
- V/Q scintigraphy
  - YES: Unmatched perfusion defects?
  - NO: Refer to PH expert center
- CTEPH likely
  - CT angiography, RHC plus PA (PEA expert center)
- PAH likely
  - Specific diagnosis tests
  - CTD
  - Drugs Toxins
  - CHD
  - Portopulmonary
  - Schistosomiasis
  - HIV
  - PVOD
  - PCH
  - Other (group 5?)
  - Idiopathic or Heritable PAH
  - Family history: consider genetic studies
  - Expert centers only
  - YES: RHC
    - PAPm ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 WU
    - Consider other causes
  - NO: Refer to PH expert center
REVEAL Registry: Most Frequent PAH Presenting Symptoms

Dyspnea at rest
- Diagnosed ≤2 years after symptom onset (n=1,967): 11.5%
- Diagnosed >2 years after symptom onset (n=526): 8.4%

Cough
- Diagnosed ≤2 years after symptom onset (n=1,967): 13.8%
- Diagnosed >2 years after symptom onset (n=526): 14.8%

Dizzy/lightheaded
- Diagnosed ≤2 years after symptom onset (n=1,967): 15.0%
- Diagnosed >2 years after symptom onset (n=526): 1.60%

Presyncope/syncope
- Diagnosed ≤2 years after symptom onset (n=1,967): 16.5%
- Diagnosed >2 years after symptom onset (n=526): 18.3%

Edema
- Diagnosed ≤2 years after symptom onset (n=1,967): 21.9%
- Diagnosed >2 years after symptom onset (n=526): 1.71%

Chest pain/discomfort
- Diagnosed ≤2 years after symptom onset (n=1,967): 22.2%
- Diagnosed >2 years after symptom onset (n=526): 21.1%

Fatigue
- Diagnosed ≤2 years after symptom onset (n=1,967): 26.7%
- Diagnosed >2 years after symptom onset (n=526): 26.2%

Dyspnea on exertion
- Diagnosed ≤2 years after symptom onset (n=1,967): 86.1%
- Diagnosed >2 years after symptom onset (n=526): 85.4%

Symptoms, signs, history suggestive of PH

Echocardiography best SCREENING tool to evaluate for possible PH

Echocardiographic Findings of PAH

- RV enlargement
- RA enlargement
- Septal straightening
- Loss of IVC inspiratory collapse
- Tricuspid regurgitation
- Pericardial effusion
- Decreased RV systolic dysfunction

TAPSE (tricuspid annular plane systolic excursion)

- TAPSE 1.5 cm: RV dysfunction
- TAPSE 2.3 cm: Relatively preserved RV function

Diagnostic Algorithm for PAH
Initial Evaluation of Patients With Suspected PH

History, Symptoms, Signs Suggestive of PH

Echo shows possible PH: First Consider Common Causes of PH

Group 2: Left Heart Disease
Tests: ECG, Cardiac MRI

Group 3: Lung Diseases and/or Hypoxia
Tests: CXR, PFTs, CT scan

Characteristic findings of PAH on ECG

RAD

RVH

RAE

RV Strain - more sensitive
Chest X-Ray and CT scan Consistent With PH

RA enlargement, prominent PA

Loss of retrosternal airspace
RV enlargement

Image courtesy of Vallerie McLaughlin, MD
PAH: CT scan

Dilated Pulmonary Artery
QUESTION 2:
What PH diagnostic group do you suspect?

A. Group 1
B. Group 2
C. Group 3
D. Not enough information

RHC:
Mean pulmonary artery pressure 42
Wedge pressure 8
PVR: 8.5 WU
QUESTION 2:
What PH diagnostic group do you suspect?

A. Group 1
B. Group 2
C. Group 3
D. Not enough information

RHC:
Mean pulmonary artery pressure 42
Wedge pressure 8
PVR: 8.5 WU
What is true regarding CTEPH?

A. CTEPH is a subgroup of PAH  
B. Most patients with CTEPH have a history of acute PE  
C. A normal VQ scan excludes chronic PE  
D. If the VQ is high probability, there is no need for a pulmonary angiogram
Question 3

What is true regarding CTEPH?

A. CTEPH is a subgroup of PAH
B. Most patients with CTEPH have a history of acute PE
C. A normal VQ scan excludes chronic PE
D. If the VQ is high probability, there is no need for a pulmonary angiogram
Screening and Diagnostic Algorithm

History, signs, risk factors
ECG, X-ray, PFT incl.
DLco, CT

Diagnosis of heart disease or lung disease confirmed with PH?

- Yes
  - No signs of severe PH/RV dysfunction
    - Treat underlying disease
  - Signs of severe PH/RV dysfunction
    - Refer to PH expert center

- No
  - V/Q scintigraphy screening method of choice to rule out CTEPH

BGA, blood gas analysis.

V/Q Scan is screening method of choice for CTEPH

Hypo-perfused regions representing perfusion defects

Normal VQ scan excludes CTEPH

Treatment Algorithm for CTEPH

CTEPH diagnosis
Continue lifelong anticoagulation

Operability assessment by CTEPH team

Operable
Pulmonary Endarterectomy
Balloon Pulmonary Angioplasty (BPA)

Non-operable

Persistent symptomatic pulmonary hypertension

Refer for lung transplantation

Targeted medical therapy

Recommend 2nd opinion by experienced center

Back to PH:
Screening and Diagnostic Algorithm

History, signs, risk factors
ECG, X-ray, PFT incl.
DLco

Diagnosis of heart disease or lung
disease confirmed?

NO

V/Q scintigraphy
Unmatched perfusion defects?

YES

No signs of severe PH/RV
dysfunction

Treat underlying
disease

CTEPH likely
CT angiography, RHC plus PA
(PEA expert center)

YES

Signs of severe PH/RV
dysfunction

Refer to PH expert
center

NO

YES

Signs of severe PH/RV
dysfunction

Refer to PH expert
center

NO

Diagnosis of heart disease or lung
disease confirmed?

YES

CTEPH likely
CT angiography, RHC plus PA
(PEA expert center)

Right heart
catheterization (RHC)

Right heart catheterization (RHC) is required when PAH is suspected

- Systemic artery pressure
- Pulmonary artery wedge pressure (or left ventricular end-diastolic pressure)
- Pulmonary artery pressure (Systolic, Diastolic, Mean)
- Right ventricle pressure (RVP), Right atrial pressure (RAP)
- CO/CI: Cardiac Output/Cardiac Index
- Pulmonary Vascular Resistance (PVR) (calculated)
- Left atrial pressure
- Oxygen saturation run including SVO2 to evaluate if shunt present
- Pulmonary vasoreactivity only for IPAH, HPAP or DT PAH

Vasoreactivity Testing

• Perform in patients with \textbf{IPAH, HPAH or DT-PAH} at experienced centers.
• Should not be done in patients in right heart failure.
• Use of NO or IV epoprostenol recommended for testing

Positive test:
  • mPAP decreases by at least 10 mm Hg to below 40 mm Hg after vasodilation given.
Role of Calcium Channel Blockers (CCBs) in PAH

- Patients with PAH who should NOT be treated with CCB
  Empiric therapy without a vasodilator trial
  Patients with right heart failure
  Non-responders to acute vasodilator challenge

- Responders to acute vasodilator challenge may be treated with high-dose CCBs
  Monitor closely
  Repeat serial RHC to evaluate for continued response

Further work up for PAH patients

PAH likely: Specific diagnostic tests

- RHC
  - mPAP \( \geq 25 \) mmHg,
  - PAWP \( \leq 15 \) mmHg,
  - PVR >3 Wood units

Yes

- CTD
- CHD
- Drugs - Toxin
- Porto-pulmonary
- HIV
- Schistosomiasis

Heritable PAH
- Idiopathic PVOD/PCH
- Idiopathic PAH

Diagnostic Algorithm for PH/PAH:

- Classify the type of PH (Group I-V)
- Establish a suspicion of PAH
- **Confirm the diagnosis (right heart catheterization)**
- Determine the disease severity
- Select the appropriate treatment

Risk assessment of severity and monitoring of PAH patients
## 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 |

Multiple risk assessment tools available for use.
None of these tools have been prospectively validated.

General Measures in PAH

- Guidelines continue to recommend against pregnancy. 
  - ERAs and GCS need to be discontinued in pregnancy 
  - Dual methods of birth control recommended

- Immunization against influenza and pneumococcal infections

- Encourage participation in a supervised physical rehabilitation program

- Psychosocial support should be offered

- Epidural anesthesia recommended for surgical procedures over general anesthesia

Supportive Therapy Recommended for PAH Patients

<table>
<thead>
<tr>
<th>ESC/ERS Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic treatment in patients with signs of RV failure and fluid retention</td>
</tr>
<tr>
<td>Continuous oxygen therapy in patients with &lt;91% O2 saturation</td>
</tr>
<tr>
<td>Oral anticoagulant therapy <strong>may be considered</strong> in patients with IPAH/HPAH or DT-PAH</td>
</tr>
<tr>
<td>Correction of anemia and/or iron status</td>
</tr>
</tbody>
</table>

PAH-specific Therapy: Factors to Consider

- Disease severity
- Route of administration
- Side-effect profile
- Consideration of patient preferences
- Physician experience and clinical judgment
- Presence and type of co-morbid conditions
- Potential drug-drug interactions

### TABLE 3: Currently Approved Medications for Treatment of Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin derivatives</td>
<td>Epoprostenol(^{a})</td>
<td>IV infusion</td>
<td>2 ng/kg/min Increase as tolerated</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhaled</td>
<td>2.5 or 5.0 μg 6-9 inhalations/d</td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Oral</td>
<td>0.25 mg bid or 0.125 mg tid Increase 0.125 mg bid every 3-4 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhaled</td>
<td>18-54 μg (3-9 inhalations) 4 times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous or IV infusion</td>
<td>1.25 ng/kg/min; increase 1.25 ng/kg/min per week based on clinical response; after week 4 increase by 2.5 ng/kg/min per week based on clinical response</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Bosentan</td>
<td>Oral</td>
<td>125 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Ambrisentan</td>
<td>Oral</td>
<td>5 or 10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Oral</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Phosphodiesterase type-5 inhibitors</td>
<td>Sildenafil</td>
<td>Oral</td>
<td>20 mg every 8 h</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>Oral</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td>Soluble cGMP stimulators</td>
<td>Riociguat</td>
<td>Oral</td>
<td>0.5-1.0 mg every 8 h (increase 0.5 mg every 2 wk as tolerated to maximum dose 2.5 mg)</td>
</tr>
<tr>
<td>Prostacyclin receptor agonists</td>
<td>Selexipag</td>
<td>Oral</td>
<td>200 μg twice daily Increase as tolerated to maximum dose of 16,000 μg twice daily</td>
</tr>
</tbody>
</table>

\(^{a}\)Available in a pH neutral (Flolan) or highly alkaline (Veletri) diluent. The latter provides increased drug stability at room temperature.
<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Drugs</th>
<th>Side Effects</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin receptor antagonists (ERA)</td>
<td>Bosentan, Ambrisentan, Macitentan</td>
<td>Teratogenic, Edema, Liver</td>
<td>Cyclosporine, Azoles, Ritonovir</td>
</tr>
<tr>
<td>Phosphodiesterase 5 inhibitors (PDE5i)</td>
<td>Sildenafil, Tadalafil</td>
<td>Headache, flushing, hypotension, priapism</td>
<td>Nitrates, Riociguat</td>
</tr>
<tr>
<td>Prostacyclins and prostacyclin receptor agonists</td>
<td>Epoprostenol, Treprostinil, Iloprost, Selexipag</td>
<td>Headache, flushing, jaw pain, hypotension, rebound if discontinued abruptly, thrombocytopenia, line infections, site pain</td>
<td></td>
</tr>
<tr>
<td>Soluble guanylate cyclase stimulator</td>
<td>Riociguat</td>
<td>Teratogenic, hypotension, hemoptysis</td>
<td></td>
</tr>
</tbody>
</table>
ERS 2018: Treatment Algorithm for PAH

CHEST 2019- ambrisentan and tadalafil.

Initial combination with ambrisentan plus tadalafil has proven to be superior to monotherapy in delaying clinical failure.
AMBITION Trial
Initial Combination Therapy
(ERA + PDE-5i compared with monotherapy with either ERA or PDE-5i)

Primary Endpoint: Time to First Clinical Failure Event
Primary Analysis Set

Atrial Septostomy for PAH

• Surgical intervention creating inter-arterial right-to-left shunt

• Decompresses right heart chambers

• Increases left ventricular preload and CO

• Improvement in $O_2$ transport despite decrease in $O_2$ saturation

• Indications:
  Severe WHO functional class IV with right heart failure refractory to medical therapy or with severe syncopal symptoms
  May be used as bridge to transplantation

ISHLT Guidelines for Lung Transplantation in PAH

Timing of referral
- Functional Class III or IV symptoms during escalating therapy
- Rapidly progressive disease
- Use of parenteral targeted PAH therapy
- Known or suspected PVOD or PCH

Timing of transplant listing:
- Functional Class III/IV despite at least 3 months of combination therapy including prostacyclins
- Cardiac index <2 liters/min/m²
- Mean right atrial pressure >15 mm Hg
- 6-minute walk test of <350 m
- Development of progressive right heart failure

Conclusions

• All of PH is not PAH. i.e: (Know how to differentiate Group 1 versus all other groups)
• New definition mPAP > 20 mmHg
• Echo is the best screening exam.
• * Diagnostic certainty of PAH is only obtained through RHC.
• Calcium channel blocker therapy is not appropriate for vast majority of patients with PAH.
• Patients must be screened for CTEPH with a VQ scan and referred to an expert center if scan is positive.
• Therapy:
  Early combination therapy for Group 1
  Group 2, 3 and 5 should not be treated with Group 1 PAH medications per guidelines to date.
  PAH therapy is based on several patient factors: severity, risk assessment, comorbidities, ability to tolerate medications
  ERA’s and SCG stimulators are contraindicated in pregnancy
  PVOD can worsen with specific PAH treatment
ευχαριστώ

Any Questions?
levines@uthscsa.edu