Recognition & Evaluation of the Patient with PAH: The need for early diagnosis

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Disclosures

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- Ikaria
- Lung Rx
- NIH-NHLBI
- Pfizer
- United Therapeutics
Objective

• Identify the necessary steps to appropriately diagnose patients with PAH earlier in the course of the disease
Pre-test Question 1

The average time between symptom onset and diagnosis in patients with pulmonary arterial hypertension is approximately:

A) 3 months
B) 6 months
C) 1 year
D) 2 years
Pre-test Question 1

• Compared to patients in NYHA functional class III or IV, treatment of PAH in NYHA class I or II results in:

A) Improved survival
B) Fewer hospitalizations
C) The need for fewer medications
D) Greater improvement from baseline in 6 min walking distance
The Challenge to Early Diagnosis of PAH

- Presenting symptoms are:
  - Insidious
  - Slowly progressive
  - Similar to other more common diseases
- PAH is a rare disease
- Extensive workup necessary to determine a cause of elevated pulmonary artery pressure
# Difficulty in Distinguishing PAH Symptoms from Other Diseases

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea with exertion</td>
<td>COPD</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>Asthma</td>
</tr>
<tr>
<td>Fatigue</td>
<td>CHF</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>CAD</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Deconditioning</td>
</tr>
</tbody>
</table>
## Prevalence of Group 1 PAH

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>PREVALENCE *</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH</td>
<td>15 per million</td>
</tr>
<tr>
<td>IPAH</td>
<td>5.9 per million</td>
</tr>
<tr>
<td>HPAH†</td>
<td>28–100 U.S. families</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>8–26.7%</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td>1–6%</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1.6-12.5 per million</td>
</tr>
<tr>
<td>HIV</td>
<td>0.5% estimate</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>32%</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>11.8–80%</td>
</tr>
<tr>
<td>Chronic hemolytic anemia</td>
<td>Highly variable; currently being studied</td>
</tr>
</tbody>
</table>

* Prevalence varies substantially depending on the type, etiology, and underlying condition
† Reported estimates are based on personal communications

Note: Numbers may also reflect differences in diagnostic criteria (e.g., ECHO vs right heart catheterization) and study design (e.g., retrospective vs prospective)

Pulmonary Arterial Hypertension is an Uncommon Cause of PH: Armadale Echocardiography Study


N = 483 of 4579 patients with sPAP > 40 mm Hg on echocardiography. PSAP = Pulmonary artery systolic pressure
The Need for Early Diagnosis
PAH is a Progressive Condition

Mild Disease
May include:
• Inflammation

Moderate Disease
May include:
• Inflammation
• Vasoconstriction
• Fibrosis
• Hypertrophy

Severe Disease
May include:
• Cell proliferation
• Plexiform lesions

Hemodynamic Progression of PAH

<table>
<thead>
<tr>
<th>Time</th>
<th>CO, cardiac output</th>
<th>PAP, pulmonary arterial pressure</th>
<th>PVR, pulmonary vascular resistance</th>
<th>RAP, right atrial pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymptomatic/Compensated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic/Decompensating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declining/Decompensated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CO, cardiac output; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.
Impact of Functional Class on Survival in IPAH

## Delay in Time to Diagnosis
### PAH Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Year</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Female (%)</th>
<th>Time to Diagnosis (months)</th>
<th>mPAP (mmHg)</th>
<th>CI (l/m²)</th>
<th>PCWP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH¹</td>
<td>1981-1985</td>
<td>187</td>
<td>36.4 ± 15</td>
<td>63</td>
<td>24</td>
<td>60 ± 18</td>
<td>2.3 ± 0.9</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>French Study²*</td>
<td>2002-2003</td>
<td>674</td>
<td>50 ± 15</td>
<td>65.3</td>
<td>27</td>
<td>55 ± 15</td>
<td>2.5 ± 0.8</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>REVEAL³*</td>
<td>2006-2007</td>
<td>2967</td>
<td>53.1 ± 14.5</td>
<td>79.5</td>
<td>34.1 ± 1.2</td>
<td>51 ± 13</td>
<td>2.4 ± 0.8</td>
<td>9.1 ± 3.5</td>
</tr>
</tbody>
</table>

*prevalent and incident cases

Three Quarters of Newly Diagnosed PAH Patients Present with Advanced Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>NYHA I</th>
<th>NYHA</th>
<th>NYHA III</th>
<th>NYHA IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>French Registry</td>
<td>1%</td>
<td>24%</td>
<td>63%</td>
<td>12%</td>
</tr>
<tr>
<td>REVEAL Registry</td>
<td></td>
<td></td>
<td>61.3%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

Diagnostic Goals

- Increased awareness
  Management of unexplained symptoms
- Detect early
  Screening in high-risk populations
- Treat early
  Treatment in WHO-FC II recommended
- Treat-to-target
  Goal-orientated approach
- Potential to improve long-term outcomes

Recognition
# Clinical Presentation

<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>


Electrocardiogram Associated With Right Ventricular Hypertrophy (RVH)

Normal sinus rhythm
Right axis deviation
Right ventricular hypertrophy with repolarization abnormality
Abnormal ECG

Image courtesy of Vallerie McLaughlin, MD
Manifestation of PAH on Echocardiogram

- 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)

Evaluation
## Patterns on Echo: PAH vs PVH

<table>
<thead>
<tr>
<th></th>
<th>PAH</th>
<th>Pulmonary Venous HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2-D echo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal LA, LV size; small LV (&lt; 3.5 cm)</td>
<td>Dilated LA and/or LV</td>
<td></td>
</tr>
<tr>
<td>No LVH</td>
<td>± LVH</td>
<td></td>
</tr>
<tr>
<td>NL to high EF</td>
<td>Variable EF</td>
<td></td>
</tr>
<tr>
<td>RV:LV &gt; 1.0</td>
<td>RV:LV &lt; 1.0</td>
<td></td>
</tr>
<tr>
<td>RV apex sharing</td>
<td>RV stops short of apex</td>
<td></td>
</tr>
<tr>
<td>Septal flattening (systole and/or diastole)</td>
<td>LV remains “round” in short axis (LV pushback)</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>No effusion</td>
<td></td>
</tr>
<tr>
<td><strong>Doppler</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable PASP</td>
<td>Variable PASP</td>
<td></td>
</tr>
<tr>
<td>No MR</td>
<td>2 plus MR or greater</td>
<td></td>
</tr>
<tr>
<td>E &lt; A</td>
<td>E &gt; A (pseudonormal or restrictive)</td>
<td></td>
</tr>
</tbody>
</table>
Right Heart Catheterization for PAH

• Measures:
  – Pulmonary arterial pressure (PAP)
  – Cardiac output (CO)
  – Right atrial pressure (RAP)
  – Pulmonary arterial wedge pressure (PAWP)
  – Pulmonary and systemic vascular resistance

• Rationale for use
  – Confirm the diagnosis
  – Assess severity of hemodynamic impairment
  – Test pulmonary vasoreactivity
  – Determine prognosis

Is There a Reason to Suspect PAH?

*Evaluation for CTEPH*

**Not a PAH subgroup, but:**

- Cannot be missed
- Is potentially curable with thromboendarterectomy (PEA)
- 3% to 4% of acute PE do not entirely resolve
- One half of those with CTEPH do not have an apparent history of acute PE
- Normal VQ scan excludes chronic PE
- CT angiogram can detect chronic clot (but the radiologist should be experienced when interpreting the imaging—distal disease can be subtle)

Is There a Reason to Suspect PAH?

**VQ Scan**

- **Idiopathic Pulmonary Arterial Hypertension**
  - Perf
  - Vent

- **Chronic Pulmonary Embolism**
  - Perf
  - Vent
Does Screening Help?
PAH Symptoms + RHC

No PAH Symptoms + TRV > 3 + RHC

Efficacy of Treatment in PAH Patients – Functional Class II
The EARLY Study

Change in PVR (primary endpoint)

Change in 6 min Walk Distance

Time to Clinical Worsening

Pitfalls of Screening by Echocardiography

570 patients screened
33 referred for RHC
14 diagnosed with PAH

Prevalence 2.5%
False positive rate 19/33 = 57.6%
False negative rate ?/537 = ???
Does the use of Multiple Diagnostic Tests Aid in the Screening of PAH?

- BNP
- 6 min walk distance
- PFTs
- Exercise stress test
Algorithm for DETECTing PAH in Systemic Sclerosis

## Screening Guidelines: Patients With Known Risk for PAH

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Further Assessment</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known BMPR2 mutation</strong></td>
<td>Echo yearly; RHC if echo shows evidence of PAH</td>
<td>Early PAH detection; 20% chance of developing PAH</td>
</tr>
<tr>
<td><strong>Systemic sclerosis</strong></td>
<td>Echo yearly; RHC if echo shows evidence of PAH</td>
<td>8% prevalence of PAH</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>Echo if symptomatic; RHC if echo shows evidence of PAH</td>
<td>0.5% prevalence of PAH</td>
</tr>
<tr>
<td><strong>Portal hypertension</strong></td>
<td>Echo if OLT considered; RHC if echo shows evidence of PAH</td>
<td>4% prevalence of PAH; predictive of poor outcome</td>
</tr>
<tr>
<td><strong>Congenital heart disease</strong></td>
<td>Echo and RHC at diagnosis; consider repair of L-R shunt defect</td>
<td>High PAH probability if unrepaird (Eisenmenger)</td>
</tr>
</tbody>
</table>

*Systemic sclerosis: consider echocardiogram if \( \frac{\% \text{ FVC}}{\% \text{ DLCO}} > 1.6 \) or unexplained declining DLCO.

Screening Recommendations for High Risk Patients - 5th WHO Conference on PH

- Annual screening for PAH is recommended in (cardiopulmonary) asymptomatic patients with the SSc spectrum of diseases, although there is a lack of evidence-based data.
- Screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH should include a 2-step approach using clinical assessment for the presence of telangiectasia, anticentromere antibodies, PFT and DLCO measurements, electrocardiogram, and biomarkers (NT-proBNP and uric acid) in the initial stage, followed by echocardiography and consideration of RHC in patients with abnormal findings, although there is a lack of data with DLCO >60%.
- The above mentioned screening programs for patients with SSc should be part of a scientific protocol, or a registry, whenever possible.
- Patients with SSc and other CTDs with clinical signs and symptoms of PH should be evaluated by RHC.

Post-test Question 1

The average time between symptom onset and diagnosis in patients with pulmonary arterial hypertension is approximately:

A) 3 months
B) 6 months
C) 1 year
D) 2 years
Post-test Question 2

- Compared to patients in NYHA functional class III or IV, treatment of PAH in NYHA class I or II results in:

A) Improved survival  
B) Fewer hospitalizations  
C) The need for fewer medications  
D) Greater improvement from baseline in 6 min walking distance
Summary

• PAH is usually diagnosed late in the course of the disease long after the onset of symptoms
• PAH should be considered in all patients with unexplained symptoms of dyspnea, fatigue, exertional chest pain or syncope
• Patients at high risk of developing PAH should be considered for regular screening with echocardiography, PFTs, BNP