Pulmonary Hypertension: Diagnosis, Treatment and Referral

16th Annual Cardiovascular Update

Lynn Brown MD, PhD
Outline

1. Definition and consequences of elevated pulmonary artery pressures
2. Pulmonary hypertension diagnostic classes
3. Evaluation of suspected pulmonary hypertension
4. Treatment options for pulmonary arterial hypertension
Pulmonary Arteries

• Compensation for increased resistance
Pulmonary Hypertension: Mean PA Pressure ≥ 25 mmHg

- **Pulmonary Arterial Hypertension**: High pulmonary artery pressure, high pulmonary vascular resistance, normal left heart.
- **Left Heart Disease**: Valvular disease, HFrEF, HFrPEF.
- **Lung Disease**: COPD, pulmonary fibrosis, sleep apnea.
- **Chronic Pulmonary Embolism**.

HFrEF = heart failure with reduced ejection fraction, HFrPEF = heart failure with preserved ejection fraction.
Location of Pulmonary Hypertension Vascular Changes

Right heart catheterization data:
- right atrial pressures
- pulmonary artery pressures
- pulmonary capillary wedge pressure / LVEDP
- cardiac output
- pulmonary vascular resistance (calculated)
*vasoreactivity

VC  RA  RV  PA  PC  PV  LA  LV  Aorta
Pulmonary Artery and Right Ventricular Changes

- **Normal**
  - RV
  - LV
  - Thin RV
  - Healthy PA endothelium
  - Thin walled-relaxed PAs
  - Large capillary network
  - Normal CO
  - Normal PVR
  - Normal perfusion

- **Compensation**
  - RV
  - LV
  - Hypertrophied RV
  - Abnormal PA endothelium
  - Constricted-stiff PAs
  - Loss of microvessels
  - Normal CO
  - Mild increase in PVR
  - Moderate decrease in perfusion

- **Failure**
  - RV
  - LV
  - Dilated RV
  - Cell proliferation in the PA wall
  - Obliterative PA remodeling
  - Severe decrease in CO
  - Severe increase in PVR
  - Severe decrease in perfusion
Dependence on Right Ventricular Function

- Progressive contractile dysfunction
- Rising filling pressures
- Failing Right Ventricle
- Diminishing cardiac output
- Pulmonary Artery Pressure
- Pulmonary Vascular Resistance
- Cardiac Output
Pulmonary Arterial Hypertension

- High pulmonary artery pressure
- High pulmonary vascular resistance
- Normal Left Heart

Left Heart Disease
- Valvular disease
- HFrEF
- HFP EF

Lung Disease
- COPD
- Pulmonary fibrosis
- Sleep apnea

Chronic Pulmonary Embolism

HFrEF = heart failure with reduced ejection fraction
HFP EF = heart failure with preserved ejection fraction
Causes of Pulmonary Arterial Hypertension

- Collagen vascular disease
- Idiopathic
- HIV
- Drugs and toxins
- Portopulmonary hypertension
- Congenital heart disease
- Heritable (BMPR2, ALK1, KCKN3)
- Other
- Pulmonary veno-occlusive disease
Causes of Pulmonary Hypertension-Lung Diseases

- Chronic obstructive pulmonary disease / emphysema
- Pulmonary fibrosis
- Pulmonary sarcoidosis
- Obstructive sleep apnea

Hypoxic Vasoconstriction
Causes of Pulmonary Hypertension-Lung Diseases

• Mean pulmonary artery pressures < 35 mmHg:
  – “proportional”

• Mean pulmonary artery pressures ≥ 35 mmHg:
  – severe pulmonary hypertension
  – “out of proportion”
## Causes of Pulmonary Hypertension-Left Heart Disorders

<table>
<thead>
<tr>
<th></th>
<th>Mean PAP</th>
<th>PCWP</th>
<th>Diastolic Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated post-capillary PH</strong></td>
<td>≥ 25 mmHg</td>
<td>&gt; 15 mmHg</td>
<td>&lt; 7 mmHg</td>
</tr>
<tr>
<td><strong>Combined pre- and post-capillary PH (CpcPH)</strong></td>
<td>≥ 25 mmHg</td>
<td>&gt; 15 mmHg</td>
<td>≥ 7 mmHg</td>
</tr>
</tbody>
</table>

Diastolic pressure gradient = (diastolic pulmonary artery pressure) – (pulmonary capillary wedge pressure)
Causes of Pulmonary Hypertension-Chronic Pulmonary Emboli

Diagnostic Delay

• No difference in time to diagnosis according to race, gender, geographic region or PAH subgroup (including heritable PAH)

• Factors associated with a delayed diagnosis:
  • Younger patients (< 36 years)
  • Those with the diagnoses of common respiratory diseases:
    • Obstructive airways’ disease
    • Obstructive sleep apnea
    • Pulmonary embolism
Symptoms of Pulmonary Hypertension

Fenstad ER et al. Pulmonary Circulation 2014;4:504-510
Suspicion for Pulmonary Hypertension: ECG

- Right axis deviation
- Right atrial enlargement
- Right ventricular hypertrophy
- Right ventricular strain
Suspicion for Pulmonary Hypertension: CXR

Normal

Abnormal
Suspicion for Pulmonary Hypertension: CT angiogram/V/Q Scan

- Normal range of main PA diameter

Males: $27.0 \pm 2.8 \text{ mm}$  
Females: $25.9 \pm 3.0 \text{ mm}$
Suspicion for Pulmonary Hypertension: pulmonary function tests

- Six minute walk distance
- Spirometry and DLCO

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Ref (LLN-ULN)</th>
<th>Pre</th>
<th>%Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC Liters</td>
<td>2.47 (1.9-3.1)</td>
<td>2.28</td>
<td>92</td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>1.87 (1.4-2.4)</td>
<td>1.47</td>
<td>78</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>77 (66.8-86.4)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>FEF25-75% L/sec</td>
<td>1.74 (0.7-2.8)</td>
<td>1.58</td>
<td>91</td>
</tr>
</tbody>
</table>

Diffusing Capacity (Hb 13.8)

| DLCO ml/mmHg/min | 20.1 (14.1-26.1) | 9.9 | 49   |
| DL Adj ml/mmHg/min | 20.1 (14.1-26.1) | 9.8 | 49   |
Suspicion for Pulmonary Hypertension: blood analysis

• CBC (anemia)
• CMP (liver disease)
• TSH (hyperthyroidism)
• HIV / HCV
• ANA with reflex (autoimmune diseases)
• BNP
Need For Non-Invasive Cardiac Imaging

• Screening
  • Suspicious cases
  • High risk populations

• Quantification /risk stratification
  • Initial treatment decision making

• Treatment monitoring
Echocardiographic Parameters (RVSP)

- Tricuspid regurgitation velocity (TRV)

  Probability of PH

  **High:** TRV ≥ 2.9 m/sec with additional TTE variables
  TRV > 3.4 m/sec with no other signs

  **Intermediate:** TRV ≤ 2.8 m/sec or immeasurable with additional TTE variables
  TRV = 2.9-3.4 m/sec with no other signs

  **Low:** TRV ≤ 2.8 m/sec with no other TTE variables

Echocardiographic Parameters (Chamber Size/Effusion)

Normal Images
Echocardiographic Parameters (Septal Flattening)

Interventricular septum

RV
LV

Image courtesy of Dr. Paul Forfia
Echocardiographic Parameters (TAPSE)

TAPSE = Tricuspid Annular Plane Systolic Excursion
Cardiac MRI

- High spatial and temporal resolution
- 3-dimensional imaging capabilities
Summation of Data

Symptoms → Heart Imaging → Chest Imaging → Laboratory Data → Referral (most frequent) → Right Heart Catheterization (with vasoreactivity testing) → Diagnostic Category → Referral
Inhaled Nitric Oxide

Primary cause of pulmonary hypertension due to vasoconstriction (reversible):
- Fall in mean PA pressure by 10 mmHg to a level < 40 mmHg

Secondary cause of pulmonary hypertension due to cell proliferation (irreversible):

Vasoreactivity Testing (First Step to a Therapy Decision)

- 20 ppm for 6 minutes
- Calcium Channel Blocker Therapy
Treatment Algorithm for PH Patients

Right Heart Catheterization
mPAP ≥ 25, PCWP ≤ 15 mmHg

Confirmed PAH

Vasodilator Testing

+ Test → Treatment with CCB

- Test

PAH Specific Therapy

No Sustained Response

Sustained Response

Continue Therapy
Categorization of PH Patients

<table>
<thead>
<tr>
<th>Clinical Determinant</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptom progression</td>
<td>No</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional</td>
<td>Repeated</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt; 440 m</td>
<td>165 – 440 m</td>
<td>&lt; 165 m</td>
</tr>
<tr>
<td>NT-proBNP Plasma levels</td>
<td>BNP &lt; 50 ng/l</td>
<td>BNP 50–300 ng/l</td>
<td>BNP &gt; 300 ng/l</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP &lt; 300 ng/ml</td>
<td>BT-proBNP 300–1400 ng/l</td>
<td>BT-proBNP &gt; 1400 ng/l</td>
</tr>
<tr>
<td>CPET peak VO₂</td>
<td>Peak VO₂ &gt; 15 ml/min/kg</td>
<td>Peak VO₂ 11–15 ml/min/kg</td>
<td>Peak VO₂ &lt; 1 ml/min/kg</td>
</tr>
<tr>
<td>Echocardiography Findings</td>
<td>RA area &lt; 18 cm²</td>
<td>RA area 18–26 cm²</td>
<td>RA area &gt; 26 cm² Pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>No pericardial effusion</td>
<td>No or minimal pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt; 8 mm Hg</td>
<td>RAP 8–14 mm Hg</td>
<td>RAP &gt; 14 mm Hg</td>
</tr>
<tr>
<td></td>
<td>CI ≥ 2.5 l/min/m²</td>
<td>CI 2.0–2.4 l/min/m²</td>
<td>CI &lt; 2.0 l/min/m²</td>
</tr>
</tbody>
</table>

6MWD — 6-minute walk distance; BNP — brain natriuretic peptide; CI — cardiac index; NT-proBNP — n-terminal brain natriuretic peptide; RA — right atrium; RAP — right atrium pressure; VO₂ — oxygen consumption

Treatment Algorithm for PH Patients

PAH Specific Therapy

Low Risk-Oral Meds

Intermediate Risk

High Risk-IV Meds

Inadequate Response

Combination Therapy

Inadequate Response

Referral for Lung Transplantation
Referral for Atrial Septostomy
Other Therapies for Pulmonary Arterial Hypertension

Prostanoids (IV, SQ, INH)
- Epoprostenol
- Treprostinil

Phosphodiesterase-5 Inhibitors (PO)
- Sildenafil
- Tadalafil (Riociguat)

Endothelin Receptor Antagonists (PO)
- Ambrisentan
- Bosentan
- Macitentan

Prostacyclin Receptor Agonist
- Selexipag
AMBITION (Dual Up-Front Therapy)

**B** Combination Therapy vs. Ambrisentan Monotherapy

- **Combination therapy**
- **Ambrisentan monotherapy**

Hazard ratio, 0.48 (95% CI, 0.31–0.72)
P < 0.001

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
<th>168</th>
<th>192</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>253</td>
<td>229</td>
<td>186</td>
<td>145</td>
<td>106</td>
<td>71</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Ambrisentan monotherapy</td>
<td>0</td>
<td>126</td>
<td>104</td>
<td>81</td>
<td>57</td>
<td>39</td>
<td>23</td>
<td>14</td>
<td>3</td>
</tr>
</tbody>
</table>

**C** Combination Therapy vs. Tadalafil Monotherapy

- **Combination therapy**
- **Tadalafil monotherapy**

Hazard ratio, 0.53 (95% CI, 0.34–0.83)
P = 0.005

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
<th>168</th>
<th>192</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>253</td>
<td>229</td>
<td>186</td>
<td>145</td>
<td>106</td>
<td>71</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Tadalafil monotherapy</td>
<td>0</td>
<td>121</td>
<td>105</td>
<td>74</td>
<td>51</td>
<td>38</td>
<td>26</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>
Other Referral Timing

Diagnostic Category

Oral Therapy

Parenteral Therapy

Lung Transplant

Referral

Referral

Patient Survival
SUMMARY

1. Pulmonary hypertension is determined by right heart catheterization
   a. Mean pulmonary artery pressure \( \geq 25 \text{ mmHg} \)

2. The diagnostic category is determined by the remaining hemodynamic data
   and other supportive data

3. Treatment of intrinsic pulmonary vascular disease is limited to patients
   primarily with pulmonary arterial hypertension

4. Referral timing is based upon a clinician’s level of comfort with the diagnostic
   evaluation and with the treatment options