Pulmonary Hypertension in 2019

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Pulmonary Critical Care
Financial disclosures

Research studies and registries:
Actelion/Canadian Heart Research Centre
United Therapeutics
Reata Pharmaceuticals
Objectives

1. Review pathophysiology, diagnosis, and evaluation of pulmonary hypertension
2. Discuss current classification system
3. Assess treatment options and goals
4. Analyze multiple clinical endpoints to determine mortality risk and success of therapy
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Pulmonary hypertension (PH)

- Pathophysiological disorder that may involve multiple clinical conditions and can complicate the majority of cardiovascular and respiratory diseases.

- Defined as an increase in mean pulmonary arterial pressure (mPAP) at rest as assessed by right heart catheterization (RHC)
  - Normal: mPAP 10-12 mm Hg
  - PH: mPAP ≥ 25 mm Hg
Proceedings of the 6th World Symposium on Pulmonary Hypertension

mPAP >20

2 standard deviations above the upper limit of normal
Overview of PH

• Obstructive lung panvasculopathy
• Prognosis is primarily determined by the functional status of the right ventricle (RV)
• Most common cause of death is RV failure

Diagnostic Issues

Misdiagnosis

– Most patients see three or more physicians over a three-year period before an accurate diagnosis is made.

Diagnostic delay

– Time to reach diagnosis has **not** improved in 20 years.

Advanced disease at diagnosis

– Approximately 75% of patients have advanced disease at diagnosis.
  • (NYHA functional class III and IV)

Most Frequent Symptoms at Diagnosis

REVEAL Database:

- Dyspnea at rest: 84%
- Cough: 26%
- Dizzy/lightheaded: 24%
- Edema: 23%
- Chest pain: 21%
- Other: 16%
- Fatigue: 13%
- Dyspnea on exertion: 11%

Physical exam findings of PH

Loud P2
Right ventricular parasternal heave
Right sided S3 or S4
Holosystolic tricuspid regurgitant murmur
  – Carvallo sign: murmur louder during inspiration
Elevated jugular venous pressure
Peripheral edema
ECG Associated with Right Axis Deviation and Right Ventricular Hypertrophy (RVH)
CXR consistent with PH
PH on CXR

Chest CT signs of PH

Pulmonary Function Tests

Normal spirometry and lung volumes

Reduced Diffusing Capacity for Carbon Monoxide

**PULMONARY FUNCTION ANALYSIS**

### Spirometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pred</th>
<th>Pred UL</th>
<th>Pred LL</th>
<th>Pre</th>
<th>%Ref</th>
<th>Post 1</th>
<th>Post 2</th>
<th>%Chg</th>
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<tbody>
<tr>
<td>FVC</td>
<td>3.16</td>
<td>3.71</td>
<td>2.50</td>
<td>2.75</td>
<td>87.0</td>
<td>87.0</td>
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<tr>
<td>FEV1</td>
<td>2.43</td>
<td>3.00</td>
<td>1.87</td>
<td>2.15</td>
<td>88.0</td>
<td>88.0</td>
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<tr>
<td>FEV1/FVC</td>
<td>77.85</td>
<td>67.86</td>
<td>60.05</td>
<td>78.44</td>
<td>100.0</td>
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<tr>
<td>PEF</td>
<td>7.74</td>
<td>2.45</td>
<td>1.06</td>
<td>3.27</td>
<td>145.4</td>
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<tr>
<td>FEF 25%</td>
<td>7.12</td>
<td></td>
<td></td>
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<tr>
<td>FEF 50%</td>
<td>5.22</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FEF 75%</td>
<td>4.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FET</td>
<td>7.14</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>FVC IN</td>
<td>3.16</td>
<td>3.83</td>
<td>2.40</td>
<td>2.47</td>
<td>78.3</td>
<td>78.3</td>
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<tr>
<td>PIF</td>
<td>8.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVV</td>
<td>87.83</td>
<td>101.01</td>
<td>74.88</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>MIP (-)</td>
<td>55.51</td>
<td>86.16</td>
<td>24.38</td>
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<td></td>
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<tr>
<td>MEP (+)</td>
<td>60.52</td>
<td>113.91</td>
<td>25.12</td>
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### Lung Volume

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Pred UL</th>
<th>Pred LL</th>
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<th>%Ref</th>
</tr>
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<tbody>
<tr>
<td>VC</td>
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<td>2.40</td>
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<tr>
<td>TLC</td>
<td>4.77</td>
<td>8.76</td>
<td>3.78</td>
<td>4.09</td>
<td>86.7</td>
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<tr>
<td>RV</td>
<td>1.87</td>
<td>2.45</td>
<td>1.03</td>
<td>1.08</td>
<td>86.7</td>
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<tr>
<td>RV % TLC</td>
<td>30.70</td>
<td>49.29</td>
<td>11.11</td>
<td>41.07</td>
<td>103.5</td>
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<tr>
<td>ERV</td>
<td>3.08</td>
<td>3.06</td>
<td>3.06</td>
<td>3.05</td>
<td>96.8</td>
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### Diffusion

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Pred LL</th>
<th>Pre</th>
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<tbody>
<tr>
<td>DLCO_SB</td>
<td>21.98</td>
<td>27.71</td>
<td>16.25</td>
<td>10.22</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.5</td>
</tr>
</tbody>
</table>

**Arterial Blood Gases**

- PaO2
- PaCO2
- pH
- SaO2
- PacO2
- Base Excess
- HCO3
- A-a Gradient
Echocardiography for PH

Modified Bernoulli’s Equation:
\[4 \times (V)^2 + \text{RAP} = \text{RVSP (PASP)}\]

V = tricuspid jet velocity (m/s)
RAP = right atrial pressure
RVSP = right ventricular systolic pressure
PASP = pulmonary artery systolic pressure
Measurement of right atrial area by echocardiography.

Ekkehard Grünig, and Andrew J. Peacock Eur Respir Rev 2015;24:653-664
ECHO assessment of PH

Pericardial effusion
TAPSE
S’
2D, 3D volumes
RV strain
Tei index
Diagnostic algorithm for PAH

Signs and/or symptoms consistent with PAH

- **ECHO**
  - Suggestive of PH
  - Not suggestive: look for other causes

Refer to PH center
Determinants of Pulmonary Hypertension

Ohm’s law:

\[ \text{PVR} = \frac{\text{P}_{\text{PA}} - \text{P}_{\text{AOP}}}{\text{CO}} \]

\[ \text{P}_{\text{PA}} - \text{P}_{\text{AOP}} = (\text{PVR}) (\text{CO}) \]

\[ \text{P}_{\text{PA}} = (\text{PVR}) (\text{CO}) + \text{P}_{\text{AOP}} \]
PA Catheter Insertion Waveforms

RA  RV  PA  PAOP
Normal Pulmonary Hemodynamics for Adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary arterial pressure</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>22 – 30 mm Hg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>6 – 12 mm Hg</td>
</tr>
<tr>
<td>Mean</td>
<td>10 – 12 mm Hg</td>
</tr>
<tr>
<td><strong>Left-ventricular end-diastolic pressure</strong></td>
<td>6 – 12 mm Hg</td>
</tr>
<tr>
<td><strong>Right-ventricular end-diastolic pressure</strong></td>
<td>0 – 6 mm Hg</td>
</tr>
<tr>
<td><strong>Cardiac index</strong></td>
<td>2.7 – 3.5 L/min/m²</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance</strong></td>
<td>&lt;1.5 Wood units</td>
</tr>
</tbody>
</table>
## Definition of PAH

<table>
<thead>
<tr>
<th>Right Heart Catheterization Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mean pulmonary arterial pressure (mPAP)*</td>
</tr>
<tr>
<td>Normal pulmonary artery occlusion pressure (PAOP)</td>
</tr>
<tr>
<td>Increased pulmonary vascular resistance (PVR)†</td>
</tr>
</tbody>
</table>

Wood units = (MPAP-PAOP)/CO (mm Hg/L/min)

Vasoreactivity

• Should only be performed in expert centers
• Recommended only for patients with IPAH, HPAH and PAH associated with drugs
• Agent of choice: Nitric oxide
  • IV epoprostenol, adenosine, inhaled iloprost are alternatives
Acute Vasoreactivity Test for PAH

Acute vasoreactive response =

Reduction of mean PAP $\geq 10$ mm Hg to reach a mean PAP $\leq 40$ mm Hg with a normalized or increased CO

Positive response in $<$10% of patients with IPAH

Long-term response to CCB =

NYHA Functional Class 1 or 2 with sustained hemodynamic improvement after at least 1 year on CCBs only

Simmoneau ERJ 2019; 53:1801913.
Objectives

1. Review pathophysiology, diagnosis, and evaluation of pulmonary hypertension
2. Discuss current classification system
3. Assess treatment options and goals
4. Analyze multiple clinical endpoints to determine mortality risk and success of therapy
5. Present newer concepts and research
Hemodynamic Profiles in PH

\[ P_{PA} = (PVR) \times (CO) + P_{AOP} \]

**Precapillary**
IPAH, HPAH, PAH in CTD, HIV, appetite suppressants, CTEPH,

**Postcapillary**
LV dysfunction, mitral or aortic valvular disease,

**Increased flow**
ASD, VSD, PDA, portopulmonary hypertension, thyrotoxicosis, anemia, systemic shunts,
### Hemodynamic Definitions of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group</th>
</tr>
</thead>
</table>
| Pre-capillary PH | Mean PAP ≥20 mm Hg, PAOP ≤15 mm Hg | 1. Pulmonary arterial hypertension  
2. PH due to left heart disease  
3. PH due to lung disease  
4. CTEPH  
5. PH with unclear or multifactorial mechanisms |

Updated from: Simmoneau ERJ 2019; 53:1801913.
World Health Organization classification

1. Pulmonary arterial hypertension
2. Pulmonary venous hypertension
3. Pulmonary hypertension due to chronic hypoxemic lung disease
4. Due to embolic disease
5. Miscellaneous
# Clinical Classification of PH

<table>
<thead>
<tr>
<th>1. PAH</th>
<th>3. PH Due to Lung Diseases and/or Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
<td>3.1 Obstructive lung disease</td>
</tr>
<tr>
<td>1.2 Heritable</td>
<td>3.2 Restrictive lung disease</td>
</tr>
<tr>
<td>1.3 Drug- and toxin-induced</td>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>1.4 Associated with:</td>
<td>3.4 Hypoxia without lung disease</td>
</tr>
<tr>
<td>CTD</td>
<td>Sleep-disordered breathing</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Chronic exposure to high altitude</td>
</tr>
<tr>
<td>CHD</td>
<td>3.5 Developmental abnormalities</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td></td>
</tr>
<tr>
<td>1.5 PAH long term responders to calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>1.6 PAH with overt features of venous/capillaries involvement (PVOD or PCH)</td>
<td></td>
</tr>
<tr>
<td>1.7 Persistent PH of newborn</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. PH due to left heart disease</th>
<th>5. PH With Unclear and/or Multifactorial Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2.1 PH due to heart failure preserved LVEF</td>
<td>5.1 Hematologic disorders: splenectomy, chronic hemolytic anemia, myeloproliferative disorders</td>
</tr>
<tr>
<td>• 2.2 PH due to heart failure reduced</td>
<td>5.2 Systemic disorders: sarcoid, LCH, LAM, NF, vasculitis and Metabolic disorders: Glycogen storage dz, Gaucher, thyroid</td>
</tr>
<tr>
<td>• 2.3 Valvular disease</td>
<td>5.3 Others: tumor, fibrosing mediastinitis, CKD, segmental PH</td>
</tr>
<tr>
<td>• 2.4 Congenital/Acquired L inflow/outflow tract obstruction/congenital cardiomyopathies</td>
<td>5.4 Complex congenital heart</td>
</tr>
</tbody>
</table>
Group 5: Unclear/multifactorial mechanisms

• **Hematologic disorders**: splenectomy, chronic hemolytic anemia, myeloproliferative disorders

• **Systemic disorders**: sarcoid, LCH, LAM, NF, vasculitis

• **Metabolic disorders**: Glycogen storage disease, Gaucher, thyroid,

• **Others**: tumor, fibrosing mediastinitis, CKD, segmental PH
Group 4 PH: Chronic Thromboembolic (CTEPH) Diagnose with Ventilation-Perfusion Scan

Group 4 PH: Chronic Thromboembolic Pulmonary Hypertension

Most treated PEs resolve over weeks
In a small percentage of patients, residual obstruction causes persistent pulmonary hypertension
  – Due to decrease in cross-sectional area of pulmonary vascular bed and development of small vessel arteriopathy

Treatment: pulmonary endarterectomy
Group 3 Pulmonary Hypertension: due to chronic hypoxemic lung disease

Second most common cause of PH

Due to destruction of lung parenchyma, entrapment of pulmonary vasculature, and hypoxemic vasoconstriction.

Treat ONLY in clinical trial. Currently investigating inhaled prostacyclin in Group 3 PAH

- Most common pulmonary cause of group 3 PH: COPD
- Fibrotic lung diseases
- OSA
Group 2 Pulmonary Hypertension

**Most common cause of PH:** left heart disease
Includes systolic dysfunction
  – Ischemic
  – cardiomyopathies
Preserved ejection fraction
  – +/- diastolic dysfunction
Valvular disease
  – Mitral or aortic
Figure 2. PAH Versus PVH: Echocardiographic and Invasive Hemodynamic Differentiation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH</th>
<th>PVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV size</td>
<td>Enlarged</td>
<td>May be enlarged</td>
</tr>
<tr>
<td>LA size</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>RA/LA size ratio</td>
<td>Increased</td>
<td>Normal (LA &gt; RA size)</td>
</tr>
<tr>
<td>Interatrial septum</td>
<td>Bows from right to left</td>
<td>Bows from left to right</td>
</tr>
<tr>
<td>RVOT notching</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>&lt;&lt; 1</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Lateral e’</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Lateral E/e’</td>
<td>&lt; 8</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Aortic pressure</td>
<td>Normal/Low</td>
<td>Normal/High</td>
</tr>
<tr>
<td>PCWP</td>
<td>≤ 15 mmHg</td>
<td>&gt; 15 mmHg</td>
</tr>
<tr>
<td>PADP-PCWP</td>
<td>&gt; 7 mmHg</td>
<td>&lt; 5 mmHg</td>
</tr>
</tbody>
</table>

Vallerie V. McLaughlin, Sanjiv J. Shah, Rogerio Souza, Marc Humbert
Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial

![Graph showing the adjudication criterion and outcomes for patients receiving sildenafil or placebo.]
# Clinical Classification of Pulmonary Hypertension

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<tr>
<th>1. PAH</th>
<th>3. PH Owing to Lung Diseases and/or Hypoxia</th>
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<td>• Developmental abnormalities</td>
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<td></td>
</tr>
<tr>
<td>− Schistosomiasis</td>
<td></td>
</tr>
</tbody>
</table>

| 1’. PVOD and/or PCH | 1”. PPHN |

<table>
<thead>
<tr>
<th>2. PH Owing to Left Heart Disease</th>
<th>4. CTEPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Valvular disease</td>
<td></td>
</tr>
<tr>
<td>• Congenital/Acquired L inflow/outflow tract obstruction/congenital</td>
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</tr>
<tr>
<td>cardiomyopathies</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>5. PH With Unclear Multifactorial Mechanisms</th>
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<tr>
<td>• Hematologic disorders: splenectomy, chronic hemolytic anemia,</td>
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<td>myeloproliferative disorders</td>
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<td>• Systemic disorders: sarcoid, LCH, LAM, NF, vasculitis</td>
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*Denotes change in classification.

Pathobiology of PAH

Vallerie V. McLaughlin, Sanjiv J. Shah, Rogerio Souza, Marc Humbert


http://dx.doi.org/10.1016/j.jacc.2015.03.540
Pathogenesis of PAH

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

1. Endothelial Dysfunction
   - ↓ Nitric Oxide Synthase
   - ↓ Prostacyclin Production
   - ↑ Endothelin 1 Production

2. Vascular Smooth Muscle Dysfunction
   - Impaired Voltage-Gated Potassium Channel (K_{V1.5})
   - Adventitial and Intimal Proliferation
   - In Situ Thrombosis
   - Plexiform Lesion
   - Advanced Vascular Lesion

NORMAL      REVERSIBLE DISEASE      IRREVERSIBLE DISEASE
Mechanisms of Pathology for PAH

Endothelin pathway

- Preproendothelin
- Proendothelin
- Endothelin
  - Endothelin-receptor A
  - Endothelin-receptor B
- Endothelin-1
- Endothelin-receptor antagonists
- Vasoconstriction and proliferation

Nitric oxide pathway

- L-arginine
- Nitric oxide
  - NOS
- cGMP
- Vasodilatation and antiproliferation
- Exogenous nitric oxide
- Phosphodiesterase type 5 inhibitor

Prostacyclin pathway

- Arachidonic acid
- Prostaglandin I₂
- Prostacyclin
  - Prostacyclin derivates
- cAMP
- Vasodilatation and antiproliferation

Type of PAH (WHO Group I) meeting traditional hemodynamic criteria

N = 2,967

UNMC Registry

N = 163

- Idiopathic: 42.2%
- CTD: 11.9%
- Portopulmonary: 11.9%
- HIV: 21.1%
- Medication
- Congenital Heart
- CTEPH
- Familial
PAH Associated With Connective Tissue Disease

Scleroderma

- Most prevalent CTD associated with PAH
- Rate of occurrence of PAH = 7 to 12% of patients with scleroderma;
- more common in limited scleroderma (CREST syndrome)
- Prognosis is poorer than other types of PAH
  - PAH is the leading cause of death; 1 year mortality rate = 30%

DETECT study: Annual screening with ECHO, DLCO and biomarkers

RALES clinic

Adult congenital heart disease

5-10% estimate of PAH in congenital heart disease

1. Eisenmenger Syndrome: PAH in the presence of a large R to L shunt accompanied by cyanosis, secondary erythrocytosis and multi-organ involvement
2. PAH associated with prevalent systemic to pulmonary shunts
3. PAH with small/coincidental defects (VSD <1 cm or ASD < 2cm)
4. PAH after defect correction

Adult congenital heart disease program accredited
Past and current cause-specific mortality in Eisenmenger syndrome

- Wood (1958)
- Daliento (1998)
- Current study, 'early' era (<July 2006)
- Current study, 'late' era (≥July 2006)

Cause-specific mortality (%)

- Heart failure
- Infection
- Sudden cardiac death
- Thromboembolism
- Haemorrhage
- Peri-procedural
- Other
## Updated Classification of Drugs and Toxins Associated with PAH

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</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>L-tryptophan</td>
</tr>
<tr>
<td>Benfluorex</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Interferon-α and –β</td>
</tr>
<tr>
<td>Toxic rapeseed oil</td>
<td>Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>Bosutinib</td>
</tr>
<tr>
<td></td>
<td>Direct-acting antiviral agents against Hep C</td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
</tr>
<tr>
<td></td>
<td>Indirubin (Chinese herb Qing-Dai)</td>
</tr>
</tbody>
</table>
Objectives

1. Review pathophysiology, diagnosis, and evaluation of pulmonary hypertension
2. Discuss current classification system
3. Assess treatment options and goals
4. Analyze multiple clinical endpoints to determine mortality risk and success of therapy
5. Present newer concepts and research
# Risk assessment in PAH

## Determinants of prognosis (estimated 1 year mortality)

<table>
<thead>
<tr>
<th>Clinical signs of right heart failure</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5-10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Symptom Progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO functional class I, II, III, IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD &gt;440 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>165-440 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;165 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPET Peak VO$_2$&gt;15 ml/min/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO$_2$ 11-15 ml/min/kg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peak VO$_2$ &lt;11 ml/min/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP &lt;50 ng/l</td>
<td></td>
<td></td>
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<tr>
<td>50-300 ng/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 ng/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECHO/MR RA area &lt;18 cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pericardial effusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA area 18-26 cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO or minimal pericardial effusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA area &gt;26 cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamics RAP &lt; 8 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI ≥2.5 l/min/m²</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RAP 8-14 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI 2.0-2.4 l/min/m²</td>
<td></td>
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</tr>
<tr>
<td>SVO$_2$ &gt;65%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVO$_2$ 60-65%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVO$_2$ &lt;60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP &gt;14 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI &lt;2.0 l/min/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVO$_2$ &lt;60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVO$_2$ &gt;65%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### REVEAL 2.0

#### Updated PAH Risk Score

<table>
<thead>
<tr>
<th>WHO Group I Subgroup</th>
<th>CTD-PAH</th>
<th>PoPH</th>
<th>Heritable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+1</td>
<td>+3</td>
<td>+2</td>
</tr>
</tbody>
</table>

#### Demographics

- Males age >60 y
  - +2

#### Comorbidities

- eGFR <60 mL/min/1.73 m² or renal ineficiency (if eGFR is unavailable)
  - +1

#### NYHA/WHO Functional Class

- I
  - +1
- II
  - +1
- IV
  - +2

#### Vital Signs

- SBP <110 mm Hg OR HR >96 BPM
  - +1

#### All-cause Hospitalizations ≤6 mo

- +1

#### 6-Minute Walk Test

- >440 m
  - -2
- 320 to <440 m
  - -1
- <165 m
  - +1

#### BNP

- <50 pg/mL or NT-proBNP <300 pg/mL
  - -2
- 200 to <800 pg/mL
  - +1
- >800 pg/mL or NT-proBNP >1,100 pg/mL
  - +2

#### Echocardiogram

- Pericardial effusion
  - +1

#### Pulmonary Function Test

- % predicted DLco <40%
  - +1

#### Right Heart Catheterization

- mRAP >20 mm Hg within 1 y OR PVR <5 Wood units
  - +1

#### SUM OF ABOVE

- + 6

#### RISK SCORE
Goals of Therapy

- Improve quality of life
- Improve functional class
- Improve survival
- Prevent clinical worsening
- Improve 6-minute walk test
- Improve hemodynamics (RV function)
- Decrease hospital admissions
# General Medical Care of PAH patients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation/Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid pregnancy</td>
<td>I C</td>
</tr>
<tr>
<td>Flu and Pneumococcal vaccination</td>
<td>I C</td>
</tr>
<tr>
<td>Psychosocial support</td>
<td>I C</td>
</tr>
<tr>
<td>Supervised exercise training in physically deconditioned patients on stable medical therapy</td>
<td>IIA B</td>
</tr>
<tr>
<td>In flight oxygen for FC III-IV and PaO2 &lt;60</td>
<td>IIA C</td>
</tr>
<tr>
<td>In elective surgery, epidural preferred over general anesthesia</td>
<td>IIA C</td>
</tr>
</tbody>
</table>
Supportive Therapy for PAH

Diuretic treatment is recommended in PAH patients with RV failure and fluid retention

Continuous long-term O₂ therapy is recommended in PAH patients when PaO₂ <60

Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens

Correction of anemia may be considered

**Medical Treatment for PAH:**
*Refer to center of excellence*

*Positive vasoreactivity*
*Calcium Channel Blockers*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>20 - 30 mg/day</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>180 - 240 mg/day</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>720 – 960 mg/day</td>
</tr>
</tbody>
</table>

# FDA-Approved PAH Therapies

**Endothelin receptor antagonists:**
- Ambrisentan ➞ Letairis (PO)
- Bosentan ➞ Tracleer (PO)
- Macitentan ➞ Opsumit (PO)

**PDE-5 inhibitor**
- Sildenafil ➞ Revatio (PO)
- Tadalafil ➞ Adcirca (PO)

**cGMP inducer**
- Riociguat ➞ Adempas (PO)

**Prostacyclin Receptor Agonist**
- Selexipag ➞ Uptravi (PO)

**Prostanoids:**
- Epoprostenol ➞ Flolan (IV), Veletri (IV)
- Treprostinil ➞ Remodulin (SC,IV)
- Treprostinil inhaled ➞ Tyvaso
- Treprostinil oral ➞ Orenitram (PO)
- Iloprost ➞ Ventavis (inhaled)
Timeline of approval of therapies for PAH

ERA
PDE-5i
sGC stimulator
Prostanoids
IP receptor agonists

Bosentan 1995
Ambrisentan 2005
Macitentan 2010
Riociguat 2015

Epoprostenol (i.v.)
Treprostinil (s.c.)
Iloprost (inh)
Treprostinil (i.v.)
Sildenafil
Tadalafil
Treprostinil (oral)#
Treprostinil (inh)#
Selexipag

Sean Gaine, and Vallerie McLaughlin Eur Respir Rev
2017;26:170095
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Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.


Selexipag: prostacyclin receptor agonist

Event = hospitalization, disease progression, death, initiation of parenteral prostanoid therapy or long term oxygen, need for lung transplant or atrial septostomy.

No. at Risk
Placebo 582 433 347 220 149 88 28
Selexipag 574 455 361 246 171 101 40

Effect of selexipag on the primary composite endpoint of morbidity/mortality by pulmonary arterial hypertension (PAH) therapy at baseline and connective tissue disease (CTD) subtype from GRIPHON study.

<table>
<thead>
<tr>
<th>p-value for interaction</th>
<th>Placebo patients/events</th>
<th>Selexipag patients/events</th>
<th>HR (95% CI)</th>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study population</td>
<td>582/242</td>
<td>574/155</td>
<td>0.60 (0.49–0.73)</td>
<td></td>
</tr>
<tr>
<td>Overall CTD</td>
<td>167/73</td>
<td>167/48</td>
<td>0.59 (0.41–0.85)</td>
<td></td>
</tr>
<tr>
<td>PAH therapy at baseline</td>
<td></td>
<td></td>
<td>0.8745</td>
<td></td>
</tr>
<tr>
<td>ERA monotherapy</td>
<td>26/14</td>
<td>40/14</td>
<td>0.78 (0.37–1.67)</td>
<td></td>
</tr>
<tr>
<td>PDE-5i monotherapy</td>
<td>43/18</td>
<td>51/14</td>
<td>0.64 (0.32–1.29)</td>
<td></td>
</tr>
<tr>
<td>ERA and PDE-5i</td>
<td>56/25</td>
<td>40/10</td>
<td>0.46 (0.21–0.98)</td>
<td></td>
</tr>
<tr>
<td>No PAH-specific therapy</td>
<td>42/16</td>
<td>36/10</td>
<td>0.59 (0.27–1.30)</td>
<td></td>
</tr>
<tr>
<td>CTD population subgroup</td>
<td></td>
<td></td>
<td>0.8926</td>
<td></td>
</tr>
<tr>
<td>PAH-SSc</td>
<td>93/46</td>
<td>77/25</td>
<td>0.56 (0.34–0.91)</td>
<td></td>
</tr>
<tr>
<td>PAH-SLE</td>
<td>37/13</td>
<td>45/11</td>
<td>0.66 (0.30–1.48)</td>
<td></td>
</tr>
<tr>
<td>Pooled PAH-MCTD and PAH-other</td>
<td>37/14</td>
<td>45/12</td>
<td>0.68 (0.31–1.47)</td>
<td></td>
</tr>
</tbody>
</table>

Kaplan-Meier curves for the time from randomisation to first adjudicated clinical failure in connective tissue disease-associated pulmonary arterial hypertension population.

HR: 0.43
95% CI (0.24, 0.77)
Risk reduction: 57%

Time (weeks)

Event-Free (%)
## PAH Therapy based on risk

<table>
<thead>
<tr>
<th>Determinants of prognosis (estimated 1 year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5-10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment</td>
<td>Monotherapy</td>
<td>Combination oral therapy</td>
<td>Combination oral therapy plus intravenous prostacyclin</td>
</tr>
</tbody>
</table>

Inadequate clinical response on maximal therapy, consider transplant referral
Initial management of pulmonary arterial hypertension in the current era.

Sean Gaine, and Vallerie McLaughlin Eur Respir Rev 2017;26:170095

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PAH: A Progressive Disease

- Pre-symptomatic/Compensated
- Symptomatic/Decompensating
- Declining/Decompensated

Symptom Threshold

Right Heart Dysfunction

Time

CO

PAP

PVR

RAP

Symptoms
ECMO

Most commonly peripheral veno-arterial to unload the RV
Bridge to transplantation
awake
Lung Transplantation

Standard: bilateral lung transplantation
Refer after inadequate clinical response on maximal combination therapy

International Society for Heart and Lung Transplant (ISHLT)

Lung transplant between 1990 and 2014: mortality risk in first 3 months was higher for IPAH (23%) than for many other indications: chronic obstructive pulmonary disease (9%) or cystic fibrosis (9%).

However, recent advances in peri- and post-operative management have resulted in considerable improvements in early post-transplant survival rates.

In a cohort of PH patients receiving a bilateral lung transplant combined with post-operative ECMO in a specialist center after 2010, post-transplant survival rates at 3 and 12 months were reported to be 100% and 96%, respectively [54].

Similar results were obtained from a recent study of IPAH patients receiving prolonged ECMO after bilateral lung transplantation. In this study, survival rates at 3 months, 1 year, 3 years and 5 years were 93%, 90%, 87% and 87%, respectively.
THE RISK is NOT KNOWING. GET TESTED.
Take Home Points

PH ≠ PAH

PAH is about cellular proliferation, not just vasoconstriction

Nonspecific symptoms: suspect early, screen with echocardiogram, and confirm with cardiac catheterization

Refer to PH center