Improving Outcomes in Pulmonary Hypertension:
Diagnostic Approaches & Treatment

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Learning Objectives
• Review the diagnosis and hemodynamic classification of pulmonary hypertension
• Review the evaluation of the patient with unexplained shortness of breath and pulmonary hypertension
• Overview of current and future approaches to treatment in PAH

Pulmonary Vascular Resistance
• The pulmonary vascular bed is a high-flow, low-resistance, low-pressure circuit
• Higher compliance of precapillary arterioles than systemic arterioles
  — Thinner media and less smooth muscle cells
  — Large cross-sectional area
  — Highly distensible
• Recruitable vessels available to accommodate increased flow

LV and RV P-V Relationships
• RV is trapezoidal, with poorly defined isovolumic periods
• Similar elastance properties as the LV
  — RV is an energetically efficient pump
  — Efficiency is dependent on the normally low pulmonary hydraulic impedance
  — RV-PV coupling
• Chronic changes lead to progressive change towards an LV pattern of P-V
• Prolonged increase in load, systolic function will decline

Updated Definition of PAH
Right Heart Catheterization Confirmed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mean pulmonary arterial pressure (mPAP)*</td>
<td>&gt;25 mm Hg at rest</td>
</tr>
<tr>
<td>Normal pulmonary capillary wedge pressure (PCWP)</td>
<td>≤15 mm Hg</td>
</tr>
<tr>
<td>Increased pulmonary vascular resistance (PVR)^</td>
<td>&gt;3 Wood units</td>
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</tbody>
</table>

*Normal resting mPAP = 8 – 20 mm Hg
^In ACC/FHH expert consensus. In 4th World Symposium on PH, increased given PVR without a value.
Significance of mPAP from 21–24 mm Hg unclear.


Disclosures
• Gilead Sciences – Investigator, Steering Committee Chair
• United Therapeutics – Investigator, Scientific Advisory Board
• Incyte Pharmaceuticals – Investigator
• Medtronic Inc. – Steering Committee, Investigator
Components of Pulmonary Vascular Remodeling

- Inflammatory Cells
- Proliferation
- Hypertrophy
- Differentiation


2.3
2.2
2.1
2. PH due to Left Heart Disease

1
1.5
1.4
1.4.6
1.4.5
1.4.4
1.4.3
1.4.2
1.4.1
1.4
1.3
1.2.3
1.2.2
1.2.1
1.2
1.1

TPG = transpulmonary pressure gradient.
CO = cardiac output.

Post-capillary PH
Pre-capillary PH

Definition
Mean PAP ≥25 mm Hg
Mean PAP ≥25 mm Hg

Characteristics
PWP ≤15 mm Hg
CO normal or reduced
PWP >15 mm Hg
CO normal or reduced
Passive = TPG ≤12 mm Hg
Reactive = TPG >12 mm Hg

Clinical group
Pulmonary arterial hypertension
PH due to left heart disease


Pulmonary Arterial Hypertension

- Disorders of increased pulmonary vascular resistance (PVR) as a consequence of structural changes to pulmonary arterial bed
- Symptoms / morbidity / mortality are determined by the effects of PVR (RV afterload) on right ventricular function and cardiac output (CO)
- Pulmonary artery pressure is not the disease but is a result of the relationship between resistance and flow (P = PVR x CO)

Classification of PH

- PH is a diverse mix of pathologies where the only unifying theme is elevated pulmonary artery pressure relative to left atrial pressure
- The categorization of pulmonary hypertension was designed by convenience for the purpose of facilitating novel treatments to be tested across different presentations
- The categorization of PH is not based on a molecular understanding of the pathology
- Not a true guide for management decisions

Clinical Classification (Dana Point, 2008)

1. Pulmonary Arterial Hypertension
   1.1 Idiopathic
   1.2 Heritable
   1.2.1 BMPR2
   1.2.2 ALK1, ENDG
   1.3 Congenital heart diseases
   1.4.1 Infectious
   1.4.2 Inflammatory diseases
   1.4.3 Portal hypertension
   1.4.4 Connective tissue disorders
   1.4.5 Hematologic disorders
   1.4.6 Chronic thromboembolic disease
   1.5 Metabolic disorders
   1.5.1 Glycogen storage disease
   1.5.2 Sarcoidosis
   1.5.3 Scleroderma
   1.5.4 Drug and toxin-induced disease
   1.5.5 Unknown
   1.6 Alveolar hypoplasia
   1.7 Developmental abnormalities

2. PH due to Left Heart Disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3. PH with lung disease/hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Intermittent 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 abnormalities

4. Chronic Thromboembolic PH (CTEPH)
   4.1 Hematologic disorders: myelo-proliferative disorders
   4.2 Systemic diseases: sarcoidosis, pulmonary hypertension, hemolytic anemias, neurofibromatosis, vasculitis
   4.3 Metabolic diseases: hypogonadal states, Gucher disease, thyroid disorders
   4.4 Others: tumor obstruction, lymphedema, chronic renal failure on dialysis

Hemodynamic Definitions of Pulmonary Hypertension

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<th>Characteristics</th>
<th>Clinical group</th>
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<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥25 mm Hg, PWP ≤15 mm Hg, CO normal or reduced</td>
<td>Pulmonary arterial hypertension, PH due to left heart disease</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥25 mm Hg, PWP &gt;15 mm Hg, CO normal or reduced</td>
<td>PH due to lung disease, CTEPH, PH with unclear or multifactorial mechanisms</td>
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</tbody>
</table>

CO = cardiac output.
PVR = pulmonary vascular resistance.

PAH: A Progressive Disease

CO
PAP
PVR
Pre-symptomatic/Compensated
Symptomatic/Degenerative
Declining/ Decompensated

Symptom Threshold
Right Heart Dysfunction

REVEAL: Initial Database Characteristics

- Median time from initial symptoms to RHC:
  - 14 months
- Median time to first visit to pulmonary hypertension clinic:
  - 15 months
- Average body mass index:
  - 28.9 + 18.4 kg/m²

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<tr>
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<th>IPAH (n=685)</th>
<th>APAH (n=760)</th>
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<td>Median age at diagnosis (years)</td>
<td>45-54</td>
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IPAH: idiopathic pulmonary arterial hypertension
APAH: associated pulmonary arterial hypertension

RHC: right heart catheterization


REVEAL Database: Most Frequent Symptoms at Diagnosis

- Dyspnea at rest: IPAH 75%, APAH 82%
- Cough: IPAH 61%, APAH 56%
- Dizzy/lightheaded: IPAH 37%, APAH 33%
- Presyncope/syncope: IPAH 20%, APAH 23%
- Edema: IPAH 22%, APAH 22%
- Chest pain/discomfort: IPAH 23%, APAH 23%
- Other: IPAH 10%, APAH 10%
- Fatigue: IPAH 35%, APAH 35%
- Dyspnea on exertion: IPAH 66%, APAH 70%

Incidence (%)

Case 1-PAH

- 33 yo woman G2P1(5-yr male) Sab1 with a history of Raynaud’s
- 3 year history of DOE, more rapidly progressing 6-months prior to presentation
- Treated for asthma with LABA / ICS without change
  - Multiple steroid tapers without effect
- 1 month prior to presentation, pre-operative CXR revealed enlarged pulmonary arteries
- Very symptomatic when climbing stairs or an incline

Impact of Clinical Worsening in First Year on Subsequent Survival

- Survival Estimate (Not Worsened vs. Worsened)

N=3012 PAH patients. Stratified by worsening or no worsening in 1st year of enrollment in REVEAL.


Case 1-PAH

- Past Medical History
  - Raynaud’s
  - “Asthma”
- Family History
  - No pulmonary or cardiac disease
- Social History
  - No history of smoking, alcohol, recreational drug, or anorexigen / stimulants use
- Medications - none

- HR: 113 SBP: 112 / 78 mmHg
- O₂ saturation: 93% (RA)
- No JVD
- Bibasilar soft rales at the bases
- Normal 1st heart sound but louder 2nd heart sound and no audible murmurs
- 1+ peripheral edema

Case 1-PAH

- Pulmonary Function Tests
  - Mild restrictive defect
  - No reversibility with bronchodilators
  - DLCO: 53% of predicted
- Normal metabolic profile, liver function tests, blood counts and thyroid function tests
- ANA + 1:320 and other auto-immune serology’s negative
- HIV negative
Patient #1: Physical Examination

- Six Minute Walk
  - 318 meters  Borg 5
  - Desat to 89% during 6MW
- Chest CT
  - No signs of interstitial lung disease or pulmonary emboli
- V/Q scan
  - No evidence of large obstructive clot
- EKG
  - RAE, RAD, RVH

6-Minute Walk Test

- 6-minute walk test is recommended at the time of diagnosis and follow-up
  - Characterize the functional impairment and response to therapy

Comparison of survival rates between high and low distance groups.

Echocardiogram

- Marked right ventricular and atrial enlargement
- Normal left ventricular size and function
- Estimated PASP 75 mm Hg
- Displaced interventricular septum
- Saline contrast study did not demonstrate right to left shunting

Accuracy of PH Diagnosis by Echocardiography in Advanced Lung Disease

- Cohort study of lung transplant patients (n=374)
- All patients
  - Doppler echo 24 to 48 hours prior to RHC
- Prevalence of PH: 25%
- Echo frequently inaccurate leading to over diagnosis of pulmonary hypertension in patients with advanced lung disease


Case 1-PAH

- RHC:
  - RA (CVP) 25
  - RV 87/12 (RVEDP: 22)
  - PAP 89/36 (54)
  - PCWP 14
  - CO/CI 4.6/1.8
  - PVR 710 (9wu); SVR 871
  - 40ppm NO – Limited response

Pulmonary Arterial Hypertension: Goals of Therapy

- Improve exercise capacity
- Improve functional class
- Prevent clinical worsening
- Improve survival
- Improve hemodynamics

Case 1-PAH

- Severe PAH, NYHA Functional Class 3b
  - 6-MWD 318m, BDS 5
- How would you treat this patient?
- How would you monitor and follow-up this patient?

General Medical Management of PAH

- Oxygen
- Warfarin (if not otherwise contraindicated)
- Diuretics
- Digoxin
- Lifestyle adjustments
  - Avoidance of stimulants
  - Assess for and treat depression
  - Encourage aerobic exercise, physical activity
  - Optimize body weight
  - Stress reduction
  - Low-salt diet
  - Assess for safety in hypoxic environments: (high altitude, airline travel)