Diagnosis of Pulmonary Hypertension

April 22, 2016
• Objectives
• Introduction
• Pathophysiology
• Diagnosis
  • Clinical presentation
  • Imaging
  • Right Heart Catherization
• Conclusion
Objectives

• Describe the different etiologies and pathophysiology of pulmonary hypertension (PH)

• Develop a method to diagnose and determine the etiology of PH
Introduction
Background

• Pulmonary Arterial Hypertension is characterized by:
  • mean pulmonary artery pressures (PA) ≥ 25mmHg at rest by right heart catheterization (RHC)

Background

- Most common reasons for referrals from general practitioners for PH include:
  - Abnormal echo findings on an echo done for other reasons
  - Screening tests in patients with connective tissue disease
  - Evaluation of symptoms such as dyspnea
Background

• Average delay between symptom onset and diagnosis is **27 months**

• For newly diagnosed PAH (idiopathic, familial, anorexigen induced) estimated survival was:
  • at 1 year - 85%
  • at 2 years - 70%
  • at 3 years - 55%


5th WSPH: Clinical Classification of Pulmonary Hypertension (2013)

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
      1.4.1 Connective tissue disease
      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 (PPHN)
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. Pulmonary hypertension due to lung diseases and/or hypoxia
   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
## Epidemiology

<table>
<thead>
<tr>
<th>Populations</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPAH</strong></td>
<td>6 cases/million population&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Systemic Sclerosis</strong></td>
<td>8% to 27%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| **Congenital Heart Disease** | 12% to 34%<sup>3</sup>  
  Approximately 50% of patients with large VSDs develop Eisenmenger syndrome<sup>4</sup>                                             |
| **HIV Infection**            | 0.5%<sup>2</sup>                                                                                                                              |
| **Sickle Cell Disease**      | 20% to 40%<sup>5</sup>                                                                                                                         |
| **Drugs/Toxins**             | 29% of IPAH patients reported stimulant use in a retrospective study of 340 PAH and PH patients<sup>6</sup>                                     |

Engelfriend PM et al. Heart 2007, 93 6820687.  4. Simonneau G et al. JACC 2004 43. 5S-12S.
PAH Distributions in the US: REVEAL Registry

Overall

- Idiopathic (46.2%)
- Associated (50.7%)
- Heritable (2.7%)
- Pulmonary veno-occlusive (0.4%)

Associated

- Connective tissue/collagen vascular (49.9%)
- Congenital heart disease (19.5%)
- HIV (4.0%)
- Other (5.5%)
- Drugs/Toxins (10.5%)
- Portopulmonary (10.6%)

Based on Venice Clinical Classification (2003); 2967 patients. Adapted from Badesch DB et al. Chest. 2010;137:376-387.
Genetic Basis of PAH

**BMPR2 Mutations**
- ~70% of familial PAH
- 10% to 40% of IPAH
- Rare in other types of PAH (eg, anorexigens)

**ALK1 Mutations**
- Shares same signaling abnormalities as BMPR2
- PAH associated with hereditary hemorrhagic telangiectasia (ie, Osler-Weber-Rendu)
PAH Associated With Scleroderma

- Overall prevalence: 10% to 15%
  - 8% to 27% in systemic sclerosis
  - Studies may overestimate prevalence due to lack of catheter confirmation
- Systemic sclerosis accounts for up to 75% of PAH associated with CTD

CTD=connective tissue disease.
PAH Associated with Congenital Heart Disease (CHD)

- In 2002, estimated up to 1.3 million Americans have congenital heart defects
  - 4 – 10 cases/1000 in general population
- 1.6 – 12.5 cases/million of PAH associated with CHD in adults
- Eisenmenger syndrome more common with large defects
  - Almost all cases of truncus arteriosus
  - Approximately 50% with large VSD (>1.5 cm)
  - Approximately 10% with large ASD (>2.0 cm)

VSD=ventricular septal defect; ASD=atrial septal defect.
PAH Associated with HIV: Epidemiology

- PAH occurs in 1 in 200 patients with HIV infection
- With improved outcomes due to highly active antiretroviral therapy (HAART), non-infectious complications are increasingly important for morbidity
- PAH has emerged as important cause of mortality and remains such despite intervention

Pathophysiology
Pathophysiologic Features

Three factors are thought to cause the increased pulmonary vascular resistance that characterizes this disease process.

• Vasoconstriction

• Remodeling of the pulmonary vessel wall

• Thrombosis in situ
Pathogenesis

Three Key Mediators

- Nitric Oxide
- Prostacyclin

Endothelin: Vasoconstriction, Proliferation, Hypertrophy, Inflammation, Fibrosis
Adventitia = Collagen fibers and fibroblasts
Media = Smooth muscle cells
Intima = Endothelial cells

Normal pulmonary artery
Note the thin media and the monolayer of endothelial cells laying down on wavy internal elastica

Internal elastica
External elastica

Pulmonary arterial changes in PAH

A
Vasconstriction
Note morphological signs of vasconstriction, including narrowed lumen and tightly folded internal elastica with endothelial cells pinched between their folds

B
Arterial remodeling and inflammation
Note adventitial and medial thickening and neointima formation, due to smooth muscle cell and fibroblast proliferation/migration, and pulmonary lymphoid neogenesis

C
Plexiform lesion
Note the glomeruloid lesion due to aberrant angiogenesis arising within a branch of small supernumerary pulmonary artery

D
Thrombotic lesion
Note the recanalized thrombus in the lumen

Tertiary lymphoid follicle
Neointima
Fibrous material

Pathogenesis of PAH

Presymptomatic: May include:
- Inflammation

Symptomatic: May include:
- Inflammation
- Vasoconstriction
- Fibrosis
- Hypertrophy

Severely Symptomatic: May include:
- Cell proliferation
- Plexiform lesions
PAH is Associated with a Dysfunction in Nitric Oxide (NO) Production*

↑ levels of eNOS in plexiform lesions

↓ levels of eNOS in vascular tissue

Proliferation of pulmonary endothelial cells

↓

NO

• Vasoconstriction
• Proliferation of tunica media

*Based on observations reported from in vitro, animal, and human trials. The clinical significance is unknown.

eNOS=endothelial nitric oxide synthase.
Prostacyclin Deficiency in PAH*

Prostaglandin H₂

↓

Prostacyclin synthase (PGIS)

↓

Prostacyclin (PGI₂)

↓

SMC prostaglandin receptor down regulation

*Based on observations reported from in vitro, animal, and human trials. The clinical significance is unknown.

SMC=smooth muscle cell.

Hata AN, Breyer RM. Pharmacol Ther. 2004;103:147-166.
Endothelin (ET) is a Key Pathogenic Mediator*

**Proliferation**
- Vascular smooth muscle
- Fibroblasts

**Vasoconstriction**
- Direct or via facilitation of other vasoconstrictor systems (renin angiotensin system, sympathetic)

**Hypertrophy**
- Cardiac/vascular

**Fibrosis**
- Fibroblast proliferation
- ↑ Extracellular matrix proteins
- ↓ Collagenase production

**Inflammation**
- ↑ Vascular permeability
- Neutrophil/mast cell activation
- Promotes cellular adhesion
- ↑ cytokine production

*Based on observations reported from in vitro, animal, and human trials. The clinical significance is unknown.
Histopathologic Alterations in Pulmonary Hypertension

SMC proliferation

Fibrosis

Plexiform lesion formation

Normal PA

SMC = smooth muscle cell.
Adapted with permission from Cool CD et al. Chest. 2005;128(6 Suppl):S65S-S71S.
Hemodynamic Changes Correlate With Disease Progression

CO=cardiac output; PAP=pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure.
Clinical Presentation
Symptoms

- Shortness of breath with exertion
- Loss of energy/fatigue
- Chest pain
- Dizziness upon standing, climbing stairs, straightening up from a bent position, or even while just sitting
- Exertional Syncope
- Peripheral edema
Symptoms

- Raynaud’s Phenomenon (chalky white and/or dusky blue fingers that may be painful and can sometimes be provoked by the cold)

- Depression

- Dry Cough

- Severity of symptoms usually correlates with the progression of the disease.
When advanced…

- Irregular heartbeat
- A racing pulse
- Passing out/syncope
- Difficulty breathing at rest
## WHO Functional Classes of Pulmonary Arterial Hypertension (PAH)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with [PAH] but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with [PAH] resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with [PAH] resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with [PAH] with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

Adapted from Rubin LJ. Chest. 2004;126(1 Suppl):7S-10S.
Diagnosis
Is it Group I (PAH)?

- Risk factors for Group I PAH?: CTD, Genetics??
- Exclude Group II (Left heart disease): Echo, heart catheterization
- Exclude Group III (Lung Disease): with PFTs, chest imaging, ABG
- Exclude Group IV (Thromboembolic PH): Ventilation/Perfusion scan
- Exclude Group V (Miscellaneous) Clinical suspicion guided eval
Diagnosis

- History and Physical Exam
- Blood tests
- Electrocardiogram
- Chest X-ray, Pulmonary function tests
- Echocardiogram
- Nuclear scan to look for blood clots
- Exercise tolerance test (6 minute walk), BNP
- Right heart catheterization
Physical Examination: Signs of PAH

- Loud pulmonic valve closure ($P_2$)
- TR murmur
- Jugular venous distention
- Right ventricular heave
- Right-sided fourth heart sound
- Peripheral edema, ascites
- Early systolic ejection click

TR=tricuspid valve regurgitation.
McGoon M et al. Chest. 2004;126(1 Suppl):14S-34S.
Standard Blood Tests for Evaluation of PAH

- Antinuclear antibody (ANA)
  - Up to 40% of patients with IPAH have positive but low (>1:80 dilutions) ANA titers
- Antiphospholipid antibodies
  - Lupus anticoagulant, anticardiolipin antibodies
- HIV serology
- CBC with platelets
- Liver function
- Thyroid function
- Hemoglobin electrophoresis, if indicated

IPAH=idiopathic pulmonary arterial hypertension; CBC=complete blood count.
The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25:2243-2278.
Screening Tests for PAH: Electrocardiogram (ECG)

- May provide prognostic information
- May indicate right-heart disease
- May show right axis deviation
- Insufficiently sensitive as a screening tool

Image courtesy of Jeffrey Sager, MD.
RV=right ventricular.
A Typical PH Chest XRay
Echocardiography

- Severe dilation of RV & RA
- Midsystolic closure of the pulmonic valve
- Paradoxical bulging of septum into the left ventricle during systole
- Hypertrophy of right ventricular free wall and trabeculae
- Septal flattening
- Tricuspid Regurgitation
V/Q Scan to Rule Out Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- Normal V/Q scan makes CTEPH unlikely
  - Sensitivity: 90% to 100%
  - Specificity: 94% to 100%
- >1 segmental-sized or larger mismatched perfusion defects seen with CTEPH
- Spiral CT may underestimate degree of obstruction in chronic CTEPH

V/Q=ventilation-perfusion; CT=computed tomography; IPAH=idiopathic pulmonary arterial hypertension; PE=pulmonary embolism.
Image courtesy of Richard N. Channick, MD.
McGoon M et al. Chest. 2004;126(1 Suppl):14S-34S.
Pulmonary Function Tests (PFTs) and Arterial Blood Gases to Rule Out Lung Disease

- Exclude or characterize contribution of underlying airway or parenchymal lung disease
- Arterial hypoxemia often present
- $D_{LCO}$ usually decreased
  - $D_{LCO}$ important to follow in scleroderma
- Mild to moderate reductions in lung volumes
- Prognostic implications unclear

$D_{LCO}=$ diffusing capacity of the lung for carbon monoxide.

McGoon M et al. Chest. 2004;126(1 Suppl):14S-34S.
The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004;25:2243-2278.
McLaughlin VV et al. Chest. 2004;126(1 Suppl):78S-92S.
Right Heart Catheterization

- Remains the “gold standard” for diagnosis of pulmonary hypertension
- Allows direct measurement of RAP, PAP, PCWP, and CO as well as calculations of CI and PVR
- Allows for determination of intracardiac shunts
- Allows for assessment of response to vasodilator challenge

RAP=right atrial pressure; PAP=pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; CO=cardiac output; CI=cardiac index; PVR=pulmonary vascular resistance.
Catheter Used in RHC

- 120 cm in length
- 1.5 cc balloon at tip
- Thermistor near tip
- 2 lumens at 19 and 30 cm
- Flushed with normal saline for pressure measurements
- Insertion requires meticulous sterile technique

- Inserted via:
  - Brachial vein
  - Right internal jugular vein
  - Left subclavian veins
  - Femoral veins

RHC=right heart catheterization.
Complications Associated With RHC

Overall associated with relatively low risk:
1.1% serious complication risk
Majority of complications from venous access

- Arterial puncture
- Pneumothorax/hemothorax
- Bleeding/hematoma
- Venous thrombosis
- Infection
- Pain
- Inability to gain access

- Pulmonary artery rupture
- Pulmonary infarction
- Ventricular tachycardia/heart block
- Perforation of atria or ventricle
- Pacemaker lead displacement

RHC=right heart catheterization.
Basic RHC Procedure

- Catheter advanced through:
  - Vena cava
  - Right atrium
  - Right ventricle
  - Pulmonary artery
  - PCWP position
- Fluoroscopic guidance
- Balloon inflated in central vein
- Measure cardiac output
- Measure oxygen saturation

## Hemodynamic Values at Rest

<table>
<thead>
<tr>
<th></th>
<th>Normal Hemodynamic Values at Rest</th>
<th>Diagnostic Criteria for PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAP</strong></td>
<td>1-5 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>RV</strong></td>
<td>15-30/1-7 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>PA</strong></td>
<td>15-30/4-12 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>mPAP</strong></td>
<td>9-19 mmHg</td>
<td>&gt;25 mmHg</td>
</tr>
<tr>
<td><strong>PCWP</strong></td>
<td>4-12 mmHg</td>
<td>≤15 mmHg</td>
</tr>
<tr>
<td><strong>CO</strong></td>
<td>4-7 L/min</td>
<td></td>
</tr>
<tr>
<td><strong>PVR</strong></td>
<td>&lt;3 Wood Units</td>
<td>&gt;3 Wood Units</td>
</tr>
</tbody>
</table>

RAP=right atrial pressure; RVP=right ventricular pressure; PAP=pulmonary arterial pressure; mPAP=mean pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; CO=cardiac output; PVR=pulmonary vascular resistance.


Waveform Progression: PA Catheterization

Normal ranges:
- Right atrium: (1–5 mmHg)
- Right ventricle
- Pulmonary artery
- Balloon inflation
- Wedge: (9-19 mmHg)
- (4-12 mmHg)

PA=pulmonary artery.
Group 1 PAH
Group 3 PH - hypoxia
Group 4 PH - CTEPH

Group 2 PH - left sided heart disease
Right PA Catheterized

Image courtesy of Harold Palevsky, MD.
PA=pulmonary artery.
Role of Vasodilator Testing

- Definition of vasodilator response:
  - Decrease in mean PAP by > 10 mmHg
  - Decrease of mean PAP to 40 mmHg or less
  - Cardiac output does not worsen
  - Prostanoids, inhaled NO, adenosine
  - Only 10% are positive responders
# PAH Determinants of Risk

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MW distance</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Very elevated</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiographic findings</td>
<td>Pericardial effusion, significant RV dysfunction</td>
</tr>
<tr>
<td>Normal/near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
</table>

**Note:**
- RV = right ventricular
- 6MW = 6-minute walk
- BNP = brain natriuretic peptide
- RAP = right atrial pressure
- CI = cardiac index
## Diagnosis: Summary

**Patient with suspected pulmonary hypertension (PH)**

- **Diagnostic evaluation to identify pulmonary arterial hypertension (PAH) patients**: Echocardiography (to evaluate cardiac causes of PH), PFT, V/Q scan, CT scan, invasive hemodynamic testing (careful cardiac catheterization), and laboratory testing (ANA, LFTs, HIV).

- **Vasoreactivity challenge for idiopathic, heritable, and anorexigen-induced PAH patients in functional class I, II, or III** to help determine which patients are more likely to be long-term responders to calcium-channel-blockers (CCBs).

- **Does IPAH patient have a positive response to acute pulmonary vasodilator testing?**
  - (Decrease in mean pulmonary arterial pressure [mPAP] to ≤40 mm Hg; Decrease in mPAP by ≥ 10 mm Hg; and Unchanged or increased cardiac output)
Collaborative Care

![Diagram showing collaborative care among primary care, EMS, rheumatology, rehabilitation programs, cardiology, pulmonary, local hospital, screening high risk populations, awareness and early diagnosis, diagnostic evaluation, and cardiac catheterization and vasodilator testing.]

Vallie V. McLaughlin, MD; Sanjiv J. Shah, MD; Rogerio Souza, MD; Marc Humbert, MD, PhD Am Coll Cardiol. 2015;65(18):1976-1997.
doi:10.1016/j.jacc.2015.03.540
PAH: Summary

- PAH is a rare and **progressive disease**, but prognosis improves with therapy.
- Suspicion of the disease given the patient’s risk factors, signs and symptoms is essential to improve outcomes.
- Symptoms are often non-specific; average 14 month - 2 yr delay from symptom onset until diagnosis.
- Evaluation must be methodical and include a **Right Heart Catherization** for diagnosis.
- The evaluation of PAH can be done **collaboratively** and is **crucial to the comprehensive care** of patients with PAH.