Pulmonary Hypertension in 2016

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Pulmonary Hypertension in 2016

- No disclosures
Pulmonary Hypertension in 2016

Learning objectives

- Identify patients at risk for development of pulmonary arterial hypertension (PAH)
- Recognize key signs and symptoms of PAH
- Utilize data obtained from echocardiography, right heart catheterization, and additional studies in the evaluation of a patient with possible pulmonary hypertension
- Understand important similarities and differences between PAH and other forms of pulmonary hypertension, particularly as related to treatment
Pulmonary Hypertension in 2016

- Pulmonary hypertension (PH) vs. pulmonary arterial hypertension (PAH)
- Pathophysiology of PAH
- Clinical manifestations and diagnosis
- Medical management
- Non-PAH pulmonary hypertension
Definitions

- Pulmonary hypertension (PH): Mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg
  - Without specification as to cause
  - V=IR (analogous to ΔP=Q x R)
  - In pulmonary circulation
    \[ mPAP - PAWP = CO \times PVR \]
    \[ mPAP = PAWP + CO \times PVR \]
  - Therefore, mPAP can be elevated in states of:
    - PAWP elevation (left sided heart failure)
    - CO elevation (hyperdynamic states, exercise)
    - PVR elevation
Definitions

- Precapillary pulmonary hypertension: PH due to elevation in PVR (high resistance state)
  - Large PA to capillary level
- Pulmonary arterial hypertension (PAH): precapillary PH fitting into WHO Group 1 classification
  - Prevalence estimates: ~15 per million adults
WHO Classification of PH

WHO Group 1: PAH
WHO Group 3: lung disease
WHO Group 1’: PVOD/PCH
WHO Group 2: left heart disease
WHO Group 4: chronic thromboembolism
WHO Group 5: unclear or variable mechanisms

**Table 1  Updated Classification of Pulmonary Hypertension**

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
WHO Group 1 PAH

- Idiopathic PAH (IPAH)
- Heritable PAH: BMPR2, others
- Drug/toxin related: anorectic agents, methamphetamines, others
- Connective tissue disease: scleroderma, MCTD
- Portopulmonary hypertension
- Congenital heart disease
- HIV
- Schistosomiasis
- (1’ PVOD/PCH)
- (1” Persistent pulmonary hypertension of the newborn)
WHO Groups 2-5

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Pathophysiology

- More than simple vasoconstriction
- Other processes
  - Endothelial dysfunction and intimal fibrosis
  - Vascular smooth muscle proliferation
  - Thrombosis
  - Inflammation
- Initiating and contributing insults
Figure 1: Proposed Multifactorial Factors Influencing Progression of Pulmonary Hypertension

In a suitable genetic background, the interplay of epigenetics and pathobiological injurious events may amplify the severity of the disease, often associated with more pronounced remodeling and worse clinical outcome.

Tuder et al.
Issues in the Pathology and Pathobiology of Pulmonary Hypertension
December 24, 2013:D4-12
Molecular predisposition:

- Altered BMPR signaling
- Mutations in other pathways involved in growth, proliferation, vasculogenesis, or apoptosis
Pathophysiology

Molecular predisposition:
- Altered BMPR signaling
- Mutations in other pathways involved in growth, proliferation, vasculogenesis, or apoptosis

Additional insults:
- Estrogens?
- Serotonergic drugs
- High flows and shear forces (CHD-PH)
- Portal hypertension/portosystemic shunting (PoPH)
- Inflammation (CTD-PH)
- Hemolysis/ROS
- Hypoxia
- HIV/other viruses
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Clinical manifestations

- **History**
  - Exertional dyspnea, lightheadedness, fatigue
  - Peripheral edema, weight gain
  - Later signs: angina, syncope

- **Exam**
  - Signs of PH: Loud P2, ejection murmur, TR or PI murmur, parasternal heave
  - Signs of RV failure: elevated JVD, edema, ascites, hepatomegaly
  - Signs pointing towards PAH etiology

- **Radiology/ECG**
  - “Incidental” finding on occasion
Diagnostic evaluation

- Diagnosis
- Etiology
- Severity
Diagnostic evaluation

- Diagnosis
  - Echocardiography
  - Right heart catheterization

- Etiology
- Severity
Echocardiography

- Estimate of pulmonary artery **systolic** pressure: relates to peak velocity of TR jet
  \[(4 \times TRV^2 + RAP)\]
- Right ventricular size and function
- Septal shift or LV impingement
- RA, PA dimensions
- Flow profiles through RVOT
- Pericardial effusion
Echocardiography
Echocardiography

- Estimate of pulmonary artery **systolic** pressure: relates to peak velocity of TR jet
  \[(4 \times TRV^2 + RAP)\]
- Right ventricular size and function
- Septal shift or LV impingement
- RA, PA dimensions
- Flow profiles through RVOT
- Pericardial effusion
- Overestimates and underestimates of PH
  - Patient 1: normal RV, PASP 28+RAP
  - Patient 2: dilated RV, PASP 53+RAP
Accuray of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension

Micah R. Fisher1*, Paul R. Forfia2†, Elzbieta Chamera2, Traci Houston-Harris1, Hunter C. Champion2, Reda E. Girgis1, Mary C. Corretti2, and Paul M. Hassoun1

TABLE 3. COMPARISON OF PH SEVERITY ACCORDING TO PASP DERIVED FROM RHC VS. PASP ESTIMATED BY DE*

<table>
<thead>
<tr>
<th>PASP Underestimates</th>
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<table>
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<th>RHC</th>
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Figure 1. Bland-Altman plot of Doppler echocardiographic estimates of pulmonary artery pressure and right-heart catheterization measurements. The bias was −0.6 mm Hg and the 95% limits of agreement were +38.8 and −40.0 mm Hg. Triangles represent excellent- and good-quality Doppler signal; circles = fair- and poor-quality Doppler signal; dotted line = bias; dash/dotted line = upper and lower limits of agreement. Abbreviations: DE = Doppler echocardiography; PASP = pulmonary artery systolic pressure; RHC = right-heart catheterization.
Right heart catheterization

- Necessary for PAH diagnosis.
- Very low morbidity and mortality
- Hemodynamic pattern:
  - $mPAP \geq 25$ mm Hg
  - $PAWP \leq 15$ mm Hg
  - $PVR \geq 240$ dyn-s/cm$^5$ (3 Wood Units)

Right heart catheterization

- Acute vasodilator testing
  - Agents: inhaled nitric oxide, IV epoprostenol, IV adenosine
  - Definition of response: decrease in mPAP by at least 10 mm Hg, to < 40 mm Hg, without decrease in cardiac output
  - Benefits of testing
    - Identification of good prognosis
    - Long term response to calcium channel blockade
    - Ensure no worsening in setting of pulmonary vasodilation
Diagnostic evaluation

- Diagnosis
- Etiology
- Severity
BMP-RI downregulation inhibits the BMP-signaling pathway that leads to antiproliferative and proapoptotic effects on PASMCs. Dysfunction of BMP signaling due to BMP-RII mutation and BMP-RII/...e.g., serotonin, endothelin, or leukotriene receptors] remains unclear. Routine screening for PAH in HIV is not...
Diagnostic evaluation

- Diagnosis
- Etiology
- Severity
  - Echo findings and RHC hemodynamics
  - WHO functional classification
  - Objective exercise capacity (6MWT, CPET)
### WHO/NYHA functional status

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

- Pretreatment era: median survival
  - Symptomatic PAH: 3 years
  - WHO functional class IV: 6 months

- Current data: [Image of survival graph]
Management

- Goals of medical therapy:
  - Produce pulmonary arteriolar vasodilation
  - Minimize vasodilation of systemic circulation
  - Maximize right ventricular performance
  - Serve anti-proliferative, anti-fibrotic, anti-inflammatory, or anti-thrombotic functions

- 13 approved therapies
  - Nitric oxide pathway (3 oral drugs)
  - Endothelin pathway (3 oral drugs)
  - Prostacyclin pathway (4 drugs - IV, SQ, inhaled, oral)
Management

- Nitric oxide pathway
  - Phosphodiesterase type 5 inhibitors (PDE-5Is)
    - Sildenafil and tadalafil
  - Soluble guanylate cyclase agonist
    - Riociguat

Management

- Endothelin pathway
  - Vasoconstrictor and smooth muscle mitogen
  - $ET_A$ (vasoconstriction) and $ET_B$ (mixed constriction and relaxation) receptors
  - Antagonists: bosentan, ambrisentan ($ET_A$), macitentan
Management

- Prostacyclin pathway
  - Epoprostenol (IV)
  - Iloprost (inh)
  - Treprostinil (IV, SQ, inh, oral)
  - Selixipag (oral): non-prostanoid prostacyclin receptor agonist
- **GRIPHON**: n=1156 with PAH
- Event driven; median treatment 71 weeks
- Primary outcome: time to first clinical worsening event
- Selexipag group: hazard ratio for primary outcome 0.60 (event in 27.0% treatment group, versus 41.6% in placebo group)
Management

- Calcium channel blockade
- Combination therapy
- Anticoagulation (?)
- Diuretics
- Oxygen
- Beta blockers (?)
- Primary anti-remodeling agents (investigational)
- Pulmonary rehabilitation
- Avoidance of pregnancy
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


Table 1. Components and Definitions of the Primary Endpoint

<table>
<thead>
<tr>
<th>Component</th>
<th>Definition</th>
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<tr>
<td>Death from any cause</td>
<td>Any death from any cause</td>
</tr>
<tr>
<td>Hospitalization for worsening pulmonary arterial hypertension</td>
<td>Any hospitalization for worsening pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Any decrease in functional class by at least one level</td>
</tr>
<tr>
<td>Unsatisfactory long-term clinical response</td>
<td>Any death or hospitalization for worsening pulmonary arterial hypertension</td>
</tr>
</tbody>
</table>

A Combination Therapy vs. Pooled Monotherapy

- Combination therapy
- Pooled monotherapy

Hazard ratio, 0.50 (95% CI, 0.35–0.72)
P<0.001

No. at Risk
- Combination therapy: 253, 229, 186, 145, 106, 71, 36, 4

Weeks
Pulmonary Hypertension in 2016

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- Pathophysiology of PAH
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PAH in internal medicine

- Overall prevalence of PAH low
- Delay in diagnosis common (median 13.6 months) (Badesch et al., Chest 2010)
- Higher risk groups within every subspecialty:
  - Cardiology and pulmonary medicine
  - Endocrinology: thyroid disorders
  - Gastroenterology: cirrhosis
  - Hematology: PE/DVT, hemolysis, MPD, chemo, obstructing tumor
  - Infectious disease: HIV, schistosomiasis, HHV8?
  - Nephrology: ESRD on HD
  - Rheumatology: SSc, SLE, MCTD, RA, sarcoid
  - Multiple: drug use, obesity, HHT, splenectomy, inborn errors of metabolism, POEMS
Non-PAH pulmonary hypertension

- More common than PAH
  - Left heart disease (Group 2)
  - Parenchymal lung disease (Group 3)
  - OSA/OHS (mixed Group 2/3)
  - Chronic thromboembolic pulmonary hypertension (Group 4)
WHO Group 2/3 PH

- PH in left heart or lung disease → increased mortality/morbidity
- For average patient, management with PAH-specific therapy not beneficial
- Is there misdiagnosis?
- Could there be two diagnoses?
- Severity of PH compared to severity of underlying disorder.
WHO Group 4 PH (CTEPH)

- Chronic thromboembolic pulmonary hypertension (CTEPH) – incidence up to 4% after acute PE
- Important to recognize
  - Implications for anticoagulation
  - Surgically curable form of precapillary PH
- Significant incidence of non-operable disease, or persistent/recurrent PH post-surgery (medical management)
Pulmonary thromboendarterectomy

- Treatment of choice for most with CTEPH
- Sternotomy, cardiopulmonary bypass, hypothermic cardiac arrest, arterial dissection
  - Mortality range 2-5%
  - Specialized centers only
Pulmonary arterial hypertension (PAH) is a rare condition, though prevalence is underestimated and delays in diagnosis are common.

Many symptoms of PAH are nonspecific, and exam signs subtle; a high index of suspicion is necessary.

While echocardiography is usually suggestive of PAH, right heart catheterization is necessary for diagnosis.
Summary

- There are currently 13 approved therapies for PAH, available in oral, inhaled, and IV/SQ administration.
- The prognosis of treated PAH has markedly improved in the modern treatment era, though progressive and uncontrolled symptoms still exist for many.
- PH ≠ PAH; PAH management should not be applied to most with non-PAH PH.
Questions?