Overview

- Background and definition
- Clinical Classification
- Diagnosis
- Treatment options—medical and surgical
Background

- Much progress has been made over the last decade
- Increased awareness
- More research about the mechanisms of disease
- More treatment options
- Center Accreditation
- Celebrity Spokesperson
Consensus Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Pulmonary Arterial Hypertension (PAH)</td>
</tr>
<tr>
<td>Group 2</td>
<td>Pulmonary Hypertension Due To Left Heart Disease</td>
</tr>
<tr>
<td>Group 3</td>
<td>Pulmonary Hypertension Due to Lung Diseases &amp;/or Hypoxia</td>
</tr>
<tr>
<td>Group 4</td>
<td>Chronic Thromboembolic PH (CTEPH)</td>
</tr>
<tr>
<td>Group 5</td>
<td>PH with unclear multifactorial mechanisms</td>
</tr>
</tbody>
</table>


PH WHO Groups IV and V

IV. Chronic Thromboembolic PH (CTEPH)

V. Other Disorders
- Hematologic disorders
  - chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- Systemic disorders
  - sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- Metabolic disorders
  - glycogen storage disease, Gaucher disease, thyroid disorders
- Others
  - luminal obstruction, fibrosing mediastinitis, chronic renal failure

*excluding pediatric PH types


Sample from Group 4 Pt S/P Pulmonary Thromboendarterectomy

Chronic pulmonary thromboembolism. Chronic thromboembolism removed by thromboendarterectomy. Note the chronic, fibrotic appearing with obstruction into multiple lobar and segmental branches. Courtesy of Harold F. Patella, MD.
World Health Organization Group 3
Pulmonary Hypertension

- Pulmonary Hypertension Associated with Respiratory Disorders and/or Hypoxemia
  - COPD
  - Interstitial Lung Disease
  - Sleep Disordered Breathing
  - Alveolar Hypoventilation Disorders
  - Chronic Exposure to High Altitude
  - Neonatal Lung Disease
  - Alveolar-Capillary Dysplasia


World Health Organization Group 2
Pulmonary Hypertension

- Pulmonary Venous Hypertension
  - Systolic Dysfunction
  - Diastolic Dysfunction
  - Left-Sided Valvular Heart Disease
  - Wedge/LVEDP is elevated


What is WHO Group 1 PAH?

- Pathophysiological condition
  - Imbalance of vasodilation and vasoconstriction
  - Smooth muscle proliferation
  - Thrombosis in the arteries

- Hemodynamic definition
  - Right heart catheterization required to make a PAH diagnosis
  - mPAP ≥25 mm Hg
  - PAWP / LVEDP ≤15 mm Hg
  - PVR >3 Wood units
WHO Group 1 PAH Stats

- No large epidemiological studies
- Registries in US and Europe estimate
  - Incidence of 1-5 per million (IPAH)
  - Prevalence of 10-15 per million (PAH Group 1)
  - Mean age of 38-50, but any age can be affected
- Female 4:1 predominance
- At the time of diagnostic RHC, 75% of pts were FC III-IV
- Symptom onset to RHC:
  - >50% of pts had sx for >1yr
  - 20% > 2yrs


PH WHO Group I
Pulmonary Arterial Hypertension

- Idiopathic PAH
- Heritable PAH
  - BMP\(\text{R2}\)
  - ALK-1, ENG, SMAD9, CAV1, KCNK3
- Drug and toxin induced

Associated with:
- Connective tissue disease
- HIV infection
- Portal hypertension
- Congenital heart diseases
- Schistosomiasis

*excluding pediatric PH


Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

- aerodrines
- Declude
- D-methylphenidate
- Dextroamphetamine
- Erythromycin
- Metoprolol
- Verapamil
- Selective serotonin reuptake inhibitors

- Amphetamines
- Deserital
- L-tryptophan
- Mephentermamine

- Caffeine
- Phenylpropanolamine
- St John's Wort
- Antidepressant/tranquilizers
- Interferon (a and b)
- Some chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide)

- Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
- Antihistamines are possible causes of pulmonary veno-occlusive disease.
REVEAL: Prevalence of PAH Subtypes


N=2525

Group 1 Pulmonary Hypertension Associated with the Scleroderma Spectrum of Disease (PAH/SSD)

- Approximately 35% of SSD pts will develop PAH
- Also associated with SLE, rheumatoid arthritis, and other connective tx disease
- Mostly female population
- Process similar to that of PPH
- PAH/SSD has worse prognosis compared to PPH pts

We know that Group 1 PAH stems from

Overzealous Growth and Pulmonary Vasoconstriction
Normal Lung Specimen

Group 1 Pathology—Overzealous Growth
- Neomuscularization of arterioles
- Medial hypertrophy
- Concentric laminar intimal fibrosis
- Lumen obliteration and vessel resorption
- “Plexiform lesions”

Therapy Targets of PAH

Plexiform lesion in Group 1 PAH from Overzealous Growth


Group 1 Pathology—Vasoconstriction

- Insufficient Nitric Oxide
- Insufficient Prostacyclin
- Too much Endothelin

Endothelin Has Detrimental Effects in Group 1

- Vasoconstriction
- Inflammation
- Fibrosis
- Neurohormonal secretion
- Cell proliferation

Acute Effects

Chronic Effects
Rationale for ET blockade in Group 1 pts

- High Endothelin-1 levels in PAH
- ET-1 induces vasoconstriction and SMC hypertrophy
- High expression of ETA and ETB receptors in the Plexiform lesions

Expression of Endothelin in the Lungs of Patients With Pulmonary Hypertension

Updated Strategy

What kind of PH is present?
Treat early and in combination
Oral and inhaled prostanoids lend to earlier start
Shift away from routine anticoagulation.

Natural History of Group 1 PAH

- Gradual onset
- DOE
- Decreased exercise tolerance
- Progressive deterioration
- Progressive Right heart remodeling
-Decline in RV function
- Ascites, edema, hypotension, syncope
- Symptoms at rest
- Death
Survival of PAH Patients in Current Era: Comparison with Historical Controls

N = 276, IPAH and FPAH patients diagnosed from 1982-2006; matched for disease variables at baseline with historical controls.


What kind of PH is present?
Diagnosis of Group 1 PAH

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical</td>
<td>Evaluate signs and symptoms, family history, associated diseases, serologies and consider sleep study</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Assess for RV enlargement, peripheral hypovascularity (pruning), and prominent pulmonary arteries</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Assess for RV and RA enlargement, RV dysfunction, TR velocity to measure RVSP</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Evaluate for right heart enlargement and strain, cardiac rhythm</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>Evaluate for CHD, measure wedge pressure or LVEDP, establish severity and prognosis, test vasodilator therapy</td>
</tr>
<tr>
<td>PFTs with DLCO</td>
<td>Assess obstructive and restrictive airway disease</td>
</tr>
<tr>
<td>VQ scan</td>
<td>Rule out thromboembolic disease</td>
</tr>
</tbody>
</table>


How high is patient's risk?

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lower risk</th>
<th>Higher risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>II, III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;400 m</td>
<td>&lt;300 m</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO2 &gt;10.4 mL/kg/min</td>
<td>Peak VO2 &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;10 mm Hg</td>
<td>RAP &gt;20 mm Hg</td>
</tr>
<tr>
<td></td>
<td>CI &gt;2.5 L/min/m²</td>
<td>CI &lt;2.0 L/min/m²</td>
</tr>
<tr>
<td>BNP</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

Echocardiogram

Importance of Right Heart Catheterization
- Vast majority of PH cases are non-Group 1
- **PAH** Group 1 characterized by
  - ↑ PVR
  - ↑ TPG
  - Normal left-sided filling pressures
  - Evaluate vasoreactivity
- **PVH** Group 2 characterized by
  - ↑ PCWP
  - ↑ LVEDP
  - ↑ LAP

Functional Classification: Assessment of PH Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of usual activities</td>
</tr>
<tr>
<td>II</td>
<td>Mild limitation of usual activities</td>
</tr>
<tr>
<td></td>
<td>No discomfort at rest</td>
</tr>
<tr>
<td></td>
<td>Normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>No discomfort at rest</td>
</tr>
<tr>
<td></td>
<td>Less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope</td>
</tr>
<tr>
<td>IV</td>
<td>Patient unable to perform any physical activity at rest and may have signs of right ventricular failure</td>
</tr>
<tr>
<td></td>
<td>Dyspnea and/or fatigue and/or syncope/near-syncope may be present at rest, and symptoms are increased by almost any physical activity</td>
</tr>
</tbody>
</table>

Management of Group 1 PAH: Goals of Therapy
- Reverse pulmonary hypertension
  - Lower pulmonary arterial pressure
  - Inhibit vasoproliferative process
- Treat/prevent RV failure
- Prevent pregnancy

Treat/prevent RV Failure
Volume Overload
- Diuretics
- Fluid and sodium restrictions
RRV systolic dysfunction
- Digoxin
  - May increase contractility
  - May reduce sympathetic activation
- Continuous IV inotropes

ABNORMALITIES
- Nitric oxide deficiency
- Prostacyclin deficiency
- Endothelin excess

THERAPIES
- PDE-5 inhibitors and guanylate cyclase stimulators
  - Restoring vasodilation through an increase in cGMP
- Prostacyclin
  - Supplemeting the deficiency in PGI2, resulting in vasodilation and inhibition of platelet aggregation
- ERAs
  - Block the binding of ET-1 to its receptors, preventing vasoconstrictor effects of ET-1

Prostacyclin analogues and Novel Delivery Systems for Group 1 PAH

- IV: Epoprostenol or Treprostinil
- SQ: Treprostinil
- Inhaled: Iloprost or Tyvaso
- Oral formulations: Orenitram and Selexipag. Beraprost is being studied

Group 1 Pt on Remodulin SQ

Group 1 Pt Using Inhaled Therapy
Group 1 Pt Using Inhaled Therapy

PAH-specific Therapies Approved for Use in the US

<table>
<thead>
<tr>
<th>Endothelin Receptor Antagonists</th>
<th>Soluble Guanylate Cyclase (sGC) Stimulator</th>
<th>Phosphodiesterase type 5 Inhibitors</th>
<th>Prostanoids – Prostacyclin Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan (PO)</td>
<td>Riociguat (PO)</td>
<td>Sildenafil (PO)</td>
<td>Epoprostenol (IV) RTS*</td>
</tr>
<tr>
<td>Bosentan (PO)</td>
<td>Tadalafil (PO)</td>
<td></td>
<td>Iloprost (inhaled)</td>
</tr>
<tr>
<td>Macitentan (PO)</td>
<td></td>
<td></td>
<td>Treprostinil (IV, SC, inhaled and PO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Selexipag PO</td>
</tr>
</tbody>
</table>

*RTS: Room temperature stable.

Prognostic Factors for Risk of PAH Disease Progression

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Lower Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO Class</td>
<td>II, III</td>
<td>IV</td>
</tr>
<tr>
<td>6-minute walk distance</td>
<td>&gt;350 m</td>
<td>&lt;350 m</td>
</tr>
<tr>
<td>Brain natriuretic peptide</td>
<td>&lt;180 pg/mL</td>
<td>&gt;180 pg/mL</td>
</tr>
<tr>
<td>Echo findings</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion; significant RV dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Normal/near normal RAP and CI</td>
<td>High RAP, Low CI</td>
</tr>
</tbody>
</table>

Kaplan-Meier estimates of survival at 36 months for IPAH patients.


Kaplan-Meier estimates of survival at 36 months for SSc-PAH patients.


Evidence based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only)


| Measure/| Combination therapy for patients not meeting goals on monotherapy. Nazzareno Galiè et al. Eur Heart J 2016;37:67-119

<table>
<thead>
<tr>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine + beta-blocker</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Other DRA + PDE-5</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Renin-angiotensin + aldosterone</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renin-angiotensin inhibitors</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other DRA + PDE-5</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Other ERA or PDE-5 inhibitors</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

Right Heart Failure

- Symptom monitoring
- Home surveillance
  - Daily weights
    - Call with change in weight
  - Assess for precipitating factors for fluid retention
- Education and Adherence
  - Diet
    - 2-3 grams/day sodium
    - 2 liters/day fluid
  - Medications
    - Tweak diuretics and potassium
    - Maintain K+ at 4.0 mEq/L
- Add PAH treatments
Longitudinal Evaluation of Group 1 PAH Patient
ACCF/AHA 2009 Expert Consensus

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Stable: no increase in symptoms or decompensation; no evidence of RV failure; FC I or II; 6MWD &gt;400 m; RAP and CI normal</th>
<th>Unstable, increase in symptoms or decompensation; signs of right heart failure; FC IV; 6MWD &lt;300 m; RAP high and CI low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of evaluation</td>
<td>Every 3-6 months</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>FC assessment</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>6MWT</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Q12 months or center dependent</td>
<td>Q6-12 months or center dependent</td>
</tr>
<tr>
<td>BNP</td>
<td>Center dependent</td>
<td>Center dependent</td>
</tr>
<tr>
<td>RHC</td>
<td>Clinical deterioration and center dependent</td>
<td>Q6-12 months or clinical deterioration</td>
</tr>
</tbody>
</table>

Collaboration

Local Care

- Diagnostic dilemmas
- Diagnostic cath/vasodilator trial
- Complex comorbidities
- Failure to achieve Rx goals
- Considering prostanoids
- Considering combination Rx
- Clinical trials

PH Center

Take Home Messages

- Much progress has been made over the last decade
- Increased awareness
- More research about the mechanisms of disease
- More treatment options
- Better survival
U of Iowa: PH Team

- Linda Cadaret, MD
- Alicia Gerke, MD, MBA
- Traci Stewart, RN, MSN
  - traci-stewart@uiowa.edu
- Anne Lovig, RN, BSN
- Page Scovell, RN, BSN
- Cyndi Larew, RN, BSN

PH Program
- Phone: 319-356-1028
- Fax: 319-356-7087