Pulmonary Arterial Hypertension: Review and Updates

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Today...
• Nomenclature review - classification
• Diagnosis
• Prognosis
• Treatment

Is it Primary vs Secondary Pulmonary Hypertension?

No!!
Dated Nomenclature
### Is it Pulmonary Arterial Hypertension (PAH) or Non-PAH?

<table>
<thead>
<tr>
<th>The 2003 Venice Classification of Non-PAH Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pulmonary hypertension (PH) with left heart disease – WHO Class 2</td>
</tr>
<tr>
<td>✔ Trigger: High LA Pressure</td>
</tr>
<tr>
<td>- PH with lung disease/hypoxemia - WHO Class 3</td>
</tr>
<tr>
<td>✔ Trigger: Hypoxemia and Parenchyma Distortion</td>
</tr>
<tr>
<td>- PH due to chronic thrombotic and/or embolic disease – WHO Class 4</td>
</tr>
<tr>
<td>✔ Trigger: Obstruction</td>
</tr>
</tbody>
</table>

### Pulmonary Hypertension Is a Disease of Triggers

<table>
<thead>
<tr>
<th>The 2003 Venice Classification of PAH - WHO Class 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td>✔ Familial PAH (FPAH)</td>
</tr>
<tr>
<td>✔ Idiopathic PAH (IPA)</td>
</tr>
<tr>
<td>✔ Associated PAH (APA)</td>
</tr>
<tr>
<td>• Connective tissue disease (CTD)</td>
</tr>
<tr>
<td>• Human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>• Portal hypertension</td>
</tr>
<tr>
<td>• Anorexigens</td>
</tr>
<tr>
<td>• Congenital heart disease (CHD)</td>
</tr>
<tr>
<td>✔ Persistent pulmonary hypertension of the newborn (PPHN)</td>
</tr>
<tr>
<td>✔ PAH with venule/capillary involvement</td>
</tr>
</tbody>
</table>

{Trigger: Mutation/Polymorphism} {Trigger: Permissive Phenotype}
### Importance of Classification: Why do it?

- Efficacy: What's the trigger? Can you change it?
- Safety: Can it hurt the patient?
- Cost: How much are we spending for limited efficacy and small changes in QOL?

### Safety: Can it hurt the patient?

- LV dysfunction: Pulmonary edema
- ILD/COPD: Worsen V/Q mismatch
- CTEPH: Delay referral for thromboendarterectomy

## Efficacy: What’s the trigger? Can you change it?

<table>
<thead>
<tr>
<th>Image 1</th>
<th>Image 2</th>
<th>Image 3</th>
</tr>
</thead>
</table>

## Cost: How much are we spending for limited efficacy and small changes in QOL?

- Bosentan: ~35-40k per year
- Sildenafil: ~12-15k per year
- Inhaled Iloprost: ~60k per year
- IV Prostacyclins: ~60-120k per year
Pulmonary Arterial Hypertension

- Classification
- Diagnosis
- Prognosis
- Treatment

Diagnosis PAH = RHC

Schema for Patient Evaluation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
<td>Left heart disease (valvular, HF, CAD)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary HTN</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Emphysema</td>
</tr>
<tr>
<td>PFTs +/- Chest CT</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Sleep study</td>
<td>Obstructive Sleep apnea</td>
</tr>
<tr>
<td>VQ scan, angiogram</td>
<td>Chronic thromboembolic disease</td>
</tr>
<tr>
<td>Serologies</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>CTD: scleroderma, SLE, RA, MCTD</td>
</tr>
<tr>
<td>LFTs</td>
<td>Portopulmonary Hypertension</td>
</tr>
<tr>
<td>Eval cirrhosis and Portal HTN</td>
<td></td>
</tr>
<tr>
<td>RHC</td>
<td>Required for diagnosis of PAH</td>
</tr>
<tr>
<td></td>
<td>Vasodilator study</td>
</tr>
</tbody>
</table>

Cardiac Catheterization to Assess Severity and Prognosis of PAH

- To measure wedge pressure or LVEDP
- Scrutinize wedge tracings!!!!
- Wedge sat; End expiration
- To exclude or evaluate CHD
- To establish severity and prognosis
- To test vasodilator therapy

Catheterization is required for every patient with suspected pulmonary HTN
Pulmonary Arterial Hypertension

- Mean Pulmonary artery ≥ 25 mmHg
- Wedge pressure ≤ 15 mmHg
- PVR > 3 Woods units

Pulmonary Arterial Hypertension

- Classification
- Diagnosis
- Prognosis
- Treatment

Natural History of PAH: NIH Registry¹,²

Predicted survival according to the NIH equation. Predicted survival rates were 66%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 221, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively.

*Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.

Survival by PAH Etiology

CHD = congenital heart disease; CVD = collagen vascular disease; HIV = human Immunodeficiency virus; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; PoPH = portopulmonary hypertension. McLaughlin et al. Chest. 2004;126:78S-92S.
**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>NYHA 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>Pencardial effusion, significant RV dysfunction</td>
</tr>
<tr>
<td>Normal/linear normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
</table>


**Correlation of Six-minute-walk Test and WHO Functional Class**

![Graph showing correlation between 6MWT and WHO Functional Class](image)

*p<0.05 vs control subjects
†p<0.05 vs WHO functional class II
‡p<0.05 vs WHO functional class III


**Impact of Functional Class on Survival**

![Graph showing survival by functional class](image)

p=0.0001 by log-rank test


**Plasma BNP as a Prognostic Indicator of Mortality in Patients With PPH**

![Graph showing baseline and follow-up BNP](image)

Baseline BNP

Follow-up BNP

p=0.0001

By multivariate analysis, higher BNP at baseline (HR=11.971, p=0.0348) and at follow-up (RR=25.880, p=0.0243) were independent predictors of mortality

Predicting Survival and Following Therapy

- Clinical parameters
  - functional class
  - exercise capacity
  - neurohormones
- Hemodynamics
- Imaging
  - right ventricle: function and size
  - pulmonary artery remodeling (future)

Schematic Progression of PAH

PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.
Courtesy of: Vallerie V. McLaughlin, MD.
Goals of Therapy

- Improve symptoms
  - 6-minute walk (>380 m)
  - functional class (I or II)
  - CPET (VO₂ max >10.4)
  - quality of life
- Improve hemodynamics
- Improve survival

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PAH Treatments - a Historical Overview

- CCB, anticoagulation, digitalis, diuretics
- Epoprostenol
- Bosentan
- Sildenafil
- SC treprostinil
- IV treprostinil
- Ambrisentan

CCB = calcium channel blocker.

When to use a Calcium Antagonist?

 Survival in IPAH
Long-term CCB Responders

- Long-term CCB responders
- Long-term CCB failure


When to use a Calcium Antagonist?

- Basic therapy: Oral anticoagulants, Diuretics, O₂, Digoxin...
- Vasodilator study:
  - Positive
    - Oral CCB
    - Sustained Response
      - Yes
        - Continue CCB
      - No
        - No CCB +++
  - Negative
    - No CCB +++
PAH

Basic therapy
Oral anticoagulants, Diuretics, O₂, Digoxin ...

Vasodilator study

Positive

Oral CCB

Sustained Response

Yes

Close monitoring of long-term clinical and hemodynamic effects

No CCB +++

Fall in mPAP > 10 mmHg + mPAP < 40 mmHg + Normal CO

Continue CCB

Positive

Vasodilator study

Negative

Other Medications?

Vascular Pathology: Balance of Powers

ET-1
Serotonin
Thromboxane A2
TGF-B
Angiopoietin 1/TE2

ADVERSE REMODELING of Vascular Tree

NO Synthase
Prostacyclin
Type-1 activity

Vasodilators
Antiproliferatives
Anticoagulants

Vasoconstrictors
Growth Factors
Procoagulants

NO Synthase
Prostacyclin
Type-1 activity

Vasodilators
Antiproliferatives
Anticoagulants

Vasoconstrictors
Growth Factors
Procoagulants

Other Medications?
What is the Optimal Treatment Strategy?

**Anticoagulate ± Diuretics ± Oxygen ± Digoxin**

**Vasodilator Study**

- **Lower Risk**
  - Oral CCB
  - Sustained Response
  - Continue CCB

- **Higher Risk**
  - No Sustained Response
  - Reassess – consider combo-therapy
  - Investigational Protocols
  - Atrial septostomy
  - Lung Transplant

**EARLY trial: Bosentan in NYHA class II**

- **Bosentan (n=85)**
- **Flaclofen (n=91)**

**McLaughlin VV and McGoon M. Circulation. 2006;114:1417-1431.**

**Rx of Heart Failure**

- **Stage A**: High risk with no symptoms
- **Stage B**: Structural disease, no symptoms
- **Stage C**: Structural disease, previous or current symptoms
- **Stage D**: Refractory symptoms requiring special intervention

Risk factor reduction, patient and family education
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
- ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
- ACE inhibitors and beta-blockers in all patients
- Dietary sodium restriction, diuretics, and digoxin
- Cardiac resynchronization if bundle-branch block present
- Inotropes, atrial septostomy
- Transplantation, VAD, transplantation
- Hospice

**Rx of Pulmonary Hypertension**

- **Stage A**: High risk with no symptoms
- **Stage B**: PAH with + VDC
- **Stage C**: PAH with - VDC

Risk factor reduction, patient and family education
- Calcium Channel Blockers
- Bosentan +/- Sildenafil +/- Ventavis
- Dietary sodium restriction, diuretics
- Aldactone and digoxin
- IV meds (Flolan or Trepostonil)
- Consider multidisciplinary team
- Inotropes, atrial septostomy
- Transplantation
- Hospice

**Goal-Oriented Therapy**

Diagnosis of PAH: Vasoreactivity test negative
NYHA II or IV

Baseline examination and 3-mo-Flexworth evaluation to assess treatment goals
- [6MWD > 380 m, peak VO2 > 10 mL/min/kg, peak systolic BP > 120 mm Hg during exercise]

Treatment goals not met
- First-line treatment bosentan
- Treatment continued
- Addition of sildenafil
- Treatment continued
- Addition of inhaled iloprost
- Treatment continued
- Transition from inhaled to intravenous iloprost
- Treatment continued
- Highly urgent lung transplantation

Early, Risk-based and Combination Therapy: Changing Paradigms for PAH?
Summary: Treatment

- Traditional therapies; diuretics, oxygen, phlebotomy still used as indicated; anticoagulants recommended
- Calcium Channel Blockers should be used in Class II or III acute responders but followed closely for safety & efficacy
- Newer agents are tailored to WHO class – ACCP Guidelines
  - Class IV – Infused prostacyclins
  - Class III – Oral endothelin receptor antagonists (ERAs), phosphodiesterase (PDE) 5 inhibitors, infused or inhaled prostacyclins
  - Class II – PDE 5 inhibitors, or ERAs
    - Consider therapy if evidence of Right Ventricular Dysfunction
- Combination therapies and an array of investigational therapies hold hope for the future
- Role of transplantation/septostomy now diminished because of new effective pharmacologic therapies

Indications for Referral to a Specialized Center for Rx of PAH

- Unexplained dyspnea on exertion with evidence of PH on Echo
- Evidence of moderate to sever PH
  - Estimate PAS pressure > 45 mm Hg on Echo
  - Symptoms consistent with NYHA functional class II or worse
  - Near-syncope or syncope
- Absence of substantial left sided cardiac disease or parenchymal lung disease
- Clinical or echocardiographic evidence of RV dysfunction
  - Lower-extremity edema
  - Ascites
  - Right ventricular enlargement or systolic dysfunction on echocardiography