A Practical Approach to Pulmonary Hypertension

Brittany Palmer, M.D.
Outline

- PH definition and classification
- Pathogenesis
- Patient assessment
- Making the diagnosis
- Therapeutic options and efficacy
- Summary
Pulmonary Arterial Hypertension:

**Definition**

- Mean PA pressure > 25 mmHg with PCW <15 mmHg
  - *(NIH Registry on PPH, 1987)*
- PVR ≥ 3 Units

\[ \text{PVR} = \frac{\text{TPG}}{\text{CO}} \]

\[ \text{TPG} = \text{PAM} - \text{PCW} \]

- Exercise mean PA pressure > 30-35 mmHg
Clinical classification of pulmonary hypertension (Nice 2013)

1. Pulmonary arterial hypertension
   - Idiopathic PAH
   - Heritable PAH (BMPR2, ALK1)
   - Drug and Toxin induced
   - Associated with:
     • Connective tissue disease
     • Congenital heart disease
     • Portal hypertension
     • HIV infection
     • Schistosomiasis

2. PH with left heart disease
   - Systolic or diastolic dysfunction
   - Valvular
   - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

1’. PVOD/PCH

Clinical classification of pulmonary hypertension (Nice 2013)

3. PH with lung diseases/hypoxemia
   - COPD
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Developmental abnormalities
   - Mixed restrictive/obstructive
   - Alveolar hypoventilation

4. PH due to chronic thrombotic and/or embolic disease
   - CTEPH

5. Miscellaneous
   Pulmonary hypertension with unclear multifactorial mechanisms
   Hematologic disorders: myeloproliferative disorders, splenectomy, chronic hemolytic anemia
   Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Pathogenesis of Pulmonary Arterial Hypertension

Gaine, JAMA 2000;284:3164
A Disease of Decline & Deterioration
IPAH Survival

Adapted from: McLaughlin et al. *CHEST*; 126: 78S-91S
Assessment of PAH: 
\textit{Signs and Symptoms}

\begin{itemize}
\item Initial signs and symptoms
  \begin{itemize}
  \item Dyspnea
  \item Syncope
  \item Dizziness
  \item Fatigue
  \item Edema
  \item Angina
  \end{itemize}
\item Non-specific nature of complaint can lead to:
  \begin{itemize}
  \item Confusion with other conditions
  \item Delayed diagnosis
  \end{itemize}
\end{itemize}
Assessment of PAH: *Physical Exam*

**Presence of PH**
- Loud P2
- RV lift
- Systolic murmur (TR)
- Diastolic murmur (PR)
- RV S4

**Presence of RV Failure**
- JVD with V wave
- RV S3
- Hepatomegaly
- Edema
- Ascites
Assessment of PAH: 

**CXR**

- Prominent Hilar Pulmonary Arteries
- Peripheral Hypovascularity (Pruning)
- RV Enlargement into Retrosternal Clear Space
- Prominent Hilar Pulmonary Arteries
Assessment of PAH: 

EKG

PAH: Making the Diagnosis

Is There A Reason to Suspect PAH?
Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

No Further Evaluation

Is PH Likely?
ECHO

TR Velocity to Measure RVSP, RVE, RAE, RV Dysfunction

Is PH Due to LH Disease?
ECHO

Echocardiogram: Parasternal Long Axis

Image courtesy of Vallerie McLaughlin, MD
Echocardiogram:
Parasternal Short Axis

Image courtesy of Vallerie McLaughlin, MD
Echocardiogram:
Apical Four Chamber

Image courtesy of Vallerie McLaughlin, MD
Echocardiogram: Tricuspid Regurgitation

Modified Bernoulli’s Equation:
\[ 4 \times (V)^2 + RAP = RVSP \text{ (PASP)} \]

\( V \)= tricuspid jet velocity (m/s); \( RAP \)= right atrial pressure; \( RVSP \)= right ventricular systolic pressure; \( PASP \)= pulmonary artery systolic pressure.

Image courtesy of Vallerie McLaughlin, MD
PAH: Making the Diagnosis

Is There A Reason to Suspect PAH?
Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG

No Further Evaluation

Is PH Likely?
ECHO

No

Is PH Due to LH Disease?
ECHO

Yes

Yes: Dx LV Systolic, Diastolic Dysfunction; Valvular Disease: 
Appropriate Treatment

No

Is PH Due to CHD?
ECHO With Bubble Study

Yes

Yes: Dx Abnormal Morphology; Shunt: Surgery, Medical Treatment of PAH or Further Evaluation for Other Contributing Causes

No

Is PH Due to CTD, HIV?
Serologies

Yes

Yes: Dx Scleroderma, SLE, HIV Infection: Medical Treatment of PAH and Further Evaluation for Other Contributing Causes

No

Is Chronic PH Suspected?
VQ Scan

Rationale

TR Velocity to Measure RVSP, RVE, RAE, RV Dysfunction

Contrast-Enhanced CT
Is Chronic PE Confirmed and Operable?
What are precise pulmonary hemodynamics?
RHC

Is PH Due to Lung Disease?
PFTs, Arterial Saturation

What Limitations Are Caused by the PH?
Functional Class; 6-minute Walk Distance Test (6MWD)

Document PA pressure, PCWP (LV or LA pressure if PCWP unobtainable or uncertain), transpulmonary gradient, CO, PVR, MVO2, response to vasodilators:
Confirm PAH, or IPAH if no other cause identified

Dx Parenchymal Lung Disease, Hypoxemia, or Sleep Disorder: Medical Treatment, Oxygen, Positive Pressure Breathing As Appropriate, and Further Evaluation for Other Contributing Causes

Document Exercise Capacity Regardless of Cause of PH:
Establish Baseline, Prognosis and Document Progression/response to Treatment With Serial Reassessments

Yes

No

PAH Definition on RHC

- Increased mean pulmonary arterial pressure (mPAP)
  - >25 mm Hg at rest or >30 mm Hg during exercise
- Pulmonary vascular resistance (PVR): >3 WU
- Normal PCWP (<15 mm Hg)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics</th>
<th>Clinical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>Mean PAP ≥25 mm Hg</td>
<td>• Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>PWP ≤15 mm Hg</td>
<td>• PH due to lung disease</td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced</td>
<td>• CTEPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PH with unclear or multifactorial mechanisms</td>
</tr>
<tr>
<td>Post-capillary PH</td>
<td>Mean PAP ≥25 mm Hg</td>
<td>• PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td>PWP &gt;15 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO normal or reduced</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive = TPG ≤12 mm Hg</td>
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<tr>
<td></td>
<td>Reactive = TPG &gt;12 mm Hg</td>
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</table>

Progression of PAH

Pre-symptomatic/Compensated

Symptomatic/Decompensating

Declining/Decompensated

Time

CO

Symptom Threshold

PAP

PVR

Right Heart Dysfunction
# Therapeutic Options for PAH

<table>
<thead>
<tr>
<th>Traditional Rxs</th>
<th>FDA Approved for PAH</th>
<th>Investigational Rxs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supplemental $O_2$</td>
<td>• Prostanoids</td>
<td>• Prostanoids</td>
</tr>
<tr>
<td>• Diuretics</td>
<td>– Epoprostenol (iv)</td>
<td>– Oral Treprostinil</td>
</tr>
<tr>
<td>• Oral vasodilators</td>
<td>– Treprostinil (iv, sq, inh)</td>
<td>– ERAs</td>
</tr>
<tr>
<td>– (CCB)</td>
<td>– Iloprost (inhaled)</td>
<td>– Sitaxsentan</td>
</tr>
<tr>
<td>• Anticoagulants</td>
<td>• ERAs</td>
<td></td>
</tr>
<tr>
<td>– warfarin</td>
<td>– Bosentan</td>
<td>• Other</td>
</tr>
<tr>
<td>• Inotropic agents</td>
<td>– Ambrisentan</td>
<td>- TKIs</td>
</tr>
<tr>
<td>– Digitalis</td>
<td>– Macitentan</td>
<td>- sGC stimulator</td>
</tr>
<tr>
<td></td>
<td>• PDE-5 Inhibitors</td>
<td>- Prostacyclin receptor agonist</td>
</tr>
<tr>
<td></td>
<td>– Sildenafil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Tadalafil</td>
<td></td>
</tr>
</tbody>
</table>
# 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</td>
</tr>
<tr>
<td>Normal/near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, low CI</td>
</tr>
</tbody>
</table>

McLaughlin and McGoon. Circulation 2006;114:1417-31
ADULT LUNG TRANSPLANTATION

Survival comparisons
COPD vs. IPF: p < 0.0001
Alpha-1 vs. CF: p = 0.0248
Alpha-1 vs. IPF: p < 0.0001
Alpha-1 vs. PPH: p = 0.0021
CF vs. COPD: p = 0.0006
CF vs. IPF: p < 0.0001
CF vs. PPH: p < 0.0001
CF vs. Sarcoidosis: p = 0.0007

J Heart Lung Transplant 2005;24: 945-982
Key Concept Summary

• Differential Diagnosis
  – Beware of the atypical patient
  – Process of Diagnosis of Exclusion
  – CTEPH - “curable”
  – Associated “risk factors”

• Treatment
  – Prostanoids
  – Endothelin Receptor Antagonism
  – Phosphodiesterase Inhibitors
  – Riociguat
  – Anticoagulation
  – RV Failure
  – Transplant
Thank you
Hemodynamic Profiles In PAH: LV dysfunction – “passive” PH

C.O. 4 L/min
TPG = 7
PVR = 1.75
Hemodynamic Profiles In PAH: LV dysfunction – after Rx

C.O. 5 L/min
TPG = 6
PVR = 1.2
Hemodynamic Profiles In PAH:  
*IPAH - compensated*

C.O. 5 L/min  
TPG = 40  
PVR = 8
What is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin → Acute Vasoreactivity Testing

Positive

Oral CCB

Sustained Response

No

Class II-III

ERAs or PDE-5 Is (oral)
Epoprostanol or Treprostinil (IV)
Iloprost (inhaled)
Treprostinil (SC)

Reassess – consider combo-therapy

Investigational Protocols

Class III-IV

Epoprostenol or Treprostinil (IV)
Iloprost (inhaled)
ERAs or PDE-5 Is (oral)
Treprostinil (SC)

Atrial septostomy
Lung Transplant

Negative

Yes

Continue CCB

PAH

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

Acute vasoreactivity test

Positive
Oral CCB
Sustained Response
Yes
Continue CCB

Negative
No CCB +++

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

Close monitoring of long-term clinical and hemodynamic effects

ACCP Guidelines. Chest 2004;126:1S-92S.
Survival in IPAH
Long-term CCB Responders

Long-term CCB responders (~50% of acute responders or ≤6% of iPAH patients)

Survival in IPAH
Long-term CCB Responders

P=0.0007

Prostacyclins

- Epoprostenol
- Treprostinil
- Iloprost
Epoprostenol (*Flolan®*)

- FDA-approved for Class III-IV PAH
- Chemically unstable, short half life
- Continuous IV Rx
- Significant SE’s
- Line complications
Treprostinil (*Remodulin*®)

- FDA-approved for Class II-IV PAH
- Chemically stable; longer half-life
- Continuous SQ or IV; inhaled (*Tyvaso*)
  - oral under investigation
- Smaller pump
- Typical prostanoid SE’s
- SQ limited by site pain
Iloprost (Ventavis®)

• FDA-approved for Class II-IV PAH
• Chemically stable; longer half-life
• Inhaled (6-9 times daily)
  • IV in Europe
• Typical (?) milder) prostanoid SE’s
• ? Favored for patients with parenchymal lung disease:
  • Provides prostacyclin activity directly to lung
  • Vasodilates (only?) ventilated pulmonary regions
• Avoids catheter complications
IV Epoprostenol in IPAH: Change From Baseline in 6MW Test


**Median change from baseline (m)**

<table>
<thead>
<tr>
<th>Epoprostenol (n=41; baseline=315 m)</th>
<th>Conventional (n=40; baseline=270 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>-29</td>
</tr>
<tr>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
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<tr>
<td>30</td>
<td></td>
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<tr>
<td>40</td>
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*P* < 0.002
Long-term Outcome in IPAH With Epoprostenol

Cumulative Survival

No. at risk:

<table>
<thead>
<tr>
<th>Months</th>
<th>178</th>
<th>129</th>
<th>85</th>
<th>57</th>
<th>36</th>
<th>21</th>
<th>7</th>
<th>3</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td>IV Epoprostenol (n=178)</td>
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<tr>
<td>Historical Control (n=135)</td>
<td></td>
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</table>

% Survival

Expected

Observed (n=162)

*P<0.001

Subcutaneous Treprostinil: Change From Baseline in 6MW Test by Dose Quartile

Inhaled Iloprost: Change from Baseline in 6MW Test (AIR Trial)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=102)</th>
<th>Iloprost (n=101)</th>
<th>( P = 0.004 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline (m)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 8</td>
<td></td>
<td></td>
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<tr>
<td>Week 12</td>
<td></td>
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</tbody>
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AIR=Aerosolized Iloprost Randomized.
6MW test was not the primary endpoint in the AIR trial.
Endothelin Receptor Antagonists

- FDA approved for class III-IV PAH
- Fluid retention
- Oral, well-tolerated
- Teratogens

• **Bosentan (Tracleer)**
  • Mixed ET$_A$/ET$_B$ antagonist
  • BID
  • LFTs

• **Ambrisentan (Letairis)**
  • ET$_A$ specificity
  • Unique metabolism, ? lack of drug-drug interaction
  • Once daily
Bosentan: 6-Minute Walk Test

Values are mean ± SEM.


PDE 5 Inhibitors

- **Sildenafil** (*Viagra, Revatio*)
  - FDA approved for class II-IV PAH
  - Oral, well-tolerated
  - Usual PDE 5 inhibitor concerns

- **Tadalafil** (*Cialis, Adcirca*)
  - Once daily
Sildenafil: Change from Baseline in 6MW Test

Mean change from baseline (m)

Placebo (n=65)
Sildenafil 20 mg tid (n=65)
Sildenafil 40 mg tid (n=63)
Sildenafil 80 mg tid (n=65)

*P<0.001

New Directions in PAH

• New treatments
• New delivery strategies
  • Treprostinil, reformulated Iloprost
• Drug combos
  • FREEDOM, COMPASS 2 (and many more)
• New assessments
  • Genomics/proteomics/etc.
  • RV studies
• New (related) disease states
  • Groups II, III, IV and V
Pregnancy in PAH

- Maternal death rate is 30-50%
- Majority of deaths occur in the first week following delivery
- Maternal mortality increased by hypovolemia, thromboemboli, and pre-eclampsia/eclampsia
- Poor fetal outcome with only 25% of all pregnancies reaching term