Pulmonary Arterial Hypertension

Mark T. Gladwin, MD
Director, Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute
Chairman, Department of Medicine
University of Pittsburgh, Institute for Transfusion Medicine, Hemophilia Center of Western Pennsylvania, and UPMC

UPMC Heart and Vascular Institute
Outline: Pulmonary Arterial Hypertension

• How does PAH present and how to diagnose in the clinic?
• The echo shows an elevated PA pressure. Do I have to do a cath?
• How do I choose initial therapy for PAH?
• How do I adjust therapy for PAH?
Referred patient from Ohio

- 18 year old with severe dyspnea, syncopal events, cyanotic lips and peripheral edema
- HbSS
- Rare painful crises or ACS; on chronic simple transfusions; no narcotics
- WBC 15.8; Hb 11.8; Plat 340; LDH 662; Haptoglobin <5.8; HbS 30%; Hb A 61%; Hb F 2%; retics 18.9% (695K absolute);
- ANA, SCL 70, RA, ANCA, SSA, SSB HIV, Hep serology all negative
RHC data

- RA: 40
- RV 144/9
- PA 147/49
- PAM 82
- PCWP 17
- TPG: 65
- Fick Index 2.63
Pulmonary hypertension: Deadly vascular disease with enigmatic molecular origins

Narrowing of pulmonary artery

Enlarged right heart
Healthy Artery

1. Endothelial dysfunction

2. Vascular remodeling

3. Plexiform lesion & In situ Thrombosis

- Muscularization / Medial Hypertrophy
- Intimal Fibrosis

- External elastic lamina
- Smooth muscle cell
- Internal elastic lamina
- Endothelial cell

- NO
- PGI2
- ET-1
- TXA2

Vasoconstriction
Diagnostic Approach

Is There a Reason to Suspect PAH?

Clinical History (Symptoms, Risk Factors), Exam, CXR, ECG
Brain Natriuretic Peptide

- Cardiomyocyte stretch (pressure or volume)
  - Pre-Pro-BNP
    - 26-108
  - Pro-BNP
    - 1-108
  - 26 aa signal sequence

- Ventricular Cardiomyocyte

- Blood
  - NT-Pro-BNP
    - 1-76
  - BNP
    - 77-108

- Vasodilation
- Natriuresis
- RAAS
Doppler Features of PH

- Peak TR velocity measured
- RVSP calculated as $4v^2 + \text{RAP}$
- RAP estimated by degree of collapse of IVC with respiration or “sniff”

Echo predicting PH:
- Sensitivity 79-100%
- Specificity 60-98%

Forfia et al. Am J Respir Crit Care Med 2006; 174:1034-41
Do I Need a RHC?

1. Accuracy
2. Necessary for diagnosis of PAH
3. Contributes prognostic information
4. Allows for provocative maneuvers

**PH**
Mean PAP ≥25 mm Hg at rest during RHC

**PAH**
Mean PAP ≥25 mm Hg plus PAWP ≤15 mm Hg plus PVR >3 Wood Units
Cons of RHC

1. Invasive

...But safe:

In > 7K RHCs
- 1% SAEs
- 0.3% hospitalization
- 0.06% fatality

Hoeper et.al. *JACC* 2006;48:2546-52

2. Limited reimbursement
So what’s the issue?

Lam SP et.al. JACC 2009; 53: 1119–26

So should I cath?

1. What’s the prior probability of PAH?
Clinical classification of PH
(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

1’. PVOD/PCH

2. PH with left heart disease
   - Atrial or ventricular
   - Valvular

3. PH with lung diseases/hypoxaemia
   - COPD
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Developmental abnormalities

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

5. Miscellaneous
   - Pulmonary hypertension with unclear multifactorial mechanisms
   - Hematologic disorders: myeloproliferative disorders, splenectomy
   - Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
So should I cath?

1. What’s the prior probability of PAH?
2. Likely alternative explanation?
So should I cath?

1. What’s the prior probability of PAH?
2. Likely alternative explanation?
3. How concerning is the echo?
So should I cath?

1. What’s the prior probability of PAH?
2. Likely alternative explanation?
3. How concerning is the echo?
4. Symptoms:
   • Severity
   • Duration
   • Unexplained

In other words, *be a doctor.*

Lastly, err on the side of doing it: it’s safe, and almost always helpful.
Question #2

How do I choose initial therapy for PAH?
Current therapeutic targets

# Therapeutic Options for PAH

<table>
<thead>
<tr>
<th>Non-PAH Targeted</th>
<th>PAH Targeted (FDA apprvd)</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Prostanoids</td>
<td>Prostanoids</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Epoprostenol</td>
<td>- Beraprost</td>
</tr>
<tr>
<td>Anticoagulants (?)</td>
<td>Treprostinil (IV, SC, Inhaled, oral**)</td>
<td>Others</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Inhaled Iloprost</td>
<td>- TKI’s</td>
</tr>
<tr>
<td></td>
<td>Selexipag +</td>
<td>- Rituximab</td>
</tr>
<tr>
<td></td>
<td>ERAs</td>
<td>- Cicletanine</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>- Inhaled NO</td>
</tr>
<tr>
<td></td>
<td>Ambrisentan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macitentan **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDE-5 Inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riociguat **</td>
<td></td>
</tr>
</tbody>
</table>

** approved 10/2013; + approved 12/2015
Choice of Initial PAH therapy

- Risk Estimation/Disease Severity
- Coverage Status
- Patient Ability
- Patient Support
- Provider Preference
- Side Effect Profile
- Patient Preference

Treatment Choice
## 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>

McLaughlin and McGoon. Circulation 2006;114:1417-31
What is the Optimal Treatment Strategy?

1. **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**
   - Oral CCB
     - **Sustained Response**
       - Continue CCB
       - Investigational Protocols
         - ERAs or PDE-5 Is (oral)
         - Epoprostenol or Treprostinil (IV)
         - Iloprost (inhaled)
         - Treprostinil (SC)
         - Reassess – consider combo-therapy

2. **Acute Vasoreactivity Testing**
   - Class II-III
     - ERAs or PDE-5 Is (oral)
     - Epoprostenol or Treprostinil (IV)
     - Iloprost (inhaled)
     - Treprostinil (SC)
   - Class III-IV
     - Epoprostenol or Treprostinil (IV)
     - Iloprost (inhaled)
     - ERAs or PDE-5 Is (oral)
     - Treprostinil (SC)
     - Atrial septostomy
     - Lung Transplant

Modified from Badesch DB et al. *Chest.* 2004;126:35S-62S
Time for a Paradigm Shift?

Current
Sequential combination therapy for deterioration or failure to show improvement with monotherapy

Future (is NOW?)
Up front combination therapy

PDE5 inhibitors + Endothelin Receptor Antagonists + Prostanoids
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


DOI: 10.1056/NEJMoa1413687
A Combination Therapy vs. Pooled Monotherapy

[Graph showing survival curves for combination therapy and pooled monotherapy with 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
Pooled monotherapy 247 209 155 108 77 49 25 5

6-Minute walk distance — m

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (IQR) change from baseline to week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>48.98 (4.63 to 85.75)</td>
</tr>
<tr>
<td>Pooled monotherapy</td>
<td>23.80 (-12.25 to 64.53)</td>
</tr>
<tr>
<td></td>
<td>27.00 (-14.00 to 63.25)</td>
</tr>
<tr>
<td></td>
<td>22.70 (-8.25 to 66.00)</td>
</tr>
</tbody>
</table>

P value
Reference <0.001 <0.001 0.003
## Combination Therapy: Ongoing or Recently Completed Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Current therapy</th>
<th>Added therapy</th>
<th>Patients (n)</th>
<th>Study duration</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEDOM-C</td>
<td>Bosentan and/or sildenafil</td>
<td>Treprostinil oral</td>
<td>300</td>
<td>16 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>AMBITION</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>300</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>COMPASS-1</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>45</td>
<td>Single dose</td>
<td>PVR</td>
</tr>
<tr>
<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
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<tr>
<td>COMPASS-3</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>100</td>
<td>16 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>ATHENA-1</td>
<td>Sildenafil or tadalafil</td>
<td>Ambrisentan</td>
<td>40</td>
<td>24 weeks</td>
<td>PVR</td>
</tr>
<tr>
<td>SERAPHIN</td>
<td>Naïve/PDE-5/PGI/combo</td>
<td>Macitentan</td>
<td>742</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>PATENT</td>
<td>Naïve/PGI/ERA</td>
<td>Riociguat</td>
<td>462</td>
<td>12 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>IMPRES</td>
<td>≥2 current therapies</td>
<td>Imatinib</td>
<td>200</td>
<td>24 weeks</td>
<td>6MWD</td>
</tr>
<tr>
<td>ATPAHSS</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>63</td>
<td>36 weeks</td>
<td>RV mass/PVR</td>
</tr>
<tr>
<td>GRIPHON</td>
<td>ERA, PDE5 or both</td>
<td>Selexipag</td>
<td>670</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
<tr>
<td>Novartis</td>
<td>Stable PAH therapy</td>
<td>Noilotinib</td>
<td>66</td>
<td>6 months</td>
<td>PVR</td>
</tr>
</tbody>
</table>
Pro-proliferative and inflammatory signaling converge on FoxO1 transcription factor in pulmonary hypertension

Rajkumar Savai1,2, Hamza M Al-Tamari1, Daniel Sedding3,4, Baktybek Kojonazarov2, Christian Muecke1, Rebecca Teske3, Mario R Capecchi5, Norbert Weissmann2, Friedrich Grimminger2, Werner Seeger1,2, Ralph Theo Schermuly2 & Soni Savai Pullamsetti1,2
Hemodynamic Progression of PAH

Pre-symptomatic/Compensated  | Symptomatic/Decompensating  | Declining/Decompensated

CO = \frac{PAP}{PVR}

CO = PAP

PVR

Symptom Threshold

Right Heart Dysfunction

Time
43 year old football coach

- Increasing dyspnea on exertion running up and down sidelines with increasing pain
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
Riociguat for the Treatment of Pulmonary Arterial Hypertension

Hossein-Ardeschir Ghofrani, M.D., Nazzareno Galiè, M.D., Friedrich Grimminger, M.D., Ekkehard Grünig, M.D., Marc Humbert, M.D., Zhi-Cheng Jing, M.D., Anne M. Keogh, M.D., David Langleben, M.D., Michael Ochan Kilama, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., and Lewis J. Rubin, M.D., for the PATENT-1 Study Group*