Pulmonary Arterial Hypertension

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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

Enlarged right heart

Narrowing of pulmonary artery
Healthy Artery

1. Endothelial dysfunction
   - External elastic lamina
   - Smooth muscle cell
   - Internal elastic lamina
   - Endothelial cell
   - NO
   - PGl2
   - ET-1
   - TXA2
   - Vasoconstriction

2. Vascular remodeling
   - Inflammatory cell
   - Muscularization / Medial Hypertrophy
   - Intimal Fibrosis

3. Plexiform lesion & In situ Thrombosis
Diagnostic Approach

Is There A Reason to Suspect PAH?
Clinical History (Symptoms, Risk Factors), Exam
Brain Natriuretic Peptide

Cardiomyocyte stretch (pressure or volume)

Ventricular Cardiomyocyte

Pre-Pro-BNP (26-108)

Pro-BNP (1-108)

26 aa signal sequence

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 %

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

**NO - sGC - cGMP Pathway**
- Endothelium
- L-arginine → L-citrulline
- eNOS
- NO
- NO inhalation
- NO synthase
- NO synthase uncoupling
- BH2
- 6R-BH4
- Sildenafil
- Tadalafil
- Riociguat
- sGC
- GTP → cGMP
- cGMP → GMP
- PDE5
- Vasodilation ↓ Proliferation

**Prostacyclin Pathway**
- NO
- Arachidonic acid
- Prostaglandins
- COX
- Prostacyclin (PGI2)
- Epoprostenol
- Treprostinil
- Iloprost
- Beraprost
- Selexipag
- IP receptor
- AC
- cAMP
- ATP

**Endothelin-1 Pathway**
- Big Endothelin-1
- ECEs
- Ambrisentan
- Endothelin-1
- ETA receptor
- ETB receptor
- Bosentan
- Macitentan

# Therapeutic Options for PAH

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

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

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

Anticoagulate ± Diuretics ± Oxygen ± Digoxin → Acute Vasoreactivity Testing

- Oral CCB
  - Sustained Response
    - Continue CCB
  - Class II-III
    - ERAs or PDE-5 Is (oral)
      - Epoprostenol 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

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

- Prostanoids
- PDE5 Inhibitors
- Endothelin Receptor Antagonists
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension


DOI: 10.1056/NEJMoa1413687
A Combination Therapy vs. 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
Pooled monotherapy: 247 209 155 108 77 49 25 5

6-Minute walk distance — m§
Median (IQR) change from baseline to week 24
Combination therapy: 48.98 (4.63 to 85.75)
Pooled monotherapy: 23.80 (−12.25 to 64.53)
Combination therapy: 27.00 (−14.00 to 63.25)
Pooled monotherapy: 22.70 (−8.25 to 66.00)
P value
Reference < 0.001 < 0.001 0.003
## Combination Therapy: Ongoing or Recently Completed Clinical Trials

<table>
<thead>
<tr>
<th>Study</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>
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<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>
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<tr>
<td>Pfizer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
<td>6MWD</td>
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<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>
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<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

CO = \frac{PAP}{PVR}

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

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