Pulmonary Arterial Hypertension: Biomarkers and Treatment

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• **Pulmonary Hypertension**
  • Mean PAP ≥ 25 mmHg

• **Post-capillary PH**
  • Mean PAP ≥ 25 mmHg
  • PAOP ≥ 15 mmHg

• **Pre-capillary PH**
  • Mean PAP ≥ 25 mmHg
  • PAOP ≤ 15 mmHg

• **Pulmonary Arterial Hypertension**
  • Mean PAP ≥ 25 mmHg
  • PAOP ≥ 15 mmHg
  • PVR > 3 wood units
<table>
<thead>
<tr>
<th>WHO Group</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Idiopathic, heritable, drugs and toxins, associated (CTD, HIV, liver disease, CHD, Schistosomiasis)</td>
</tr>
<tr>
<td>2</td>
<td>Left heart disease</td>
</tr>
<tr>
<td>3</td>
<td>Lung disease or hypoxia</td>
</tr>
<tr>
<td>4</td>
<td>Chronic thromboembolic</td>
</tr>
<tr>
<td>5</td>
<td>Other (CKD, Sarcoid, hematologic or metabolic disorders, etc.)</td>
</tr>
</tbody>
</table>
Epidemiology

PH TYPES BY ECHO

- **Left Heart Disease**: 68%
- **Respiratory Disease**: 9%
- **PAH**: 3%
- **CTEPH**: 2%
- **Unknown or Miscellaneous**: 18%

Strange et. al. heart 2012;98:1805
PAH = Group 1
PVR>3; mPAP>25; PAOP<15

Etiology:
Idiopathic, heritable, drugs & toxins, associated (CTD, HIV, liver disease, CHD, Schistosomiasis)

Adapted from Gaine S. JAMA. 2000;284:3160-3168.
PH Diagnosis

- **High index of suspicion!**
- **Echo (to screen)**
- **Supportive tests to assess etiology**
  - PFT
  - CXR or CT chest
  - Polysomnogram
  - VQ scan
- **RHC (to confirm diagnosis)**

![Echocardiogram images](WNL vs. PH)

**UC San Diego Health System**
• **REQUIRED**
  • PAH specific Rx should **not** be initiated without a RHC

• Detailed oriented RHC is important: **consider doing at expert center**
  • Diagnostic (mPAP, PAOP) and prognostic (RAP, CO/CI)
  • Need to assess vasoreactivity (iNO, etc.) for patient and insurance purposes
  • Accurate PAOP measurement is very important
  • Perform CO/CI via thermodilution & Fick methodologies
  • Multiple technical details need to be addressed (zeroing, wedge tracing and end-expiratory measurement rather than mean, sat. run, etc.)
PAH Management

• General measures
  • Rehab/activity maintenance
  • Avoiding pregnancy, surgeries
  • Support groups, vaccinations, genetic counseling if heritable

• Supportive measures
  • Diuretics
  • Oxygen
  • Anticoagulation
  • Digoxin

• Pharmacotherapy for PAH
Therapy – PAH specific medications

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan(^6^1)</td>
<td>5.4 h</td>
</tr>
<tr>
<td>Ambrisentan(^6^2)</td>
<td>9–15 h</td>
</tr>
<tr>
<td>Macitentan, ACT-064992 (2 h)(^1^7)</td>
<td></td>
</tr>
<tr>
<td>active metabolite, ACT-132577 (8.4 h)</td>
<td></td>
</tr>
<tr>
<td>Sildenafil (for PAH)(^6^6)</td>
<td>3.7 h</td>
</tr>
<tr>
<td>Tadalafil (for PAH)(^6^7)</td>
<td>18 h</td>
</tr>
<tr>
<td>Riociguat(^6^8)</td>
<td>5–10 h</td>
</tr>
</tbody>
</table>

Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol(^5^3,5^4)</td>
<td>2–3 min</td>
</tr>
<tr>
<td>Iloprost(^5^4)</td>
<td>30 min</td>
</tr>
<tr>
<td>Treprostinil(^6^4,6^5)</td>
<td>4.5 h</td>
</tr>
<tr>
<td>Beraprost(^5^9,6^4)</td>
<td>35–40 min</td>
</tr>
<tr>
<td>Selexipag</td>
<td>0.8–2.5 h</td>
</tr>
<tr>
<td>metabolite</td>
<td>6.2–13.5 h</td>
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</table>
PAH Management

• Multidimensional approach
  • Looking at all the variables described above
  • Risk stratification correlates with prognosis

• Make decisions on management/Rx based on goals
  • No Si/Sx of heart failure, no progression of Sx
  • WHO FC I or II
  • 6MWD > 440 m (other thresholds include 380m or 400m)
  • Normal proBNP or BNP
  • Normalization of RV size and function on Echo/RHC
  • RAP<8 mmHg and CI>2.5 l/min/m²
  • CPET criteria
### PAH biomarkers are based on PAH pathophysiology

<table>
<thead>
<tr>
<th>Myocyte insult</th>
<th>Endothelial dysfunction</th>
<th>Inflammation and Oxidative stress</th>
<th>End-organ dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-prBNP *</td>
<td>Nitric Oxide (NO)</td>
<td>Osteopontin</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>BNP *</td>
<td>Endothelin 1</td>
<td>Galectin-3</td>
<td>Total bilirubin</td>
</tr>
<tr>
<td>Troponins I and T</td>
<td>cGMP</td>
<td>RDW</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Asymmetric dimethylarginine (ADMA)</td>
<td>Interleukins (1B, 6, 8, 12p70)</td>
<td>PaCO2</td>
</tr>
<tr>
<td>ANP</td>
<td></td>
<td>C-reactive protein</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>ST2</td>
<td></td>
<td>Growth differentiation factor 15</td>
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<tr>
<td></td>
<td></td>
<td>Soluble CD40 ligand</td>
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<tr>
<td></td>
<td></td>
<td>TNF-a</td>
<td></td>
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<td></td>
<td>High-density lipoprotein cholesterol</td>
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<tr>
<td></td>
<td></td>
<td>CXC chemokine ligand 10</td>
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</tr>
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<td></td>
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<td>PDGF</td>
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NT-proBNP and BNP

- Has significant prognostic impact (REVEAL registry – Circulation 2010)

- BNP < 50 pg/ml or NT-proBNP < 300 pg/ml → increased survival
- BNP > 180 pg/ml or NT-proBNP > 1500 pg/ml → increased morbidity/mortality
  - These cutoffs were incorporated in the 1 year mortality risk calculator generated by REVEAL
- Baseline BNP < 340 pg/ml strongly predicted 5 year survival (Frantz 2018)
- Change of BNP in 1 year, correlated with change in survival (Frantz 2018)

- BNP and NT-proBNP are used in every day practice
  - Guidelines recommend regular follow up of these
  - Escalation of therapy to normalized BNP/NT-proBNP values is recommended
NT-proBNP and BNP studies

- Multiple studies show promising results
  - Lower values correlate with
    - Improved survival (Nagaya, 2000)
    - Better hemodynamics (Leuchte 2007)
    - Improved exercise capacity (Leuchte 2004)
    - Lower disease severity (Souza 2007)
    - Positive response to treatment (Souza 2005)

- NT-proBNP vs. BNP
  - More stable fragment in plasma
  - Remains a prognostic indicator if renal dysfunction present (Fijalkowska 2006)
    - BNP does not
    - Loses correlation with hemodynamics

- Clinical trials looking at combination Rx for PAH show proBNP improvements
  - ATHENA-1, TRIUMPH, AMBITION, etc.
Other Biomarkers

- **Uric Acid**
  - Increased levels correlate with worse prognosis and hemodynamics (Nagaya 1999)

- **Troponin I (sensitive assay)**
  - Detectable levels correlated with worse prognosis and disease (Heresi 2012)

- **Troponin T**
  - Similar results with lower survival if detectable levels are present (Torbicki 2003)

- **Endothelin-1 and Endothelin-3**
  - Higher ET-1 and ET-1/ET-3 levels correlate with worse hemodynamics/prognosis (Montani 2007)

- **ADMA (asymmetric dimethylarginine) – NOS inhibitor**
  - Higher levels correlate with worse prognosis and hemodynamics in PAH (Pullamsetti 2005) and CTEPH (Kielstein 2005)
Other Biomarkers

• Soluble ST2 (circulating form of ST2, an IL-1 receptor family protein)
  • Independent predictor of mortality in idiopathic PAH (Zheng 2014)

• Osteopontin (extracellular structural protein)
  • Higher in PAH, correlated with FC and mortality predictor in PAH (Resenberg 2012)

• Cystatin C (mostly renal function biomarker)
  • Higher in PAH, correlates with RVSP and RV volumes (Fenster 2014)

• Others?
  • Serum cAMP or cGMP, exhaled NO, PCO₂, heart-type fatty acid-binding protein, HDL,
    urinary F(2)isoprostane, inflammatory markers (CRP, RDW), adrenomedullin, angiopoietin-2,
    MMPs, PDGF
Micro-RNAs

- Small, non-coding RNAs that regulate gene expression post-transcriptionally
- Multiple are associated with PAH
- miRNA-424(322) recently associated with HIF/BMPR path and PAH
Thank you!

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