Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

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PHPN 2015 Symposium
19 September 2015
Disclosures

• Deedre’ Boekweg has no financial interests to disclose.

• Kerri Akaya Smith has no financial interests to disclose.

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Summarize the physiologic effect of hypoxic pulmonary vasoconstriction in chronic obstructive pulmonary disease and other related pulmonary diseases.

2. Recognize challenges specific to the assessment of pulmonary hypertension in chronic obstructive pulmonary disease and other related pulmonary diseases.

3. Distinguish between pulmonary hypertension “within proportion” and “out of proportion” to pulmonary disease.

4. Describe specific challenges and benefits of PAH specific therapies in patients with chronic obstructive pulmonary disease and other related pulmonary diseases.
Defining Pulmonary Hypertension

- Mean pulmonary artery pressure (PAP):
  - RHC: PA mean \( \geq 25 \text{ mmHg} \) at rest
  - Echo: Systolic PAP by Echo \( \geq 40 \text{ mmHg} \) at rest

\[
mPAP = CO \times PVR + PCWP
\]

PH is not a SPECIFIC diagnosis but rather a group of diseases
Updated Clinical Classification of Pulmonary Hypertension (Nice, 2013)

1. Pulmonary Arterial Hypertension
   - Idiopathic PAH
   - Heritable
   - Drug- and toxin-induced
   - Associated with:
     - CTD
     - HIV infection
     - portal hypertension
     - CHD
     - Schistosomiasis

   1’. PVOD and/or PCH
   1”. Persistent PH of newborn

   PH
   Mean PAP ≥25 mm Hg

   PAH
   Mean PAP ≥25 mm Hg plus PCWP/LVEDP ≤15 mm Hg plus PVR > 3 WU

   “PAH” like hemodynamics can be found in other WHO groups → Diagnosis must be made in clinical context
1. Pulmonary Arterial Hypertension
   - Idiopathic PAH
   - Heritable
   - Drug- and toxin-induced
   - Associated with:
     - CTD
     - HIV infection
     - portal hypertension
     - CHD
     - Schistosomiasis

1’. PVOD and/or PCH
1’’. Persistent PH of newborn

2. PH Owing to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease
   - Congenital L heart inflow/outflow/ CMP

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   - ILD
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. Chronic Thromboembolic PH (CTEPH)

5. PH With Unclear Multifactorial Mechanisms
   - Hematologic disorders
   - Systemic disorders (Sarcoid, LAM)
   - Metabolic disorders
   - Chronic hemolytic anemia
   - Others (tumor, ESRD)

Etiology of PH

Left Heart disease 78.7%

COPD/OSA/ILD 9.7%

Unknown 6.8%

PAH 2.3%

CTEPH 0.6%

Congenital HD 1.9%

Adapted from Gabby, AJRCCM 2007:175:A713
Pulmonary Hypertension Owing to Lung Disease/Hypoxia

- 3.1: Chronic obstructive lung disease
- 3.2: Interstitial lung disease
- 3.3: Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4: Sleep-disordered breathing
- 3.5: Alveolar hypoventilation disorders
- 3.6: Chronic exposure to high altitude
- 3.7: Developmental abnormalities

Mechanism of PH in COPD and Lung Diseases

• **Chronic hypoxic**
  – Vasoconstriction
    • Intracellular calcium

• **Vascular remodeling**
  – Intimal thickening and fibrosis, smooth muscle proliferation

• **Endothelial Dysfunction**
  – ↓eNOS and exhaled NO
  – ↑Endothelin-1 in circulation

Using ECHO in PH

- 65 PH pts: accuracy of ECHO with RHC 48%
  - 38% of overestimates >20 mmHg
  - 80% of underestimates >20 mmHg
  - 6 pts without an appreciable TR jet, 4 of these with PH
- 74 paired caths and ECHOs in COPD patients
  - Sensitivity 60%
  - Specificity 74%
  - 38% not included in study
    - RVSP could not be estimated
    - Thought due to hyperinflation
- Similar error exists in the context of IPF

Considerations for RHC in Lung Diseases

• Preventing Hypoxia
  – Prevent acute vasoconstriction

• Careful measurement and review of tracings for respiratory variation. Increased in this population due to:
  – Hyperinflation
  – Increase work of breathing
  – Possible Valsalva
Considerations for RHC in Lung Diseases

Pulmonary Vascular Resistance is calculated not measured

\[ \text{PVR} = \frac{\text{mPAP} - \text{PCWP}}{\text{CO}} \]
Just how common is PH in COPD?
Definitions

• COPD/IPF/CPFE without PH
  – mPAP < 25 mm Hg

• COPD/IPF/CPFE with PH = PH-COPD, PH-IPF, and PH-CPFE
  – mPAP 25 mm Hg
  – PH-COPD, PH-IPF, and PH-CPFE

• COPD/IPF/CPFE with severe PH = “out of proportion”
  – mPAP 35 mm Hg or mPAP 25 mm Hg with low CI (<2.0 l/min/m2)
  – Severe PH-COPD, severe PH-IPF, and severe PH-CPFE.
# PH-COPD

<table>
<thead>
<tr>
<th>Author, Yr</th>
<th>N</th>
<th>Population</th>
<th>Definition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thabut, 2005</td>
<td>215</td>
<td>Txp/LVRS Eval</td>
<td>mPAP &gt; 25, PCWP &lt; 16</td>
<td>50</td>
</tr>
<tr>
<td>Lederer, 2008</td>
<td>4395</td>
<td>Listed for Txp</td>
<td>mPAP &gt; 25, PCWP &lt; 15</td>
<td>22</td>
</tr>
<tr>
<td>Sims, 2009</td>
<td>362</td>
<td>Txp Eval</td>
<td>mPAP &gt; 25, PCWP &lt; 16</td>
<td>23</td>
</tr>
<tr>
<td>Minai, 2014</td>
<td>797</td>
<td>LVRS Eval</td>
<td>mPAP ≥ 25, PCWP &lt; 16, ≥ 35 or ≥ 25 with CI &lt; 2</td>
<td>26</td>
</tr>
<tr>
<td>Cuttica, 2010</td>
<td>4930</td>
<td>Listed for Txp</td>
<td>mPAP ≥ 35</td>
<td>4</td>
</tr>
<tr>
<td>Chaouat, 2005</td>
<td>998</td>
<td>Resp failure, FEV1/VC &lt; 0.60</td>
<td>mPAP &gt; 40, PCWP &lt; 15</td>
<td>1</td>
</tr>
</tbody>
</table>

Seeger, JACC 2013
Hoeper, Int J Card 2011
Clinical implications of PH in COPD

Adjusted for age, gender, race, height, weight, FEV$_1$, and PAOP.

6MWD dropped 11 m for every 5 mm Hg increment in mPAP.

(Sims, Chest 2009)
Clinical implications of PH in COPD

<table>
<thead>
<tr>
<th></th>
<th>HR*</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PH</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>Pulmonary Venous</td>
<td>1.4</td>
<td>1.1-1.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>1.3</td>
<td>1.04-1.6</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, ethnicity, BMI, FEV1, FVC, NYHA, DM

(Cuttica, Resp Medicine 2010)
**Management of PH in COPD**

<table>
<thead>
<tr>
<th>Lung Disease</th>
<th>mPAP &lt; 25 mm Hg</th>
<th>mPAP ≥ 25 and &lt; 35 mmg Hg</th>
<th>mPAP ≥ 35 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Consider referral for lung transplant eval for all IPF, CPFE groups and severe PH-COPD

*Seeger, JACC 2013*
Role of PH-specific therapies

- **Endothelin receptor antagonists**
  - Stolz, ERJ 2008- RCT of bosentan, 20 bos, 10 placebo for 12 wks
  - No change in 6MWT, bos- lower O2 sats, worse HRQOL

- **Prostacyclin analogues**
  - Dernaika, Respiration 2009- 10 males with RVSP > 35 and RV changes
  - Acute dosing of iloprost- reduced shunt fraction, dead space, reduced A-a gradient

- **Phosphodiesterase inhibitors**
  - Sildenafil does not improve exercise tolerance or QOL in COPD without sev PH *(Blanco, ERJ 2013; Lederer, COPD 2012)*
### Role of PH-specific therapies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PH specific drug</th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean Difference</td>
<td>IV, Fixed, 95% CI</td>
<td>Mean Difference</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
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<td></td>
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<tr>
<td><strong>3.1.1 Bosentan</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stolz 2008</td>
<td>-2</td>
<td>9.3</td>
<td>14</td>
<td>-4</td>
<td>15.4</td>
<td>9</td>
<td>2.3%</td>
<td>2.00 [-9.18, 13.18]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valerio 2009</td>
<td>-6</td>
<td>5.6</td>
<td>16</td>
<td>2</td>
<td>6.2</td>
<td>16</td>
<td>16.9%</td>
<td>-8.00 [-12.09, -3.91]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>30</strong></td>
<td></td>
<td><strong>25</strong></td>
<td><strong>19.1%</strong></td>
<td><strong>-6.82 [-10.66, -2.97]</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Heterogeneity: Chi² = 2.71, df = 1 (P = 0.10); I² = 63%</td>
<td></td>
<td>Test for overall effect: Z = 3.48 (P = 0.0005)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

| **3.1.2 Sildenafil** |                  |         |                  |                    |                  |
| Rao 2010           | -11.7            | 10.5    | 15               | -3.8               | 12.8             | 18              | 4.5%  | -7.90 [-15.85, 0.05] |                  |
| Zhang 2012         | -9.3             | 7.2     | 36               | -4.7               | 7.9              | 35              | 22.8% | -4.60 [-8.12, -1.08] |                  |
| Zhen 2011          | -18              | 5.3     | 30               | -6.3               | 3.9              | 30              | 51.0% | -11.70 [-14.05, -9.35] |                  |
| **Subtotal (95% CI)** | **111**         |         | **113**          | **80.9%**          | **-9.55 [-11.42, -7.68]** |                  |
|                   | Heterogeneity: Chi² = 11.57, df = 3 (P = 0.009); I² = 74% | | Test for overall effect: Z = 10.00 (P < 0.00001) |

| **Total (95% CI)** |                  |         |                  |                    |                  |
|                   |                  |         | **141**          | **100.0%**         | **-9.02 [-10.71, -7.34]** |                  |
|                   | Heterogeneity: Chi² = 15.85, df = 5 (P = 0.007); I² = 68% | | Test for overall effect: Z = 10.52 (P < 0.000001) |
|                   | Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21); I² = 36.1% | | | | |
Role of PH-specific therapies

- Dernaika, et al 2010
  - n=10 men with COPD at VA in Oklahoma City with PH by echo \(\rightarrow\) PFT, dead space, ABG and 6MWT pre and post
  - PH determined by echocardiography with RVSP > 35 mm Hg plus findings of right ventricle (RV) morphologic changes (RV dilation and/or hypertrophy)
  - Baseline: mean FEV1 47\%, mean PaO2 67, mean PCO2 38, mean RVSP

Iloprost given in divided dose 30 minutes apart:
- Improved Aa gradient, mean 6MWT (by 49.8 m)
- Stable: ABG, venous admixture, dead space fraction and lung functions
- Effects resolved at 2 hours

Dernaika. Respiration 2010;79:377–382
Role of PH-specific therapies

- Tadalafil in COPD, n=120, with RVSP > 30 mm Hg

No significant change in quality of life or exercise capacity

<table>
<thead>
<tr>
<th></th>
<th>At 12 wks</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSP</td>
<td>-12</td>
<td>-20- -4</td>
<td>0.007</td>
</tr>
<tr>
<td>mPAP</td>
<td>-3.5</td>
<td>-7—0.4</td>
<td>0.025</td>
</tr>
<tr>
<td>TAPSE</td>
<td>0.1</td>
<td>-0.1-0.3</td>
<td>0.32</td>
</tr>
</tbody>
</table>

(Goudie, Lancet Resp Med 2014)
What about PH in interstitial lung disease?
PH in IPF: Mild

- mPAP in most mildly elevated
- Unlike PAH, CO tends to be preserved, RA pressure normal
- Prevalence of PH 20-40% however prevalence of severe PH only 5-10% -- severe PH-IPF

Lettieri C et al. Chest 2006; 129:746-52
Clinical implications of PH in IPF

6MWT still correlates with PH even when controlled for severity of IPF (FVC)

Mortality worse in those with PH and IPF vs IPF alone


Lettieri. Chest 2006. 128:746
## Vasodilator Trials in IPF

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>n</th>
<th>Study Type</th>
<th>Group</th>
<th>PH</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghofrani, Lancet ’02</td>
<td>sildenafil</td>
<td>8</td>
<td>RCT, open label</td>
<td>Fibrosis mPAP&gt;35</td>
<td>Improved hemos, V/Q, PaO2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epo IV</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>Worsened V/Q, PaO2</td>
</tr>
<tr>
<td>Minai, Resp Med ‘08</td>
<td>Bosentan vs Epo IV</td>
<td>19</td>
<td>Case Series</td>
<td>IPF   mPAP&gt;25</td>
<td>Improved 6MWT, WHO class</td>
<td></td>
</tr>
<tr>
<td>Collard Chest 07</td>
<td>sildenafil</td>
<td>14</td>
<td>Case series</td>
<td>IPF   mPAP&gt;25 (10), RVSP&gt;35</td>
<td>57% improved 6MWT 20% @ 3mo</td>
<td></td>
</tr>
<tr>
<td>Krowka Chest 07</td>
<td>illoprost</td>
<td>51</td>
<td>RCT, phase II, abstract (ACTIVE)</td>
<td>IPF   mPAP&gt;25 (10), RVSP&gt;35</td>
<td>Trend to worse 6MWT/ WHO</td>
<td></td>
</tr>
<tr>
<td>Jackson 2010</td>
<td>sildenafil</td>
<td>29</td>
<td>RCT, DB</td>
<td>IPF   mPAP&gt;25</td>
<td>No diff 6MWT/ borg</td>
<td></td>
</tr>
<tr>
<td>Badesch Cv Rx 12</td>
<td>Ambri-sentan</td>
<td>24</td>
<td>RCT</td>
<td>mPAP&gt;25</td>
<td>Trend to worse 6MWT</td>
<td></td>
</tr>
<tr>
<td>IPFnet NEJM ‘10</td>
<td>Sildenafil</td>
<td>180</td>
<td>RCT, DB (STEP-IPF)</td>
<td>IPF   mPAP&gt;25</td>
<td>No diff in 6MWT</td>
<td></td>
</tr>
</tbody>
</table>
Who do I consider therapy in?

- **RARELY**
  - Severe PH, low CI, abnormal RV size and function, nl PCWP/LV, mild lung disease

- PDE-5 inhibitor or inhaled prostacyclin, not ERA or IV prostacyclin

- **Re-evaluate frequently**
  - Be open to stopping treatment if ineffective/harmful
  - Follow 6MWD, sats, patient self-assessment
Case Study
Case Study

• 66 YO male
• Presents with increasing dyspnea and recurrent syncope with exertion
  – Dx: COPD, OSA, Mild CAD, Hypertension
  – History:
    • 80 pack smoking history, quit 12 years ago.
    • ETOH use on weekends
    • Over the last year Oxygen needs have increased from 2 L to 8-10 L
    • CPAP in use for Tx OSA
Case Study-Testing

• Vital Signs:
  – BP 94/62, HR 106, SpO2 84-90 on 8-10 L NC

• Significant Labs:
  – BNP 1334, Creatinine 1.5, Hematocrit 42.3
  – ABG PH 7.44, CO2 40, PO2 99 (50% Oxygen)
  – Mildly elevated CK-MB

• Unable to complete a 6MWT

• WHO functional class 4
Case Study-Imaging

- **CXR**
  - Evidence of large PA, suggestive of pulmonary hypertension

- **CTPA**
  - Negative for PE
  - Consistent with obstructive airway and mild interstitial disease
• Severely dilated RV with moderate to severe RV dysfunction with signs of RV pressure and volume overload
  – RVSP estimate 65 mmHg
  – No evidence of intracardiac shunt
What would you do?
Right Heart Catheterization

• What considerations are needed?

<table>
<thead>
<tr>
<th>Diagnostic RHC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RA, mmHg</td>
<td>16</td>
</tr>
<tr>
<td>PA, mmHg</td>
<td>113/53 (74)</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>12</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.8</td>
</tr>
<tr>
<td>CI, lpm</td>
<td>1.9</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>16.3</td>
</tr>
<tr>
<td>Vasoreactivity testing</td>
<td>Negative</td>
</tr>
</tbody>
</table>

• Would you treat with PAH specific therapy?  
  – If so which one?
Case Study: The N of One

- 66 yo male with COPD:
- Inhaled Iloprost at 5 μg 6x/d
  - Careful monitoring

<table>
<thead>
<tr>
<th>Variables</th>
<th>February 2006 (Baseline)</th>
<th>February 2008 (Iloprost Therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO functional class</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>Unable</td>
<td>300</td>
</tr>
<tr>
<td>Right-heart catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Diastolic/systolic PAP, mm Hg</td>
<td>113/53 (mean, 74)</td>
<td>96/52 (mean, 67)</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood U</td>
<td>16.3</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Chest 2009; 135: 536-537
In summary, PH in Lung Disease

- **Prevalence**
  - Occurs in ~ 15 % of patients with COPD or ILD
  - 30-40% with combined pulmonary fibrosis and emphysema (CPFE)

- **PH is generally mild → SEVERE PH occurs in less than 5%**

- At any severity, the presence of PH is a poor prognostic sign

- No data that PH specific therapy changes outcome and most data suggest harm
Thank you for your attention!

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