Pulmonary Hypertension in Interstitial Lung Disease

Richard Wells
Objectives

• Prevalence of pulmonary hypertension (PH) in interstitial lung disease (ILD)

• Pathogenesis of PH in ILD

• Predictive factors and clinical implications of PH in ILD

• Treatment and role of advanced therapies in PH associated with ILD
Interstitial Lung Disease

• Comprises a heterogeneous group of disease with restrictive physiology and impaired gas exchange

• Pulmonary hypertension (PH) in this setting is designated group 3 based on Dana Point 2008 PH classification
Interstitial Lung Disease

• PH in ILD causes dyspnea, fatigue and exercise limitation

• Significant symptom overlap with ILD symptoms

• PH may be missed in ILD until signs of right heart failure develop
Definition of PH in ILD

• Presence of PH in an ILD patient without an alternative cause

• PH is defined as a mean PAP (mPAP) of $\geq 25\text{mmHg}$ at rest

• PH is considered severe when mPAP $\geq 25\text{mmHg}$ with cardiac index $<2\text{L/min/m}^2$ or if mPAP $\geq 35\text{mmHg}$
Prevalence of PH in ILD

• Actual prevalence is uncertain

• Depends on the type of ILD, the differences in patient populations, modality used to detect PH


Prevalence of PH in ILD

• Idiopathic pulmonary fibrosis
  – Nathan et al in 2008 retrospective cohort of 44 patients with RHC data on initial transplant evaluation
    – 38.6% had PH at baseline
    – During follow up the majority of non-PH patients developed PH → incidence of 77.8%
  – Overall prevalence of 86.4% at the time of transplant

Prevalence of PH in ILD

• Idiopathic pulmonary fibrosis
  – In 79 IPF patients studied retrospectively 31.6% met criteria for PH
  – >2000 IPF patients on the UNOS registry, the prevalence of PH was around 25%

Prevalence of PH in ILD

• Sarcoidosis
  – Prospective study in 246 sarcoidosis patients the frequency was 5.7% based on PASP>40mmHg by doppler ultrasound

Prevalence of PH in ILD

• Connective tissue disease (CTD) with ILD
  – 5-38% of patients with systemic sclerosis
  – 4.3-43% of patients with SLE
  – 21% patients with rheumatoid arthritis

• PH in CTD can also be due to:
  – group 1 pulmonary arteriopathy
  – group 2 cardiac disease

Pathogenesis of PH in ILD

• Normally
  – Pulmonary hypertension develops under conditions of global hypoxia that cause widespread pulmonary vasoconstriction

  – Additionally there are ablative changes to the pulmonary vasculature secondary to fibrosis that contribute PH

  – PH here is an adaptive/secondary phenomenon
Pathogenesis of PH in ILD

• “Disproportionate PH in ILD”

• Not just hypoxemia and fibrosis

• Derangement in the balance of angiogenesis and pro-fibrotic mediators drives PH

• Disproportionate PH suggests a role for pulmonary vasodilators

Nathan SD and King CS. Treatment of pulmonary hypertension in idiopathic pulmonary fibrosis: shortfall in efficacy or trial design? Drug Design, Development and Therapy 2014; 8: 875-885
Pulmonary Hypertension in Interstitial Lung Disease

• Most data about PH in ILD comes from IPF studies

• Unclear how much IPF data can be applied to other ILDs

• Additionally clinical studies of PH in IPF typically involve lung transplant patients who are typically younger, have few comorbidities and more severe ILD
Mortality in IPF with PH

• PH is a significant predictor of mortality in IPF
• 1 year mortality of 28% with PH versus 5.5% without PH


PH in IPF

• Are there any clinical indices that are less invasive to obtain that may aid diagnosis, inform decisions and determine prognosis in IPF associated PH?
Echocardiography
Echocardiography in PH associated with IPF

• Echocardiography is a useful diagnostic tool for studying pulmonary hypertension

• Not a perfect test
Echocardiography in PH associated with IPF

Figure 2  Accuracy of the RVSP\textsubscript{echo} compared to the PASP\textsubscript{cath} pressure as measured by right-heart catheterization in relation to the mean PAP.

Figure 3  Diagnostic accuracy of incremental thresholds of the RVSP\textsubscript{echo} for the detection of PH in IPF depicted as a receiver operator characteristic curve.

Nathan SD et al. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respiratory Medicine 2008; 102: 1305-1310
Echocardiography in PH associated with IPF

• RVSP overestimated $\text{PASP}_{\text{cath}}$ in 48.3% and underestimated in $\text{PASP}_{\text{cath}}$ in 11.8% of cases

• Positive predictive value of RVSP can be improved when combined with PFT and 6MWT data

Nathan SD et al. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respiratory Medicine 2008; 102: 1305-1310
Echocardiography in PH associated with IPF

• Cohort of 374 lung transplant candidates
• Comparing echo to RHC
• Echo overestimated PASP by more than 10mmHg in 52% of cases

Echocardiography in PH associated with IPF

- Other echo measures are useful to identify PH-related abnormalities
  - RA enlargement
  - RV enlargement
  - Right ventricular dysfunction
Echocardiography in PH associated with IPF

• Rivera-Lebron et al in 2013

• Retrospective cohort of 135 IPF patients receiving RHC and TTE each within 24 hours of each other

• 29% had PH (mean mPAP 31+/- 6mmHg)

## Echocardiography in PH associated with IPF

**Table 3—Cox Proportional Hazards Models for RV Echocardiographic Predictors of Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Model</th>
<th></th>
<th></th>
<th>Adjusted Model&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th>Censored at Lung Transplantation&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
<td>HR</td>
</tr>
<tr>
<td>RV:LV</td>
<td>3.8</td>
<td>1.5-9.7</td>
<td>.006</td>
<td>4.5</td>
<td>1.7-11.9</td>
<td>.003</td>
<td>5.6</td>
</tr>
<tr>
<td>TAPSE &lt; 1.6 cm</td>
<td>2.0</td>
<td>1.0-3.7</td>
<td>.05</td>
<td>1.9</td>
<td>1.0-3.7</td>
<td>.06</td>
<td>1.5</td>
</tr>
<tr>
<td>TAPSE (continuous)</td>
<td>0.7</td>
<td>0.4-1.2</td>
<td>.22</td>
<td>0.8</td>
<td>0.5-1.5</td>
<td>.56</td>
<td>0.8</td>
</tr>
<tr>
<td>Moderate to severe RA dilation</td>
<td>2.4</td>
<td>1.2-4.7</td>
<td>.009</td>
<td>2.9</td>
<td>1.4-5.9</td>
<td>.004</td>
<td>3.0</td>
</tr>
<tr>
<td>Moderate to severe RV dilation</td>
<td>2.6</td>
<td>1.4-4.6</td>
<td>.001</td>
<td>2.7</td>
<td>1.4-5.4</td>
<td>.004</td>
<td>3.2</td>
</tr>
<tr>
<td>Moderate to severe RV dysfunction</td>
<td>4.9</td>
<td>2.5-9.6</td>
<td>&lt;.001</td>
<td>5.5</td>
<td>2.6-11.5</td>
<td>&lt;.001</td>
<td>7.5</td>
</tr>
<tr>
<td>RVSP, for 5 mm Hg increase</td>
<td>1.1</td>
<td>1.1-1.2</td>
<td>&lt;.001</td>
<td>1.2</td>
<td>1.1-1.3</td>
<td>&lt;.001</td>
<td>1.2</td>
</tr>
<tr>
<td>RVOT VTI</td>
<td>0.9</td>
<td>0.9-1.0</td>
<td>.16</td>
<td>0.9</td>
<td>0.9-1.0</td>
<td>.17</td>
<td>0.8</td>
</tr>
<tr>
<td>RVOT AT</td>
<td>1.0</td>
<td>0.9-1.0</td>
<td>.46</td>
<td>1.0</td>
<td>0.9-1.0</td>
<td>.64</td>
<td>1.0</td>
</tr>
<tr>
<td>Notching of RVOT</td>
<td>1.4</td>
<td>0.8-2.3</td>
<td>.27</td>
<td>1.4</td>
<td>0.8-2.4</td>
<td>.25</td>
<td>2.4</td>
</tr>
</tbody>
</table>

HR = hazard ratio. See Table 2 legend for expansion of other abbreviations.

<sup>a</sup>Adjusted for age, sex, race/ethnicity, height, weight, FVC and transplant status.

<sup>b</sup>Adjusted for age, sex, race/ethnicity, height, weight, FVC.

Pulmonary Function Tests
PFT in PH associated with IPF

- Patients with SPAP>50mmHg had more impaired DLCO and PaO2
- FEV1, FVC and FEV1/FVC ratio had no correlation with SPAP

PFT in PH associated with IPF

Table 1—Patient Characteristics Based on the Presence or Absence of PAH*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MAP ≤ 25 mm Hg (n = 54)</th>
<th>MAP &gt; 25 mm Hg (n = 25)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56.2 ± 1.0</td>
<td>54.7 ± 3.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>72.2</td>
<td>64.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Supplemental oxygen, %</td>
<td>17.6</td>
<td>66.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>52.5 ± 11.9</td>
<td>49.3 ± 11.0</td>
<td>0.13</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>55.5 ± 10.7</td>
<td>57.8 ± 12.1</td>
<td>0.27</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>37.6 ± 11.3</td>
<td>31.1 ± 10.1</td>
<td>0.04</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>19.1 ± 3.7</td>
<td>29.5 ± 3.3</td>
<td>n/a</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>4.3 ± 2.8</td>
<td>5.3 ± 3.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.8 ± 0.4</td>
<td>3.2 ± 1.3</td>
<td>0.20</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>8.4 ± 3.5</td>
<td>9.3 ± 3.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>61.5 ± 5.9</td>
<td>59.4 ± 5.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>29.9</td>
<td>60.0</td>
<td>0.001</td>
</tr>
<tr>
<td>1-yr mortality rate, %</td>
<td>5.5</td>
<td>28.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Values are given as the mean ± SD, unless otherwise indicated. RAP = right atrial pressure; MAP = mean arterial pressure.

• The presence of RHC diagnosed PH correlated with an impaired DLCO and need for supplemental oxygen

PFT in PH associated with IPF

- Measures of restrictive lung disease fail to correlate with the presence of PH in IPF

PFT in PH associated with IPF

- Retrospective study of 118 patients with IPF of whom 48% had RHC-confirmed PH
- Again showed a correlation of DLCO with presence of PH
- FVC/DLCO performed less well than DLCO alone
- FVC was not predictive

Six Minute Walk Test
PFT in PH associated with IPF

- The presence of PH in IPF correlates with 6 minute walk distance and nadir desaturation

<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP ≤ 25 mm Hg (n = 10)</th>
<th>MAP &gt; 25 mm Hg (n = 24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP, mm Hg</td>
<td>18.2 ± 3.6</td>
<td>29.8 ± 5.1</td>
<td>NA</td>
</tr>
<tr>
<td>6MWT distance, m</td>
<td>365.9 ± 81.8</td>
<td>143.5 ± 65.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO2, nadir on 6MWT, %</td>
<td>88.0 ± 3.5</td>
<td>80.1 ± 3.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mortality rate, %</td>
<td>37.5</td>
<td>70.0</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Values are given as the mean ± SD, unless otherwise indicated. NA = not applicable.

Radiographic Findings
CT Findings in PH with associated IPF

- No relationship between the presence of PH in IPF
  - Chest CT-determined fibrosis score
  - Ground-glass opacity score
  - Diameter of the main pulmonary artery
  - Ratio of the pulmonary artery to aorta diameter

Zisman D A et al. High-resolution chest CT findings do not predict the presence of pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Chest 2007; 132(3): 773-779
Treatment of PH in ILD

• Therapy for the underlying ILD if possible

• Supplemental O$_2$ for exercise and resting hypoxemia

• Diuretic therapy
Treatment of PH in ILD

• Listing for lung transplantation
  
  – Decline in FVC≥10% during 6 months of follow up
  
  – Decline in DLCO≥15% in 6 months follow up
  
  – Desaturation to <88% or distance <250m on 6 minute walk test or >50m decline in 6 minute walk distance over 6 month period
  
  – Pulmonary hypertension on RHC or 2D echocardiography
  
  – Hospitalization because of respiratory decline, pneumothorax or acute exacerbation

Treatment of PH in ILD

• Advanced therapies – vasoactive agents
  – ILD patients have not been systematically assessed in studies of pulmonary vasoactive agents

  – Potential for harm from worsened VQ mismatch
Treatment of PH in ILD

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

- IPF with DLCO<35% (no echo or RHC data reported)
- DB-RCT of 12 weeks of sildenafil (n-89) versus placebo (n-91)
- No effect on 1° outcome of 20% improvement of 6 minute walk distance
- Secondary outcomes including QOL, DLCO and PaO₂ favored treatment arm

Treatment of PH in ILD

Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

MeiLan K. Han, MD; David S. Bach, MD; Peter G. Hagan, MD; Eric Yow, MS; Kevin R. Flaherty, MD, FCCP; Galen B. Toews, MD; Kevin J. Anstrom, PhD; and Fernando J. Martinez, MD, FCCP; for the IPFnet Investigators*

• STEP-IPF Subgroup: RV dysfunction on TTE on sildenafil had a favorable effect on 6min walk distance at 12 weeks compared to placebo

Han MK et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013; 143(6): 1699-1708
Treatment of PH in ILD

- Endothelin receptor antagonists have been studied

- Primarily, the anti-fibrotic effects of ERAs in IPF and not necessarily the effects on PH
Treatment of PH in ILD

BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., Kevin K. Brown, Ganesh Raghu, Roland M. du Bois, David A. Lynch, Fernando Martinez, Dominique Valeyre, Isabelle Leconte, Adele Morganti, Sébastien Roux, and Juergen Behr

1Department of Medicine, University of California San Francisco, San Francisco, California; 2Department of Medicine; 3Division of Radiology, National Jewish Health, Denver, Colorado; 4Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; 4Imperial College, London, United Kingdom; 6Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan; 7Department of Pneumology, Avicenne Hospital, University of Paris, Bobigny, France; 8Clinical Development, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; and 9Department of Respiratory and Critical Care Medicine, Ruhr-University, Bochum, Germany

- DB-RCT
- 616 IPF patients with no reported PH indices
- No effect on time to clinical worsening or all cause mortality

Treatment of PH in ILD

• Artemis-IPF looked at ambrisentan in IPF but stopped early due to a lack of efficacy and evidence of harm

• Artemis-PH geared toward IPF patients with RHC-diagnosed PH
  – Also stopped early

  – Difficulty with recruiting patients with a confident diagnosis of IPF and associated PH

  – Evidence of a lack of efficacy from the PH subgroup (mPAP≥25) of Artemis-IPF
    • Over 48 weeks on ambrisentan no statistically significant differences in hemodynamic parameters on repeat RHC
    • Baseline mean mPAP 29.6 +/-7.53

Treatment of PH in ILD

- In IPF, PH is usually mild
- Does not require PAH meds
Treatment of PH in ILD

• Severe disproportionate PH is rare, is a different disease that may respond to PAH medications
Treatment of PH in ILD

• Disproportionate PH in ILD
  – Is the patient suffering from ILD with resultant disproportionate PH or from PAH with concomitant non-causative ILD?
Treatment of PH in ILD

• Disproportionate PH in ILD

Table 2
Criteria for the presence of severe pulmonary hypertension in patients with chronic lung disease*.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 of the following criteria must be met:</td>
</tr>
<tr>
<td>1. Mean PA pressure (PAPm) &gt; 35 mmHg</td>
</tr>
<tr>
<td>2. PAPm ≥ 25 mmHg with limited cardiac output (CI &lt; 2.0 l/min/m²)</td>
</tr>
<tr>
<td>3. Pulmonary vascular resistance (PVR) &gt; 480 dyn s cm⁻⁵</td>
</tr>
</tbody>
</table>

*As a rule, these criteria only apply if other causes of PH (e.g. chronic thromboembolic PH or left ventricular failure) have been excluded.

Treatment of PH in ILD

• Prescribed vasoactive PAH drugs when
  – Invasive assessment and the aforementioned criteria were met
  – Mild to moderate severity in ventilatory limitation (TLC>60%)
  – Rule out left heart disease and CTEPH

• Treat for 3-6 months and re-assess efficacy and justification to continue

# Treatment of PH in ILD

## 5th World Symposium on PH 2013 – Expert Guideline – Management of PH in Chronic Lung Disease

<table>
<thead>
<tr>
<th>Degree of ventilatory impairment</th>
<th>mPAP &lt;25 at rest</th>
<th>mPAP ≥25 and &lt;35 at rest</th>
<th>mPAP≥35 at rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF FVC≥70%</td>
<td>No PH</td>
<td>PH classification uncertain</td>
<td>Differentiate disproportionate PH from PAH with concomitant non-causative ILD</td>
</tr>
<tr>
<td></td>
<td>No PAH treatment</td>
<td>No data to support treatment with PAH drugs</td>
<td>Referral to expert center and undergo a comprehensive evaluation (HRCT, RHC, Complete PFT and CPET) and consideration for PAH meds</td>
</tr>
<tr>
<td>IPF FVC≤70%</td>
<td>No PH</td>
<td>PH classification uncertain</td>
<td>Severe IPF</td>
</tr>
<tr>
<td></td>
<td>No PAH treatment</td>
<td>No data to support treatment with PAH drugs</td>
<td>Prognosis is very severe – refer to an expert PH and ILD center.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Analysis of hemodynamics RHC and CPET and if CO is low or inadequately increasing CO with activity → Reducing PVR</td>
</tr>
</tbody>
</table>

- Thorough monitoring of gas exchange as patients may experience VQ MM and hypoxemia or normoxia due to higher ScvO₂ from improved CO

Summary Points

• PH is common in IPF and mostly mild and does not require PAH meds

• PH based on RHC and echo data predicts increased mortality in IPF/ILD

• DLCO, PaO2, 6MWD, and nadir desat correlate with PH in IPF/ILD

• FVC and CT radiographic indices do not correlate with PH in IPF/ILD

• Disproportionate PH in IPF is a unique diagnosis requiring thorough investigation and consideration for PAH medications in select cases
Thank You