Pathophysiology of pulmonary vasculature in IPF and Sleep Disorders: the role of pulmonary hypertension

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## CLASSIFICATION

### 4th World Symposium 2008

1. Pulmonary Arterial Hypertension

   - **Idiopathic PAH**
     - Disorders of the respiratory system and hypoxemia
       - Chronic obstructive pulmonary disease
       - **Interstitial lung diseases**
       - Sleep disorders
         - Alveolar hypoventilation
         - Chronic exposure to high altitude
         - Others...

2. Pulmonary hypertension due to left heart disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear or multifactorial mechanisms

   1: Hematologic disorders, myeloproliferative disorders, splenectomy
   2: Systemic disorders: vasculitis, sarcoidosis, PLCH, LAM, neurofibromatosis
   3: Metabolic disorders: GD, thyroid disorders, glycogen storage disease
   4: Others: tumoral obstruction, fibrosing mediastinitis, dialysis
Sleep apnea and PH

Experimental intermittent hypoxia administered for part of the day for just a few weeks in rodents results in:

- Pulmonary Hypertension
- Pulmonary arteriolar remodeling
- Right ventricular hypertrophy

- J Appl Physiol 99:2028-2035, 2005
Exposure to intermittent hypoxia was shown to decrease the relaxation to Acetylcholine, in pulmonary arteries pre-treated with phenylephrine.

ET-1 was found to induce a significant dosedependent contraction of the pulmonary artery.

Vessels from CIH rats were more sensitive to ET-1 than those from normoxia rats.

Thus, the hypoxic conditions used (2 min. cycles of 9%/21% O2, 8 h/day, 3 wks) eventually impaired endothelium-dependent vasodilation and increased vasoconstrictor responsiveness, which is in agreement with the pathology observed in human OSA.
CIH decreases eNOS expression and NO level in pulmonary arteries

- CIH increases ET-1 expression in the rat pulmonary artery
In the pulmonary artery segments from the CIH group, there were histopathological changes of the endothelial monolayer with cellular enlargement and edema, denudation of some endothelial cells.

PLoS One 2013; 8 (3)
The imbalance of between NO and ET pre-disposes the vasculature to increased tone, altered remodeling, proliferation and endothelial injury.
Individual values for the Doppler echocardiography-derived pulmonary artery systolic pressure (PASP) after crossover trial of 3-month sham vs 3-month effective CPAP treatment in 21 patients with OSA

Eur Heart J 2006. 27:1106-1113
During CPAP treatment there was a fall of daytime Ppa (room air breathing) in the 20 compliant patients with OSA, which reached statistical significance after 4 mo of treatment.

The biggest drop in Ppa was observed in pulmonary hypertensive patients with mean Ppa ≥ 20 mm Hg.

Total pulmonary vascular resistance (TPVR) fell significantly during CPAP treatment.

Daytime mean Ppa (estimated by Pulsed Doppler echocardiography) during room air breathing in 20 patients with OSA over 4 mo of CPAP treatment.

Am J Respir Crit Care Med 2002; 165: 152-158
## Frequency of PH in patients with OSAS

Table 1. Prevalence of PHT in OSAs

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>PH prevalence (%)</th>
<th>mPAP (mm Hg)</th>
<th>mPAP in PH</th>
<th>FEV₁ (% predicted)</th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Schroeder et al&lt;sup&gt;64&lt;/sup&gt;</td>
<td>22</td>
<td>59</td>
<td>21</td>
<td>25</td>
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<td>Tilkian et al&lt;sup&gt;28&lt;/sup&gt;</td>
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<td>Fletcher et al&lt;sup&gt;65&lt;/sup&gt;</td>
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<td>Podsusz et al&lt;sup&gt;36&lt;/sup&gt;</td>
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<td>Weitzenblum et al&lt;sup&gt;54&lt;/sup&gt;</td>
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<td>Krieger et al&lt;sup&gt;53&lt;/sup&gt;</td>
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<td>Sajkov et al&lt;sup&gt;59&lt;/sup&gt;</td>
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<td>Laks et al&lt;sup&gt;56&lt;/sup&gt;</td>
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<td>45</td>
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<td>Chaouat et al&lt;sup&gt;52&lt;/sup&gt;</td>
<td>220</td>
<td>17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>73</td>
<td>39</td>
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<tr>
<td>Sanner et al&lt;sup&gt;61&lt;/sup&gt;</td>
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<td>22</td>
<td>92</td>
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<td>Bady et al&lt;sup&gt;58&lt;/sup&gt;</td>
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<td>Sajkov et al&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>Arias et al&lt;sup&gt;63&lt;/sup&gt;</td>
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<td>-</td>
<td>40</td>
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</tbody>
</table>

Am J Cardiol. 2009;104:1300-6
Frequency and impact of PH in patients with OSAS
A retrospective study

Flow diagram showing hemodynamic characteristics (measured by right heart catheterization) in a cohort of 83 patients with OSA

Am J Cardiol. 2009;104:1300-6
All PH groups experienced significantly more frequent nocturnal desaturation than did the non-PH group (p < 0.05 for PH and PAH compared to non-PH group).

The PH group had the longest duration of nocturnal desaturation (i.e., percentage of total sleep time with oxygen saturation 90%; PAH 34 33% vs PVH 14 24% of total sleep time).

No significant difference was observed in the depth of desaturation (i.e., no significant difference was found in the minimum recorded oxygen saturation) and apnea-hypopnea index.
Most patients had mild or moderate elevations in pulmonary arterial pressure; however, 33% of patients had a mean pulmonary arterial pressure $\geq$ of 40 mm Hg

Am J Cardiol. 2009;104:1300-6
Frequency and impact of PH in patients with OSAS

Kaplan-Meier survival estimates in 83 patients with OSA (A) with and without PH and (B) those without PH compared to those with PAH and PVH.

Am J Cardiol. 2009;104:1300-6
In addition to factors such as age, forced expiratory volume in 1 second, diffusion capacity for carbon monoxide, and the apneahypopnea index, pulmonary hemodynamics are important correlates of increased mortality in patients with OSA.

Functional capacity is decreased and dyspnea is greater in patients with OSA and PH than in those with OSA but without PH agrees with observations regarding PH in other diseases such as idiopathic pulmonary fibrosis and sarcoidosis.
Methods: 169 patients with a diagnosis of PH confirmed by right heart catheterisation and clinically stable in NYHA classes II or III were prospectively investigated by polygraphy. Recruitment was independent of sleep-related symptoms and the use of vasodilator drugs or nasal oxygen.
Based on the AHI cutoff value of >10/hour of sleep, 45 PH patients (i.e. 26.6%) were found to suffer from sleep-disordered breathing. Of these, 27 patients (i.e. 16%) had OSA and 18 patients (i.e. 10.6%) had CSA. The severity of sleep-disordered breathing was mild-to-moderate with a mean AHI of 20/hour. OSA mainly occurred in patients with chronic thromboembolic PH (CTEPH) and COPD-associated PH. The majority of cases with CSA were seen in patients with IPAH, CTEPH and “other” diagnoses of PH.

Sleep Medicine 2013; 14: 247–251
Poor sleep quality and daytime sleepiness are extremely common in patients with IPF.

Poor sleep quality however does not seem to be associated to the degree of lung impairment.

Strong correlation has been found between oxygen saturation during sleep and Fatigue Severity Scale.

Chest 2008; 134: 693-698

Med Princ Pract 2009; 18: 10-15
Several studies show that nocturnal hypoxiemia is often present in DPLD and that these desaturations may lead to sleep fragmentation and impairment of sleep quality.
Pulmonary hypertension in IPF

- Frequency
- Prognosis
- Diagnosis
- Treatment
The prevalence of PH complicating the course of patients with IPF has been reported as occurring in 32 to 85% of patients.

9% of patients having a mPAP of greater than 40 mm Hg.

Initial prevalence of 41% increasing to more than 90% at follow-up.
Correlates of PH in IPF

- It appears that PH may not correlate with lung volumes in patients with IPF.
- Factors aside from progressive fibrosis are responsible for PH in IPF.
- Pulmonary artery remodeling might play a more relevant role than vasoconstriction, yet the two pathogenetic processes might be intimately interrelated.
The incidence and prevalence of PH in IPF remain unclear, with widely varying estimates. The differences reflect:

- varying patient populations
- varying underlying disease severity
- differing diagnostic modalities
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>N</th>
<th>Diagnosis</th>
<th>Definition of PH</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leutche et al.</td>
<td>2004</td>
<td>IPF</td>
<td>28</td>
<td>RHC</td>
<td>mPAP &gt; 35 mmHg</td>
<td>21.4</td>
</tr>
<tr>
<td>Nadrous et al.</td>
<td>2005</td>
<td>IPF</td>
<td>88</td>
<td>Echo</td>
<td>sPAP &gt; 35 mmHg, sPAP &gt; 50 mmHg</td>
<td>84, 31</td>
</tr>
<tr>
<td>Hamada et al.</td>
<td>2007</td>
<td>IPF</td>
<td>70</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>8.1</td>
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<tr>
<td>Zisman et al.</td>
<td>2007</td>
<td>IPF</td>
<td>65</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>41.5</td>
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<tr>
<td>Patel et al.</td>
<td>2007</td>
<td>IPF</td>
<td>41</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg + PCWP ≤ 15 mmHg</td>
<td>20</td>
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<tr>
<td>Shorr et al.</td>
<td>2007</td>
<td>IPF</td>
<td>2.5</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>46.1</td>
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<tr>
<td>Nathan et al.</td>
<td>2008</td>
<td>IPF</td>
<td>118</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg</td>
<td>40.7</td>
</tr>
<tr>
<td>Song et al.</td>
<td>2009</td>
<td>IPF</td>
<td>131</td>
<td>Echo</td>
<td>sPAP &gt; 40 mmHg</td>
<td>25</td>
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<tr>
<td>Minai et al.</td>
<td>2009</td>
<td>IPF</td>
<td>148</td>
<td>RHC</td>
<td>mPAP &gt; 25 mmHg, mPAP &gt; 40 mmHg</td>
<td>45.9, 14.2</td>
</tr>
<tr>
<td>Kimura et al.</td>
<td>2012</td>
<td>IPF</td>
<td>101</td>
<td>RHC</td>
<td>mPAP &gt; 20 mmHg</td>
<td>34.6</td>
</tr>
</tbody>
</table>
Pulmonary hypertension in IPF

- 118 patients with IPF and RHC (FVC% 54.6 and Dlco% 36.3)
- 48 patients (40.7%) qualified as having PH

- 79 patients with IPF and RHC (FVC% 49.3 and Dlco% 31.1)
- 25 patients (31.6%) qualified as having PH

Hamada K et al. Chest 2007, 131:650-656
- 70 patients with IPF and RHC (early stage of IPF: FVC% 76 and Dlco% 45)
- 6 patients (8.1%) qualified as having PH

- 2525 patients with IPF and RHC (FVC% 48.4) Patients undergoing assessment for lung transplantation
- 932 patients (46.1%) qualified as having PH
Patients assessed at the time of transplantation evaluation: PH prevalence of 36%

At the time of transplantation, 85% of the same patient cohort had PH

Conclusions

PH is progressive and the prevalence and severity of PH is temporally related to the progression of IPF

Nathan SD et al. Respiration 2008; 76: 288-94
### Pulmonary Hypertension in IPF

<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP ≤ 25 mmHg (n= 10)</th>
<th>MAP &gt; 25 mmHg (n= 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP, mmHg</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>

The presence of PH in IPF is associated with higher mortality and its development contributes to the deterioration of IPF patients.
As opposed to PAH, the PH in IPF tends to be mild in most patients.

In one series, approximately 50% of the patients with PH had an mPAP in the 25 to 30 mmHg range, while only about 10% of patients with IPF listed for transplantation have severe PH as defined by a mPAP > 40 mmHg.

Lettieri CJ et al. Chest 2006;129: 746-752
Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883
Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic disease and suspected pulmonary hypertension

Corte TJ et al. Thorax 2009; 64: 883

In severe diffuse lung disease, raised PVR strongly predicts death within 1 year independent of disease severity or diagnosis of IPF. PVR is superior to other measurements at RHC and also to non-invasive tests (alone or in combination). These findings suggest that, in advanced lung disease, prognostic information that is only obtainable by RHC has important management implications.
Pulmonary rare diseases
Ospedale San Giuseppe Experience (2001-2012)
Tot. 996 patients

- IPF 363 pts
- Sarcoidosis
- BOOP
- LAM
- PLCH
- Pulmonary hypertension
- Others IIP
- IPF
- Vasculitides
<table>
<thead>
<tr>
<th>Variables</th>
<th>MAP ≤ 25 mmHg (n= 17)</th>
<th>MAP &gt; 25 mmHg (n= 13)</th>
<th>MAP &gt; 35 mmHg (n= 4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP, mmHg</td>
<td>19.4 ± 3.6</td>
<td>32.4 ± 6</td>
<td>40.5 ± 2.6</td>
<td>NA</td>
</tr>
<tr>
<td>6MWT distance, m</td>
<td>222.0 ± 118.5</td>
<td>222.3 ± 118.5</td>
<td>203.7 ± 128.3</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>FVC, %</td>
<td>51.6 ± 13.8*</td>
<td>63.8 ± 16*</td>
<td>56.0 ± 6.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1, %</td>
<td>58.3 ± 16.3</td>
<td>65.8 ± 18.8</td>
<td>55.2 ± 3.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>31.4 ± 9.6</td>
<td>24.2 ± 13.0</td>
<td>29.0 ± 7.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CI, l/min/m2</td>
<td>3.4 ± 0.55*</td>
<td>2.9 ± 0.7*</td>
<td>2.8 ± 0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVR, wood units</td>
<td>3.5 ± 1.1*</td>
<td>6.9 ± 1.4*</td>
<td>10.3 ± 2.0</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Harari S. submitted
In the PH group 4 pts had out of proportion PH (mean PAP >35 mmHg) and walked 203.7 meters ±128.3 that did not statistically differ from the latters - mean survival in those pts was 8 months.

Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with or without PH. 6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.
## Trials of therapy for PH in IPF

<table>
<thead>
<tr>
<th>Type of lung disease</th>
<th>Investigator/year</th>
<th>Type of study</th>
<th>N</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Lung fibrosis</td>
<td>Ghofrani et al, 2002</td>
<td>OL-RCT</td>
<td>16</td>
<td>Sildenafil, iNO, epoprostenol</td>
<td>Sildenafil improved pulmonary hemodynamics and gas exchange</td>
</tr>
<tr>
<td>IPF</td>
<td>Krowka et al, 2007 (multicenter)</td>
<td>DB-RCT</td>
<td>51</td>
<td>Inhaled iloprost</td>
<td>No improvement in 6MWT, NYHA/WHO Class</td>
</tr>
<tr>
<td>IPF</td>
<td>Collard et al, 2007</td>
<td>OL trial</td>
<td>14</td>
<td>Sildenafil</td>
<td>57% had significant increase in 6MWT</td>
</tr>
</tbody>
</table>
STEP-IPF - Sildenafil in IPF

- Prospective, randomized, clinical trial: to evaluate effectiveness of sildenafil at improving breathing function, exercise capacity and QoL in patients with advanced IPF

- Primary endpoint: Change in 6-MWD (defined as $\geq 20\%$ improvement or $\leq 20\%$ improvement)

STEP-IPF Results

<table>
<thead>
<tr>
<th>≥ 20% improvement in 6MWD</th>
<th>Sildenafil</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/89 (7%)</td>
<td>9/89 (10%)</td>
<td>6/91 (7%)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

- No significant change in **6MWD** at 12 or 24 weeks
- No difference in mortality or acute exacerbations after 12 or 24 weeks
- **QOL**
  - Improvement with treatment on St. George’s Respiratory Questionnaire \((P = 0.01)\)
  - No improvement on SF-36 or EQ-5D tests
- **Dyspnea**
  - Improvement with treatment on SOB Questionnaire \((P = 0.006)\)
  - No improvement on Borg Dyspnea Index after walk test
- **Gas exchange** at 12 weeks
  - Improvement in \(D_{LCO}\) \((P = 0.04)\)
  - Improvement in arterial oxygen saturation \((P = 0.05)\)
- Serious adverse events were similar in the two study groups.

This study was intended to examine the effects of sildenafil in a population with advanced IPF, defined as a DLCO of less than 35% of the predicted value, not a population with IPF and documented PH.

PH is common, although not universally present, in patients with advanced IPF.

The lack of RHC before and after the study intervention precluded the ability to determine whether the potential benefits of sildenafil in patients with advanced IPF (e.g., decreased dyspnea, improved quality of life, and improved gas transfer) were driven by the subgroup with elevated PAP.
Methods:

Of 180 subjects enrolled into STEP-IPF, echocardiograms from 119 were available for independent review (sildenafil, n 56; placebo, n 63)

Right ventricular hypertrophy (RVH), right ventricular systolic dysfunction (RVSD), and right ventricular systolic pressure (RVSP) were assessed.

Multivariable linear regression models estimated the relationship between RV abnormality, sildenafil treatment, and changes in 6MWD, St. George’s Respiratory Questionnaire (SGRQ), the EuroQol instrument, and SF-36 Health Survey (SF-36) from enrollment to 12 weeks.

Chest 2013; 146: 1699
Patients with any evidence of RVSD treated with sildenafil demonstrated a 99.3 m greater 6MWD as compared with those treated with placebo.

Treatment with sildenafil in subjects with RVSD resulted in a significantly lower SGRQ total score.
Ambrisentan PH-IPF trial was interrupted prematurely because of a lack of superior activity of the experimental arm (unpublished data)
**Objective:** To determine whether ambrisentan, an ETA receptor–selective antagonist, reduces the rate of IPF progression.

**Design:** Randomized, double-blind, placebo-controlled, event driven trial (ClinicalTrials.gov: NCT00768300)

**Participants:** Patients with IPF aged 40 to 80 years with minimal or no honeycombing on HRCT.

**Intervention:** Ambrisentan, 10 mg/d, or placebo.

**Measurements:** Time to disease progression, defined as death, respiratory hospitalization, or a categorical decrease in lung function.

**Conclusion:** Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations.
Out-of-proportion pulmonary hypertension
A paradigm for rare diseases

we can highlight some of the limitations of this study design, which have also been observed in other studies.

First, patients who were deemed eligible for enrollment included not only those with a PAP > 35 mm Hg, but also subjects with a mPAP > 25 mm Hg.

Second, the 6-MWT, which is a non validated and probably misleading test, was chosen as the primary end point.

This test has not yet been validated as a useful screen for PH in IPF, and its prognostic significance is still unknown.

Harari S. Chest, 2012; 142:1087-1088
### Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial


<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline demographics and clinical characteristics of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>22</td>
</tr>
<tr>
<td>Age years</td>
<td>60.5 (33.0–80.0)</td>
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<tr>
<td>White ethnicity</td>
<td>22 (100.0)</td>
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<tr>
<td>Male sex</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>BMI kg·m⁻²</td>
<td>26 ± 4</td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>19 (86.4)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>6-min walk distance m</td>
<td>316 ± 96</td>
</tr>
</tbody>
</table>

**Underlying disease**

- Idiopathic pulmonary fibrosis | 13 (59.1)
- Non-specific interstitial lung disease | 5 (22.7)
- Sarcoidosis | 3 (13.6)
- Systemic sclerosis | 1 (4.5)

**Pulmonary function**

- TLC % pred | 67 ± 12
- FVC % pred | 67 ± 20
- FEV₁ % pred | 67 ± 17
- DLCO* mmol·min⁻¹·kPa⁻¹ | 2.7 ± 1.5

**Haemodynamics and blood gases**

- Mean pulmonary artery pressure mmHg | 40 ± 10
- Pulmonary vascular resistance dyn·s⁻¹·cm⁻⁵ | 656 ± 201
- Cardiac output L·min⁻¹ | 4.3 ± 1.4
- Systolic blood pressure mmHg | 136 ± 16
- Heart rate beats per minute | 78 ± 14
- SPO₂ % | 94 ± 3
- SvO₂ % | 62 ± 12
- PaCO₂ mmHg | 39 ± 7
Objective: to assess the safety, tolerability and preliminary efficacy of riociguat, in patients with PH-ILD

Design: open-label, uncontrolled pilot trial

Intervention: patients received oral riociguat (1.0–2.5 mg three times daily) for 12 weeks (n=22), followed by an ongoing long-term extension (interim analysis at 12 months) in those eligible (n=15)

Conclusions: Riociguat was well tolerated by most patients and improved cardiac output and PVR, but not mPAP. Further studies are necessary to evaluate the safety and efficacy of riociguat in patients with PH-ILD.
Conclusions

- OSA can be complicated by the development of PH
- PH in the context of OSA has prognostic implications for the patient
- PH in OSA is usually mild-moderate, but sometimes it can be severe
- CPAP treatment can reduce PH values
Conclusions

◆ IPF is commonly complicated by the development of PH
◆ PH in the context of IPF has functional and prognostic implications for the patient
◆ There is no sufficient evidence that the drugs currently used for PAH are safe and effective in patients with PH associated with IPF
◆ Patients with PH and IPF disease should be treated in the setting of clinical trials whenever possible
Conclusions

- The use of drugs currently approved for PAH, in patients with IPF is not recommended until further data are available.
- Lung transplantation is the best option for these patients.
Occlusion of a vascular lumen by intimal hyperplasia and fibrosis

PH due to:
- granulomatous vasculitis
- mechanical compression of the large pulmonary artery
- distortion of the vascular bed

Sarcoidosis

PLCH

LAM

PH in LAM is rare and mild
# PULMONARY HYPERTENSION IN LUNG TRANSPLANT CANDIDATES WITH INTERSTITIAL LUNG DISEASE

## 43 IDIOPATHIC FIBROSIS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>43.6% ± 13.8 S.D.</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>52.3% ± 21.7 S.D.</td>
<td></td>
</tr>
<tr>
<td>Tiffenau</td>
<td>93.7% ± 18.7 S.D.</td>
<td></td>
</tr>
<tr>
<td>PaO2</td>
<td>56.8% ± 14.09 S.D.</td>
<td></td>
</tr>
<tr>
<td>PAPm</td>
<td>33.6% ± 9.8 S.D.</td>
<td></td>
</tr>
<tr>
<td>C.I.</td>
<td>3.18% ± 0.69 S.D.</td>
<td></td>
</tr>
<tr>
<td>PVRi</td>
<td>8.3% ± 3.45 S.D.</td>
<td></td>
</tr>
</tbody>
</table>

Harari S., Simonneau G. Brenot F. et Coll.  
J Heart Lung Transplant 1997 Apr;16(4):460-463
The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis

- 88 pts with IPF submitted to EcoCG
- sPAP = 48 ± 16 mmHg
- sPAPs correlated to DLco
- Pts with sPAP > 50 mmHg have bad survival than the others (p=0.009)

Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected PH

- 66 pts with RVSP > 40 mmHg and/or RVD with dyspnea or hypoxia not correlated to fibrosis
- 50 pts (76%) with mPAP >25 mmHg (mPAP 33.5±11.8 mmHg, PVR 5.9±4.3 Wood units)
- Elevated PVR values are prognostic factor of mortality

Sildenafil Improves Walk Distance in Idiopathic Pulmonary Fibrosis

Harold B. Collard, MD, FCCP; Kevin J. Austrom, PhD; Marvin I. Schwarz, MD, FCCP; and David A. Zisman, MD, FCCP

(CHEST 2007; 131:897–899)

Table 1—Clinical Characteristics*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>72 (7); 71 (63, 85)</td>
</tr>
<tr>
<td>Female gender</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Duration of symptoms, mo</td>
<td>40.4 (30.0); 34.5 (10, 84)</td>
</tr>
<tr>
<td>Surgical lung biopsy-proven disease</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Right-heart catheterization performed</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Mean PA pressure, † mm Hg</td>
<td>30.7 (5.7); 29.5 (29.0, 43.0)</td>
</tr>
<tr>
<td>FVC L % predicted</td>
<td>2.65 (1.18); 2.39 (0.99, 5.31)</td>
</tr>
<tr>
<td>DLCO mL/min/mm Hg % predicted</td>
<td>69.6 (18.4); 71.5 (41.0, 100.0)</td>
</tr>
<tr>
<td>DLCO mL/min/mm Hg % predicted</td>
<td>7.39 (3.92); 7.25 (2.90, 17.90)</td>
</tr>
<tr>
<td>DLCO mL/min/mm Hg % predicted</td>
<td>32.4 (17.0); 33.0 (13.0, 79.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>RHC</th>
<th>Dose (tid), mg</th>
<th>6MWD, m</th>
<th>BDI</th>
<th>AE(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Y</td>
<td>50</td>
<td>40</td>
<td>20</td>
<td>15, 13</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>50</td>
<td>60</td>
<td>40</td>
<td>15, 13</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
<td>50</td>
<td>382</td>
<td>-8</td>
<td>7, 7</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>50</td>
<td>100</td>
<td>-40</td>
<td>11, 13</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>50</td>
<td>135</td>
<td>40</td>
<td>12, 12</td>
</tr>
<tr>
<td>6</td>
<td>Y</td>
<td>20</td>
<td>55</td>
<td>45</td>
<td>12, 11</td>
</tr>
<tr>
<td>7</td>
<td>Y</td>
<td>20</td>
<td>75</td>
<td>15</td>
<td>10, 7</td>
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<tr>
<td>8</td>
<td>Y</td>
<td>20</td>
<td>60</td>
<td>125</td>
<td>11, 9</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>50</td>
<td>518</td>
<td>7</td>
<td>6, 6</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>20</td>
<td>65</td>
<td>15</td>
<td>13, 12</td>
</tr>
<tr>
<td>11</td>
<td>Y</td>
<td>20</td>
<td>70</td>
<td>205</td>
<td>6, 7</td>
</tr>
<tr>
<td>12</td>
<td>Y</td>
<td>40</td>
<td>155</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>Y</td>
<td>20</td>
<td>105</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>N</td>
<td>25</td>
<td>250</td>
<td>8</td>
<td>None</td>
</tr>
</tbody>
</table>

*CHEST 2007; 131:897–899

†CHEST 2007; 131:897–899

‡CHEST 2007; 131:897–899
The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease

TAMERA J. CORTE, MICHAEL A. GATZOU LIS, LISA PAR FITT, CARL HARRIES, ATHOL U. WELLS AND S. JOHN WORT

15 ILD pts and PAH submitted to six month-therapy of sildenafil:

1 IPF
5 NSIP
2 ILD associated to polymiositis
1 chronic hypersensitivity pneumonia
5 Sarcoidosis
1 histyocitosis

Table 1 Clinical data before and after 6-month sildenafil therapy

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Pre-sildenafil</th>
<th>n</th>
<th>Post-sildenafil</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain natriuretic peptide (pmol/L)</td>
<td>15</td>
<td>37 (5–452)</td>
<td>12</td>
<td>15.5 (3–220)</td>
<td>0.03†</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>13</td>
<td>156 ± 101</td>
<td>6</td>
<td>256 ± 57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Right ventricular systolic pressure (mm Hg)</td>
<td>11</td>
<td>73.8 ± 17.8</td>
<td>11</td>
<td>72.6 ± 28.0</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>14</td>
<td>23.8 ± 12.8</td>
<td>9</td>
<td>26.4 ± 16.5</td>
<td>NS</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>14</td>
<td>52.6 ± 15.4</td>
<td>11</td>
<td>55.9 ± 13.8</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>11</td>
<td>7.3 ± 1.8</td>
<td>9</td>
<td>7.8 ± 2.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

In this retrospective review of intention to treat ILD patients with PH, we report that 6-month oral sildenafil therapy was safe and well tolerated, and was associated with a significant improvement in 6MWD and BNP levels, but no change in echocardiographic haemodynamic values (RVSP). Our results suggest that sildenafil may have a role in the management of PH in ILD patients. However, prospective placebo-controlled trials in patients with PH and ILD are warranted before therapeutic recommendations can be made for this patient group.