Pulmonary Hypertension and Sleep Apnea

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Pulmonary Division, University Hospital of Zurich
## Prevalence & Severity of PH in OSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>PH % prevalence</th>
<th>mPAP (mm Hg)</th>
<th>mPAP in PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder et al</td>
<td>22</td>
<td>59</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Tilkian et al</td>
<td>12</td>
<td>67</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Fletcher et al</td>
<td>24</td>
<td>79</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Podszius et al</td>
<td>65</td>
<td>20</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Weitzenblum et al</td>
<td>46</td>
<td>20</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Krieger et al</td>
<td>114</td>
<td>19</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Sajkov et al</td>
<td>27</td>
<td>41</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Laks et al</td>
<td>100</td>
<td>42</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Chaouat et al</td>
<td>220</td>
<td>17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sanner et al</td>
<td>92</td>
<td>20</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Bady et al</td>
<td>44</td>
<td>27</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Sajkov et al</td>
<td>32</td>
<td>34</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Alchanatis et al</td>
<td>29</td>
<td>21</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Arias et al</td>
<td>23</td>
<td>43</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>

Prevalence: 79% in the entire cohort, 17% in patients with PH

Mean PAP: ≤32 mmHg

Sakov & McEnvoy. Prog Cardiovasc Dis 2009;51:363
Sleep Apnea

Daytime Pulmonary Hypertension

Coexisting Disorders

1

2

3
Cardio-Vascular Consequences of Sleep Apnea

Obstructive Apnea

- Intrathoracic Pressure Swings
  - Shear Stress
- Arousals
  - Sympathetic activation
- Intermittent Hypoxia
  - Oxydative Stress Inflammation

Endothelial Dysfunction, Cardiovascular Diseases
PAP During REM-Sleep OSA

Subj. A.S.

Niijima et al AJRCCM 1999;159:1766
Association of OSA and PH

Fig. 1. – Pulmonary artery pressure (Ppa), respiratory function, RDI and Sao2: min, age and BMI in the entire patient group (n=100). Paco2: arterial oxygen tension; Paco2: arterial carbon dioxide tension; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; RDI: respiratory disturbance index; Sao2: min; minimal arterial oxygen saturation during apnoea; BMI: body mass index.

Laks et al. Eur Respir J 1995;8:537
# OSA and PH: Determinants of PAP

## Table 6—Univariate and Multivariate Prediction of PAP*

<table>
<thead>
<tr>
<th>(1) Linear Correlations Between PAP and Several Variables</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.17 (NS)</td>
<td>BMI</td>
</tr>
<tr>
<td>VC</td>
<td>-0.51 (p&lt;0.001)</td>
<td>VC %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>predicted</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>-0.53 (p&lt;0.001)</td>
<td>FEV$_1$/VC</td>
</tr>
<tr>
<td>TLC</td>
<td>-0.43 (p&lt;0.001)</td>
<td>Raw</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>-0.42 (p&lt;0.001)</td>
<td>PaCO$_2$</td>
</tr>
<tr>
<td>AI</td>
<td>0.24 (p&lt;0.001)</td>
<td>AHI</td>
</tr>
<tr>
<td>MSaO$_2$</td>
<td>-0.54 (p&lt;0.001)</td>
<td>Minimal SaO$_2$</td>
</tr>
</tbody>
</table>

## (2) Stepwise Multiple Regression Analysis of PAP

\[
PAP = 0.31 \text{PaCO}_2 - 0.0015 \text{FEV}_1 + 0.72 \text{Raw} - 0.26 \text{MSaO}_2 + 29.98
\]

- $r^2=0.50$; PaCO$_2$ accounts for 0.32; FEV$_1$ for 0.12; Raw for 0.04; MSaO$_2$ for 0.02; Complete set data available for 142 patients.
- SEE=4.2 mm Hg.

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*For definition of abbreviations: see Tables 1 through 3.

Units: PaCO$_2$: mm Hg; FEV$_1$: mL; Raw: cm H$_2$O/L/s; MSaO$_2$: %.

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## OSA + COPD: „Overlap Syndrome“

<table>
<thead>
<tr>
<th></th>
<th>OSA, normal PFT n=235, 89%</th>
<th>Overlap Syndr. n=30, 11%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV1/FVC</strong></td>
<td>75 ±7</td>
<td>50 ±6*</td>
</tr>
<tr>
<td><strong>AHI, 1/h (&gt;20/h)</strong></td>
<td>76 ±32</td>
<td>89 ±37</td>
</tr>
<tr>
<td><strong>Age, y (males)</strong></td>
<td>53 ±10 (91%)</td>
<td>58 ±9 (100%) *</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>33 ±7</td>
<td>31 ±5</td>
</tr>
<tr>
<td><strong>PaO₂, mmHg</strong></td>
<td>74 ±10</td>
<td>66 ±10*</td>
</tr>
<tr>
<td><strong>PaCO₂, mmHg</strong></td>
<td>38 ±4</td>
<td>42 ±6*</td>
</tr>
<tr>
<td><strong>Nocturnal SpO₂, %</strong></td>
<td>91 ±4</td>
<td>89 ±4</td>
</tr>
<tr>
<td><strong>PAP, mmHg</strong></td>
<td>15 ±5</td>
<td>20 ±6</td>
</tr>
</tbody>
</table>

Chaouat et al. AJRCCM 1995;151:82
Consequences of "Overlap Syndrome"

- COPD
- OSAS
- Hypoxia
- Oxydative stress
- TNFα
- IL-8
- CRP
- IL-6
- Endothelial dysfunction
- Atherosclerotic plaques
- Cardiovascular disease

Cigarette smoking
Adipose Tissue

McNicholas. AJRCCM 2009;180:692
OSA&PH And Patients With Normal PFT

92 OSA patients
AHI>10/h, normal PFT, Normal daytime ABG

n=18 PAP>20 mmHg
AHI 44 ±28/h
Time SpO2<90% 41 ±37%

n=74: PH Absent
AHI 39 ±23/h
Time SpO2<90% 19 ±25%

Sanner et al. Arch Int Med 1997;157:2483
PH in Mice Exposed to Hypoxia

- **Normoxia**: FiO2 21%
- **Intermitt**: every 2 min FiO2 10% & 21% 2min 8/24h
- **Continuous**: FiO2 10% (5’600m)

* Fagan. JAP 2001;90:2502
Vascular Remodelling in Mice Exposed to Intermittent and Continuous Hypoxia

Number of myosin positive vessels

Fagan. JAP 2001;90:2502
### Characteristics of Patients with OSA & PH w/o Cardiopulmonary Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>21 OSA Pat. mPAP&lt;20</th>
<th>11 OSA Pat. mPAP≥20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 ±3</td>
<td>54 ±3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32 ±1</td>
<td>31 ±1</td>
</tr>
<tr>
<td>AHI, 1/h (&gt;10/h)</td>
<td>47 ±5</td>
<td>45 ±7</td>
</tr>
<tr>
<td>tSpO₂&lt;90, %</td>
<td>34 ±11</td>
<td>38 ±17</td>
</tr>
<tr>
<td>PaO₂, PaCO₂ mmHg</td>
<td>79 ±2; 41 ±1</td>
<td>77 ±3; 40 ±1</td>
</tr>
<tr>
<td>FEV1% (FEV1/FVC&gt;75%)</td>
<td>101 ±2</td>
<td>105 ±4</td>
</tr>
<tr>
<td>FRC-Closing Capacity, L</td>
<td>0.27 ±0.09</td>
<td>-0.16 ±0.11*</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>15 ±1</td>
<td>24 ±1*</td>
</tr>
</tbody>
</table>

Sajkov et al. AJRCCM 1999;159:1518
Characteristics of Patients with OSA & PH w/o Cardio-Pulmonary Disease

Hypoxic Vasoreactivity

PAP Response to Dobutamin

Sajkov et al. AJRCCM 1999;159:1518
Effect of CPAP in OSA with PH

22 patients of 32 in initial study

Sajkov et al. AJRCCM 2002;165:152
Effect of CPAP on Hypoxic Vasoreactivity

ΔPAP/ΔSO₂ = 10 mmHg/%
ΔPAP/ΔSO₂ = 6 mmHg/%

Baseline w/o CPAP
Months on CPAP

Inspired Oxygen Concentration

Sajkov et al. AJRCCM 2002;165:152
Effect of CPAP on Pulmonary Flow Reserve

all, n=20

n=5, initial PAP>20

Sajkov et al. AJRCCM 2002;165:152
Randomized Trial on Effect of CPAP on PAP in OSA

Inclusion criteria:
- AHI > 10/h
- Epworth > 10

Exclusion criteria:
- Lung disease
- Heart disease
- Systemic hypertension
- Diabetes

Arias et al. Eur J Cardiol 2006;27:1106
PH in OSA: Effect of CPAP

PAPs>30mmHg
AHI 69 ±25/h
BMI=33.6 ±4.4 kg/m²
FVC 94 ±12 %pred

PAPs<30mmHg
AHI 25 ±15/h
BMI=28.9 ±2.9 kg/m²
FVC 117 ±15 %pred
all P<0.05 vs. PAP>30

n=23

Arias et al. Eur J Cardiol 2006;27:1106
Sleep Apnea

1. Coexisting Disorders

2. Daytime Pulmonary Hypertension

3.
Control of Breathing

Alterations in LV and RV failure that destabilize ventilation

Medullary & Central Controller

Chemo-Receptors

Dead Space

Lung

Heart & Vasculature

Body Tissues

P_{\text{aCO}_2}

↓↓ Pa_{\text{O}_2}

dead space ventilation

V'/Q' mismatch

transport delay due to low CO RV & LV dysfunction

Khoo et al JAP 1982;53:644
Cheyne-Stokes Respiration in IPAH

Schulz et al. ERJ 2002;19:658
## Cheyne-Stokes Respiration in IPAH

<table>
<thead>
<tr>
<th>Metric</th>
<th>No CSR, n=14</th>
<th>CSR, n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAPm, mmHg</strong></td>
<td>53 ±4</td>
<td>63 ±2*</td>
</tr>
<tr>
<td><strong>AHI, 1/h (&gt;20/h)</strong></td>
<td>9 ±3</td>
<td>37 ±5*</td>
</tr>
<tr>
<td><strong>Nocturnal SpO₂, %</strong></td>
<td>92 ±1</td>
<td>89 ±1*</td>
</tr>
<tr>
<td><strong>DLCO, %pred.</strong></td>
<td>70 ±4</td>
<td>57 ±5*</td>
</tr>
<tr>
<td><strong>PaO₂, mmHg</strong></td>
<td>9.1 ±0.7</td>
<td>6.6 ±0.9</td>
</tr>
<tr>
<td><strong>PaCO₂, mmHg</strong></td>
<td>3.9 ±0.2</td>
<td>3.9 ±0.1</td>
</tr>
<tr>
<td><strong>CI, L/min/m²</strong></td>
<td>2.21 ±0.2</td>
<td>1.38 ±0.1*</td>
</tr>
<tr>
<td><strong>RVEF, %</strong></td>
<td>20 ±2</td>
<td>7 ±1%*</td>
</tr>
</tbody>
</table>

Schulz et al ERJ 2002;19:658
Oxygen Therapy in IPAH with CSR

Schulz et al ERJ 2002;19:658
38 patients with PH
PAPm 43 mmHg
PAH, n=23
CTEPH, n=15

No difference in hemodynamics, PaO2, PaCO2, PFT

Ulrich et al. Chest 2008;133:1375
## QoL in Patients with PH & CSR

<table>
<thead>
<tr>
<th></th>
<th>No SA</th>
<th>CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=19</td>
<td>Central AHI ≥10/h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=15 (39%)</td>
</tr>
<tr>
<td>Epworth score</td>
<td>6 (4-10)</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>MSLHF physical</td>
<td>19 (18-24)</td>
<td>24 (21-28)**</td>
</tr>
<tr>
<td>emotional</td>
<td>7 (3-16)</td>
<td>10 (7-14)</td>
</tr>
<tr>
<td>SF-36 physical</td>
<td>37 (31-45)</td>
<td>29 (26-35)**</td>
</tr>
<tr>
<td>mental</td>
<td>48 (39-59)</td>
<td>55 (46-59)</td>
</tr>
</tbody>
</table>

Ulrich et al. Chest 2008;133:1375
Daytime Cheyne-Stokes Respiration in LVF

Brack et al., Chest 2007;132:1463
Diagnostic Performance of Ambulatory Polygraphy Compared to PSG

Performance to predict Polysomnography $\text{AHI}>10/h$

Polygraphy ROC area $0.93 \pm 0.06$

Pulse oximetry alone ROC area $0.66 \pm 0.16$

Ulrich et al. Chest 2008;133:1375
Conclusions OSA & PH

• <20-80% of OSA patients have PH
  – Confounders: obesity, COPD, CHF
  – Predictors: FEV1, PaO$_2$, PaCO$_2$, BMI

• PH may occur in OSA patients w/o cardiopulmonary disease
  – but is rare and mild
  – poor correlation with AHI
  – associated with increased hypoxic pulmonary vasoreactivity, may lead to vascular remodelling
  – is reversible with CPAP

• PH patients may have CSR and OSA
  – evaluation with ambulatory polygraphy
  – Treatment ? (oxygen)
Summary Cheyne-Stokes Respiration

- CSR and OSA are both common in CHF, stroke, pulmonary hypertension.
- Predictors of nocturnal CSR: age, severe CHF, atrial fibrillation, daytime CSR, low PaCO$_2$.
- CSR in CHF is associated with reduced physical activity and QoL and increased mortality.
- Since symptoms of CSR in CHF are non-specific patients at risk should undergo a sleep study.
Characteristics of Patients with PH and OSA

Sajkov et al. AJRCCM 1999;159:1518
• Pathophysiological link
  – Response of pulmonary circulation to hypoxia
  – OSA as a cause of PHTN
  – PHTN as a cause of CSR

• Clinical relevance PHTN in OSA, causal relationship?
  – Prevalence, association: in general in overlap syndrome
  – Symptoms, QoL
  – First studies in unselected patients: PH associated with poor lung function, impaired gas exchange and obesity
  – Subsequent studies in OSA with normal lung function and normal daytime PO2 also had PH.
  – Some OSA patients may show hyperreactive PA to hypoxia; see also OSA at altitude.
  – Recent studies reveal reduction in PH with CPAP

• Clinical relevance CSR&OSA in PHTN
  – Prevalence
  – Symptoms, QoL
  – Treatment

• Diagnosis

• 35'max
Mechanisms of CSR in Heart Failure

- Increased circulatory delay
- Sympathetic overstimulation
- Modulation of chemoreflex
- Altered gas stores, dead space ventilation
- Supine posture
- Combined LV and RV dysfunction
  elevated PVP
Links between PH and Sleep Apnea

• PH through coexisting disorders
  – OSA, COPD, Obesity-Hypoventilation, Cardiovascular Disease (postcapillary PH)

• PH is induced By OSA

• SA is induced by PH
Intermittierende Hypoxie beim OSAS

Ryan et al. Circulation 2005;112:2660
Sleep Apnea in CHF, Stroke & PHTN

- **AHI >15/h**
- **AHI >10/h**
- **AHI >5/h**

**Congestive heart failure, LVEF <45-55%**

- Yumino, 2009
- Javaheri, 2006
- Vazir, 2007
- Macdonal, 2008
- Ferier, 2005
- Sin, 1999
- Mared, 2004
- Paulino, 2009
- Roebuck, 2004
- Oldenburg, 2007
- Luo, 2009

**Stroke**

- Parra, 2000
- Ulrich, 2008

**Pulmonary hypertension**
Prevalence of CSR/CSA & OSA

- AHI >15/h
- AHI >10/h
- AHI >5/h
- AHI >10/h

Congestive heart failure, LVEF <45-55%

Stroke
Pulmonary hypertension

Patients with sleep apnea (OSA & CSA)
Prevalence of **CSR/CSA**

Prevalence of sleep apnea (OSA & CSA) among different AHI levels and conditions:

- **Congestive heart failure, LVEF <45-55%**
- **Stroke**
- **Pulmonary hypertension**
- **Community >65yo men**

- **AHI >15/h**
- **AHI >10/h**
- **AHI >5/h**
- **AHI >10/h**
# Characteristics of Patients with CHF & CSR

<table>
<thead>
<tr>
<th></th>
<th>no SA (AHI&lt;5/h)</th>
<th>CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=169, 24%</td>
<td>n=278, 40%</td>
</tr>
<tr>
<td>AHI</td>
<td>2±2</td>
<td>30±15*</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±11</td>
<td>66±11*</td>
</tr>
<tr>
<td>Men, %</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8±3.7</td>
<td>26.3±4.1</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.6±0.5</td>
<td>2.9±0.5*</td>
</tr>
<tr>
<td>LVEF, % (≤40)</td>
<td>28±7</td>
<td>27±7*</td>
</tr>
<tr>
<td>Atrial Fibr., %</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>6 min walk, m</td>
<td>377±118</td>
<td>331±111*</td>
</tr>
</tbody>
</table>

* P<0.05

Intermittent und Sustained Hypoxia

A  
Sustained Normoxia  
~90% \( \rightarrow \) HIF-1\( \alpha \)  
\( \sim 10\% \) \( \rightarrow \)

B  
Sustained Hypoxia  
\( \downarrow \text{O}_2 \sim 100\% \)
\( \uparrow \text{HIF-1}\alpha \)

C  
Intermittent Hypoxia  
\( \uparrow \text{O}_2 \)
\( \downarrow \text{HIF-1}\alpha \)

Adaptive

Inflammatory

Ryan et al. Circulation 2005;112:2660
Mechanisms of PH in OSA

- Intrathoracic pressure swings
- Transmural gradient ↑
- Sleep fragmentation, Sympathetic activation ↑
- Blood pressure ↑
- Insulin resistance
- Shear stress ↑
- Arousals
- Systemic inflammation
- Oxidative stress
- Intermittent hypoxia
OSA&PH And Patients With Normal PFT

92 OSA patients
AH\(I\)>10/h, normal PFT, Normal daytime ABG

- \(n=18\) PAP>20 mmHg
  - AHI 44 ±28/h
  - Time SpO\(_2\)<90% 41 ±37%

- \(n=74\): PH Absent
  - AHI 39 ±23/h
  - Time SpO\(_2\)<90% 19 ±25%

Sanner et al. Arch Int Med 1997;157:2483
Hemodynamic Effects of Obstructive Apnea

Podzus et al. Marcel Decker, 1994
OSA, PH and Obesity

44 OSA patients, AHI>5/h, FEV1>70%, FEV1/FVC>60%
PH associated with: ↑BMI, ↓VC, ↓ERV, ↓PaO2, ↑PaCO2

Bady et al. Thorax 2000;55:934
PH in OSA: Effect of CPAP

Alchanatis et al. Respiration 2001;68:566
Effect of CPAP on Hypoxic Vasoreactivity

Sajkov et al. AJRCCM 1999;159:1518

Sajkov et al. AJRCCM 2002;165:152
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