Sleep disordered breathing in patients with precapillary pulmonary hypertension (PH)

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Agenda

- **Sleep apnea** leading to PH
  - Obstructive
  - Hypoventilation

- **PH** with sleep disordered breathing (SDB)
  - Pathophysiology and mechanisms
  - Prevalence
  - Potential treatment strategies

To be differentiated!
Does Obstructive Sleep Apnea lead to PH?

- Coccagna & Lonsdorfer 1972: catheters during PSG
  - Oscillations in PAP due to intrathoracic pressure swings
  - PAP highest immediate post apnea and in REM-sleep
  - PAP normalized in the morning awake
- Marone 1989 & Schäfer 1998: catheters and esophageal pressure to assess transmural vascular pressure
  - Mildly increased PAP during sleep (SPAP 28 to 38 mmHg), changes significantly correlated to Δ SpO₂
- Guilleminault 1986: catheter in OSAS
  - Marked decrease in cardiac output during apnea (by 35%)

Apnea episodes lead to mild temporary PH
Obstructive Sleep Apnea leading to PH

• Variations in transmural PAP during OSA episodes may be a consequence of multiple factors:
  – variation in intrathoracic pressure
  – variations in heart rate
  – variation in cardiac output
  – possibly variation in left heart filling pressure

• But the major factor for transmural PAP increase during an OSA episode seems to be:
  – Hypoxic Pulmonary Vasoconstriction (HPV)

Apneas lead to mild temporary PH due to HPV  

Weitzenblum & Chaouat 2005
Is permanent PH a feature of OSA?

• Bradely 1985: 50 OSA patients:
  – Cor pulmonale only in 6 patients (12%) with daytime hypoventilation and obstructive ventilatory defect

• Chaouat 1996: catheters in 220 OSA patients:
  – PH defined as mPAP > 20 mmHg found in 37 Pts (17%)
  – 24/37 daytime hypoxemia
  – 15/37 additional hypercapnia, mostly with additional obstructive or restrictive lung disease
  – no correlation of PAP with AHI

The majority of OSA patients without significant daytime hypoxemia will not develop precapillary PH!
CPAP treatment to improve PH in OSA?

- Sajkov AJRCCM 2002: prospective, uncontrolled, 22 patients with OSA, mean AHI 48/min,

<table>
<thead>
<tr>
<th>N=22</th>
<th>Before CPAP</th>
<th>After CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP mmHg</td>
<td>16.8 ± 1.2</td>
<td>13.9 ± 0.6</td>
</tr>
<tr>
<td>PVR dynes<em>s</em>cm-5</td>
<td>231 ± 88</td>
<td>186 ± 55</td>
</tr>
</tbody>
</table>

Treatment of OSAS by CPAP is moderately effective in ameliorating pulmonary hemodynamics
Does hypoventilation lead to PH?

- Kessler 2001: PH often found in Obesity - Hypoventilation Syndrome with concomitant daytime hypoxemia and hypercapnia
  - 26 patients, 59% PH
  - 23 concomitant OSA
- Common in PH-clinic (Held M, ERS 2012)
  - 126 PH patients, 19 with OHS
  - mPAP 49mmHg, VO$_2$max 63 Watt
  - mPAP correlated to PaCO$_2$
Therapy of Obesity Hypoventilation Syndrome

Increase CPAP to eliminate obstructive apneas, hypopneas, and flow limitation

$S_{\text{PO}_2}$ persistently below 90% in the absence of obstructive apneas or hypopneas

Switch to bi-level PAP and increase IPAP over the last CPAP pressure that eliminated obstructive apneas until $S_{\text{PO}_2} > 90$

Add supplemental oxygen if $S_{\text{PO}_2}$ is persistently < 90% despite an IPAP – EPAP difference of 8–10 cm H$_2$O, or try AVAPS

Weight-loss surgery or tracheostomy with or without mechanical ventilation and/or respiratory stimulants in patients who fail positive-airway-pressure therapy

Non-invasive ventilation ameliorates pulmonary hemodynamics in small series
Agenda

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  – Obstructive
  – Hypoventilation

• PH with sleep disordered breathing (SDB)
  – Pathophysiology and mechanisms
  – Prevalence
  – Potential treatment strategies

To be differentiated!
Sleep disordered breathing in PH – potential mechanisms

• Hypoxemia in PH
  – pulmonary capillary bed ↓, V/Q- Mismatch
  – intrapulmonary Shunts
  – respiratory muscle weakness

• Effect of Sleep on lung diseases
  – Respiratory drive ↓, airway stability ↓, ventilation stability ↓ → sleep disordered breathing

Sleep worsens daytime hypoxemia and may lead to intermittent apnea or periodic breathing
Sleep disordered breathing in PH – different manifestations

- Nocturnal hypoxemia
- Sleep apnea / Periodic Breathing /Cheyne-Stokes-Respiration
- ....
Nocturnal hypoxemia in PH

- Rafanan Chest 2001: 13 IPAH-Pts (12♀)
  - Desaturators = pts with >10% of TST with SpO$_2$ <90%
  - 10 Patients (77%)
  - not associated with sleep apnea
Nocturnal hypoxemia in PH

- Minai Chest 2007: 43 Patients (36♀), 88% IPAH, 12% APAH
  - desaturators = pts with >10% of TST with SpO₂ <90%
  - 30 desaturators (69.7%), only 1 sleep apnea
    - older
    - higher BNP, higher Hb
    - lower cardiac index on last RHC
  - desaturation in 6MWT: not good predictor of nocturnal hypoxemia
  - Resting daytime SpO₂ 95±3.4
Nocturnal Hypoxemia in PH- very common even in preserved daytime SpO₂

63 patients (68% female), 54% idiopathic, 30% CTEPH, 16% APAH

Hildenbrand & Ulrich Respiration 2012
<table>
<thead>
<tr>
<th>Data given in Numbers (%)</th>
<th>Non-Desaturators</th>
<th>Desaturators</th>
<th>Sustained Desaturators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients (%)</td>
<td>14 (22)</td>
<td>49 (76)</td>
<td>33 (52)</td>
</tr>
<tr>
<td>Females</td>
<td>9 (56)</td>
<td>34 (71)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (40;72)</td>
<td>61 (53;71)</td>
<td>61 (54;71)</td>
</tr>
<tr>
<td>WHO functional class II / III / IV</td>
<td>6 / 8 / 0</td>
<td>18 / 23 / 8</td>
<td>12 / 17 / 4</td>
</tr>
<tr>
<td>(43 / 57 / 7)</td>
<td>(37 / 47 / 16)</td>
<td>(38 / 53 / 12)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 (26;29)</td>
<td>26 (22;29)</td>
<td>26 (23;28)</td>
</tr>
<tr>
<td>Tricuspid pressure gradient (mmHg)</td>
<td>43 (38;55)</td>
<td>66 (66;50;83)*</td>
<td>75 (58;89)# §</td>
</tr>
<tr>
<td>NT-pro-BNP (ng/l, &lt; 130)</td>
<td>563 (240;1716)</td>
<td>718 (206;1371)</td>
<td>1048 (206;1689)</td>
</tr>
<tr>
<td>6 minute walking test (m)</td>
<td>529 (385;568)</td>
<td>450 (363;506)</td>
<td>450 (367;516)</td>
</tr>
<tr>
<td>Daytime resting SpO₂ (%)</td>
<td>96 (95;97)</td>
<td>94 (92;96)</td>
<td>93 (91;96)#</td>
</tr>
<tr>
<td>Exercise SpO₂ (% end of 6MWT)</td>
<td>95 (89;97)</td>
<td>87 (80;91)**</td>
<td>86 (78;91)# §</td>
</tr>
<tr>
<td>Mean desaturation during exercise (%)</td>
<td>-2 (-7;0)</td>
<td>-6 (-11;-2)*</td>
<td>-6 (-15;-2)</td>
</tr>
<tr>
<td>Exercise Desaturators (≥ 4% &amp; absolute &lt;90%)</td>
<td>5 (33)</td>
<td>28 (58)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Mean nocturnal SpO₂ (%)</td>
<td>94 (93;95)</td>
<td>88 (85;90)**</td>
<td>86 (84;88)# ## §</td>
</tr>
<tr>
<td>Oxygen desaturation index (ODI, events/h)</td>
<td>2 (1;4)</td>
<td>3 (1;9)</td>
<td>3 (1;9)</td>
</tr>
<tr>
<td>ODI &gt;10 events/h</td>
<td>0</td>
<td>10 (21) *</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Apnea/hypopnea index (AHI, events/h)</td>
<td>9 (5;18)</td>
<td>10 (6;19)</td>
<td>10 (6;19)</td>
</tr>
<tr>
<td>AHI &gt;10 events/h</td>
<td>3 (38)</td>
<td>13 (54)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Periodic breathing (PB, % time in bed)</td>
<td>5 (4;9)</td>
<td>11 (4;13)</td>
<td>12 (5;15)</td>
</tr>
<tr>
<td>Patients with PB ≥10 % of time in bed</td>
<td>3 (38)</td>
<td>12 (50)</td>
<td>9 (56)</td>
</tr>
</tbody>
</table>
Nocturnal Hypoxemia in PH- very common even in preserved daytime SpO₂

Hildenbrand & Ulrich Respiration 2012
Nocturnal Hypoxemia in PH- correlation to tricuspid pressure gradient

Hildenbrand & Ulrich Respiration 2012
Nocturnal hypoxemia in PH - Summary

- Very common
- Daytime SpO₂ underestimates nocturnal hypoxemia
- Nocturnal hypoxemia is correlated to hemodynamic disease severity
- Nocturnal hypoxemia is common even in the absence of sleep disordered breathing

Treatment of nocturnal hypoxemia in PH??????
Sleep disordered breathing in left heart disease

- CSR/CSA is very common in patients with left heart failure (33-45%, Javaheri 1995, Lofaso 1994)
- CSR more prevalent if ejection fraction and VO₂ max are low
- CSR/CSA in left heart failure associated with:
  - arrhythmias↑
  - deterioration of LHF
  - worse prognosis
  - Quality of life ↓

CSR marker of severity in left heart disease
Pathogenesis of CSR/CSA

- Stimulation of sympathetic nerve activity → increase in blood pressure & catecholamines
- Low cardiac output → prolonged blood circulation time → delayed sensing of blood gas changes → oscillatory behavior ↑
- Other potentially contributing factors:
  - impaired cardiac afferents
  - water salt balance
  - hormones involved in body fluids
  - increased left atrial pressure
The vicious cycle of CSR/CSA

Periodic loss of neural drive to respiratory muscles

- Blood gas changes (pO₂↑, pCO₂↓)
- Recurrent apneas
- Hyperventilation
- Blood gas changes (pO₂↓, pCO₂↑)
What about right heart failure in PH?
Sleep disordered breathing in right heart disease due to PH

- Schulz ERJ 2002: 6 out of 20 (30%) patients with PH had nocturnal CSR (PSG)

CSR associated with:
- worse hemodynamic
- lower DLCO
- lower PaO₂
Sleep disordered breathing in right heart disease due to PH

• Schulz ERJ 2002:
• 5 patients agreed to be re-examined under oxygen therapy (2l via nasal cannula):
• 4 responded with almost complete resolution

• Schulz Chest 2004: case-report of reversal of CSR after LTPL in a 56y old woman

Fig. 2.—Effects of nasal oxygen administration on the apnoea/hypopnoea index (AHI) in five patients with primary pulmonary hypertension and periodic breathing. Data are presented as individual values and as mean±SEM before and after nasal oxygen (O₂). **: p<0.01.
# Sleep related breathing disorders in Zürich PH collective

<table>
<thead>
<tr>
<th>38 patients with PH</th>
<th>Numbers or median (quartiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>27 (71%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (51-72)</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)*</td>
<td>43 (33-51)</td>
</tr>
<tr>
<td>WHO functional class II / III / IV</td>
<td>14 / 16 / 8</td>
</tr>
<tr>
<td>6 minute walking distance (m)</td>
<td>481 (429-550)</td>
</tr>
</tbody>
</table>

### Sleep studies

<table>
<thead>
<tr>
<th>Apnea/hypopnea index (AHl, events/h)</th>
<th>8 (4-19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- obstructive</td>
<td>0 (0-0.03)</td>
</tr>
<tr>
<td>- central</td>
<td>8 (4-16)</td>
</tr>
<tr>
<td>Time spent with CSR (% time in bed)</td>
<td>8 (4-13)</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>90 (87-92)</td>
</tr>
<tr>
<td>Time spent with SpO₂ &lt; 90% (% time in bed)</td>
<td>34 (3-78)</td>
</tr>
<tr>
<td>Patients with AHI &gt; 10 /h (%)</td>
<td>45 10 40</td>
</tr>
<tr>
<td>- obstructive AHI &gt; 10/h (%)</td>
<td></td>
</tr>
<tr>
<td>- central AHI &gt; 10/h (%)</td>
<td></td>
</tr>
<tr>
<td>Patients with time spent with CSR &gt; 10 % of time in bed (%)</td>
<td>42</td>
</tr>
<tr>
<td>Patients with time spent with SpO₂ &lt; 90% &gt; 10% time in bed (%)</td>
<td>68</td>
</tr>
</tbody>
</table>
Sleep related breathing disorders in Zürich PH collective

Ulrich, Chest 2008
Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- Circulation time: delay in transport of blood to brain resp. carotid sensors (lung to ear time)
  - Crowell Am J Physiol 1956: large prolongation of circulation time necessary to receive CSR in only 30%

Circulation time influences time of breathing cycle and length of hyperpneic episodes
Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- Hyperventilation with low PaCO₂ (below apneic threshold)
  - breathing with low CO₂ (2-3%) during sleep increases CSR
- But: PaCO₂ alone is not crucial, e.g. liver cirrhosis patients with the same PaCO₂ do not have CSR

Δ PaCO₂ may be more important and the combination with other factors

- increased ventilatory response to CO₂ during exercise (VE/VCO₂) best correlation to CSR
Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- **Hypoxemia:** may promote instability due to a stimulating effect on carotid chemoreceptors
  - High altitude induces CSR
  - However, hypoxemia not mandatory to develop CSR in HF and oxygen therapy attenuates but not completely suppresses CSR
- **Arousal response:** magnitude determines lengths of subsequent interruption of ventilation
- **Catecholamine hypersecretion:**
  - Noradrenalin infusion increases ventilation
  - Important for self-perpetuating effect of CSR-CSA

Pepin Sleep Medicine 2006
Treatment options for CSR in patients with PH

- The indication, type and benefits of potential treatments for CSR/CSA in PH are currently not known

In lack of treatment strategies, it is not know whether screening PH for CSR is sensible

- Extrapolating from left heart failure-associated CSR/CSA
  - nocturnal oxygen therapy (NOT)
  - Acetazolamide
  - non-invasive positive pressure ventilation via a mask

may all be potentially effective
Treatment of and sleep disordered breathing in PH

• Main inclusion criteria: Patients with precapillary PH and sleep disordered breathing defined as: SpO2 < 90% and/or oxygen desaturation index > 10/h during ambulatory pulse oximetry

• Main exclusion criteria: Wedge ≥15mmHg, significant lung disease, co-morbidities, not able to walk, ….

• Actually: > 60 PH-patients screened, 23 patients actually includes
Treatment of and sleep disordered breathing in PH

Ulrich NF Study 2011-13
Treatment of and sleep disordered breathing in PH

• Primary Outcomes:
  – 6 minute walk distance
  – SF36 (1-week recall form) physical component

• Secondary Outcomes:
  – vigilance, sleepiness, QoL (SF-36, MLHF, Camphor)
  – prevalence and severity of sleep disordered breathing
  – hemodynamics by echocardiography
  – changes in arterial and venous blood parameters
  – actimetry

Results awaited soon
Take Home Messages

• OSA may lead to mild PH, significant PH only with concomitant diseases (which are not seldom!)
• Nocturnal hypoxemia is very common in PH, underestimated by daytime measurements and associated with hemodynamic severity
• SDB is common in severe PH, but not the only reason for nocturnal hypoxemia
• Treatment strategies widely unknown