Asthma and sleep disorders

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Disclosure of Interest

• I have no conflict of interest to disclose
Objectives

- Are OSA and Asthma related?
- Respiratory activity in Sleep
- Nocturnal Asthma and OSA
- Difficult to control Asthma and OSA
- Does CPAP have a role in the treatment of Asthma?
What is he talking about?

- In 1698, Dr. (later Sir) John Floyer, wrote: "I have observed the fit always to happen after sleep in the night.... At first waking, about one or two of the clock in the night, the fit of "?" more evidently begins, the breath is very slow ... the diaphragm seems stiff and tied... It is not without much difficulty moved downwards."

Respiratory activity in NREM sleep

- VE decreased in sleep
  - $W = 1081 \pm 25\text{ ml}$;
  - NREM $= 883 \pm 9.9$;
  - REM $= 806 \pm 19$

- end-tidal CO$_2$ increases in NREM sleep

Respiratory activity in NREM sleep

• It is unclear whether the decrease in minute ventilation is caused by a:
  • decrease in tidal volume or
  • a decrease in respiratory frequency,
  • or both.

• Most studies report a decrease in tidal volume that averages 16% in stage 2 and 18.5% in stage 3 to 4
Respiratory muscles in NREM sleep

• As compared with wakefulness:
  – Intercostal muscle activity increases by a mean of 34%
  – Diaphragmatic muscle activity increased by 11% indicating an increase in the respiratory work load

• A substantial increase in rib cage contribution to VT

Respiratory muscles in REM sleep

• REM sleep was associated with a
  – marked decrease in intercostal muscle activity (P < 0.05)
  – diminished rib cage contribution

Ventilatory response to hypoxia

In adult humans, the ventilatory response to hypoxia falls during sleep.

**Ventilatory response to Hypercapnea**

In adult humans the hypercapnic ventilatory response is depressed during sleep.

Arousal from Sleep

Arousal from REM sleep after airway occlusion is far more rapid than arousal from NREM sleep

Upper airway resistance in NREM

- Large increase (230%) has been shown to occur in total airway resistance during NREM sleep.
- The resulting increase in upper airway resistance has a role in the decrease in ventilation during sleep.

Blood gases in NREM

- Arterial PCO$_2$ values increase by 3 to 7 mm Hg
- Arterial PO$_2$ decreases from 3.5 to 9.4 mm Hg
- SaO$_2$ decreases 2% or less
- Metabolic rate decreases, reflected by
  - 10% to 20% decreases of O$_2$ consumption and CO$_2$ production

REM Sleep Ventilation

The breathing irregularities do not occur at random but are linked to bursts of rapid eye movements.
Why do we care about Nocturnal Asthma?

- There are more asthmatic deaths per hour at night than by day.
- The death rate is higher at night than by day in the general population, but the average increase between midnight and 8:00 AM is only 5% in general population, in contrast to the 28% increase observed in asthmatic patients.

Nocturnal Asthma

• Patients with asthma are often troubled by
  – nocturnal cough
  – wheeze
  – Breathlessness

• This results from sleep-related nocturnal narrowing of the lower airways
Nocturnal Asthma

• The forced expiratory volume in 1 second (FEV\textsubscript{1}) and peak flow rates fall overnight in patients with asthma

• > 50% in some patients

Pathogenesis of nocturnal asthma

• Supine posture:
  – patients who lie in bed throughout the 24-hour period continue to exhibit overnight bronchoconstriction

• Interruption of medications:
  – regular spacing of treatments throughout the 24 hours does not abolish nocturnal bronchospasm

• Allergens in bedding:
  – avoidance of such allergens does not abolish nocturnal airway narrowing
Pathogenesis of nocturnal asthma

• Cold, dry air produces bronchoconstriction:
  – overnight bronchoconstriction persists in healthy subjects when temperature and humidity are kept constant throughout the 24-hour day

• Kerr HD: Diurnal variation of respiratory function independent of air quality: Experience with an environmentally controlled exposure chamber for human subjects. Arch Environ Health 1973;26:144-152

• Nevertheless, it has been reported that breathing warm, humid air (36° C to 37° C, 100% saturation) overnight, compared with breathing room air (23° C, 17% to 24% saturation) overnight, abolished nocturnal bronchoconstriction in six of seven asthmatic patients
  – Chen WY, Chai H: Airway cooling and nocturnal asthma. Chest 1982;81:675-680
Pathogenesis of nocturnal asthma

• GERD: high incidence of gastroesophageal reflux (GER) in people with asthma, especially in those with nocturnal wheeze.

• Gastric acid suppression with the proton pump inhibitor omeprazole produced a small improvement in nocturnal but not daytime asthma symptoms.
Pathogenesis of nocturnal asthma

• Circulating catecholamine levels show diurnal changes, with a nocturnal nadir.
• Urinary catecholamine excretion falls to a minimum coincident with the lowest peak flow rates in some patients.
• However, catechol infusion does not abolish nocturnal airway narrowing.
Pathogenesis of nocturnal asthma

- **Cortisol**: Nocturnal breathlessness in asthmatic patients is most marked when the urinary excretion of 17-hydroxycorticosteroid is at its nadir and peak flow rates parallel changes in the levels of circulating steroids.

- Therapy with large doses of steroids does not abolish morning dipping.

- Circadian changes in circulating cortisol levels are not important in the pathogenesis of nocturnal bronchoconstriction.
Circadian changes in airway caliber

- Normal people have circadian changes in airway caliber with mild nocturnal bronchoconstriction.
- The amplitude of the peak flow rate changes is far greater in asthmatic patients (50%) than in healthy subjects (8%).
- Nocturnal bronchoconstriction in asthma appears to be an exaggeration of the normal circadian changes in airway caliber.

Circadian changes in airway caliber
Circadian changes in airway caliber

- Amplitude of variation is greater in asthmatics than in simple bronchitis.
- It is reduced by about 20% with bronchodilators.
- Treatment with corticosteroids does not appear strongly to influence either characteristic patterns or amplitude of variation.

Circadian changes in airway caliber affected by sleep

Morning peak flow was higher after the awake night

Is Nocturnal Wheeze Related to Sleep Stage?

Asthmatic attacks being randomly distributed throughout the stages of sleep in proportion to the amount of time spent in each sleep stage

OSA and Nocturnal Asthma

• Could it be that recurrent upper airway obstruction and snoring may be important triggering mechanisms of nocturnal asthma attacks?
Asthma and OSA

• Reduced asthma symptoms and bronchodilator use, and improved PEFR after 2 weeks of CPAP in nine patients.
• Cessation of CPAP returned PEFR to baseline levels.
Asthma and OSA

Some nocturnal asthmatic patients who snore or have obstructive sleep apnea may develop worsening of their asthma.

Nasal continuous positive airway pressure therapy may be extremely helpful.

Prediction of Nocturnal Oxygenation

Difficult to control Asthma

• The National Asthma Education and Prevention Program guidelines 2007 recommend evaluation for OSA in patients with asthma with suboptimal control. (Grade D)
How Could OSA aggravate Asthma?

- OSA could promote GERD
- OSA-related increase in the resistive load on lower airways over imposed on an already more challenged airway system especially during sleep
- Upper-airway-triggered vagally mediated bronchoconstriction, and increased bronchial responsiveness
- Altered chemical arousal thresholds
- OSA may lead to oxidative stress and inflammation in the lower airway as it does in the cardiovascular system
Is OSA associated with to difficult to control Asthma?

• A high OSA risk was associated with a 3.60 times higher odds for having not well-controlled asthma (95% C, 2.16-5.98; $P$, .0001)
  
  • Mihaela Teodorescu, David A. Polomis, Stephanie V. Hall, et al; Association of obstructive sleep apnea risk with asthma control in adults. *Chest 2010;138;543-550*
Not well controlled asthma if:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High OSA risk</td>
<td>3.60 (2.16-5.98)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99-1.03)</td>
<td>.14</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>0.69 (0.42-1.13)</td>
<td>.14</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>2.46 (1.50-4.01)</td>
<td>.00003</td>
</tr>
<tr>
<td>Black (vs all other)</td>
<td>3.45 (1.19-9.99)</td>
<td>.02</td>
</tr>
<tr>
<td>Nasal condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0.27 (0.11-0.66)</td>
<td>.004</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>1.11 (0.68-1.83)</td>
<td>.67</td>
</tr>
<tr>
<td>Polyps</td>
<td>1.95 (1.10-3.48)</td>
<td>.02</td>
</tr>
<tr>
<td>GERD</td>
<td>3.03 (1.83-5.01)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>1.99 (1.18-3.36)</td>
<td>.01</td>
</tr>
</tbody>
</table>
OSA = not well controlled asthma

• Subjects with high OSA risk compared with those without high OSA risk had higher scores on all ACQ versions, with differences uniformly greater than the validated minimal clinically important difference of 0.5 (P < .0001 in all cases)
The graph shows the ACQ Score (Mean ± SEM) for different versions of the ACQ (ACQf, ACQsf, ACQsb, ACQs) for subjects with and without High OSA Risk. The table below provides the mean scores for each version:

<table>
<thead>
<tr>
<th>ACQ Version</th>
<th>High OSA Risk</th>
<th>No High OSA Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACQf</td>
<td>1.31</td>
<td>0.73</td>
</tr>
<tr>
<td>ACQsf</td>
<td>1.40</td>
<td>0.78</td>
</tr>
<tr>
<td>ACQsb</td>
<td>1.26</td>
<td>0.67</td>
</tr>
<tr>
<td>ACQs</td>
<td>1.36</td>
<td>0.71</td>
</tr>
</tbody>
</table>
OSA = not well controlled asthma

• 13 clinical and environmental factors potentially associated with recurrent exacerbations were investigated in 136 patients with difficult-to-treat asthma.

• Patients with more >3 severe exacerbations (n=539) in the previous year were compared with those with only one exacerbation per year (n=524)
OSA = not well controlled asthma

- OSA was considered a potential contributing factor if the criteria were met by polysomnography, or in case of a history of daytime sleepiness and heavy snoring at night with frequent apnoea periods of .10 s reported by the partner.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR# (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological dysfunctioning</td>
<td>10.8 (1.1–108.4)</td>
</tr>
<tr>
<td>Recurrent respiratory infections</td>
<td>6.9 (1.9–24.7)</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>4.9 (1.4–17.8)</td>
</tr>
<tr>
<td>Severe chronic sinus disease</td>
<td>3.7 (1.2–11.9)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>3.4 (1.2–10.4)</td>
</tr>
<tr>
<td>Hormonal influences</td>
<td>2.8 (0.5–15.8)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1.9 (0.2–19.6)</td>
</tr>
<tr>
<td>Occupational sensitisers</td>
<td>0.7 (0.2–2.1)</td>
</tr>
<tr>
<td>Poor inhaler technique</td>
<td>0.6 (0.1–2.9)</td>
</tr>
<tr>
<td>Food allergens</td>
<td>0.6 (0.1–3.5)</td>
</tr>
<tr>
<td>Ongoing allergen exposure</td>
<td>0.5 (0.2–1.3)</td>
</tr>
<tr>
<td>Relative immune deficiency</td>
<td>0.4 (0.1–1.7)</td>
</tr>
<tr>
<td>Drugs</td>
<td>0.2 (0.1–1.9)</td>
</tr>
</tbody>
</table>

CI: confidence interval. \#: OR adjusted for age and asthma duration.
CPAP is a treatment for Asthma

• In stable asthmatics:
  • Clinical improvement for each QOL questionnaire is established by a score increase of 0.5.
CPAP is a treatment for Asthma

**TABLE 2**

Functional and clinical characteristics of the subjects at baseline (pre-) and after 6 weeks of treatment (post-) with continuous positive airway pressure (CPAP)

<table>
<thead>
<tr>
<th></th>
<th>Pre-CPAP</th>
<th>Post-CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 % pred</td>
<td>82.2 ± 13.6</td>
<td>80.4 ± 13.6</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>77.3 ± 8.3</td>
<td>76.3 ± 10.1</td>
</tr>
<tr>
<td>PC20 mg·mL⁻¹</td>
<td>2.2 (1.3–3.5)</td>
<td>2.5 (1.4–4.5)</td>
</tr>
<tr>
<td>AHI</td>
<td>48.1 ± 23.6</td>
<td>2.6 ± 2.5***</td>
</tr>
<tr>
<td>QOLAs</td>
<td>5.0 ± 1.2</td>
<td>5.8 ± 0.9***</td>
</tr>
<tr>
<td>QOLAp</td>
<td>4.1 ± 1.4</td>
<td>6.0 ± 1.0***</td>
</tr>
</tbody>
</table>
P = 0.3
P = 0.001
CPAP is a treatment for Asthma

- Patients who had nocturnal symptoms in spite of the optimal medical treatment according to the GINA guidelines and associated with snoring were studied.
- PFTs, asthma nighttime symptom scores, and polysomnography were performed on all patients.
- Patients with an apnea-hypopnea index (AHI) X15 (moderate–severe OSAS) with CPAP during 2 months.
- After 2 months, PFT, asthma nighttime symptom scores were reperformed.
CPAP is a treatment for Asthma

- There was no significant difference in PFT values before and after CPAP treatment in OSAS patients.
- Asthma nighttime symptom scores were improved significantly (P<0.05) after CPAP treatment

CPAP is a treatment for Asthma

Table 2  PFT values and nighttime symptoms scores of asthmatic patients with OSAS, before and after CPAP treatment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline no. 16</th>
<th>After 2 months of CPAP treatment no. 16</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% of predicted value)</td>
<td>70.25±21.17</td>
<td>71.25±21.85</td>
<td>0.64</td>
</tr>
<tr>
<td>FVC (% of predicted value)</td>
<td>83.68±17.93</td>
<td>88.81±20.64</td>
<td>0.34</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>66.68±15.64</td>
<td>70.75±15.37</td>
<td>0.12</td>
</tr>
<tr>
<td>FEF25–75 (% of predicted value)</td>
<td>39.87±24.7</td>
<td>40.4±20.77</td>
<td>0.14</td>
</tr>
<tr>
<td>Nighttime symptom scores</td>
<td>2.19±1.07</td>
<td>1.44±1.15</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

*P<0.05
OSA and difficult to control Asthma is a new phenotype!

- Symptomatic patients with asthma and comorbid OSA have lower levels of exhaled nitric oxide, an indicator of eosinophilic inflammation.
- OSA may contribute to the noneosinophilic phenotype increasingly recognized among patients with uncontrolled asthma.
- Respiratory efforts against an obstructed upper airway lead to neutrophilic airway inflammation which may contribute to loss of asthma control.