Sleep and Asthma/COPD

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No COI or disclosures for this lecture
Learning Objectives

- Understand how sleep and circadian rhythms affect both respiratory physiology and pathology
- Identify key clinical features of nocturnal asthma and COPD
- Learn about the assessment and management of nocturnal asthma and COPD
Introduction

- Relationship between sleep and respiratory disorders is bidirectional
  - Sleep quality is affected by respiratory disorders and by medications and vice versa
- Other factors
  - Sleep deprivation
  - Circadian rhythms
  - Comorbid sleep disorders
Pulmonary Physiology during Sleep
Respiratory System

Behavioral input is lost leaving only metabolic processes (O₂ and CO₂) to control respiration during sleep.

- **PaO₂** (by 2-12 mmHg)
- **SaO₂** (by 2%)
- **Tidal volume**
- **Minute ventilation**
- **Ventilatory response to hypoxia/hypercapnia**
- **UA dilator muscle tone**

- **PaCO₂** (by 2-8 mmHg)
Ventilatory Response to Hypoxia

Ventilation (L/min) vs Oxygen Saturation (%)

Awake
3/4
2
REM

Principles and Practice of Sleep Med 2010
Ventilatory Response to Hypercapnia

- **Awake**
- **Stage 3/4**
- **Stage 2**
- **REM**

Circadian Variation in Lung Function

Spengler C et al. AJRCCM 2000;162;1038-1046
## Respiration During Sleep

<table>
<thead>
<tr>
<th>Sleep stage</th>
<th>Respiratory pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Periodic breathing with episodes of hypopneas and hyperpneas</td>
</tr>
<tr>
<td>N3</td>
<td>Regular frequency and amplitude</td>
</tr>
<tr>
<td>REM</td>
<td>Irregular pattern of respiration</td>
</tr>
<tr>
<td></td>
<td>Variable RR and TV</td>
</tr>
<tr>
<td></td>
<td>Periodic breathing may occur during phasic REM sleep</td>
</tr>
</tbody>
</table>
Asthma
Asthma

- Airway hyperreactivity to specific and nonspecific stimuli
- **Reversible** bronchoconstriction
- Episodic dyspnea, wheezing or coughing
Nocturnal Asthma

- **Sleep complaints**
  - Insomnia
    - 3/4 have nocturnal awakenings ≥ once weekly
    - 2/3 have nocturnal awakenings ≥ three times a week
  - Excessive sleepiness
  - Nocturnal hypoxemia
Nocturnal Asthma

- **Causes** of poor sleep quality
  - Coughing, dyspnea, wheezing and chest discomfort
  - Majority report having poor sleep quality even in the absence of nighttime asthma attacks

*Luyster FS. Sleep Breath 2012*
Nocturnal Asthma

- Nocturnal symptoms indicate sub-optimally treated asthma
  - Inverse correlation between asthma control and presence and severity of sleep disturbance
  - Sleep disturbance present in 11-20% with totally controlled asthma

- Asthma attacks not specific to any sleep stage

*Braido F. Asian Pac J Allergy Immunol 2009*
Nocturnal Asthma

- **Mechanisms for nocturnal asthma**
  - **Circadian** variability in airflow
    - Lowest levels in the early morning
  - **Sleep-related changes in**
    - Autonomic nervous system activity
      - Increased parasympathetic tone
      - Decreased sympathetic activity
  - Lung capacity
  - Inflammatory mediators
- **Other disorders** – nocturnal GERD or OSA
Nocturnal GERD

Emilsson et al. Eur Respir J 2013
Nocturnal Asthma

- **Diagnosis** of nocturnal asthma
  - Monitoring morning and evening PEF or FEV1 over several days to weeks
  - Reduced evening values compared to daytime
Polysomnography

Arousals and awakenings

Sleep efficiency; total sleep time
Nocturnal Asthma: Therapy

- Avoid precipitants
- Inhaled corticosteroids
- Long-acting bronchodilators
- Leukotriene inhibitors
- Short-acting beta-agonists for acute control
- PAP therapy for concurrent asthma and OSA
Asthma and OSA

- Patients with OSA were 3.6 times more likely to have uncontrolled asthma
  
  *Teodorescu Chest 2010*

- Nocturnal CPAP in stable mild-to-moderate asthmatics and newly diagnosed OSA
  - Did not alter airway responsiveness or FEV$_1$
  - Did improve AHI and asthma quality of life
  
  *Lafond Eur Respir J 2007*

- Poorly controlled asthma and symptoms of OSA should undergo evaluation

*US National Asthma Education and Prevention Expert Panel Report 3*
In this pilot study, CPAP therapy reduced peak flow variability and improved symptom control in non-apneic patients with severe asthma.


PEF amplitude (P < 0.05) and PEF morning dip (P < 0.001)

PEF: peak expiratory flow
Chronic Obstructive Pulmonary Disease
Chronic Obstructive Pulmonary Disease

- Progressive, not fully reversible, airflow limitation
- Due to injury to the small airways and alveoli from noxious particles or gases
- Includes chronic bronchitis and emphysema
- Dyspnea, chronic cough and chest tightness – common complaints
COPD: Nighttime Symptoms

- Prevalence of nighttime symptoms and sleep disturbance – not well understood
  - Frequently unreported
  - No uniform definition
- May exceed 75%
COPD: Sleep Disturbance

- Sleep-related complaints are common
- Insomnia
  - Difficulty falling asleep
  - Repetitive awakenings
  - Early awakening
  - Non-restorative sleep
- Excessive sleepiness

Cormick W et al. Thorax 1986
Bella V et al. Sleep 2003
Prevalence of Insomnia

Tucson Epidemiologic Study of Chronic Lung Disease

- 53% Two symptoms
- 39% One symptom
- 28% Asymptomatic

Klink M et al. Chest 1987
Causes of Sleep Disturbance

Nocturnal coughing

Increased work of breathing

Dyspnea or orthopnea

Medication use

Other sleep disorders

Klink M et al. Chest 1984
Causes of Sleep Disturbance

- Frequency of arousals does not appear to be related to the degree of nighttime hypoxemia

Mulloy E et al. ARRD 1993
Martin RJ et al. ARRD 1992
Berry RB et al. ARRD 1991
Known adverse effects of current pharmaceuticals on respiratory function in COPD patients

<table>
<thead>
<tr>
<th>Drug subclass</th>
<th>Effects on sleep</th>
<th>Adverse pulmonary effects in COPD patients</th>
</tr>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>↓ sleep latency, ↑ sleep efficiency,</td>
<td>↓ tidal volume, ↓ arousal response to hypercapnia, ↑</td>
</tr>
<tr>
<td></td>
<td>↓ arousals</td>
<td>hypoxia, ↑ hypercapnia</td>
</tr>
<tr>
<td>Non-benzodiazepines</td>
<td>↓ sleep latency, ↑ sleep efficiency,</td>
<td>↑ apneas&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>↓ arousals</td>
<td></td>
</tr>
<tr>
<td>Melatonin receptor agonists (ramelteon)</td>
<td>↓ sleep latency, ↑ sleep efficiency</td>
<td>No effect on apnea or P&lt;sub&gt;A&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trazodone</td>
<td>↑ sleep efficiency (only in patients</td>
<td>Unknown&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>with depression)</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Further research is needed.
Insomnia Therapy

Kapella et al. Int J COPD 2011
Restless Legs Syndrome

- Diagnostic criteria
- Primary (idiopathic and often hereditary)
- Secondary
  - Nutritional deficiencies (iron, folate, vitamin B12)
  - Medical conditions (ESRD, pregnancy, rheumatologic disorders, or neurologic conditions)
Restless Legs Syndrome

Prevalence of RLS-type Symptoms in COPD

- 29-36% during stable disease
- 54% during acute exacerbations

Aras G. COPD 2011
## RLS in COPD

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>36%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severity (IRLSS)</td>
<td>20.5</td>
<td>18</td>
<td>0.016</td>
</tr>
<tr>
<td>EDS (ESS)</td>
<td>11.8</td>
<td>8.6</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Lo Coco D. Sleep Med 2009
Consequences in COPD

- Poorer sleep quality (PSQI > 5 in 59%)
- More fatigue (FSS > 27 in 51%)
- Worse depression (BDI >10 in 14%)

RLS in COPD

Cavalcante AG. Sleep Med 2012
Aras G. COPD 2011
Consequences in COPD

Cavalcante et al. Sleep Med 2012
COPD: Nocturnal O2 Desaturation

- Less hypoxia
  - NREM sleep
  - Chronic bronchitis

- Worse hypoxia
  - Moderate to severe
  - REM sleep
  - Emphysema
Oxygenation During Wakefulness is the Major Predictor of Mean and Lowest Oxygen Saturation During Sleep in COPD

\[ P < 0.0001 \]
\[ R = 0.75 \]

Mechanisms for Nocturnal Hypoxemia

- Diminished Lung Volumes
- VQ Mismatching
- Hypoventilation
  - Most Important Factor
COPD: Overlap Syndrome

- Presence of both COPD and OSA
  - Prevalence of OSA in COPD is similar to general population

- Compared to isolated COPD
  - Lower PaO2
  - Higher PaCO2
  - Higher mean PA pressures
Overlap Syndrome

- Compared to isolated COPD
  - *Increased risk of death* and hospitalization
  - More extensive RV remodeling
  - Increased arterial stiffness
  - *Higher economic burden*
    - Higher medical service claims and medical costs

Sharma B. COPD 2012
Shiina K. Respir Med 2012
Shaya FT. Sleep Breath 2009
Overlap Syndrome

- Prevalence of OSA in COPD is similar to that in the general population, and *vice versa*

- Decreased pulmonary function in COPD is **not** an independent risk factor for OSA
  - No correlation between FEV$_1$ % predicted and risk for OSA, AHI and ODI

*Sharma B. Lung 2011*
COPD: Evaluation

- PSG is **not** routinely indicated in persons with COPD
- Should be considered if
  - Clinical suspicion for OSA
  - Complications from unexplained hypoxemia
  - Severity of pulmonary hypertension out of proportion to degree of airflow limitation
- Home sleep apnea testing **not** recommended

_Celli BR et al. Eur Respir J 2004_
Polysomnography

- Sleep latency; sleep stage changes; arousals and awakenings
- Sleep efficiency; total sleep time; REM sleep

Fleetham J. ARRD 1982
McSharry DG. Respirology 2012
Indications for Overnight Oximetry

- Daytime hypercapnia and/or hypoxemia
- Pulmonary and systemic hypertension
- Right heart failure
Actigraphy

SE, TST and sleep activity correlated with severity of dyspnea

Low SE
Prolonged SOL
Short sleep duration
Increased mean activity
More WASO

Budhiraja R. Sleep 2012
Nunes DM. Sleep Breath 2012
COPD: Therapy

- Symptoms
  - Breathlessness, wheezing, cough

- Hypoxia

- Hypoventilation

- Respiratory mechanics
  - Expiratory flow limitation

- Comorbid sleep disorders
COPD: Indications for Oxygen Therapy

- $\text{PaO}_2 \leq 55 \text{ mmHg}$, or $\text{SaO}_2 \leq 88$

- $\text{PaO}_2 \leq 59 \text{ mmHg}$, or $\text{SaO}_2 \leq 89\%$ plus
  - Cor pulmonale
  - Right heart failure, or
  - Erythrocytosis (Hct > 55\%)
Figure 2 Correlation between the changes in apnoea-hypopnoea index (delta-AHI) and the changes in walking distance (delta-distance) with CPAP treatment in the patients with overlap syndrome.

Wang et al.  Resp Res 2013
Home NPPV (BPAP 15/5 cmH2O) improved quality of life in stable COPD patients with nonhypercapnic respiratory failure (PaCO2 < 52 mmHg).

**NPPV arm**

<table>
<thead>
<tr>
<th>Dyspnea</th>
<th>Quality of life</th>
<th>PaO2</th>
</tr>
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<tbody>
<tr>
<td>Improved Transitional Dyspnea Index (TDI)-Task at 6 months (P = 0.03)</td>
<td>Improved Chronic Respiratory Disease Questionnaire (CRQ)-Mastery domain (P = 0.04)</td>
<td>Remained stable (P=0.02)</td>
</tr>
</tbody>
</table>

Many patients present with disturbances in duration, timing or quality of sleep.

Evaluation of sleep complaints relies chiefly on a comprehensive sleep history.

Frequent follow-up is recommended to determine response to therapy as well as development of new sleep complaints.