Sleep Medicine Update: Interactions Between Physiology and Genetics

Jaime Boero, MD PhD
Phiroze L Hansotia Sleep Medicine Center
Department of Neurology
Marshfield Clinic
WHAN that Aprille with his shoures soote
The droghte of Marche hath perced to the roote,
And bathed every veyne in swich licour,
Of which vertu engendred is the flour
Whan Zephirus eek with his swete breeth
Inspired hath in every holt and heeth
The tendre croppes, and the yonge sonne
Hath in the Ram his halfe cours y-ronne,
And smale fowles maken melodye,
That slepen al the night with open ye...

Geoffrey Chaucer
We need to Sleep

• Biological function common to all animals.
• Biological need (hunger, thirst, reproduction, thermal regulation, sleep)
• Under neural control like all complex body functions
• Serves a restorative function for both body and nervous system. We need to sleep.
We all may fall asleep during the day
We all fall asleep at different times as we age.
Whan happens when we don’t sleep?

- We don’t perform well
  - Tasks affected are:
    - Long, monotonous, without feedback
    - Newly learned, need to remember (memory component)
    - Example: driving, placing a line in the ICU, talking to a patient, rounds after call
  - What happens to my driving
    - 49% of residents on call (2.7 hrs sleep)
      - FALL ASLEEP AT THE WHEEL (90% after call)
        - Marcus & Loughlin, 1996)
    - Residents had 67% more driving tickets and 82% more car accidents. (worse than attorneys!)
The less we sleep the less when can pay attention

- Performance deficits still increased at day 14 of the restricted sleep schedule.
- 4 and 6 hrs of time in bed per night for 14 days produced cognitive Decrements equivalent to what occur when awake for 24-48 hours.
What happens when we have Obstructive Sleep Apnea syndrome?

• Signs and symptoms associated with sleep apnea:
  – Snoring
  – Witnessed apneas
  – Gasping for air
  – Sleepiness
  – Nocturia
  – Mood, memory, learning problems
  – Impotence
  – Recent weight gain
  – Dry mouth or dry throat in the morning
  – Obesity, hypertension, crowded oropharynx
  – Retrognathia
Airway Collapse
Obstructive Sleep Apnea syndrome

- **Diagnostic criteria:**
  
  A. Excessive daytime sleepiness not explained by other factors
  
  B. Two or more
     
     A. Choking or gasping for air during sleep
     
     B. Recurrent awakenings from sleep
     
     C. Unrefreshing sleep
     
     D. Daytime fatigue
     
     E. Impaired concentration
  
  C. **Sleep study with 5 or more apneas/hr of sleep**
Obstructive Sleep Apnea syndrome

- Consequences of untreated Obstructive Sleep Apnea syndrome
  - Impaired cognitive function
  - Impaired quality of life
  - Daytime sleepiness
  - Increased risk of automobile accidents
  - Increased health care costs
  - Hypertension
  - Cardiovascular disease
  - Worsened glucose tolerance
  - Increased mortality rates
  - Impotence
Do we need to be sleepy to have Obstructive Sleep Apnea syndrome?

• NO

• Very alert people can still have Obstructive Sleep Apnea syndrome and not be sleepy

• They have the same higher risk of strokes and heart attacks
Obstructive Sleep Apnea syndrome
Diagnosis
• Sleep study
Obstructive Sleep Apnea: Benefits of Treatment

- Increased alertness
- Decreased accidents
- Improved memory and learning
- Less irritability
- Blood pressure control: no difference
- Improved diabetes control: lower glucose in AM
- Decreased mortality from heart failure, strokes and heart attacks
Pathophysiology of Sleep Apnea

- Inflammation
- Autonomic overactivity
- Sleep Apnea
- Endothelial dysfunction
- Metabolic dysregulation
Immediate Effects of Sleep Apnea

• Obstructive SA:
  – Intermittent arterial gas changes:
    • Hypoxemia/reoxygenation
    • Hypercapnia/hypocapnia
    • Increased sympathetic activity and pulmonary arterial vasoconstriction
    • Decreased myocardial oxygen delivery and release of inflammatory mediators such as endothelin
  – Arousals
  – Large swings in intra-thoracic pressure
Sleep Apnea and Coronary Artery Disease

• Co-morbid sleep apnea has an additive synergistic factor for development of coronary artery disease
• Identification of sleep apnea for new primary and secondary prevention models of CAD
Circadian pattern of sudden cardiac death in sleep apnea

- Angina pectoris or acute coronary syndrome are more frequent during the late hours of sleep or early in the morning.
- Obstructive Sleep Apnea syndrome patients have a peak in sudden death from cardiac cause during sleeping hours (midnight to 6am).

Sleep apnea and CAD association

- Sleep apnea may provide a synergistic risk factor for development of CAD
- Sleep Heart Health Study (SHHS)
  - 1.42 increased odds ratio for self reported cardiovascular disease and Apnea/Hypopnea Index

Sleep Apnea and Heart Failure

- Obstructive Sleep Apnea as a cause of left ventricular systolic and diastolic dysfunction

- Mechanisms:
  - Sympathetic overactivity
  - Change in left ventricular preload and afterload
  - Hypoxemia

- Clinical implications and effects of treatment with nasal CPAP
Sleep apnea and heart failure

• Sleep apnea is more frequent in patients with congestive heart failure (11-38%)

• Javaheri et al (1995)
  – Prospective study of 81 men with stable systolic HF (LVEF<45%)
  – 51% had mean AHI > 44/h
  – 40% had central apneas
  – Increased atrial fibrillation with HF and sleep apnea

Mechanisms

- **Hemodynamic**
  - Hypertension
  - Cardiac myocyte necrosis
  - B-adrenoreceptor desensitization
  - Cardiac arrhythmias

- **Neurohumoral**
  - Increased sympathetic activity
  - Reduced parasympathetic modulation
Mechanisms

- Inflammatory & Oxidative stress
  - Increased IL-6, CRP and TNF-a
  - Decreased IL-10
  - Increased oxygen free radicals

- Endothelial dysfunction
  - Impaired endothelial-mediated vasodilation
  - Increased endothelin, ICAM-1, VCAM-1 and adhesion of leucocytes to the endothelium

CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule; IL-6, interleukin-6; TNF-a, tumor necrosis factor a; VCAM, vascular cell adhesion molecule

Obstructive Sleep Apnea and Left Ventricular Systolic and Diastolic Dysfunction by Francisco Garcia-Rio and Miguel Arias. Sleep Medicine Clinics 2 (2007) 565-574
Sleep apnea and arrhythmias

- **Sleep Heart Health Study:**
  - Individuals with severe sleep apnea have a 2-4 fold higher risk of developing complex arrhythmias

- **Atrial fibrillation is strongly associated with obstructive sleep apnea.**

- **Predisposing factors include:**
  - hypoxemia, intrathoracic pressure oscillations with cardiac wall stress, autonomic imbalances during apnea, diastolic dysfunction and long term atrial remodelling

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Mechanisms

- Prothrombotic
  - Increased plasminogen, activator inhibitor, platelet activity and aggregation
  - Increased frequency of pulmonary embolism and retinal vein thrombosis
Fatal cardiovascular events in non-treated sleep apnea

### Mortality in Sleep Apnea

Fully adjusted odds ratio for cardiovascular death associated to clinical variables and diagnosis status, according to the logistic-regression analysis

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>1.09 (1.04-1.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diagnostic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td>1.03 (0.31-1.84)</td>
<td>0.88</td>
</tr>
<tr>
<td>Mild-moderate OSA</td>
<td>1.15 (0.34-2.69)</td>
<td>0.71</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>2.87 (1.17-7.51)</td>
<td>0.025</td>
</tr>
<tr>
<td>CPAP</td>
<td>1.05 (0.39-2.21)</td>
<td>0.74</td>
</tr>
<tr>
<td>Presence of CV disease</td>
<td>2.54 (1.31-4.99)</td>
<td>0.005</td>
</tr>
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What is the interaction between the environment and genes?
DNA Methylation in Inflammatory Genes among Children with Obstructive Sleep Apnea

Jinkwan Kim¹, Rakesh Bhattacharjee¹, Abdelnaby Khalyfa¹, Leila Kheirandish-Gozal¹, Oscar Sans Capdevila¹, Yang Wang¹, and David Gozal¹

¹Section of Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, The University of Chicago, Chicago, Illinois
What can we learn from sleep apnea in children?

• Sleep apnea in some children leads to cumulative end organ damage caused by inflammation and oxidative stress.

• Chronic intermittent hypoxia induces the expression of inflammation related genes: IL-6, CRP.
  – Not all children have increased inflammatory markers
Epigenetics

• Potential mechanism underlying phenotypic variations of disease presentations
• Chemical modification of DNA without altering the primary DNA sequence:
  – DNA methylation
  – DNA acetylation
  – Hystone acetylation
  – Chromatin remodeling
DNA methylation

- Methylation of CpG dinucleotides
- Addition of methyl group to Cytosine residue without changing the primary DNA structure
- Methylated CpG in promoter regions: modify expression of genes
- What happens in sleep apnea and inflammatory related genes?
Methylation of inflammatory related genes in sleep apnea

Figure 1. Semi-DNA methylation array data. Heatmap of DNA methylation profile that includes 24 inflammatory related genes in children with obstructive sleep apnea (OSA) and high levels of high-sensitivity C-reactive protein (hsCRP) (n = 6) and matched children with OSA and low hsCRP levels (n = 6) (see Table E1).
FOXP3 gene methylation associated to apnea severity

Figure 2. Prevalence of Forkhead box P3 (FOXP3) DNA hypermethylation in children with obstructive sleep apnea (OSA) and control subjects. *FOXP3 DNA hypermethylation is defined as > 24%. hsCRP = high-sensitivity C-reactive protein.
FOXP3 gene methylation associated to disease status in sleep apnea

Figure 3. Prevalence of Forkhead box P3 (FOXP3) DNA hypermethylation in children according to the categorical severity of obstructive sleep apnea (OSA). *FOXP3 DNA hypermethylation was defined as \( \geq 24\% \).
Obstructive Sleep Apnea

- Chronic inflammatory condition
- Increased CRP and IL-6 in adults and children with sleep apnea
- FOXP3: transcription factor methylated in children with high inflammatory reaction to sleep apnea
- Methylation of FOXP3 CpG residues represses FOXP3 expression
- Hypoxia-induced transcription factors also mediate gene methylation
Epigenetics:

- Lifestyle and/or disease-induced changes in gene expression can have long term positive or negative health consequences
- Opportunity to improve the lifestyle of our patients
He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.

William Osler