Sleep Apnea: Bi-directional Risk with Stroke

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Bi-directional

- Sleep apnea <-> Stroke
- Therefore sleep apnea is a risk for stroke and...
- Stroke is a risk factor for sleep apnea and often unmasks it
- Treating sleep apnea before stroke reduces risk and...
- Treating sleep apnea after stroke improves stroke recovery

Sleep apnea definition

- Recurrent pauses in breathing or periods of shallow breathing during sleep.
- 10 seconds or longer per event
- Mild is ≥ 5/hr, able to treat with co-morbidities, moderate ≥15/hr and no additional criteria needed, severe ≥30/hr.
- Apnea is >50% decrease in flow, hypopnea >30% with SaO₂ drop of ≥4%
- May be central (10%), mixed or obstructive (90%)
- Airway remains open in central and blocked in obstructive.
Pickwickian Syndrome

- Joe, the Fat Boy from *The Pickwick Papers* by Charles Dickens in 1836
- Snoring
- Sleepy, even while standing
- Constantly hungry

Not only obesity

- Large tongue
- Small airway behind the tongue
- Large tonsils
- Longer and thicker soft palate
- Low position of the hyoid bone (long necks)
- Brachycephaly (head is wider than it is longer)
- Asians tend to have smaller, more restrictive facial structures

Sleep apnea

- Common and under-diagnosed.
- May be as high as 20-30% in the middle aged.
- Increases risk by 2-3 times in several prospective studies.
- Presence of sleep disordered breathing in stroke patients leads to poor outcomes and increased risk of recurrent stroke.
- Associations with:
  - Increased cardiovascular and cerebrovascular disease
  - Atrial fibrillation
  - Obesity and metabolic syndrome
  - Increased dyslipidemia
- Treatment may result in:
  - Improvement in blood glucose levels
  - Inflammation
  - Dyslipidemia
Many symptom consequences of sleep apnea

Obstructive sleep apnea

- Prevalence may be as high as 20-30% in middle-aged (34% of men and 17% of women) and largely undiagnosed
- Increasingly linked to cardiovascular and cerebrovascular disease
- Associated with obesity and metabolic syndrome, most likely from reduced androgens
- Increased dyslipidemia associated with untreated OSA
- Treatment can result in improvement in lipid levels
- This may result in improvement in multiple areas: Blood glucose levels, inflammation and dyslipidemia

Before the Stroke...
Medical Consequences of Sleep Apnea

![Image of medical consequences of sleep apnea]

Prevalence (%) of OSA in CVD

Normal Cardiovascular Changes in NREM and REM Sleep

![Image of normal cardiovascular changes in NREM and REM sleep]

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![Image of medical consequences of sleep apnea]

Prevalence (%) of OSA in CVD

Normal Cardiovascular Changes in NREM and REM Sleep

![Image of normal cardiovascular changes in NREM and REM sleep]
Sleep Apnea and Patent Foramen Ovale

- Prevalence of PFO in sleep apnea significantly higher (69 vs 17%)
  - Possibly due to transient infrequent elevation of right-sided pressure during apnea and subsequent opening of PFO
  - Possible right-left shunt as well as increased blood this causes to be in sleep apnea may raise the likelihood of embolism
Atrial fibrillation recurrence after cardioversion

- Recurrence 82% in non-compliant or untreated vs. 42% in treated OSA (P=0.009)
- Worse sleep apnea predicted recurrence in untreated OSA.
  - SaO₂ drop 8% vs 18% (P=0.034)
  - 4% vs 23% of night with SaO₂ <90% (P=0.063)


OSA and Dyslipidemia

Gündüz C, Basoglu OK et al. Obstructive sleep apnoea independently predicts lipid levels. Data from the European Sleep Apnea Database. Respirology 2018 doi:10.1111/resp.13372

Patient Characteristics

According to Sleep Apnea Severity

Gündüz C, Basoglu OK et al. Obstructive sleep apnea independently predicts lipid levels. Data from the European Sleep Apnea Database. Respirology 2018 doi:10.1111/resp.13372
Effect of CPAP Treatment on CV Risk


- In the McEvoy study, the significant CV improvement in patients who used CPAP ≥4 h/day was only achieved in the risk of a cerebrovascular event, but not in cardiovascular outcome.

Sleep Apnea is Prevalent in Left Ventricular Dysfunction

CPAP Treatment Reduces Incidence of CV events

(A) Incidence of stroke. (B) Incidence of cardiac disease. (C) Incidence of overall CVE.

CPAP Treatment Reduces Mortality of CV Events

(A) Mortality from stroke. (B) Mortality from cardiac disease. (C) Mortality from overall CVE

And don’t forget this one!
As if the others weren’t enough

- Erectile dysfunction seen in 69% with OSA vs. 34% without OSA (p<0.001)
- OR was 0.45 to have ED in absence of OSA.
- Correlates with mean nocturnal SaO\textsubscript{2} so intermittent hypoxemia may be specific contributor.
- Treatment with CPAP improved ratings of erectile function and sexual satisfaction


After the Stroke... or CPAP
What’s unique about OSA after stroke?

Sleepiness, snoring and obesity are less prevalent in stroke patients. Relationship between BMI and OSA severity less apparent after stroke!

BMI ≥ 30 and OSA: Non-stroke population: OR 4.7 (3.4-6.2) vs Stroke population: OR 1.1 (0.4-2.9)

Arzt M, Young T et al. Dissociation of Obstructive Sleep Apnea From Hypersomnolence and Obesity in Patients With Stroke. Stroke 2010 41(3) e129-134.

How common is it?

Table 3—Percentage of stroke or TIA patients with SDB stratified by AHI

<table>
<thead>
<tr>
<th>AHI Cutpoint</th>
<th># Studies (# patients)</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI &gt; 5</td>
<td>9 (908)</td>
<td>72 (60-81)</td>
</tr>
<tr>
<td>AHI &gt; 10</td>
<td>24 (1660)</td>
<td>63 (58-68)</td>
</tr>
<tr>
<td>AHI &gt; 20</td>
<td>15 (1465)</td>
<td>38 (31-46)</td>
</tr>
<tr>
<td>AHI &gt; 30</td>
<td>10 (865)</td>
<td>29 (21-37)</td>
</tr>
<tr>
<td>AHI &gt; 40</td>
<td>3 (316)</td>
<td>14 (7-25)</td>
</tr>
<tr>
<td>Central*</td>
<td>17 (1286)</td>
<td>7 (5-12)</td>
</tr>
</tbody>
</table>

*Percentage of patients who had primarily central apnea


Effect of CPAP Therapy on BP in Patients With Hypertension
Effect of CPAP Therapy on BP in Patients With Resistant Hypertension

Cardiovascular Survival after Stroke

Cardiovascular Events and Mortality

<table>
<thead>
<tr>
<th>5 year follow-up</th>
<th>CPAP group (n = 55)</th>
<th>Control group (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Angina</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Other events</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Deaths</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Cardiovascular-related deaths</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Non-cardiovascular-related deaths</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>
Comparative Survival of HF Patients Treated for and Not Tested for Sleep Apnea

![Graph showing survival rates of HF patients treated and not treated for sleep apnea](Image1)

**Source:** Lu J et al. Heart Failure: Treatments, Mechanisms, and Clinical Applications. Institute of Cardiology, Paris, France. 2018

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Stroke outcomes if treated with CPAP

![Graph showing stroke recovery outcomes with CPAP](Image2)


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Early Improvement in Stroke Recovery with CPAP

**Table 2:** Percentage of patients with improvement in neurological parameters 1 month after stroke

| Table 2 Percentage of patients with improvement in neurological parameters 1 month after stroke |
|---------------------------------|--------------|----------------|----------------|
| CPAP group | Control group | OR (95% CI) | p-value |
| Bithermal, improvement in point at disability | | | |
| Relatives | 401 (40.1) | 411 (41.2) | 0.967 |
| Excluding patients with two scores | 306 (30.9) | 307 (30.7) | 0.520 |
| Risk units, reduction in point per category | | | |
| All patients | 291 (29.3) | 292 (29.2) | 1.02 (1.01-1.03) | 0.032 |
| Excluding patients with two scores | 219 (21.9) | 220 (21.9) | 1.00 (0.95-1.05) | 0.904 |
| Cranial scores, increase in area points | | | |
| All patients | 261 (26.2) | 265 (26.7) | 2.41 (2.11-2.77) | 0.006 |
| Excluding patients with two scores | 209 (20.9) | 211 (21.0) | 2.19 (1.94-2.48) | 0.006 |

Data are presented as n (%) unless otherwise stated. CPAP = continuous positive airway pressure. * between the CPAP group and the control group (Dichotomous).

Lipid metabolism and OSA/CPAP

Chronic intermittent hypoxia (reversed by CPAP):
• Upregulates lipoprotein secretion
• $\uparrow$ free fatty acid flux to the liver
• Induces sympathetic activity which may induce lipolysis

Insulin resistance (improved with CPAP):
• $\uparrow$ total cholesterol and LDL by $\downarrow$ LDL receptors and $\downarrow$ LDL catabolism
• $\downarrow$ inflammatory markers

Hypersomnia improvements with increased activity
Hypersomnia with effects on leptins and ghrelin.

Total cholesterol and LDL pre- and post-Tx

Stroke Recurrence (25% of total stroke) and OSA

<table>
<thead>
<tr>
<th></th>
<th>Strokes +</th>
<th>Strokes -</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.77</td>
<td>55.63</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38/62</td>
<td>34/68</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking</td>
<td>15/19</td>
<td>28/34</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12/24</td>
<td>15/20</td>
<td>0.27</td>
</tr>
<tr>
<td>Alcohol</td>
<td>14/26</td>
<td>16/24</td>
<td>0.55</td>
</tr>
<tr>
<td>Female</td>
<td>20/30</td>
<td>25/35</td>
<td>0.30</td>
</tr>
</tbody>
</table>


Sleep apnea screening uncommon after stroke

- Non-academic stroke center
- Only 17% of patients reported being offered sleep apnea testing pre-stroke.
- After stroke: 5% report being questioned about snoring, 9% about sleepiness, 6% offered sleep studies.
- But likelihood is 72% (AHI >5)


All it takes is a pulse oximetry (to screen)

- Of 115 stroke patients, 75 with oxygen desaturation index >4% of >10/hr, mean was 29 ± 30.
- Association with atrial fibrillation and ↑ODI (P=0.005)
- Association between discharge disposition rehab vs. home and ↑ODI (P=0.005, OR 3.76)


Summary

- Sleep apnea is a risk for stroke and many conditions that predispose to stroke
- Treatment of sleep apnea can reduce the risk of new or recurrent stroke when present
- Treatment of sleep apnea can lead to improved stroke outcomes
- Current screening is inadequate
Thanks! Your lecture cured my sleep disorder.

Excessive sleepiness in OSA

- OSA is associated with structural changes in gray and white matter that are linked to compromised neurocognitive performance and activity in patients with OSA.

Oxidative Injury

- In an animal model of severe sleep apnea, chronic intermittent hypoxia showed significant oxidative injury.

Degeneration of wake-promoting neurons

- Chronic fragmented sleep caused a significant loss of 50% (P < 0.001) of orexinergic neurons and 25% of noradrenergic neurons involved in wake promotion in an animal model, which persisted after 4 weeks of recovery sleep.

Reduced gray matter

- As compared to healthy controls, studies have indicated that untreated OSA is associated with reduced gray matter volume in brain regions including frontal lobes and subcortical areas.

Structural changes to white matter

- In patients adherent to CPAP (≥6 hours), ES was associated with structural changes to white matter, potentially indicating compromised neuroconnectivity. Some structural changes correlated with clinical measures of ES.
And a bit on stroke during sleep...

• Now you may have the luxury of tPA or IR if you wake with a stroke.
• EXTEND allows for tPA up to 9 hours from onset using RAPID software in non-LVO stroke.
• WAKE-UP

• Gündüz C, Basoglu OK et al. Obstructive sleep apnoea independently predicts lipid levels. Data from the European Sleep Apnea Database. Respirology 2018 doi:10.1111/resp.13372