Sleep Apnea and Stroke: A ‘sleeping’ epidemic- consequences and management challenges

Kanika Bagai, MD, MS
Assistant Professor
Department of Neurology
Vanderbilt University Medical Center
Nashville, TN

- I have no financial disclosures for this talk.

Case

75 year old man with chief complaints of:
- loud snoring
- witnessed apneas
- frequent nocturnal awakenings
- daytime sleepiness in sedentary situations.

Obstructive Sleep Apnea: Cessation or reduction in airflow during sleep with continued ventilatory efforts

Past Medical History
- HTN
- Pontine stroke on MRI
- Glucose intolerance with FBS up to 131
- Paroxysmal atrial fibrillation
- CAD, s/p CABG in 1992, s/p stent placement to RCA
- Echocardiogram: nml wall motion, dilated LA/LV, EF > 55%

Examination
- BMI = 34.5, Friedman palate position of 4
**Overnight Polysomnogram**

- Apneas - >90% decrement in the thermistor, for at least 10 seconds.
- Hypopneas - 30-90% decrement in the nasal pressure transducer for at least 10 seconds, with concurrent oxyhemoglobin desaturation of 3% or greater or an EEG arousal, as defined by the American Sleep Disorders Association arousal criteria.

**Central Sleep Apnea (CSA):** Cessation or reduction in airflow during sleep with cessation/reduction in ventilatory efforts

**Mixed Sleep Apnea:** Initial cessation or reduction in airflow during sleep with cessation/reduction in ventilatory efforts followed by return of ventilatory effort but continued obstruction

**Epidemiology of OSA**

- Sleep apnea is a common disorder.
- Affects up to 20% of the general population.

**Obstructive Sleep Apnea**

<table>
<thead>
<tr>
<th>AHI</th>
<th>Classification of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>Normal</td>
</tr>
<tr>
<td>5-15</td>
<td>Mild</td>
</tr>
<tr>
<td>15-30</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Severe</td>
</tr>
</tbody>
</table>

AHI: Apnea-hypopnea index
The prevalence of sleep apnea is high in stroke patients—estimated to be between 50-70%.

It may predate the stroke, worsen during the acute stage, and persist after the acute phase.

Sleep Apnea is Highly Prevalent (and Largely Unrecognized) in Stroke

- 1991: Retrospective study¹ found that 72% of patients with stroke (n = 47) had AHI ≥ 10.
- 1996: Prospective study² on 24 consecutive patients admitted with recent stroke (mostly ischemic) found AHI ≥ 10 in:
  - 77% of men and 64% of women with strokes
  - 23% of men and 14% of women (age and gender-matched controls)

¹ Kapen et al, 1991, Neurology 41 (suppl 1):125

Sleep Apnea and Stroke

- 1996: Comparison of sleep apnea in three groups³:
  - Acute Stroke (n = 48)
    - AHI = 32 (0-140)
  - TIA (n = 32)
    - AHI = 23 (0-81)
  - Age/gender-matched controls (n = 25)
    - AHI = 5 (0-24)
  - Stroke and TIA did not significantly differ in AHI.
  - This result suggested that sleep apnea is the cause of stroke, rather than its consequence

³ Bassetti et al, 1996; Neurology, 27:401-407

Obstructive Sleep Apnea is an Independent Risk Factor for Stroke and Death

- Enrolled 1022 patients referred for sleep studies
- 68% had OSA (AHI of 5 or greater)
- Compared outcomes in groups with and without OSA
- Adjusted for co-morbid conditions

Yaggi H, NEJM, 2005

Obstructive Sleep Apnea and Incident Stroke

The Sleep Heart Health Study

- Served 11,000 participants in 47 centers.
- Followed over 4 years.
- Correlated sleep apnea with stroke incidence.

Am J Respir Crit Care Med Vol 182, pp 269–277, 2010
Un玘treated OSA affects Survival after Stroke

-161 patients underwent portable respiratory monitoring 48-72 hrs after admission for stroke
- Four independent variables associated with mortality:
  - Presence of CAD
  - AHI
  - MCA involvement
  - Age

OSA is an independent risk factor for HTN

- Sleep apnea
- Drug-induced or drug-related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease


Does treating OSA improve HTN?

- Small (5 mm Hg) improvements in mean blood pressure seen in normotensive cohort, driven by those with more frequent oxyhemoglobin desaturation episodes.
  - Peppard J, Lancet, 2002

- Larger reductions in mean blood pressure (9.9 ± 11.4 mm Hg) were seen in those with severe OSA treated for 60 days.

Impact of Treating OSA on Cardiovascular Events

Pts had CAD (>70% stenosis) and AHI > 15
N = 54
Pts not randomized

Milledon O, European Heart Journal, 2004
**Sleep Apnea and Arrhythmias**

- The entire spectrum of arrhythmias is increased in sleep apnea.
- About half of patients undergoing elective cardioversion for atrial fibrillation had significant sleep disordered breathing.
- Patients with both atrial fibrillation and sleep disordered breathing are more likely to remain in sinus rhythm after cardioversion if treated with CPAP. (Gami A, Circulation, 2004)

**OSA and Obesity/Insulin Resistance**

- AHI and minimum oxygen saturation are independent determinants of insulin resistance, even after controlling for obesity.
- CPAP improves insulin sensitivity in patients with OSA and Type 2 DM. (Harsch I, Respiration, 2004)

**Sleep Apnea and Cardiovascular Disease: Putative Mechanisms**

- Sympathetic nervous system overactivity and RAAS.
- Impaired glucose tolerance, increased insulin resistance.
- Endothelial dysfunction.
- Blood coagulation abnormalities, such as elevated PAI-1.
- Altered systemic inflammatory markers that promote atherosclerosis, such as C-reactive protein and tumor necrosis factor.
- Oxidative stress.

**Increased Nocturnal Sympathetic Activity with OSA**

- Somers V, J Clin Invest. 1995

**Endothelial function and OSA**

- Endothelial dysfunction plays an important role in the pathogenesis of CVD.
- Abnormal endothelial function in patients with OSA.
- Flow-mediated dilatation significantly lower than in OSA patients.

**Molecular Mechanisms of Endothelial Dysfunction in OSA**

- *Endothelium-derived nitric oxide (NO)*
  - NO is a major mediator of endothelium-dependent vasodilatation.
  - Anti-inflammatory and antithrombotic properties.
  - Lower levels of NO in patients with OSA and an increase in levels following treatment with CPAP.
- Lavie L, J Mol Neurosci 2003
Molecular Mechanisms of Endothelial Dysfunction in OSA

Reactive oxygen species (ROS)

- Intermittent hypoxia in OSA patients may alter endothelial function by promoting the formation of reactive oxygen species.
- Inflict injury to surrounding tissues.
- Activate signaling pathways that can initiate adaptive responses to hypoxia, such as hypoxia inducible factor-alpha (HIF-1 alpha) or inflammatory pathways via NFkB.

Inflammation and OSA

- TNF-a: Serum TNF-a is the downstream product of activation of the NF-kB pathway
- TNF-a levels are reported to be elevated in OSA and fall with CPAP. Ryan S. Circulation. 2005;112:2660–2667.
- CRP: CRP is a marker of inflammation and a strong predictor of future CVD.
- In patients with OSA, CRP levels are reported to be elevated and decrease with CPAP treatment. Yako et al., Circulation. 2003

Fibrinolytic system, CVD and OSA

- Majority of strokes and MIs are due to atherothrombotic events, with impaired fibrinolytic activity increasing the propensity for these events.
- Plasminogen Activator Inhibitor-1 (PAI-1) is the major physiologic inhibitor of the body’s fibrinolytic system.
- PAI-1 is released from platelets and endothelial cells in response to thrombin.

Activation and Inhibition of the Fibrinolytic Pathway

- Overall fibrinolytic activity follows a diurnal variation.
- PAI-1 activity is highest and t-PA activity is lowest in the morning.

PAI-1 and CVD

- PAI-1 expression has been observed in atherosclerotic plaques in humans and may contribute to the progression of vascular disease.
- PAI-1 levels are elevated in patients with cardiovascular events such as myocardial infarction (MI) and stroke
- Elevated PAI-1 appears to be a risk factor for recurrent MI.
- Extent of PAI-1 elevation independently correlates with mortality in acute MI.

Circadian Rhythm of PAI-1

- Overall fibrinolytic activity follows a diurnal variation.
- PAI-1 activity is highest and t-PA activity is lowest in the morning.
PAI-1 and OSA

- Studies have shown that PAI-1 levels are significantly higher in patients with OSA and correlate with the severity of disease.
- Morning PAI-1 levels were significantly increased in patients with OSA.

Molecular Mechanisms of fibrinolytic imbalance in OSA

- Circadian Clock Genes
- Hypoxia

Mechanisms of fibrinolytic imbalance in OSA

- Hypoxia
  - Hypoxia is a potent stimulus for the PAI-1 gene in endothelial cells.
  - Plasma PAI-1 antigen and activity were measured in mice placed in a hypoxic environment with Po2 < 40 mmHg.
  - PAI-1 antigen and activity levels increased in a time-dependent fashion after hypoxic exposure with an increase in PAI-1 mRNA, compared with normoxic controls.
  - Transcripts for both tPA and uPA decreased under hypoxic conditions.

- Circadian Clock Genes
  - Studies have implicated the molecular components of the body's endogenous circadian clock as a key determinant of PAI-1 rhythmicity.
  - These include the transcriptional activators BMAL1, BMAL2 and CLOCK, which directly regulate PAI-1 gene expression.
  - Changes in sleep-wake cycles are known to alter the amplitude of PAI-1's oscillations.
  - The heightened circadian variation in PAI-1 levels noted in patients with OSA may be mediated via an effect on the circadian clock genes.

Overnight PSG showing Hypoxia

- Overnight polysomnography (PSG) showing hypoxia.
Specific Aims

- Assess the relationship between endothelial dysfunction and OSA.
- Characterize the relationship between circadian variation of fibrinolytic markers and OSA, to determine the circadian rhythm of PAI-1 and t-PA in patients with OSA and normal controls.
- To determine the correlation between severity of OSA and fibrinolytic balance and the correlation between severity of OSA and endothelial function.

- History of MI, stroke, TIA or peripheral vascular disease.
- History of DM, uncontrolled HTN (SBP >160, DBP >120), ESRD on dialysis, cancer, autoimmune or liver disease.
- Significant medical or psychiatric disease that may impair participation in the trial.
- Evidence of medical instability (cardiac arrhythmias, CHF, pulmonary disease) that requires expedited evaluation and treatment of OSA.
- History of alcohol or drug abuse during the one-year period prior to trial participation.
- Current use of tobacco products.
- Current treatment with ACE inhibitors and or chronic NSAID use.
- Another primary sleep disorder that can cause disrupted sleep.
- Patients with unusual sleep or wake habits, including shift work.
- Trans meridian travel in the previous 3 months.
- Patients with OSA who have already received treatment with CPAP, surgery or oral appliance.
- Pregnancy, as hormonal changes affect sleep disordered breathing.

Flow Mediated Vasodilation

- The brachial artery was imaged using a high-resolution ultrasound equipped with a 7.5 MHz linear-array transducer.
- Endothelial-dependent vasodilatation was assessed by measuring the change in caliper of the brachial artery during reactive hyperemia.

Endothelial Function

<table>
<thead>
<tr>
<th></th>
<th>OSA</th>
<th>Non-OSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>19 (625-48)</td>
<td>0.44 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Min O2</td>
<td>0.0057</td>
<td>0.30 (2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean O2</td>
<td>0.00 (0.03)</td>
<td>0.19 (0.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time below 80</td>
<td>0.05 (2.33)</td>
<td>0.40 (0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N1</td>
<td>13.0 (13.41)</td>
<td>11.1 (6.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>N2</td>
<td>81.7 (11.6)</td>
<td>61.29 (7.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>N3</td>
<td>7.0 (6.1)</td>
<td>10.1 (6.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Arousal index</td>
<td>23.4 (23.74)</td>
<td>7.8 (2.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean O2</td>
<td>90.0 (3.38)</td>
<td>94.19 (2.21)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Bagai et al, SLEEP, in press
The rhythm adjusted mean levels of PAI-1 activity and antigen in the OSA group was significantly higher and t-PA activity levels were significantly lower than the non-OSA group.

The mean peak time of the PAI-1 antigen and activity and t-PA antigen and activity did not differ significantly between the two groups.

Results indicate an alteration of the circadian rhythm of fibrinolytic markers in OSA patients as compared with control subjects confirmed by overnight polysomnography.

Using Spearman correlation, PAI-1 activity was strongly correlated to the minimum oxygen levels and the severity of OSA (as measured by AHI).

Alteration in fibrinolytic balance, mediated by PAI-1, may be one of the key links between OSA and CVD.

No significant differences in the markers of endothelial function were noted.

Based on the results of this study, treatment strategies to favorably shift the fibrinolytic balance can be expected to result in primary and secondary prevention of CVD in OSA.
OSA Management

- PSG/Ambulatory PSG confirming OSA
- CPAP/Follow up program
- Alternative Therapy: Provent
  - Oral
  - Appliance
  - Surgery
  - Weight loss

Clinical Guidelines for Portable Monitoring

- PM for the diagnosis of OSA should be performed only in conjunction with a comprehensive sleep evaluation.
- May be used as an alternative to polysomnography (PSG) for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA.
- PM is not appropriate for the diagnosis of OSA in patients with significant comorbid medical conditions that may degrade the accuracy of PM, including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure.

J Clin Sleep Med 2007;3(7):737-747

Portable Monitoring

- PM is not appropriate for the diagnosis of OSA in patients with significant comorbid medical conditions that may degrade the accuracy of PM, including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure.

STOP BANG Questionnaire

- Height _____ inches/cm Weight _____ lb/kg
- Age _____ Male/Female BMI _____
- Collar size of shirt: S, M, L, XL, or _____ inches/cm , Neck circumference* _____ cm
- 1. Snoring 2. Tired 3. Observed Apneas
- 4. Blood pressure 5. BMI > 35 kg/m²? 6. Age > 50 yr old?
- * Neck circumference is measured by staff
- High risk of OSA: answering yes to three or more items
- Low risk of OSA: answering yes to less than three items
- Adapted from:
- STOP Questionnaire A Tool to Screen Patients for Obstructive Sleep Apnea
  - Frances Chung, F.R.C.P.C.,* Balaji Yegneswaran, M.D.,† Pu-Liao, M.D.,§ Sharon A. Chung, Ph.D.,||
  - Santhira Vairavanathan, M.B.B.S., Sazzadul Islam, M.Sc., Ali Khajehdehi, M.D.,† Colin M. Shapiro,

OSA and management

- PSG/Ambulatory PSG confirming OSA
- CPAP/Follow up program
- Alternative Therapy: Provent
  - Oral
  - Appliance
  - Surgery
  - Weight loss
Consider Positional Therapy

- CPAP troubleshooting
- Mild OSA
- Provent or Oral appliance
- Mod/Severe OSA
- Oral Appliance
- Weight loss
- Surgery
- Surgery
**Positional Therapy**

- Expiratory resistor with adhesive for each nostril.
- Minimal Inspiratory resistance.
- Disposable after each night’s use.
- FDA approved for OSA treatment.

**Nasal End Expiratory Pressure**

- Expiratory resistor with adhesive for each nostril.
- Minimal Inspiratory resistance.
- Disposable after each night’s use.
- FDA approved for OSA treatment.

**Mandibular Advancement Splints**

- Nasal Surgery: Correction of nasal problems such as a deviated septum.
- Uvulopalatopharyngoplasty (UPPP): A procedure that removes soft tissue on the back of the throat and palate, increasing the width of the airway at the opening of the throat.
- Tonsillectomy
- Mandibular maxillary advancement surgery: Surgery to correct certain facial problems or throat obstructions that contribute to sleep apnea.

**Oral Appliance**

- Correction of nasal problems such as a deviated septum.
- Uvulopalatopharyngoplasty (UPPP): A procedure that removes soft tissue on the back of the throat and palate, increasing the width of the airway at the opening of the throat.
- Tonsillectomy
- Mandibular maxillary advancement surgery: Surgery to correct certain facial problems or throat obstructions that contribute to sleep apnea.
Case Presentation

- 75 year old man with loud snoring, witnessed apneas, frequent nocturnal awakenings, and daytime sleepiness in sedentary situations.
- Begun on BIPAP but felt like he was “fighting machine” to breathe.
- Came back for a trial of adaptive servo ventilation (ASV) and did very well.
- Using ASV device every night with improved alertness and more consolidated sleep.

Summary

- Sleep apnea and stroke are interrelated, with shared risk factors as well as plausible mechanisms that await further research.
- Treatment of sleep apnea may impact favorably on management of their condition and prevention of cardiovascular events.

Bagai K, The Neurologist 2010