Sleep, Obstructive Sleep Apnea, and Stroke

Leroy Seaux, M.D.
Winston Neurology
What Is Sleep For?
What is Sleep For? Ecologic Theories

• A planned inactivity may be protective against predators (stay out of harm’s way)
• But also more vulnerable
• Dolphins swim while sleeping with half a brain at a time
What is Sleep For?

- Energy conservation: only conserves 120 calories in 8 hours of sleep
- Thermoregulation: total sleep deprivation in experimental animals results in severe abnormalities of temperature control
- Prevention of cornel damage: stirring fluid behind the closed eyelids during REM keeps it from drying out
What is Sleep For? Immunity

- Infection activates substances that have an effect on sleep
- Mammals that sleep longer have enhanced immune responses and lower rates of parasitic infection
- Sleep restriction decreases fever in response to infection
- The immune system response to flu vaccine is 50% lower 10 days after the vaccine when sleep deprived
What is Sleep For? The Brain

- Smaller animals with smaller brains have higher metabolic rates and require more sleep
  - Small Brown Bat, over 19 hours
  - Mouse, 14 hours
  - Human, 7-8 hours
  - Elephant, 4 hours
What is Sleep For? The Brain

- During sleep the space between cells in the brain increases by 60%, allowing better cerebrospinal fluid flow and more effective clearance of metabolites
What is Sleep For? Life

- In animals, sleep deprivation is fatal in 4-6 days for puppies, 9-17 days in adult dogs and 7-31 days in adult rabbits
- In rats, death occurred in 11-32 days (21) versus 17 days without food
- In rats, recovery occurred in 1-3 days in those allowed to sleep
What is Sleep For? Life

- Rats deprived of sleep lost weight despite eating more, became scrawny and disheveled, and were unable to maintain their body temperature despite expending more energy.
- Mechanism of death unknown.
Sleep Deprivation
How Much Sleep Do We Need?

- Infants: 15-19 hours
- 1-3 years: 12 hours
- Children: 10 hours
- Teens: 9-10 hours
- Adults: 7-8 hours
- Based on research on alertness, sleep-wake cycles, hormones and circadian rhythms
Is America Sleep Deprived?

- CDC “Insufficient Sleep is a Public Health Epidemic”
  - Multiple studies show 18% of adults report receiving insufficient sleep
  - Based on surveys between 1977-2004, the % of men and women who sleep <6 hours has increased significantly over the last 20 years
Is America Sleep Deprived?

- In 2008 and 2009, 35% of adults reported <7 hours of sleep during a typical 24 hour period
  - 38% reported unintentionally falling asleep at least once in the preceding month
  - 5% reported nodding off or falling asleep while driving at least once in the preceding month
- In contrast, more than 35 years ago, adults reported sleeping >7.7 hours of sleep per night
Why Are We Sleep Deprived

1. Lifestyle/Occupational
   - Shift work: the number of workers departing for work between midnight and 5:30 am grew over a 10 year period by 24%
   - Longer working hours
   - Social/recreational activities
   - Around the clock access to technology
   - Among adolescents
     - Extensive television viewing
     - Growing social, recreational and academic demands
Why Are We Sleep Deprived?

2. Medical
   - Sleep disorders
   - Other medical disorders
   - Drug/alcohol induced
Increasing Obesity in America
What Does Sleep Deprivation Do To Us?

- Decreased memory
- Impaired ability to learn
- Decreased attention
- Decreased executive control/irritability/poor decision making
- Anxiety
- Lack of coordination
- Depressed mood
- Lack of energy
What Does Sleep Deprivation Do To Us?

- Sleep deprivation causes at least 10-15% of fatal vehicle accidents.
- Drowsy driving causes more than 100,000 crashes, resulting in 40,000 injuries and 1,550 deaths each year in the US (NHTSA.gov).
- Drowsy driving crashes tend to occur at night, on highways at higher speeds and in young men.
- At highway speeds, lapses of not more than 2 seconds can result in crossing the highway lane.
What Does Sleep Deprivation Do To Us?

- Staying awake for just 17-19 hours straight impacts performance more than a blood alcohol level of .05%
- 24 hours of continuous wakefulness equals blood alcohol level of .10%
- Alcohol intensifies the effects of sleep deprivation
- Accidents related to sleep loss have been estimated to have an annual economic impact of $43-56 billion
Cumulative adverse effects of chronic sleep restriction were greater in objective performance than subjective awareness

**Objective Performance**

- PVT performance lapses

**Subjective Performance**

- KSS subjective sleepiness
Neurogenesis

- Adult neurogenesis observed in humans
- Sleep loss has been reported to inhibit hippocampal cell proliferation and neurogenesis
- Inhibited by stress and enhanced by exercise
- Learning and memory?
What is Obstructive Sleep Apnea?
What is Obstructive Sleep Apnea

- Repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstructions during sleep
- Generally daytime symptoms
- Snoring (often described as periods of silence alternating with noisy, snorting or gasping respirations, accompanied by gross motor movements)
- Clinical pearl: the sleepy patient who snores has OSA until proven otherwise
Diagnostic Criteria for OSA

- One of the following:
  - Unintentional sleep, daytime somnolence, unrefreshing sleep, fatigue or insomnia
  - Awakenings with breath-holding, gasping or choking
  - The bed partner reports loud snoring, interruptions in breathing, or both
- Polysomnogram shows 5 or more apneas or hypopneas per hour with preserved respiratory effort
- Not better explained by another current sleep disorder, medical or neurologic disorder, medication or substance use
Diagnostic Criteria for OSA

OR

- Polysomnogram shows 15 or more apneas or hypopneas per hour with preserved respiratory effort
- Not better explained by another current sleep disorder, medical or neurologic disorder, medication or substance use
Demographics of OSA

- 2-5% of population
- 2% of middle aged women and 4% of middle aged men
- 5 or more respiratory events per hour without symptoms: 9% of women and 24% of men
- Prevalence increases with age
- Prevalence in children reported to be around 2%; highest in preschool ages when the tonsils and adenoids are largest relative to airway
- Increased prevalence reported in African-Americans, East Asians, Mexican-Americans and Pacific Islanders
- East Asians reported to have greater severity despite lower BMI than Caucasians
Nighttime Symptoms of OSA

- Snoring
  - Weight gain, alcohol, supine posture worsens
- Night sweats
- Restless sleep
- Nightmares of drowning, suffocating or being buried alive
- Sleepwalking and sleep talking
- Nocturia
  - Arousals
  - Increased intra-abdominal pressure
  - Increased secretion of atrial natriuretic peptide
- Esophageal reflux
Daytime Symptoms of OSA

- Daytime sleepiness and fatigue most common complaint
- Decreased dexterity, concentration, attention, memory and judgment
- Morning headache (can be nocturnal as well)
- Morning dry mouth
- Personality changes such as irritability
- Marital discord
- Decreased libido or impotence
“Laugh and the world laughs with you, snore, and you sleep alone.”

Anthony Burgess
“The magnitude of the AHI generally reflects the severity of excessive daytime sleepiness”

Review of Sleep Medicine, by Teri Barkoukis & Alon Avidan
“The frequency of apneas and hypopneas during sleep correlates poorly with daytime symptom severity and quality of life.”

International Classification of Sleep Disorders
“It is possible for any severity level of OSA to occur with any degree of symptomatic sleepiness and in some cases, with no subjective complaints.”

*International Classification of Sleep Disorders*
Pathology of OSA

- Reduced cross-sectional area of the upper airway lumen due to either excessive bulk of soft tissues (tongue, soft palate, lateral pharyngeal walls) or craniofacial anatomy or both
- Activity of pharyngeal dilating muscles decreases with sleep and decreases further with REM sleep
- Patients with normal or below normal body weight are more likely to have OSA due to anatomic abnormalities such as retrognathia or adenotonsillar enlargement
Clinical Evaluation of OSA

- Increased BMI
  - The major predisposing factor
- Neck
  - Mean neck circumference in patients with OSA was 43.7 cm and without it 39.6
  - The 40 cm threshold used in the Stop Bang has a sensitivity of 61% and a specificity of 93%
Clinical Evaluation of OSA

- Head and neck exam
  - Significant nasal obstruction
  - High arched palate
  - Tonsillar hyperplasia
  - Engorgement of pharyngeal tissue
  - Large uvula
  - Retrognathia
  - Macroglossia
The Mallampati Classification

Class 1

Class 2

Class 3

Class 4
The Incidence of Sleep Apnea in Patients with CVA or TIA

- Poland
- n=43
- AHI <5 in 16, 5-10 in 10, 10-20 in 8, >20 in 9
- 63%
- Mean age 63.2 in those with AHI <5, 71.3 in rest
- No significant difference in BMI, hyperlipidemia, hypertension, CAD, arrhythmias, DM, smoking
Benefits of OSA Treatment in CAD: A Long Term Follow Up Study

- 54 patients with OSA and CAD
- 2 OSA groups: accepted or rejected treatment with CPAP or upper airway surgery
- Endpoints: cardiovascular death, acute coronary syndrome, hospitalization for heart failure, and revascularization procedures
- 2^{nd} events in the same patient weren’t counted
- Severity of OSA similar in the 2 groups
- All but one patient were men
Benefits of OSA Treatment in CAD: A Long Term Follow Up Study

- Clinical characteristics and cardiac features at the time of diagnosis of OSA similar in the 2 groups
- Median follow up 86 and 90 months in treated and untreated groups
- At the end of follow up neither cardiovascular treatment nor risk factor control different between the 2 groups
- At least 1 cardiovascular event occurred in 24% of the treated patients vs. 58% of the untreated patients
- All 3 CV deaths were in the untreated group
- The time to first event was significantly longer in the OSA-treated group (median 26.5 months vs 13 months)
Risk of Stroke in Patients with CAD and Sleep Apnea

- 392 patients with CAD followed for 10 years
- Sweden; data complete
- AHI $\geq 5$ in 54%
- Hazard ratio for CVA 3.92, 2.89 adjusted for age, sex, LV function, other variables
  - 2.44 AHI 5-15
  - 3.56 AHI $>15$
- Only 9 of the patients were treated
- MI and death not increased in this study
OSA and Cardiovascular Disease & Stroke

- A larger study of OSA patients without CAD at baseline followed for 7 years
  - CAD developed in 16% of OSA patients vs 5% of snorers without OSA
  - CAD confirmed in 25% of incompletely treated cases vs 4% of efficiently treated cases
OSA and Cardiovascular Disease

- Long Term Cardiovascular Outcomes in Men With OSA With or Without Treatment With CPAP: An Observational Study by Marin, J.M. et.al.
  - Men with OSA, simple snorers and a population of healthy men matched for age and BMI with untreated OSA patients
  - Participants followed for a mean of 10 years
  - Endpoints were fatal cardiovascular events (MI or stroke) and nonfatal cardiovascular events (nonfatal MI, nonfatal stroke, CABG, and PTCA)
OSA and Cardiovascular Disease

Results:

- Participants with severe untreated disease had higher incidence of fatal and nonfatal cardiovascular events than all other categories; odds ration 3 vs healthy participants
CPAP in Elderly Patients with Moderate to Severe OSA

- China
- 130 patients >60 years old with moderate to severe OSA (AHI ≥ 20)
- CPAP vs untreated
- No significance difference in age, sex, BMI, pre-existing cardiovascular disease
- Endpoints: fatal and nonfatal MI and CVA and revascularization procedures
- AHI, snoring, ESS score higher in treated group
- Mean follow up 5 years
- Risk of death 21.6% without CAP, 5.6% treated
- All cardiovascular events 55.7% vs 13.9% (4.2% with good compliance, 16.7% with poor compliance)
Wisconsin Sleep Cohort Study: Stroke

- 1475 participants had PSGs at baseline and 4, 8, and 12 years later, with measurements of BP and cholesterol, and recording of age, sex, BMI, smoking history, alcohol use, and presence of diabetes.
- 76% had AHI <5, no SDB
- 17% had AHI 5-20, mild SDB
- 7% had AHI >20, moderate to severe SDB
Wisconsin Sleep Cohort Study: Stroke

- Prevalence of stroke odd ratio 3.83 controlling for all potentially confounding variables
- In the 4 year prospective analysis odds ratio was 4.48 for incident stroke controlled for all variables except BMI; 3.08 including BMI
OSA as a Risk Factor for Stroke and Death

- Observational cohort study of patients referred to Yale Center for Sleep Medicine for suspected sleep apnea
- >50 years old, 1022 in study
- AHI cutoff 5, mean 35
- Endpoints: CVA, TIA death from any cause
- Most patients were treated but efficacy of treatment was not described
OSA as a Risk Factor for Stroke and Death

- Median follow-up duration 3.4 years for those with SDB and 3.3 years for controls
- Hazard ratio 1.97 for all end points, 1.70 for death
- Risk for all endpoints was 3x that of controls in most severe quartile
Cohort Studies and Stroke

- Sleep Heart Health Study: odds ratio 1.58 for stroke
- A recent meta analysis of 12 prospective cohort studies with >25,000 subjects: RR of stroke for severe vs no OSA 2.15
Sleep Disordered Breathing and Recurrence of Cerebrovascular Events, Case Fatality, and Functional Outcome in Patients with Ischemic Stroke or TIA
• Poland
• 91 patients with CVA or TIA without previously diagnosed sleep apnea
• 61 with SDB, AHI >5, mean 20.8
• No significant difference in other risk factors
• Odds ratio for recurrent CVA or TIA 1.52 over 2 year follow-up period for those with SDB
• No significant difference in functional outcomes or case fatality
Severe Sleep Apnea and Risk of Ischemic Stroke in the Elderly

- Patients aged 70-100, median age 77, 57% male
- Cut off AHI 30; those treated with CPAP excluded
- No previous CVA, controlled for other risk factors
- Hazard ratio 2:52
AHI: An Independent Predictor of Mortality in CAD

- Swedish study Yuksel Peker et. al.
- PSGs done on patients admitted to ICU with CAD, 4-21 months later when stable
- AHI cut off 10; successfully treated patients excluded
- Matched for other risk factors
- 5 year follow up study
- Cardiovascular death in patients with CAD 37.1% over five years versus 9.3%
OSA and Cardiovascular Disease

- Long Term Effects of Nasal CPAP on Cardiovascular Outcomes in Sleep Apnea Syndrome by Doherty et. al.
  - 61 patients intolerant of CPAP versus treated patients
  - Matched for age, BMI and time since diagnosis
  - Deaths from cardiovascular events 14.8% vs 1.9%
OSA is a Risk Factor for Death in Patients with CVA

- 132 patients admitted for stroke had PSG mean of 23 days later
- Followed over 10.6 years
- With AHI 15 cut off, 1.76 hazard ratio independent of other risk factors
- Most did not continue CPAP
Possible Mechanisms

- Heightened cardiovascular activity during sleep, including sympathetic activation and catecholamine release
- CBF velocity increases during an obstructive apnea and decreases after apnea termination; CBF, arterial pressure changes and hypoxemia after an apnea may predispose to nocturnal cerebral ischemia
Possible Mechanisms

- Periodic intermittent hypoxia generates reactive oxygen species and oxidative stress
  - Increase in inflammatory factors including CRP
  - Increase in transcription factors that in turn increase production of VEGF among other proteins
  - Decreases NO synthase, decreasing circulating NO, which alters vascular reactivity, inhibits platelet aggregation, and attenuates adhesion of platelets and WBCs to vessel walls
Possible Mechanisms

- Negative intrathoracic pressure during apnea increases venous return to the heart, which can increase right to left shunt through a patent forearm ovale
- One study found evidence of early atherosclerosis with increased intima-media thickness in OSA; treatment with CPAP for 4 months decreased the thickness of the carotid intima-media layer and reduced CRP and catecholamine levels
OSA and Arrhythmias

- Afib odds ratio 4; 82% vs 42% recurrence rate untreated versus treated
- A case control study of patients with OSA and first time ischemic stroke: 5.34 times increase in afib after controlling for other risk factors
- NSVT odds ratio 3.4
- AV block (increased vagal tone due to persistent breathing effort vs closed upper airway)
- Severe sinus bradycardia
- Prolonged sinus pauses
Risk of sudden death from cardiac causes as well as MI in the general population peaks from 6 am to noon and has a nadir from midnight to 6 am

Reviewed PSGs and death certificates of 112 Minnesota residents who died suddenly from cardiac causes

For 4 intervals of the day, compared rates of sudden death from cardiac causes among people with OSA with:

- Rates among people without OSA
- Rates in general population
- Expectations according to chance
Day-Night Pattern of Sudden Death in OSA

- For each interval assessed median AHI and relative risk of sudden death from cardiac causes
- Similarly analyzed sudden death from cardiac causes during three time intervals that correlate with usual sleep-wake cycles
Day-Night Pattern of Sudden Death in OSA

- From midnight to 6am, sudden death from cardiac causes occurred in:
  - 46% of people with OSA
  - 21% of people without OSA
  - 16% of general population
  - 25% expected by chance

- The AHI correlated directly with the relative risk of sudden death from cardiac causes from midnight to 6am
OSA Treatment: PAP

- PAP: Positive Airway Pressure
- The gold standard for moderate to severe OSA
- Pneumatic splint preventing airway collapse
- MRI has confirmed CPAP increases airway volume and area and decreases lateral pharyngeal wall thickness and edema (from chronic vibration and occlusion of the airway)
PAP Improves

- Sleepiness
- Cognitive function
- Driving
- GERD
- Hypertension (=1 med/ approved for mild OSA without symptoms with comorbid hypertension)
- Cardiovascular events with stroke
- Glucose control
- Pulmonary hypertension
- Arrhythmias
- Depressive symptoms
- Nocturia
Continuous Positive Airway Pressure (CPAP) Machine

CPAP machine with nasal pillow mask, ballcap-style straps

- Full face mask, side straps
- Nasal pillow mask, ballcap-style straps
- Nasal pillow mask, side straps

© 2009 RelayHealth and/or its affiliates. All rights reserved.
OSA Treatment: Mandibular Advancement Devices (MADs)

- Patients with mild to moderate OSA who prefer them to PAP
- Patients who can’t tolerate PAP
- Follow-up study recommended
- Regular follow up with dentist and sleep specialist recommended to watch the device and monitor for worsening symptoms
MADs: Mechanism

- Advance mandible and tongue
- Increase dilator muscle activity
- Decrease pharyngeal tissue folds
MADs: Side Effects

- Increased saliva
- TMJ discomfort
- Altered occlusion
- Loosening of dental work
- Compliance data better than PAP in studies
OSA Treatment: Surgery

- **Tracheostomy**
  - Universally effective; bypasses the obstruction
  - Only when other options don’t exist, have failed, are refused or necessary by clinical urgency

- **UPPP (uvulopalatopharyngoplasty)**
  - Doesn’t reliably treat moderate or severe OSA as a single procedure
  - May be combined with MMA (MLS – multi level surgery)
OSA Treatment: Surgery

- MMA (maxillomandibular advancement)
  - Indicated for severe OSA in patients intolerant of CPAP or mild-moderate OSA when MAD ineffective or undesirable
  - Evidence for effectiveness in severe OSA
  - Can be effective by itself

- RFA
  - Nasal turbinates, tongue and soft palate
  - Mild-moderate OSA if PAP not tolerated or MAD not tolerated or ineffective
Medical OSA Treatment: Weight Loss

- 10% weight loss translates to 26-32% decrease in AHI
- Remember, non obese patients with OSA due to other factors will not benefit from weight loss
Medical OSA Treatment: 
Smoking Cessation

- Smokers are 4-5 times more likely to have at least moderate OSA
- May contribute to upper airway dysfunction by eliciting mucosal edema and increased upper airway resistance
Medical OSA Treatment: Upper Airway Exercises

- Oropharyngeal exercises developed by speech pathologists
- Learn to play the didgeridoo
- Studies show moderate reduction in AHI in mild to moderate OSA
Medical OSA Treatment: Sleep Hygiene

- Upper airway collapsibility increases after sleep fragmentation
- Sleep deprivation is associated with blunted hypoxic and hypercapnic ventilatory chemoresponsiveness; may prolong apneas and hypopneas with greater oxygen desaturations by depressing the arousal response
Sleep Hygiene

- Stick to the same sleep schedule, even on weekends
- Avoid napping, especially during the day
- Healthy diet
- Exercise daily
Sleep Hygiene

- Optimize the sleep environment
  - Bedroom should be cool, quiet and dark
  - Consider blackout curtains, eye shades, ear plugs, “white noise” machine, fans
  - Mattress should be comfortable and supportive
  - Take work materials, computer, tv, out of the sleep environment
- Avoid alcohol, nicotine, excessive fluids and heavy meals in the evening
- Wind down with a calming activity, such as reading
Medical OSA Treatment: Body Position

- In many patients, OSA is substantially worse in the supine position.
- Gravity may cause the tongue to move posteriorly and anterior cervical tissue similarly to compromise the airway.
- More a factor in NREM than REM.
- Elevating the head of the bed 30-60 degrees increases the magnitude of the negative pressure required to compromise the airway.
Medical Therapy of OSA: Substances

- Alcohol: increases frequency and duration of events
- Sedatives: conflicting data with different meds; prudent to avoid if possible
- Narcotics?
Nasal EPAP for OSA (Provent)

- Single use nasal device with a valve that is applied to each nostril with adhesive
- Valve has low inspiratory but high expiratory resistance, resulting in positive pressure during expiration to splint open the upper airway, making it more resistant to collapse on subsequent inspiration
Nasal EPAP for OSA (Provent)

- A large study showed reduction of AHI at week 1 and month 3 of 52.7% and 42.7% respectively but the baseline AHI was 14.
- In a small group of severe patients, the AHI decreased from 48 to 19.
- ESS score decreased significantly.
- FDA approved but not covered by Medicare or major insurers.
- 30 day supply costs $65-$80.
- Not effective in mouth breathers or those with severe nasal allergies.
- 1/3 don’t end up using it.
“Some people talk in their sleep. Lecturers talk while other people sleep.”

Albert Camus