Sleep apnea (and other sleep demons): Its impact on cardiovascular disease: Interactive Cases

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Conflict

• No conflict of relevance to this presentation
Audience response question

• Does sleep apnea cause stroke?
  – Yes (1)
  – No (2)
  – Need more information (3)
Sleep apnea and stroke
(Am J Respir Crit Care Med 2010;182:269-77)

• Sleep Heart health Study
• Baseline PSG between 1995 and 1998
• 5,422 without stroke at the baseline
• Median follow-up 8.7 years, 193 ischemic strokes
• Men in the highest AHI quartile (>19) had an adjusted hazard ratio of 2.86 (95% confidence interval, 1.1-7.4).
• In the AHI range 5-25, each one-unit increase in AHI in men was estimated to increase stroke risk by 6% (95% confidence interval, 2-10%).
• In women, stroke risk only increased with AHI > 25.
Audience response question

• Does sleep apnea cause congestive heart failure?
  – Yes (1)
  – No (2)
  – Need more information (3)
Sleep apnea and IHD CHF
(Circulation 2011;123:1280-6)

• Sleep Heart Health Study
• 1927 men and 2495 women ≥40 years of age and free of coronary heart disease and heart failure
• Followed up for a median of 8.7 years
• OSA a significant predictor of incident IHD only in men < or =70 years of age (adjusted HR 1.10 [95% CI 1.00 to 1.21] per 10-unit increase in AHI (not in women)
• OSA predicted incident heart failure in men but not in women (adjusted HR 1.13 [95% CI 1.02 to 1.26] per 10-unit increase in AHI).
• Men with AHI > or =30 were 58% more likely for CHF
Why is the risk from sleep apnea “not much” or “needs a lot”? 

• Aha! Ischemic preconditioning!  
• (Sleep Breath 2012, in Press, First Author: Shah)  
• 136 acute MI  
• 35 % had an AHI >5  
• Higher AHI was associated with lower peak troponin-T levels ($p = 0.0085$) (“adjusted for everything”)  
• This makes clinical sense  
• Most with profoundly severe sleep apnea wake up the next say and get on with it  
• Does not mean apnea is “good for you”.....
Audience response question

- Does pathological sleep cause dysglycemia or diabetes?
  - Yes (1)
  - No (2)
  - Need more information (3)
Respirology 2012 (Wang, E-pub)
Sleep apnea causing diabetes

- Meta-analysis of six prospective cohort studies, 5,953 participants
- Follow-up periods of 2.7-16 years
- 332 incident cases of type 2 diabetes
- Moderate-severe OSA was associated with a greater risk of diabetes [relative risk (RR) 1.63; 95% confidence interval (CI) 1.09-2.45], as compared with the absence of OSA.
J Clin Endocrinol Metab 2012 (Myhill, E-pub)
No quick fix

- Fremantle Diabetes Study Phase II
- 59 at high risk for OSA
- Randomized to a 3-month CPAP intervention initiated early (<1 week) or late (1-2 months).
- Data were pooled
- Improved: sleepiness, blood pressure, resting heart rate
- Unchanged: Glycemic control and serum lipids
Sleep apnea causing problems in diabetics

- Sub-study of Look AHEAD (Sleep AHEAD)
- 350 diabetics, 86% had OSA (AHI > 5)
- The AHI was associated with stroke with an adjusted odds ratio (95% confidence interval) of 2.57 (1.03, 6.42).
- Not with heart disease in this small cohort
CPAP for extreme sleep apnea + metabolic syndrome

- Double-blind, placebo-controlled trial
- OSA, 3 months CPAP / sham, flip after a month
- 86 patients completed the study, 75 (87%) of whom had the metabolic syndrome
- CPAP: significant decreases in SBP (3.9 mm Hg), DBP (2.5 mm Hg), serum total cholesterol (13.3 mg / dL), LCL-C (9.6 mg per deciliter; 95% CI, 2.5 to 16.7; P=0.008), triglycerides (18.7 mg / dL), and HbA1c (0.2%)
- MS reversal: 11/86 real, 1/86 sham
- Enrolled 90! Perfect CPAP use! Unrealistic in real life
- Extreme sleep apnea (AHI > 50, severe desaturations)
Diabetes Care 2012; (Pamidi, E-pub)
Sleep apnea impact on lean diabetics

- Prospective, 52 healthy men (age 18-30 years; BMI 18-25 Kg/M²)
- Polysomnogram + OGTT
- Matched, 20 control men without OSA and 12 men with OSA
- OSA had 27% lower insulin sensitivity (estimated by Matsuda index) and 37% higher total insulin secretion (AUC) than the control subjects, despite comparable glucose levels.
Sleep apnea and HbA1c in non-diabetics

- HbA1c data in 1599 patients, PSG
- Dose-response relationship was observed between AHI and the percentage of patients with HbA1c >6.0%
- Range: from 10.8% for AHI <5 to 34.2% for AHI ≥50.
- Statistical adjustment for age, sex, smoking habits, BMI, waist circumference, cardiovascular morbidity, daytime sleepiness, depression, insomnia, sleep duration.
- Odds ratios (95% CIs) for HbA1c >6.0% were 1 (reference), 1.40 (0.84-2.32), 1.80 (1.19-2.72), 2.02 (1.31-3.14), and 2.96 (1.58-5.54) for AHI values <5, 5 to <15, 15 to <30, 30 to <50, and ≥50, respectively.
Nocturnal hypoxia and incident diabetes risk

- Circulatory Risk in Communities Study (CIRCS)
- 4,398 community residents aged 40 to 69 years
- Nocturnal hypoxia by pulse-oximetry, 2001-2005
- ODI3 < 5, 5-15 (mild), or greater
- By the end of 2007, 92.2% of participants had been followed up 3.0 [2.9-4.0] years), 210 persons identified as having developed diabetes.
- The multivariable-adjusted hazard ratio (95% CI) for developing type 2 diabetes was 1.26 (0.91-1.76) and 1.69 (1.04-2.76) for mild / greater hypoxia
CPAP improves glycemic control only if....

- 50 subjects, AHI > 15, impaired glucose tolerance
- 8 weeks of CPAP or sham CPAP, flip after 1 month
- 2-hour OGTT
- 42% men, age 54± 10, BMI of 39 ±8, and AHI 44 ±27
- Seven subjects normalized their mean 2-h OGTT after CPAP but not after sham CPAP, while 5 subjects normalized after sham CPAP but not after CPAP
- No overall insulin sensitivity index improvement
- AHI ≥ 30 (n = 25): 13.3% (p < 0.001) improvement in ISI (0,120) and 28.7% (95%CI: [-46.5%, -10.9%], P = 0.002) reduction in the 2-h insulin level
Mediators of sleep pathology

• Deprivation
• Fragmentation
• Hypoxia
• Hemodynamics
• Inflammation
• Vascular function
• Metabolic function
• Neurogenesis (hippocampal)
• Gene-environmental interaction: apo\(\varepsilon4\)
Sleep Hypnogram

Normal Young Adult

OSA->Fragmentation
Fragmented sleep
Consolidated sleep
Sympathetic Activation and OSA

Recordings of sympathetic nerve activity, respiratory rate, and intra-arterial blood pressure in the same individual when awake, with OSA during rapid eye movement (REM) sleep, and with elimination of OSA episodes by continuous positive airway pressure (CPAP) therapy during REM sleep. Sympathetic nerve activity is very high during wakefulness, but increases even further secondary to obstructive apnea during REM sleep. Blood pressure increases from 130/65 mm Hg when the individual is awake to 256/110 mm Hg at the end of the apneic episode. Elimination of apneic episodes by CPAP therapy results in decreased sympathetic activity and prevents blood pressure surges during REM sleep. Reproduced with permission from Somers et al.²

Audience Response Question

• Does sleep apnea cause hypertension?
  – Yes
  – No
  – Need more clinical human data
  – Need more experimental data
Does sleep apnea cause hypertension?

• Yes
  – Longitudinal data (Sleep Heart Health Study, etc)

• Effects on blood pressure
  – Nocturnal
  – Daytime

• Mediators (dominant)
  – Hypoxia for daytime
  – Fragmentation for nocturnal

• Time scales
  – Hypoxia has very complex time scales of effects
  – Carotid bodies important
  – Increased sympathetic drive
Glucose metabolism and sleep

• Deprivation, restriction, fragmentation, hypoxia and circadian mismatch leads to dysmetabolism and increased insulin resistance

• Sleep apnea extremely common in obese type II diabetics

• Treatment trials have been generally disappointing
  – Seems only really severe apnea (e.g., AHI ≥ 30 / hour) clearly matters

• Likely responsive and unresponsive phenotypes
Atrial fibrillation

- Complex interactions
- More common in OSA
- Strong association in hypertrophic cardiomyopathy
- Strong CSA association with idiopathic central sleep apnea syndrome
  - Suggests chemoreflex activation is important
- Increase in recurrence risk with untreated sleep apnea
- Nocturnal triggering is almost always sleep apnea
- No coherent clinical approach advocated, in part due to sheer numbers to deal with
Atrial fibrillation – sleep apnea
Heart Rhythm 2013;10(3):331-7

• “Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: Clinical impact of continuous positive airway pressure therapy”

• 153 patients (128 men; 60±9 years)

• Extensive encircling pulmonary vein isolation for drug refractory AF.

• 116 patients were identified as having OSA

• Mean follow-up period of 18.8±10.3 months, 51 (33%) patients experienced AF recurrences after ablation

• A Cox regression analysis: LA volume (HR 1.11; 95% CI 1.01-1.23; concomitant OSA (HR 2.61; 95% CI 1.12-6.09), usage of CPAP therapy (HR 0.41; 95% CI 0.22-0.76;) were associated with AF recurrences.
Stroke

• Bidirectional interactions
• Sleep apnea causes stroke
  – Acute stroke: nearly universal, at least half “resolve”

• Sleep apnea causes stroke
  – Best data from SHHS
  – Needs plenty of sleep apnea

• Sleep apnea in stroke patients is often “mixed” and hard to treat

• Possible stroke recurrence risk
Sleep in aging and Alzheimer’s disease

- Sleep fragmentation
  - Macro-fragmentation
  - Micro-fragmentation
  - Standard stages not too useful as vast majority of sleep in elderly is “light, stage II”

- Sleep apnea
  - Role in subcortical white matter injury

- Circadian dysregulation

- Depression

- High risk conditions for increased afferent sensory input
  - Pain, drugs
  - Motor disorders and disability
  - Heart failure, dyspnea
Sleep and beta amyloid

• Sleep restriction and fragmentation increase Aβ
• Hypoxia increases Aβ
• Hypoxia reduces Aβ clearance
• Sleep apnea increases incident MCI/AD diagnosis risk (Study of Osteoporosis Fractures; SOF)
Sleep and vascular dementia

- Data from Korean Genome and Epidemiology Study and Framingham Heart Study
So.....

- Hypertension
- Diabetes
- Congestive heart failure
- Atrial fibrillation
- Stroke
- Dementia
What can you do

• It seems that everyone has sleep apnea!
• Everyone with diabetes gets an eye exam
  – Routine now but is a parallel medical industry in its own right
• So why not a sleep physiology/pathology assessment?
• Oximetry is cheap, practical and a good screen-in
• Once screened, then comes the “problem”
• Sleep management is complex, time intensive, expensive, requires substantial ongoing patient effort
• Mildly symptomatic individuals will find this burdensome
• It needs a parallel system run from within the diabetes centers
Some nuts and bolts

• Several insurance specific issues
  – A real pain, time sink
• Home testing vs. lab testing
  – Former reasonable for uncomplicated sleep apnea
• Lab titration vs. auto-CPAP
  – Key is to track clinical and device based outcomes
  – Onerous compliance / adherence requirements
• Current devices track useful respiratory parameters
The circadian system

Normal Sleepiness

Sleep Drive

Wake Propensity

Circadian Drive for Wakefulness

[Diagram showing the relationship between circadian drive, sleep drive, and wake propensity over a 24-hour period, with a focus on the peak of sleepiness around 3 am and the dip during the work hours.]
Must read for circadian-metabolism link


The circadian system

• Sleep effects more intuitive
• Profound whole body effects
• Much of new research focused on clock mechanisms outside sleep-wake regulation
• Circadian dysregulation effects (experimental models)
  – Metabolic syndrome
  – Hypertension
  – Vascular dysfunction
  – Cardiac failure
  – Renal failure
Diabetes and the circadian system

- Nothing good in shift work for diabetics
- Circadian disruption accelerates diabetes development in human islet amyloid polypeptide transgenic (HIP) rats
- Increased risk for incident diabetes in shift workers?
  - Obesity major confounder
- More metabolic syndrome in former night-shift workers
- Food intake is misaligned – dysglycemic, dysmetabolic
- Using bright light, consistent schedules and perhaps hypnotics could help
Summary

- Sleep management needs to be integrated into cardiometabolic management
- Challenges of cost effectiveness, administrative burden
- Point-Of-Care testing and treatment
Thank you

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