Sleep Apnea and Cardiovascular Disease

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Sleep Disorders – Socioeconomic Consequences

- 40 million Americans suffer from chronic disorders of sleep and wakefulness.
- 95% of these remain unidentified and undiagnosed.
- The annual direct cost of sleep-related problems is $16 billion, with an additional $50-$100 billion in indirect costs (accidents, litigation, property destruction, hospitalization, and death).

Impact of Cardiovascular Disorders

- 900,000 deaths annually in US
- Hypertension alone affects 75 million Americans, many misdiagnosed as “essential”
- Research has discovered evidence of bidirectional relationship of sleep apnea and cardiovascular disorders
- Mechanisms: Arousals > neuro-hormonal activation > release of inflammatory mediators (cytokines) and adhesion molecules > reactive oxygen species and transcription factors due to oxidative stress

Javaheri Principles and Practice of Sleep Medicine 2004
Possible Cardiovascular Complications of Sleep Apnea

- Endothelial dysfunction
- Hypertension
- Pulmonary hypertension
- Systolic or diastolic heart failure
- Arrhythmias
- Coronary artery disease
- TIA and stroke
- Dementia
- Death


- Retrospective chart review of a hospital-based sleep center
- Patients referred by general IM or FP
- 65 out of 68 patients had OSA (95%)

- These patients represented 0.13% of the primary care patient panel

Prevalence
- Sleep apnea (AHI>5)
  - 9% of middle-aged women
  - 25% of middle-aged men
- Sleep apnea syndrome (AHI>5 and EDS)
  - 2% of women
  - 4% of men
- Sleep apnea in elderly (>65 years old)
  - between 20% and 62%

Young T, et al. The occurrence of sleep-disordered breathing among middle-aged adults. NEM 1993

Mean apnea-hypopnea index at baseline and the increase 8 years later in 282 participants in the Wisconsin Sleep Cohort

Defining Sleep Apnea

Hypopnea  1) 30% drop in signal excursion from baseline; 2) durations is 10 or more seconds; 3) the event is associated with an arousal and/or oxygen desaturation of at least 3% (4% for Medicare).
Obstructive Apnea  A complete blockage of the airway despite efforts to breathe. Ten second cessation of airflow.

Central Apnea

Mixed Apneas

<table>
<thead>
<tr>
<th>Type of Apnea</th>
<th>Central</th>
<th>Obstructive</th>
<th>Mixed</th>
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</thead>
<tbody>
<tr>
<td>Central Apnea</td>
<td></td>
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<tr>
<td>Obstructive Apnea</td>
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<tr>
<td>Mixed Apnea</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Sleep Study</td>
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<tr>
<td>Arterial Oxygen Saturation</td>
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Apnea Severity Scale

<table>
<thead>
<tr>
<th>AHI</th>
<th>Rating</th>
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<tr>
<td>&lt;5</td>
<td>Normal (no Sleep Apnea)</td>
</tr>
<tr>
<td>5-15</td>
<td>Mild Sleep Apnea</td>
</tr>
<tr>
<td>15-30</td>
<td>Moderate Sleep Apnea</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Severe Sleep Apnea</td>
</tr>
</tbody>
</table>

Clinical features of OSAS

- Habitual snoring
- Excessive daytime sleepiness
- Obesity (BMI>30)
- Age (increases in 5th decade)
- Gender (male:female = 2:3:1)
- Race (African-Americans, Hispanics)
- Depression
- Decreased:
  - memory
  - vigilance
  - motor coordination
- Nocturnal gasping, choking
- Morning headache
- Loss of libido/secondary impotence
Mimics of Apneas

- Nocturnal heartburn
- Chest pain, palpitations
- Coughing and choking
- Asthma attacks
- Night sweats
- Insomnia
- Jerks

Diagnosis

- Physical findings
  - neck circumference
    - 17 inches in males
    - 16 inches in females
  - craniofacial anatomy
  - posterior oropharynx
  - body mass index (weight in kg/height in m\(^2\))
    - BMI>30 with 8-12 fold increase in risk

Enlarged Tonsils
Sleep Apnea Questionnaires

- **STOP Questionnaire**
  - 6 questions regarding the following symptoms:
    - Snoring
    - Sleepiness
    - Obstructed apneas or choking
    - Hypertension
  - Patients classified as low, intermediate, or high risk for CSA

- **STOP BANG Questionnaire**
  - 6 questions regarding apneas/symptoms plus four clinical attributes:
    - Snoring
    - Sleepiness
    - Obstructed apneas or choking
    - Hypertension
    - Obesity (BMI > 35 kg/m²)
    - Age (≥ 50 y)
    - Neck size
    - Sex
  - Patients classified as low, intermediate, or high risk for CSA

- **Braun & Siegemund Scale**
  - 5 questions asking patients to rate the likelihood of falling asleep in various settings:
    - Home, road, bathroom, office, or hospital
  - Patients classified as low, medium, or high risk for CSA

**STOP Bang QUESTIONNAIRE**

- **Snoring**: Do you snore loudly loud enough to be heard through closed doors or your bed partner awake you for snoring at night? (Yes/No)
- **Tired**: Do you feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving)? (Yes/No)
- **Obstructed**: Has anyone observed you stop breathing or choking/gasping during your sleep? (Yes/No)
- **Pressure**: Are you or your partner being treated for high Blood Pressure? (Yes/No)
- **Body Mass Index**: More than 30% over ideal range? (Yes/No)
- **Age**: Older than 50? (Yes/No)
- **Neck Size**: Measure around Adams apple
  - Men is your shirt collar 17” or larger? (Yes/No)
  - Women is your shirt collar 16” or larger? (Yes/No)
- **Gender**: Male? (Yes/No)

0-3 low risk
4-5 intermediate
6+ high risk
Medicare requirements for sleep study (PSG or HST)

Sleep Apnea is Deadly

MORTALITY FROM OSA
Wisconsin Sleep Cohort Study

- 18 year follow up of 1522 middle aged patients ages 30-60
- All cause mortality - 2-3 times greater in those with OSA vs. no OSA
- Cardiovascular mortality - 5-6 times greater
Day-Night Pattern of Sudden Death in OSA

Midnight to 6AM

- OSA patients: 46%
- No OSA: 21%
- General Population: 16%
- Chance: 25%

8-h Epochs of MI Occurrence

Morbidity and Mortality

- Ischemic heart disease
- Congestive heart failure
- Cerebrovascular disease
- Pulmonary hypertension
Pathophysiologic events in obstructive sleep apnea


Prevalence of SDB in CVD Patients

Drug-Resistant Hypertension
Congestive Heart Failure
Acute Hypertension
Coronary Artery Disease
Angina

80%
50%
35%
30%
30%

80%
50%
35%
30%
30%

Logan et al. J Hypertension 2001
Javaheri et al. Circulation 1999
Sjostrom Thorax 2002
Schafer et al. Cardiology 1999
Sanner et al. Clin Cardiology 2001

Angina

The New England Journal of Medicine

Prospective Study of the Association Between Sleep-Disordered Breathing and Hypertension

Ran A. Reiner, MD; Dean V. Vasey, MD; Eric F. Vergamini, MD; and David B. Redline, MD

Copyright, 1999, by Massachusetts Medical Society.
New England Journal of Medicine, 2000
Peppard et al

The Apnea-Hypopnea Index at Base Line

<table>
<thead>
<tr>
<th>Baseline Apnea-Hypopnea Index</th>
<th>Odds Ratio, Adjusted for Baseline Hypertension Status</th>
<th>Odds Ratio, Adjusted for Baseline Hypertension Status, Non-regular Sleep, And Heavy Alcohol and Cigarette Use</th>
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</thead>
<tbody>
<tr>
<td>0.5 – 4.0 events/hr</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td>5.5 – 15.9 events/hr</td>
<td>2.74(1.82–4.12)</td>
<td>2.83(1.95–3.97)</td>
</tr>
<tr>
<td>&gt;16 events/hr</td>
<td>4.54(4.46–5.36)</td>
<td>2.89(1.46–5.64)</td>
</tr>
</tbody>
</table>

SDB and Hypertension

- Independent risk factor for heart disease
  - As strong a risk factor as obesity, smoking, and HTN
- Evident in 30-50% of patients with CAD
- Increased incidence of both bradyarrhythmias and tachydyrhythmias
Sleep-disordered Breathing and Cardiovascular Disease
Cross-sectional Results of the Sleep Heart Health Study

EYAL SHAHAR, CORALYN W. WHITNEY, SUSAN REDLINE, ELIZABETHA L. NEEF, ANNE B. NEWMAN, F. JAVIER NIETO, GEORGE T. O’CONNOR, LORI L. SLOCKARD, JOSEPH S. SCHMIDT, and JONATHAN M. SANET for the Sleep Heart Health Study Research Group

Sleep Disordered Breathing and A Fib

New data on mechanisms and impact:
• Upper airway collapse > hypoxia > ventilator overshoot > hypercapnia > autonomic instability and intrathoracic pressure alterations
• Increased state of thrombosis, inflammation, and oxidative stress produce a pro-arhythmogenic milieu, atrial macro-reentry, and automaticity
• OSA is a powerful predictor of ablation failure, independent of atrial enlargement, obesity, or hypertension
• A fib will affect up to 16 million patients by 2050
• A fib will cost $6.7 billion per year
• In a cardiology practice the majority of OSA patients have been referred by electrophysiologists
• Future strategies?

Mehra ACC Cardiosource 2014

Pulmonary Hypertension (PAH) and Sleep Apnea

• OSA recognized by WHO in 1998 as a secondary cause of PAH
• 15 – 70% of OSA patients have PAH
• COR pulmonale may occur in cases of severe OSA, especially if associated with high PaCO₂
• Several but not all studies show compliant, effective treatment of OSA improves PAH
Obstructive and Central OSA and Heart Failure HF_{REF} HF_{P-EF}

- Major public health issue
- High mortality and morbidity
- Frequent hospital admissions and readmissions
- High economic impact
- Obstructive sleep apnea is the most common, least recognized co-morbidity — 70% of HF patients have OSA/CSA
- Similar symptoms in heart failure and OSA
- CSA associated with higher mortality
- PAP may not improve mortality in HF patients

Obstructive and Central OSA and Heart Failure HF_{REF} HF_{P-EF} (cont’d)

- CSA is suppressed in 50% of HF patients by CPAP
- In HF patients OSA is not associated with daytime sleepiness
- ASV is recommended for CPAP non-responders with CSA
Coronary Heart Disease and Sleep Apnea

- CAD estimated to be present in 20–25% of OSA patients
- Prevalence is 30% in case controlled studies with an independent association
- Direct causality is not well established
- Major cardiac events are more likely in patients with severe OSA
- CPAP may significantly reduce cardiovascular events
- AHI severity is an independent predictor of mortality in patients with CAD
- Screening for both disorders in patients with risk factors for one is suggested as well as co-management strategies
- Impaired sleep in men and disturbed sleep in women may be related to moderately higher risk of poor cardiac prognosis after first AMI

Patent Foramen Ovale and Sleep Apnea

- Congenital cardiac defect present in approximately 25% of healthy adults and usually asymptomatic
- Patients with PFO might have left to right shunt which can lead to systemic embolization
- It is little known and poorly studied
- Severe OSA may raise the risk of complications in patients with elevated right heart pressures
Dyken et al
Stroke 1996

OSA and Stroke


OSA and Diabetes

- After adjustment for body weight, higher prevalence of insulin resistance and diabetes
- Odds ratio of DM with AHI >15 versus AHI < 5 was 2.30
Mortality
40% of patients with OSA (AHI>20) died during a follow-up period of 8 years
Patients with CPAP or trach had improved survival compared with patients treated with weight loss or uvulopalatopharyngoplasty

Studies
- Overnight oximetry (Profox)
- Nurse observation record
- “Poly-G” (ox, airflow, thoracic, abd)
- Home Sleep Test (HST)
- Portable
- In-lab polysomnogram

Therapy
- Behavioral
  - Etoh
  - tobacco
  - weight reduction
  - positional sleep therapy
- PAP therapy
- Surgical interventions
Positional Therapy: Raise HOB

CPAP/BiPAP therapy
PAP therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Aim</th>
<th>Feature</th>
<th>Pressure Profile</th>
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</thead>
<tbody>
<tr>
<td>Continuous Positive Airway Pressure (CPAP)</td>
<td>Maintain open upper airway</td>
<td>Fixed pressure</td>
<td></td>
</tr>
<tr>
<td>Automatic Positive Airway Pressure (APAP)</td>
<td>Maintain open upper airway</td>
<td>Continuously adjusting pressure to optimize pressure level to the patient's needs</td>
<td></td>
</tr>
<tr>
<td>Variable Positive Airway Pressure (VPAP)</td>
<td>Support breathing in long distance-related respiratory insufficiency</td>
<td>Fixed expiratory pressure and pressure support of inspiration usually with fixed back-up rate</td>
<td></td>
</tr>
<tr>
<td>Adaptive Servo-ventilation (ASV)</td>
<td>Stabilize breathing and keep upper airway open</td>
<td>Continuously adjusting inspiratory and expiratory pressure with variables (on-demand, back-up rate)</td>
<td></td>
</tr>
</tbody>
</table>

CPAP and Hypertension

- Studies of therapeutic versus sham CPAP in normotension and mild hypertension have shown an effect in decreasing nighttime and daytime blood pressure
  

- JNC VII identified OSA as first on the list of identifiable causes of hypertension
  

Baseline Arm

Therapeutic Arm

Sleep Quality in Patients with Hypertension
Before and after sleep apnea treatment

Blood Pressure Improvement and Medication Usage
Before and after sleep apnea treatment

CPAP and CHF

- CPAP treatment of patients with CHF will reduce LV afterload, increase stroke volume, reduce cardiac sympathetic tone, reduce atrial natriuretic peptide, and increase LVEF.
Comparison of Transplant Free Survival in CHF Patients: CPAP vs Control

(Sin et al. Circulation 2000)

75% five-year survival rate for CHF patients with CSA/CSR on CPAP
25% five-year survival rate for CHF patients with CSA/CSR not on CPAP

Sleep Apnea Cardiovascular Endpoints study (SAVE)

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea.

McEvoy RD, et al.


SAVE

- 2,717 adults (mostly men ages 45 to 75 years with minimal sleepiness)
- From 7 countries (though only 4 patients were from the United States) who had moderate to severe OSA and coronary or cerebrovascular disease.
- Half the patients received CPAP plus usual care or usual care alone.
• The primary composite endpoint was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack.
• Secondary endpoints included other cardiovascular outcomes, quality of life, snoring, daytime sleepiness, and mood.

• After a mean follow-up of 3.7 years, no significant effect on any individual or other composite cardiovascular endpoint was observed between the CPAP group and the usual care group.

• The authors concluded that CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate to severe OSA and established cardiovascular disease.
• However, in the CPAP group there was significantly reduced snoring and daytime sleepiness, improved health-related quality of life and mood, and a suggestion that the stroke risk was lower.
Limitations

• Mean CPAP duration of 3.3 hours per night.
• Even the so-called “rule” of 4 hours/night for at least 70% of the nights (primarily used to justify payment or occupational fitness and apparently adopted without objective basis) is not sufficient PAP adherence.
• The goal should be all night every night.
Limitations

- Both risk factors and response to treatment for OSA, as well as frequency and types of comorbid conditions, may vary among ethnic groups.
- Patients were excluded from the study for severe daytime sleepiness, severe hypoxemia, or Cheyne–Stokes respiration.

Central sleep apnea
Cheyne-Stokes respirations

Treatment of Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) trial

Adaptive servoventilation for central sleep apnea in systolic heart failure.
SERVE-HF trial

1325 patients with heart failure with reduced ejection fraction (HFrEF) and co-existing central sleep apnea (CSA) treated with ASV

Primary end point: the composite of all-cause mortality, life-saving cardiovascular interventions, or unplanned hospitalizations for worsening heart failure.

SERVE-HF trial

• The intention-to-treat analysis showed no significant difference between individuals randomly assigned to ASV and those randomly assigned to control for the primary end point (P=0.10). However, the ASV group experienced significantly higher all-cause and cardiovascular mortality than the control group (HR 1.28 [P=0.01], and HR 1.34 [P=0.006], respectively), and no improvement in quality of life.

• The authors concluded that the ASV device used (Auto CS, ResMed, USA) increased mortality without improving quality of life and, therefore, should not be used in HFrEF patients with CSA (in patients with LVEF<45%).

Limitations

• Substantial nonadherence to the study protocol: 29% of patients either discontinued or never used ASV, while 16% of patients randomly assigned to control crossed-over to positive airway pressure therapy.

• ASV compliance was low, averaging only 3.4 h per night one year postrandomization. This low adherence suggests that subjects remained exposed to CSA during a substantial length of time when ASV was not worn.
Limitations

- ASV device used has relatively high default pressures as part of its ventilation algorithm (minimum end-expiratory pressure of 5 cmH₂O and minimum inspiratory pressure support of 3 cmH₂O), making it more likely to induce hyperventilation and to lower cardiac output in those with normal or low left ventricular filling pressures than a device with lower default pressures.

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Treating sleep apnea is cheap: cost per quality-adjusted life-year (QALY)

- Med management of ischemic heart disease: $8,300
- Intensive lifestyle intervention for preDM: $8800
- Drug treatment of hypertension: $4,800-$50,000
- Implantation of AICD in pt with low EF: $47,000
- Diagnosis and treatment of OSA: $9,200-$13,400


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Costs Associated with OSA in United States in 2015

$162.0 B

Annual per patient diagnosis and treatment costs are 67% less than leaving patients undiagnosed.

Diagnosed/ Treated
5.9 M People, $12,4B

Undiagnosed/ Untreated
23.5 M People, $149.6B

Source: Primary research with experts, secondary clinical review by J.J. Viera (2015); Frost & Sullivan Patient Survey.
Cost Burden of OSA in the Undiagnosed vs. Diagnosis & Treatment Costs

<table>
<thead>
<tr>
<th></th>
<th>Undiagnosed</th>
<th>Diagnosed</th>
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</thead>
<tbody>
<tr>
<td># People with OSA</td>
<td>23,500,000</td>
<td>5,900,000</td>
</tr>
<tr>
<td>Cost of Undiagnosed OSA ($US Bil)</td>
<td>23.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Comorbidities &amp; Mental Health</td>
<td>$30.0</td>
<td>$6.6</td>
</tr>
<tr>
<td>Motor Vehicle Accidents</td>
<td>$26.2</td>
<td>$6.2</td>
</tr>
<tr>
<td>Workplace Accidents</td>
<td>$6.5</td>
<td>$5.4</td>
</tr>
<tr>
<td>Lost Productivity</td>
<td>$86.9</td>
<td>$0.8</td>
</tr>
<tr>
<td>Total Costs ($US Bil)</td>
<td>$149.6</td>
<td>$12.4</td>
</tr>
<tr>
<td>Cost per Person</td>
<td>$6,336</td>
<td>$2,105</td>
</tr>
</tbody>
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Quality of Sleep - Overall
Before and after sleep apnea treatment

Quality of Sleep Across Comorbidities
Before and after sleep apnea treatment
Substance Abuse and Weight
Before and after sleep apnea treatment

Then
(Per week)
Sleeping Pills: 2.9
Alcoholic Drinks: 22.3
Cigarettes: 1.4

Vs
Now
(Per week)
Sleeping Pills: 2
Alcoholic Drinks: 8.5
Cigarettes: 1.1

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Dental Devices

Snoreplasty
(Injection sclerotherapy)
Mandibular Osteotomy with Genioglossus advancement
Maxillomandibular advancement osteotomy

- Morbid obesity
- Severe facial deformity
- Significant cardiac arrhythmias
- CPAP/BiPAP intolerance