




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



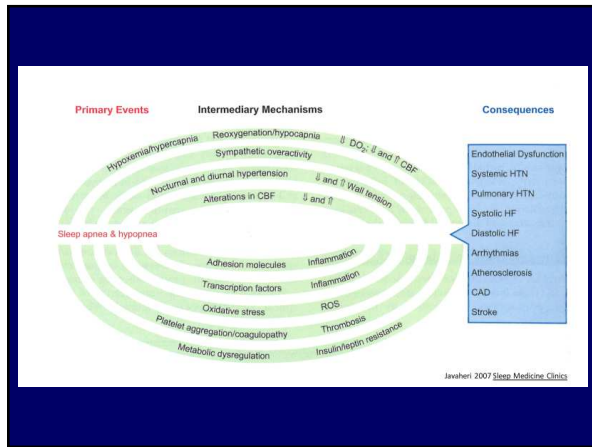
- 900,000 deaths annually in US
- Hypertension alone affects 75 million Americans, many misdiagnosed as "essential"
- Research has discovered evidence of bidirectional relationship of sleep apnea and cardiovascular disorders
- Mechanisms: Arousals > neuro-hormonal activation > release of inflammatory 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





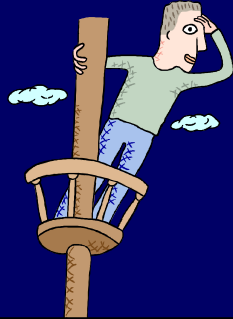
Kramer, NR et al. **The role of the primary care physician in recognizing obstructive sleep apnea.** Arch Intern Med. 1999.

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



Kramer, NR et al. **The role of the primary care physician in recognizing obstructive sleep apnea.** Arch Intern Med. 1999.

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

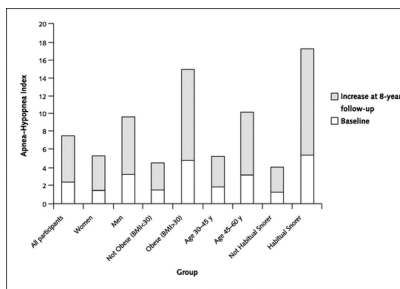


Prevalence

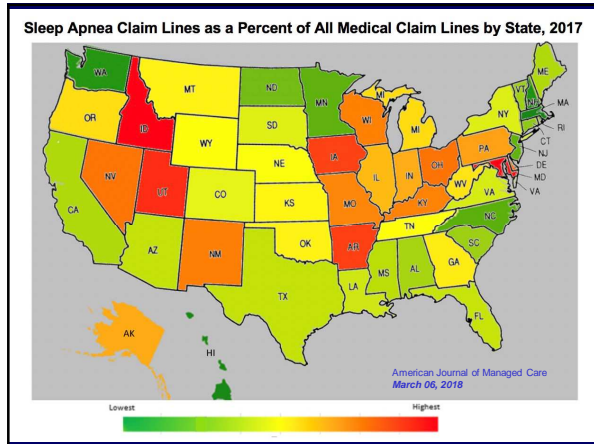
- Sleep apnea (AHI>5)
 - 9% of middle-aged women
 - 25% of middle-aged men
- Sleep apnea syndrome (AHI>5 and EDS)
 - 2% of women
 - 4% of men
- Sleep apnea in elderly (>65 years old)
 - between 20% and 62%

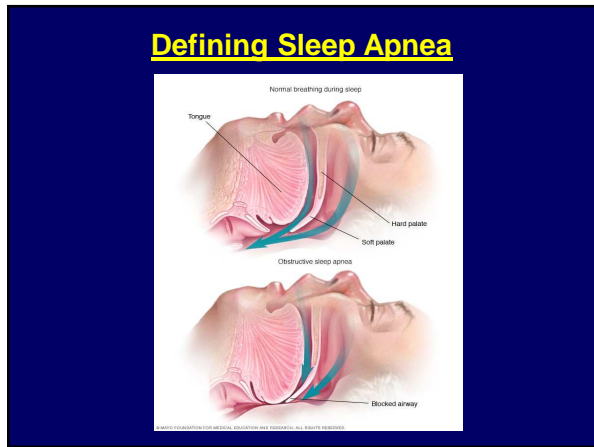
Young T, et al. The occurrence of sleep-disordered breathing among middle-aged adults. NEJM 1993

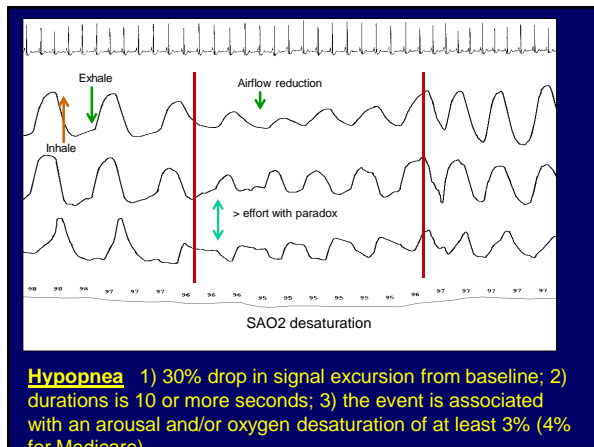
Mean apnea-hypopnea index at baseline and the increase 8 years later in 282 participants in the Wisconsin Sleep Cohort



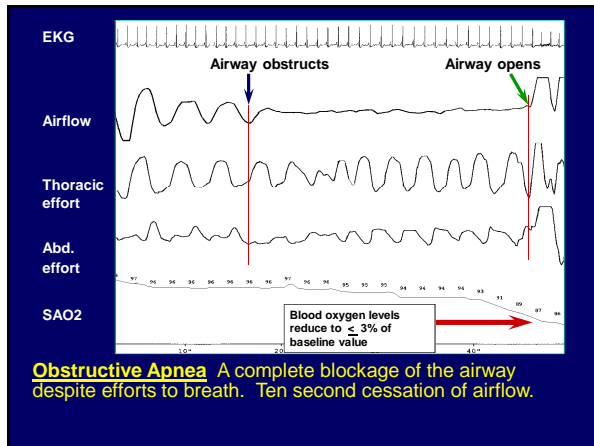
Caples, S. M. et al. Ann Intern Med 2005;142:187-197

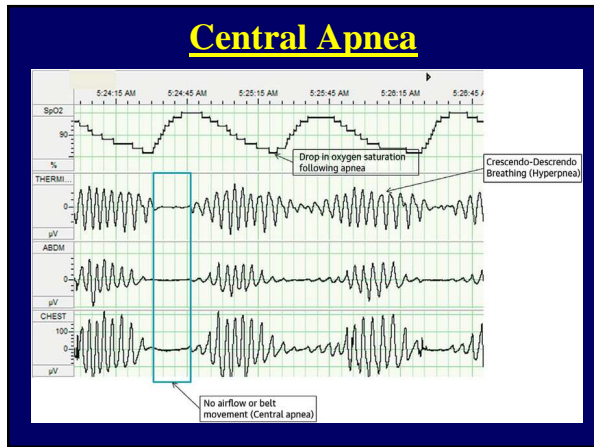


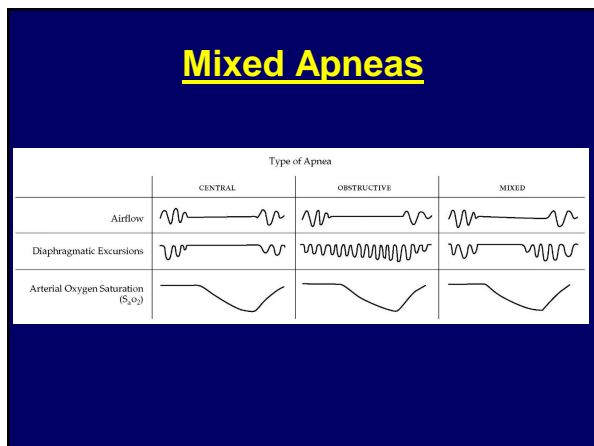




Hypopnea 1) 30% drop in signal excursion from baseline; 2) durations is 10 or more seconds; 3) the event is associated with an arousal and/or oxygen desaturation of at least 3% (4% for Medicare)







Apnea Severity Scale

AHI	Rating
<5	Normal (no Sleep Apnea)
5-15	Mild Sleep Apnea
15-30	Moderate Sleep Apnea
>30	Severe Sleep Apnea

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)

Clinical features

- 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



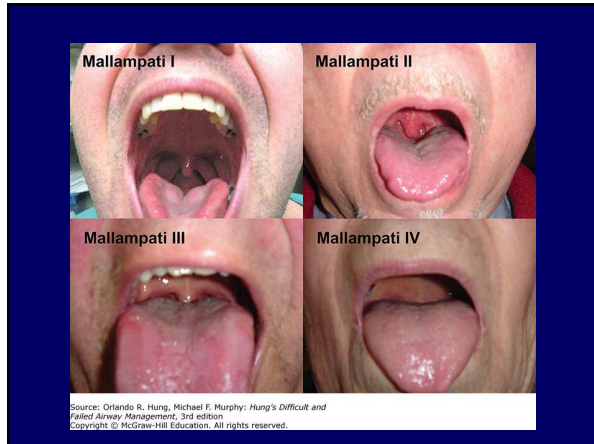
Diagnosis

- Physical findings
 - neck circumference
 - 17 inches in males
 - 16 inches in females
 - craniofacial anatomy
 - posterior oropharynx
 - body mass index (weight in kg/height in m²)
 - BMI>30 with 8-12 fold increase in risk



Enlarged Tonsils





Sleep Apnea Questionnaires

Questionnaire	Summary of Questionnaire Contents	Diagnostic Accuracy Compared With AHI (≥ 15 events/h) ^a
Berlin Questionnaire	10 questions pertaining to the following 3 symptoms/signs: • Snoring • Daytime sleepiness • Hypertension Patients classified by score as having low risk or high risk of OSA	• Sensitivity: 0.77 (0.73-0.81) • Specificity: 0.44 (0.38-0.51)
STOP Questionnaire	4 questions regarding the following signs/symptoms: • Snoring • Sleepiness • Observed apneas or choking • Hypertension	• Sensitivity: 0.89 (0.81-0.94) • Specificity: 0.32 (0.19-0.48)
STOP-BANG Questionnaire	4 questions regarding signs/symptoms plus 4 clinical attributes: • Snoring • Sleepiness • Observed apneas or choking • Hypertension • Obesity (BMI ≥ 35 kg/m ³) • Age (≥ 50 y) • Neck size • Sex Patients classified as low, intermediate, or high risk for OSA	• Sensitivity: 0.90 (0.86-0.93) • Specificity: 0.36 (0.29-0.44)
Epworth Sleepiness Scale	8 questions asking patients to rate the likelihood of falling asleep in various daytime contexts Patients classified as having normal sleep, average sleepiness, or severe and possibly pathologic sleepiness	• Sensitivity: 0.47 (0.35-0.59) • Specificity: 0.62 (0.56-0.68)

STOP BANG QUESTIONNAIRE

Snoring - Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbow you for snoring at night)? o Yes o No

Tired - Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving)? o Yes o No

Observed - Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep? o Yes o No

Pressure - Do you have or are being treated for High Blood Pressure? o Yes o No

Body Mass Index - more than 10% over ideal range. o Yes o No

Age - Older than 50? o Yes o No

Neck Size - (Measure around Adams apple)
Male is your shirt collar 17" or larger? Female, is your shirt collar 16" or larger? o Yes o No

Gender = Male? o Yes o No

After you have completed the STOP-BANG questionnaire, please return it to the front desk for a quick risk assessment of possible sleep apnea.

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

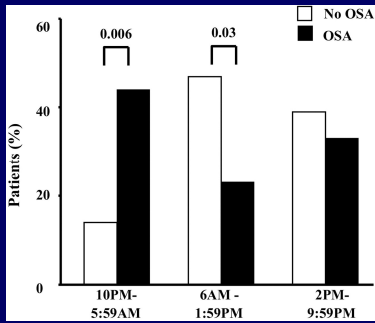


Day-Night Pattern of Sudden Death in OSA

Midnight to 6AM

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

8-h Epochs of MI Occurrence



Sert Kuniyoshi, F. H. et al. J Am Coll Cardiol 2008;52:343-346

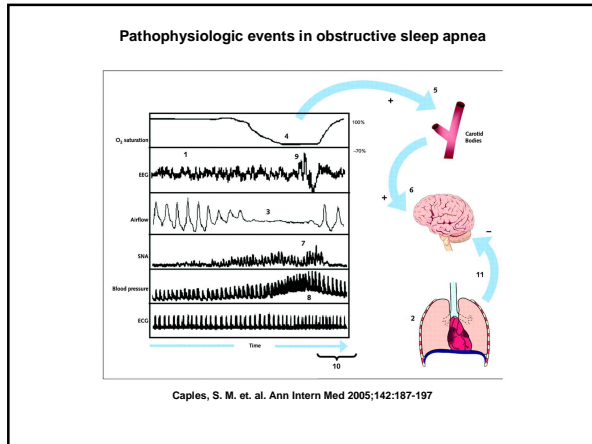
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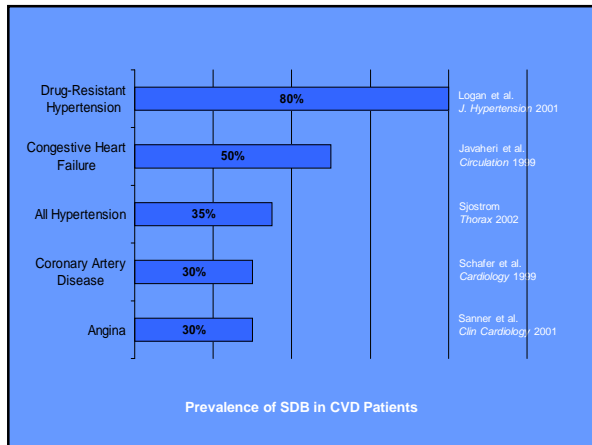


Morbidity and Mortality

- Ischemic heart disease
- Congestive heart failure
- Cerebrovascular disease
- Pulmonary hypertension





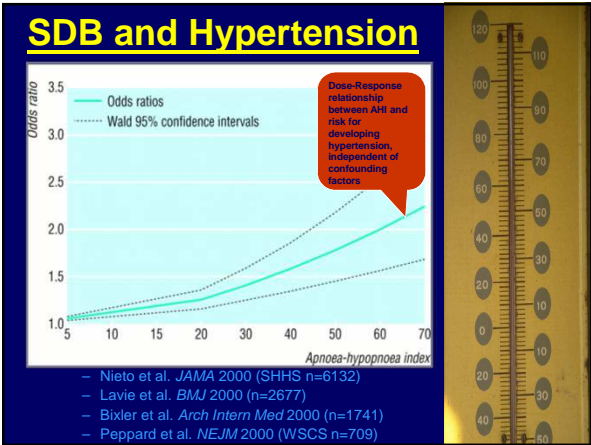




New England Journal of Medicine, 2000
Peppard et al

The Apnea-Hypopnea Index at Base Line

Base-Line Apnea-Hypopnea Index	Odds Ratio, Adjusted for Base-Line Hypertension Status	Odds Ratio, Adjusted for Base-Line Hypertension Status, Non-modifiable Risk Factors, Habitus, and Weekly Alcohol and Cigarette Use
0 events / hr	1.0	1.0
0.1 – 4.9 events / hr	1.66 (1.35 – 2.03)	1.42 (1.13 – 1.78)
5.0 – 14.9 events / hr	2.74 (1.82 – 4.12)	2.03 (1.29 – 3.17)
≥15.0 events / hr	4.54 (2.46 – 8.36)	2.89 (1.46 – 5.64)
P for trend	< 0.001	0.002



CAD and OSA

- Independent risk factor for heart disease
 - As strong a risk factor as obesity, smoking, and HTN
 - Hung J, et al. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990.
- Evident in 30-50% of patients with CAD
 - Andreas S, et al. Prevalence of obstructive sleep apnoea in patients with coronary artery disease. *Coron Artery Dis.* 1996
- Increased incidence of both bradyarrhythmias and tachyarrhythmias
 - Guilleminault C, et al. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol.* 1983.

Sleep-disordered Breathing and Cardiovascular Disease
Cross-sectional Results of the Sleep Heart Health Study
 EYAL SHAHAR, CORALYN W. WHITNEY, SUSAN REDLINE, ELISA T. LEE, ANNE B. NEWMAN, F. JAVIER NIETO, GEORGE T. O'CONNOR, LORI L. BOLAND, JOSEPH E. SCHWARTZ, and JONATHAN M. SAMET 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-arrhythmogenic 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

Guidelines featuring sleep apnea and heart failure disease

AHA-ASA Guideline

Primary Prevention of Ischemic Stroke

Questioning bed partners and patients, particularly those with abdominal obesity and hypertension, about symptoms of SDB and referral to a sleep specialist for further evaluation as appropriate may be reasonable, especially in the setting of drug-resistant hypertension. Treating potential stroke patients with CPAP may reduce the risk of stroke.

U.S. Department of Health and Human Services

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

Sleep Apnea is an identifiable cause of Hypertension.

Heart Failure Society of America

Comprehensive Heart Failure Practice Guideline

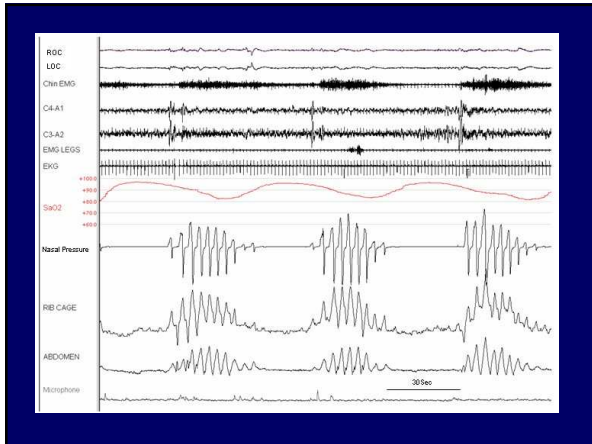
Continuous positive airway pressure to improve daily functional capacity and quality of life is recommended in patients with HF and obstructive sleep apnea documented by approved methods of polysomnography. (Strength of Evidence = B).

Obstructive and Central OSA and Heart Failure HF_REF HF_PEF

- 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_PEF (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

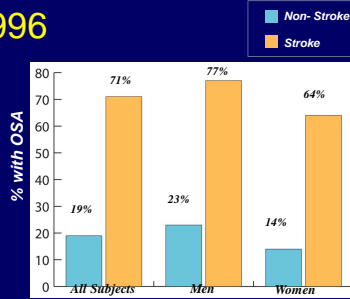
- CAD estimated to be present in 20– 25% of OSA patients
- Prevalence is 30% in case controlled studies with an independent association
- Direct causality is not well established
- Major cardiac events are more likely in patients with severe OSA
- CPAP may significantly reduce c-v events
- AHI severity 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

(A. Clark SLEEP2014)

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

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).^a

Severity of Syndrome	Stroke or Death		Mean Follow-up Period yr	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4-12	21	258	3.06	1.75 (0.88-3.49)
AHI 13-36	20	243	3.09	1.74 (0.87-3.51)
AHI >36	34	250	2.78	3.30 (1.74-6.26)

^a P=0.005 by the chi-square test for linear trend. AHI denotes apnea-hypopnea index, and CI confidence interval.

Yaggi K, et al. Obstructive Sleep Apnea as a Risk Factor for Stroke and Death. NEJM 2005;353:2034-41.


OSA and Diabetes

- After adjustment for body weight, higher prevalence of insulin resistance and diabetes

Punjabi N, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Resp Crit Care Med 2002.

- Odds ratio of DM with AHI >15 versus AHI < 5 was 2.30

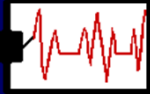
Reichmuth K, et al. Association of Sleep Apnea and Type II Diabetes. Am J Resp Crit Care Med 2005.

 **Mortality**

He J, Kryger M, et al. Mortality and apnea index in obstructive sleep apnea. Chest 1988

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 uvulopalatopharyngeoplasty

Studies 

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

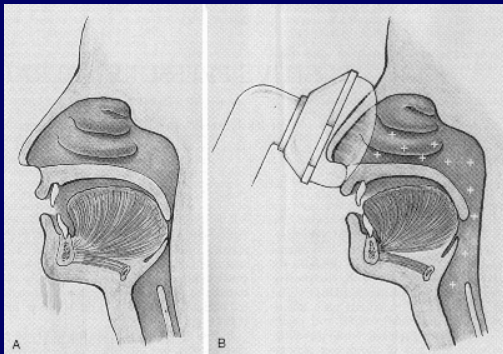
Therapy

- Behavioral
 - Etoh
 - tobacco
 - weight reduction
 - positional sleep therapy
- PAP therapy
- Surgical interventions



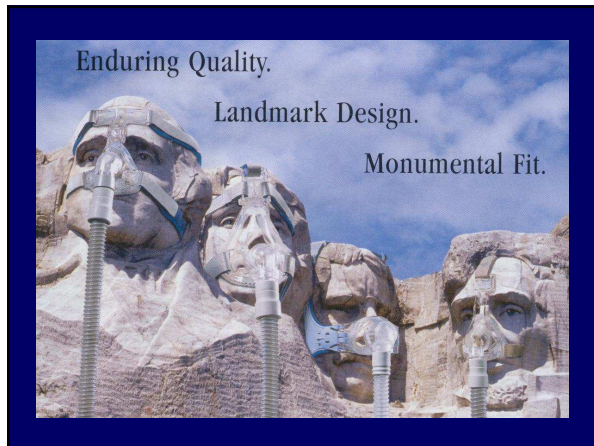


Positional Therapy: Raise HOB



CPAP/BiPAP therapy



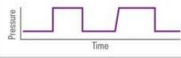
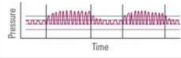






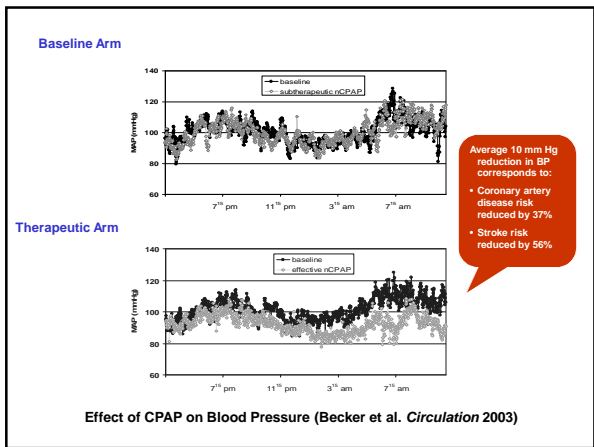


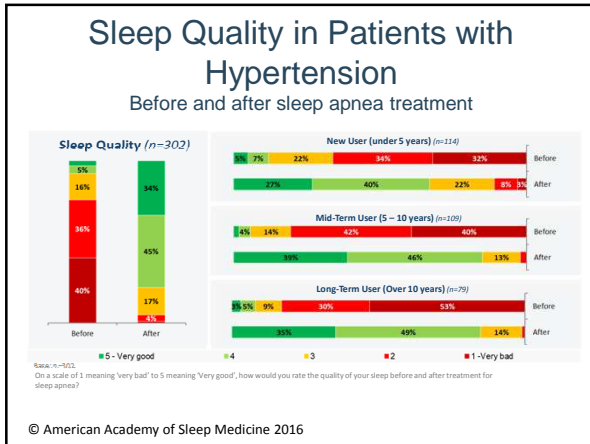
PAP therapy

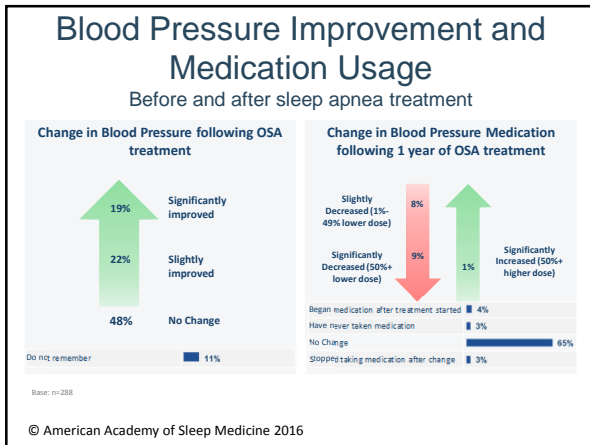
Therapy	Aim	Features	Pressure Profile
Continuous Positive Airway Pressure (CPAP)	Maintain open upper airways	Fixed pressure	
Automatic Positive Airway Pressure (APAP)	Maintain open upper airways	Continually adjusting pressure to optimize pressure level to the patient's needs	
Variable Positive Airway Pressure (VPAP)	Support breathing in lung disease-related respiratory insufficiency	Fixed expiratory pressure and pressure support at inspiration, usually with fixed back-up rate	
Adaptive Servo-Ventilation (ASV)	Stabilise breathing and keep upper airway open	Continually adjusting inspiratory and expiratory pressure with variable, on-demand, back up rate	

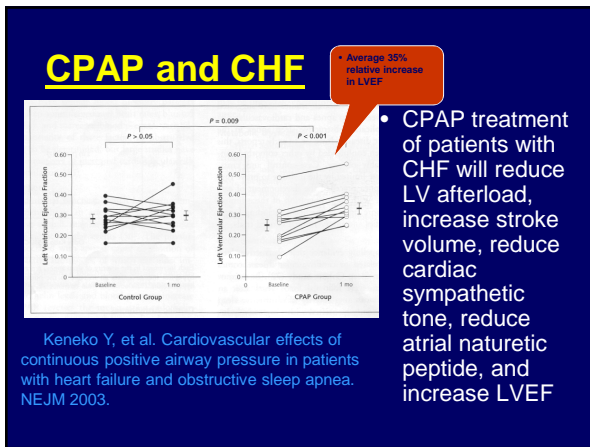
CPAP and Hypertension

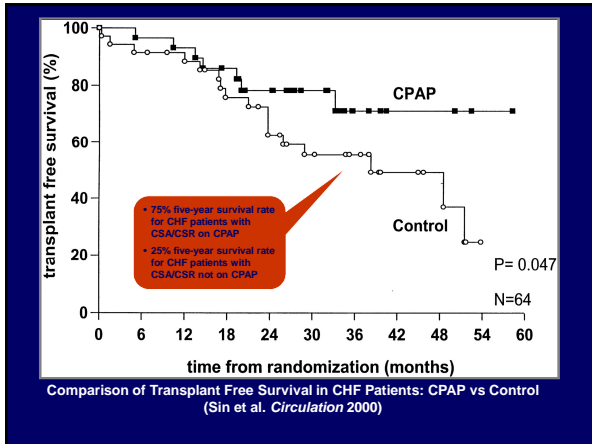
- Studies of therapeutic versus sham CPAP in normotension and mild hypertension have shown an effect in decreasing nighttime and daytime blood pressure
 - Becker H, et al. Effect of continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003.
- JNC VII identified OSA as first on the list of identifiable causes of hypertension
 - The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure: the JNC 7 report. *JAMA* 2003.











Sleep Apnea Cardiovascular Endpoints study (SAVE)

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea.

McEvoy RD, et al.

N Engl J Med. 2016 Sep 8; 375(10):919-31.

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.

SAVE

- 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.

SAVE

- 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.

SAVE

- 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

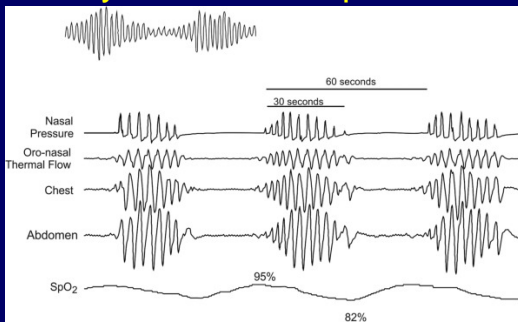
- Mean CPAP duration of **3.3 hours** per night.
- Even the so called “rule” of 4 hours/night for at least 70% of the nights (primarily used to justify payment or occupational fitness and apparently adopted without objective basis) is not sufficient PAP adherence.
- The goal should be all night every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

Cowie MR, Woehrle H, Wegscheider K, et al.

N Engl J Med. 2015;373:1095–105



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

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

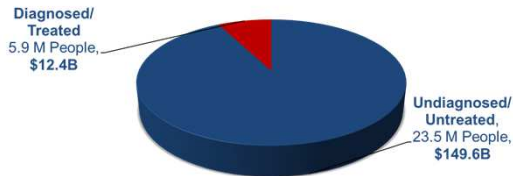
- Med management of ischemic heart disease ➤ \$8,300
- Intensive lifestyle intervention for preDM ➤ \$8800
- Drug treatment of hypertension ➤ \$4,800-\$50,000
- Implantation of AICD in pt with low EF ➤ \$47,000
- Diagnosis and treatment of OSA ➤ \$9,200-\$13,400

Cost justification for diagnosis and treatment of obstructive sleep apnea: position statement of the American Academy of Sleep Medicine. Sleep. 2000;23:1017-1018.

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.



Source: ¹Primary research with experts, secondary clinical research, U.S. Census (2014), Peppard "Increased Prevalence of Sleep-disordered Breathing in Adults." American Journal of Epidemiology (2013), Frost & Sullivan Patient Survey

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Cost Burden of OSA in the Undiagnosed vs. Diagnosis & Treatment Costs

	Undiagnosed	Diagnosed
# People with OSA	23,500,000	5,900,000
Cost of Undiagnosed OSA (\$US Bill)	\$30.0	Cost of Diagnosed OSA (\$US Bill)
Comorbidities & Mental Health	\$30.0	Diagnosis, Testing and Follow Up
Motor Vehicle Accidents	\$26.2	Non-surgical Treatment
Workplace Accidents	\$6.5	Surgical Treatment
Lost Productivity	\$86.9	
Total Costs (\$US Bill)	\$149.6	\$12.4
Cost per Person	\$6,336	\$2,105

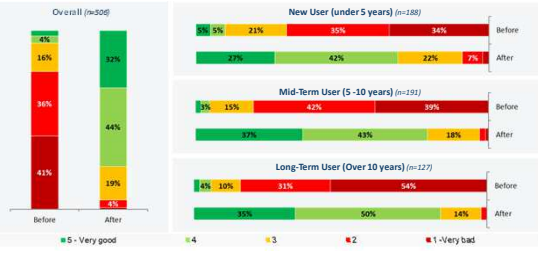
Source: ¹Primary research with experts, secondary clinical research, U.S. Census (2014), Peppard "Increased Prevalence of Sleep-disordered Breathing in Adults." American Journal of Epidemiology (2013), Frost & Sullivan Patient Survey.

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Quality of Sleep - Overall

Before and after sleep apnea treatment

76% reported the quality of their sleep as 'good'/'very good' after treatment (vs. 7% before treatment). While all user groups indicate improvement, long-term users have the most positive impact after treatment (85%).



On a scale of 1 meaning 'very bad' to 5 meaning 'very good', how would you rate the quality of your sleep before and after treatment for sleep apnea? (Percentages under 2% not shown for transparency.)

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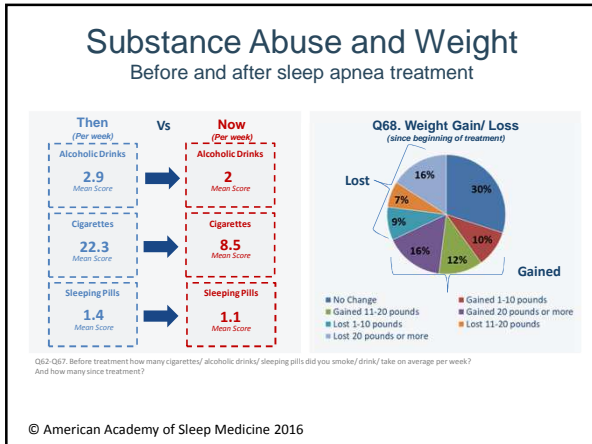
Quality of Sleep Across Comorbidities

Before and after sleep apnea treatment

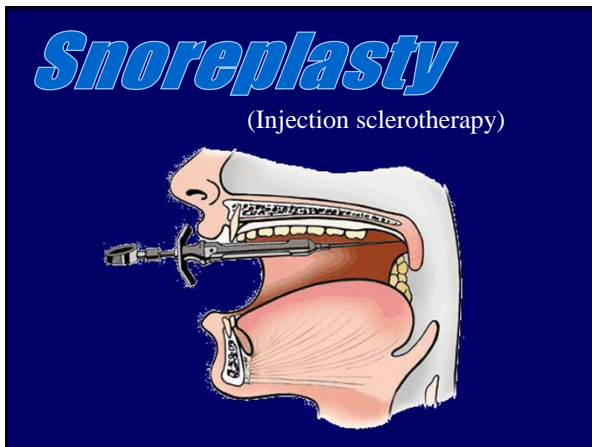
A high proportion of respondents with comorbidities declare their sleep quality as 'good'/'very good' after treatment. The biggest difference is among High Blood Pressure patients (79% vs 8% before treatment), and the smallest among Insomnia patients (65% vs. 8% before treatment.)

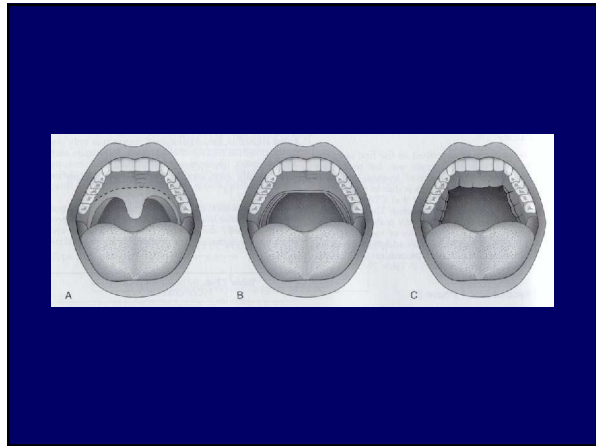


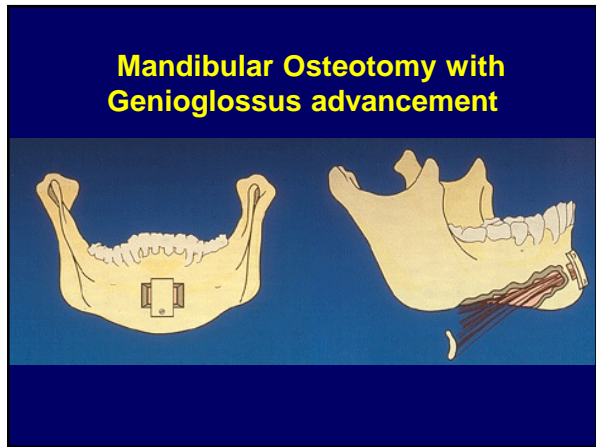
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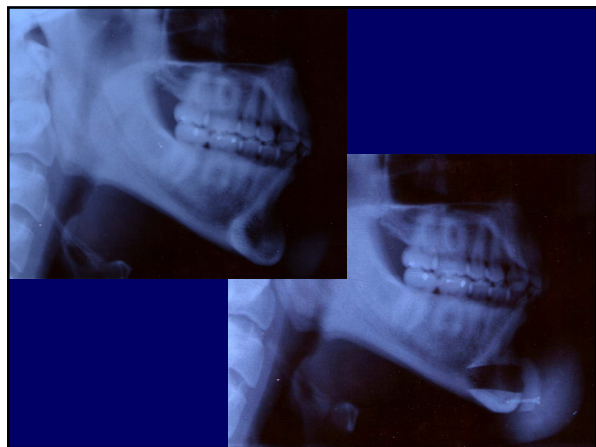




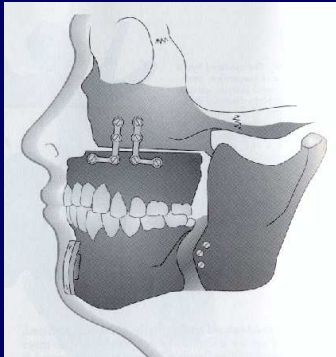








Maxillomandibular advancement osteotomy



Tracheostomy

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

