Cardiovascular Effects of sleep Disorders

Ram C Sharma, MD, DNB (Med), FRCP (Edin.), FACC, FSCAI
Associate Professor of Medicine
Div. Of cardiology, Quillen College of Medicine
East Tennessee State University
Johnson City, TN USA

Historical Medical Accounts of Sleep Apnea

When a person, especially advanced in years, is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails to overcome the resistance in the pharynx, of which stridor or snoring is the audible sign, and there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally air enters with a loud snort, after which there are several compensatory deep inspirations....

Broadbent, WH
Lancet, 1877

History

• 1978: Guilleminault & Dement reported hemodynamic and CV effects of sleep apnea
• 1979 (Chest) Deedvania: AV block as a manifestation of sleep apnea syndrome
• 1980 (Sleep) Lugaresi: Cardiocirculatory disturbances
• 1984 (Lancet) Kales: Sleep apnea in hypertensive pts.
• 1985 (Lancet) Partinin: snoring & cerebral infarction
• 1987: Finnish study in BMJ: Snoring a risk factor for CAD and stroke.

How I got into the Sleep Medicine?
Clinical Scenario 1
• Patients in advanced heart failure clinic
  • Euvolemic
  • On evidence based treatment
  • Documented improvement in EF
• Continue to feel fatigued and weak. Diagnosis:
  • Low cardiac output state
  • Depression
  • Metabolic derangement
  • Sleep apnea
• Treated for sleep apnea with remarkable improvement in symptoms

Clinical Case 2
• 45 yr American Indian male presented to ER 3rd time with heart failure in 3 months
• Medications: Loop diuretic & ACEI
• Normal EF, poorly controlled HTN
• PSG: Severe OSA, AHI 96 with severe desaturations. Prescribed CPAP & LSM
• No admission during 2yr F/U

Clinical Case 3
• 32 yr female morbidly obese long standing HTN and headache.
• Extensive neurological work up suggested pseudotumor cerebri
• Patient had multiple lumbar punctures
• “Sleep study” c/w severe sleep apnea
• Remarkable improvement with CPAP

Sleep Physiology
– NREM Sleep: Decreased sympathetic & Unopposed parasympathetic activity
  – Lower BP and HR
– REM Sleep: Intermittent surge in sympathetic activity
  – Surge in BP and HR

CV Effects of Arousal
• Sudden surge in sympathetic output
• Withdrawal of parasympathetic tone
**Effects of hypoxia**
- Pulmonary vasoconstriction
- Pulmonary hypertension
- Decreased VO2 max
- Decreased myocardial contractility

**Effects of Sleep Deprivation**
- Increase in HR
- Increase in BP
- Increase in inflammatory markers
  - Leukocytes
  - IL-6
  - CRP

**Sleep Apnea**
- Repetitive arousals
- Chronic sleep deprivation
- Nocturnal hypoxemia

**Sleep Apnea: Autonomic NS**
- “Diving reflex”
  - Apnea
  - Increased sympathetic drive to maintain BP and tissue perfusion
  - Increased parasympathetic drive (HR) to reduce MVO
**Cardiovascular Effects of SA**

- HTN
- CHF
- CAD
- Arrhythmias
  - Atrial and ventricular ectopy
  - Bradycardia
  - Atrial fibrillation
  - Ventricular tachycardia
- Stroke

**Causative Role of Severe Untreated OSA in Cardiovascular Events**

(Marin et al, Lancet 365:1046, 2005)

**Clinical Pearl**

- Heart failure and sleep apnea both should be treated appropriately as one condition worsens the other.
- CPAP is not the primary treatment for advanced heart failure

**OSA and Cardiovascular disease**

- There is increased incidence of sleep apnea in patients with cardiovascular disease
- Higher incidence of adverse cardiovascular events in untreated patients with sleep apnea

Postgrad Med J 2008; 84:15-22
SLEEP 2007;30(3):291-304
CHEST 2008; 133:793-804
OSA and Cardiovascular disease

Peker: 7 yrs f/u; Marin and Doherty: 10 yrs f/u Postgrad Med J 2008; 84:15-22

Hypertension: OSA

Epidemiology

- >30% of patients with hypertension have OSA (independent of obesity: Carlson)
- 20-40% patients with OSA fail to drop BP at night (non dippers): implication for LVH
- >50% of patients with OSA have hypertension
  - ??Causal
  - ??Co-morbidities

Snoring and Hypertension: Finnish Twin Study

KOSKENVOO et al, Lancet, 1985

OSA and Hypertension

- 40% of people with OSA have daytime HTN
- 40-80% of people with poorly controlled HTN have OSA
- Wisconsin prospective sleep cohort (709 pts.). Risk of developing HTN over 4 yrs:
  - Minimal OSA: 1.42 x normal
  - Mild-moderate: 2.03 x normal
  - Moderate-severe: 2.89 x normal

After adjusting for other risk factors

Table 1. Prevalence studies on cardiovascular disease and obstructive sleep apnoea/hypopnoea syndrome (OSAH)

Table 2. Prevalence studies on hypertension and obstructive sleep apnoea/hypopnoea syndrome (OSAH)

SDB and Incident Hypertension

Adjusted Odds Ratios for Hypertension at Follow-up


After adjusting for other risk factors
OSA and Hypertension

- Effective CPAP therapy can reduce BP
- One study showed a fall in systolic BP by 10 mm after 4 weeks of CPAP
- Improvement in blood pressure correlated with improvement in sleepiness

Take Home Message

- Patients with hypertension should be screened for sleep apnea
- Patients with resistant hypertension should have sleep study as part of evaluation.
- Treatment with CPAP has small but statistically significant effect on hypertension.

Sleep Apnea and Heart Failure: OSA Epidemiology

- Sleep Heart Study (6424 men and women)
  - RR of Heart Failure in OSA: 2.38 (independent of other risk factors for HF)
- Heart Failure patients undergoing PSG
  - 37% of 450 patients
  - Higher prevalence in men 38% Vs 31%
  - Risk factor: obesity in men, age in women

Prevalence of OSA in Stable Outpatients with Heart Failure

SA and Heart Failure

- CSA is the SDB most commonly associated with HF (Javaheri 2006, 49% with CHF have SDB, 37% CSA, 12% OSA)
- Heart Failure is 2.38 x more common in “mild-moderate OSA” then in “no OSA”
Pathophysiology: Sleep Apnea in Heart Failure

- Hypertension
- Left ventricular diastolic dysfunction
- Atrial fibrillation
- Increasing obesity is a predictor of development of new onset HF (Framingham study)

Sleep Apnea and Heart Failure: OSA

- Pathophysiology
  - Obesity
  - Withdrawal of pharyngeal muscle tone during waning of ventilation
  - Fluid shifts to more central structures (no direct evidence)
- Mechanical and Hemodynamic effects
  - Negative intrathoracic pressure (afterload)
  - Increased venous return (preload)
  - Decrease in stroke volume

Sleep Apnea and Heart Failure: OSA

- Neurohormonal effects: Increased Sympathetic activity
  - Apnea: pulmonary stretch receptors : disinhibits central sympathetic outflow
  - Hypoxemia and hypercapnia: peripheral and central chemoreceptors
  - Arousal: excitatory input from cortical center: burst of BP, HR in immediate post apneic period

Sleep Apnea and Heart Failure

- Repeated episodes of apnea-hypopnea-arousal:
  - Repeated amplitudes oscillations in central sympathetic nerve traffic, BP and HR
  - Adverse effects not confined to sleep
  Sustained reduction in heart rate variability
  Day time elevation in BP

Sleep Apnea and Heart Failure: OSA

- Increased C-reactive protein
- Increased oxidative stress: reactive oxygen species production in neutrophils and monocytes
  - ICAM-1, VCAM-1, E-selectin
  - Monocyte CD 15, CD 11c
- Endothelial dysfunction
  - Low plasma nitrite concentration
  - Enhanced responsiveness to neurogenic vasoconstrictor stimuli

Sleep Apnea and Heart Failure: Conclusion

- Heart Failure adversely affected by OSA due to Hemodynamic alterations, potential for improvement with CPAP, more studies needed
- OSA more common in patients with HF: screening implications
Sleep Apnea & Heart Failure: CSA

**Epidemiology**

- **Prevalence of CSA in Heart Failure**
  - 33% of 450 patients
  - 40% of 81 patients
- **Risk factors**
  - Male gender: RR-4.33 (rare in women with HF)
  - Hypocapnia: day time PCO2 <38: RR-4.33
  - Atrial fibrillation: RR-4.08
  - Advancing age: >60: RR-2.37

**Sleep Apnea and Heart Failure: Progression of HF**

- **Increased Mortality**
- **Higher urinary and circulating catecholamine levels during sleep and wakefulness** (controlled for other risk factors and proportional to frequency of arousals and degree of apnea related hypoxia)

**Sleep Apnea and Heart Failure: CSA**

**Treatment**

- Optimize drug therapy
- Nocturnal supplemental oxygen
- ?? Theophyllin: small, short, study, reduced severity of CSA but no beneficial cardiac effects, (potential for increase in arrhythmia)
- CPAP; small short trials: beneficial hemodynamic effects are seen, no long term end point trials

**Sleep Apnea and Heart Failure: CSA**

**Conclusion**

- CSA common in patients with HF
- Indicative of severe HF
- Increased mortality: independent risk factor for lower life expectancy in HF patients
- Screening implications

OSA and Abnormal Heart Rhythms

- Abnormal heart rhythms have been associated with OSA
- 1983 Guilleminault et al.:  
  - 400 pts with OSA  
  - 48% had cardiac arrhythmias at night  
  - 2% sustained VT, 11% sinus arrest, 8% AV block, 19% PVC
OSA and Abnormal Heart Rhythms: Atrial Fibrillation

- Four times increased risk of AF in pts with OSA (AHI>30) (Sleep Heart Health Study 2006)
- Onset of >75% of persistent Afib episodes in pts with OSA occur at night (8pm-8am)
- A fib recurrence after cardioversion twice as high in untreated OSA
- Observational review over 17 yrs suggests that nocturnal hypoxemia influences the onset of A fib

Postgrad Med J 2008; 84:15-22

OSA and Abnormal Heart Rhythms: Ventricular arrhythmias

- Reported in pts with OSA
- Causative role not proven
- NEJM 2005 study observed higher incidence of sudden death during night hours (12am-6am) in pts with OSA, suggesting but not proving a causative effect


Recurrence of Atrial Fibrillation Following Cardioversion Is Higher in Patients with Untreated Obstructive Sleep Apnea

![Graph showing recurrence of AFib following cardioversion](image)

Recurrence of AFib (12 mo)

- Untreated pt – mean nocturnal fall in O2 sat
- Recurrence – 18%
- No recurrence – 8%

Kanagala and Somers

Obstructive Sleep Apnea and Recurrence of AFib

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>4.64 (1.48-14.57)</td>
<td>3.72 (1.13-12.2)</td>
<td>3.40 (1.03-11.2)</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>1.96 (1.29-3.08)</td>
<td>1.81 (1.16-2.84)</td>
<td>1.74 (1.11-2.74)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.66 (1.56-20.52)</td>
<td>3.85 (1.00-14.93)</td>
<td>4.02 (1.03-15.74)</td>
</tr>
</tbody>
</table>

BMI=body mass index; CHD=coronary heart disease

*Results of logistic regression analysis with SDB as the exposure; N=338 without SDB, N=228 with SDB

Association Between Severe OSA (AHI >30) and Arrhythmias in Sleep Heart Health Study
(Mehra et al, AJRCCM, doi:10.1164/rccm.200509-1442OC)

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>4.64 (1.48-14.57)</td>
<td>3.72 (1.13-12.2)</td>
<td>3.40 (1.03-11.2)</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>1.96 (1.29-3.08)</td>
<td>1.81 (1.16-2.84)</td>
<td>1.74 (1.11-2.74)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.66 (1.56-20.52)</td>
<td>3.85 (1.00-14.93)</td>
<td>4.02 (1.03-15.74)</td>
</tr>
</tbody>
</table>

BMI=body mass index; CHD=coronary heart disease

*Results of logistic regression analysis with SDB as the exposure; N=338 without SDB, N=228 with SDB

Diagram showing proposed pathophysiologic interaction between OSA, cardiovascular risk mechanisms, and acute/critical illness

Figure 7: Proposed pathophysiologic interaction between OSA, cardiovascular risk mechanisms, and acute/critical illness. OSA, obstructive sleep apnea; BMI, body mass index; BP, blood pressure; WBC, white blood cell count; SDB, sleep-disordered breathing; SDB in TIA, sleep-disordered breathing in transient ischemic attack; SDB in stroke, sleep-disordered breathing in stroke; SDB in cancer, sleep-disordered breathing in cancer; SDB in TBI, sleep-disordered breathing in traumatic brain injury; SDB in other, sleep-disordered breathing in other conditions; BMI, body mass index; BP, blood pressure; WBC, white blood cell count; SDB, sleep-disordered breathing; TIA, transient ischemic attack; stroke, acute stroke; cancer, cancer; TBI, traumatic brain injury; other, other conditions.
Incident CHD and OSA

Although there was an increased risk of incident CHD in clinic-derived samples, those who were treated with CPAP had the same risk as controls.

MedianFollow-up

Treated with CPAP

12 year follow-up
All Men
N=1651

Martin, Lancet 2005

Major Adverse CV Events (MACE) in Patients with CAD and OSA

- 407 consecutive patients with CAD
- 38% with ODI >5
- Increased 5-year MACE
  - ♂ AHI ≥10: 28% vs. 16%
  - ♂ AHI ≥10: 20% vs. 14%

Major Adverse CV Events (MACE) In Patients with CAD and OSA

- 407 consecutive patients with CAD
- 38% with ODI >5
- Increased 5-year MACE
- ♂ AHI ≥10: 28% vs. 16%

- ♂ AHI ≥10: 20% vs. 14%

Unadjusted Kaplan-Meier survival curves for AHI clinical categories, by sex and event type.

Mooe T, AJRCCM 2001:164

Cardiologists report new guidelines on treatment for high blood pressure.

Blood Pressure Guideline Update

- New guidelines for blood pressure management
- Increase in the number of patients needing treatment
- Focus on personalized care

Cardiology Career Network

- Resources
- Newsletters
- Opportunities
- News
- Articles
- Event Calendar
- My Job Alerts
- My Resources

Damage Blood Vessels as a Result of Sleep Apnea

Moderate

Sleepiness

Med-CRP

- Low
- Medium
- High

P<0.001

- Low
- Medium
- High

P<0.001
Effects of CPAP therapy on protein expression in venous endothelial cells

Jelic S et al. Circulation 2010;121:1014-1021

Copyright © American Heart Association

CAD and Treatment of OSA


OSA Increases Risk of MACE and Re-stenosis After PCI

- 89 consecutive pts with ACS followed for mean 227 days,
- 57% OSA (AHI>10)
- Higher CRP but otherwise comparable

- MACE in OSA vs non-OSA:
- 23.5% vs. 5.3%
- HR: 11.6 (2.2,62.2)

- Quantitative Coronary Arteriography
- Late Loss: 1.28 vs 0.69 mm MLD
- Binary restenosis: 37% vs 15%


Yumino, D. AJC 2007:99