Obstructive Sleep Apnea and Cardiovascular Disease

~What Probing deep has ever solved the mystery of sleep?~
(Thomas Aldrich (1836-1907) Human Ignorance)

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Objectives

1. To describe the acute cardiovascular changes that occur with apnea.
2. To understand the pathophysiology of the acute cardiovascular changes associated with apnea.
3. To describe the chronic cardiovascular abnormalities associated with sleep-disordered breathing (SDB), with particular reference to the Sleep Heart Health Study.
4. To identify the potential pathophysiologic mechanisms underlying chronic cardiovascular disease in SDB.
5. To understand the clinical relevance of cardiovascular abnormalities in SDB.
Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., M.P.H., John Concato, M.D., M.P.H., Walter N. Kernan, M.D., Judith H. Lichtman, Ph.D., M.P.H., Lawrence M. Brass, M.D. and Vahid Mohsenin, M.D.

N Engl J Med
Volume 353;19:2034-2041
November 10, 2005
Day-Night Pattern of Sudden Death in Obstructive Sleep Apnea

Apoor S. Gami, M.D., Daniel E. Howard, B.S., Eric J. Olson, M.D. and Virend K. Somers, M.D., Ph.D.

N Engl J Med
Volume 352;12:1206-1214
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Sleep Apnea and Insulin Resistance

OSA patients have higher levels of fasting insulin.

The fasting insulin levels correlate with sleep variables such as RDI and lowest oxygen saturation. AHI is associated with insulin mediated glucose uptake.

OSA subjects are insulin resistant.

Plasma Leptin is increased in OSA.

Insulin resistant cytokines tumor necrosis factor-alpha and interleukin-6 are increased in OSA.
HYPERTENSION AND OSA

- An association between OSA and hypertension has been observed. However, the association of OSA as an independent risk factor for hypertension has always been controversial because of multiple confounding variables for hypertension that are usually also characteristic of patients with OSA, such as age, sex, body mass index (BMI), alcohol use, and smoking. In many studies of the association between hypertension and OSA, these variables have not been controlled adequately. Because of the difficulty in accounting for multiple confounding factors, the association between OSA and hypertension has remained controversial with conflicting findings in multiple studies.

Obstructive sleep apnea (OSA) is a common medical condition characterized by abnormal collapse of the pharyngeal airway during sleep, causing repetitive arousals from sleep. A key feature of OSA is that patients will make persistent efforts to breathe against the occluded upper airway.
• These recurrent and strenuous efforts at inspiration contribute substantially to disturbed sleep. In contrast, central sleep apnea, not a focus of this review, is characterized by the absence of any breathing effort and occurs secondary to central inhibition of the drive to breathe.
• The chief pathophysiologica l event is abnormal narrowing and collapse of the upper airway during sleep due to anatomical narrowing of the upper airway and a loss of tone in the pharyngeal muscles, including the genioglossus.
The oropharynx is the principal site of obstruction in the upper airway, in patients with obstructive sleep apnea syndrome. The soft palate can be enlarged, thickened and elongated. The uvula can be swollen and bulbous. The base of the tongue can protrude backwards and obstruct the airway. The posterior pharyngeal lining can go into folds of redundant tissue. The pillars of fauces may be prominent and close to the midline. The tonsils can be enlarged and in some patients the lingual tonsils may be enlarged and cause obstruction.
• Complete collapse of the upper airway for at least 10 seconds with persistent effort to breathe is termed obstructive apnea. Often, OSA is associated with snoring, which represents near collapse of the upper airway, high resistance to airflow, and rapid vibration of the soft tissues of the airway.
• Hypopnea, partial collapse of the airway during sleep, is defined as a 30% or greater reduction in airflow and a 4% desaturation.
Obstructive Sleep Apnea Syndrome

- C4-A1.A2
- C3.A1.A2
- ROC-LOC
- Chin EMG
- R. Ant. Tib.
- L. Ant. Tib.
- Microphone
- R Nasal Flow
- L Nasal Flow
- Oral Airway
- Abdomen
- ECG
- Oximetry

Arousal

Apnea

Compressed recording - 2.5mm/sec
Obstructive Sleep Apnea Syndrome

C4-A1-A2
O2-A1-A2
ROC-A1-A2
LOC-A1-A2
Chin EMG
ECG
RAT
R Nasal Flow
L Nasal Flow
Chest Mvt.
Abd Mvt.
ET CO2
SAO2

Arousal

Apneic phase

Paradoxical movements
• The severity of OSA is measured by the apnea-hypopnea index (AHI), obtained by counting the total number of apneas and hypopneas during sleep and dividing that by the hours of sleep. An AHI lower than 5 per hour is normal; an AHI of 5 to 15 is mild disease, 15 to 30 is moderate disease, and greater than 30 is severe disease.

• A condition termed *upper airway resistance syndrome* has been described and is characterized by abnormal respiratory-related arousals that do not meet the accepted definition of apneas or hypopneas.\textsuperscript{10}
Prevalence of Sleep-Disordered Breathing

n = 3513 questionnaires (1843F, 1670M)
602 underwent PSG (250F, 352M)
Age 30-60 years

<table>
<thead>
<tr>
<th>Percent</th>
<th>Female</th>
<th>Male</th>
</tr>
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<tbody>
<tr>
<td>25</td>
<td></td>
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<tr>
<td>20</td>
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<td>0</td>
<td>4</td>
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</tbody>
</table>

AHI > 5 + EDS
AHI > 5

References
Young et al, 1993
SYMPTOMS of SLEEP APNEA SYNDROME
Obstructive Sleep Apnea Syndrome

SYMPTOMS

Excessive Sleepiness
Snoring
Apneic Episodes
Choking or Gasping in Sleep
Nocturia
Tiredness upon Awakening
Obstructive Sleep Apnea Syndrome

Features in Children

Hyperactivity or excessive sleepiness
Noisy breathing during sleep
Irregular body positions in sleep
Rib cage retractions
Flaring of the ribs
Predisposing Factors

- Age (40 - 60 years)
- Obesity
- Gender (male:female 2:1)
- Anatomical abnormalities
  - Upper airway obstruction
  - Craniofacial abnormalities
- Medications
- Alcohol
- Smoking
- Family history
<table>
<thead>
<tr>
<th></th>
<th>NREM Sleep</th>
<th>REM Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of ventilation</td>
<td>Metabolic</td>
<td>Metabolic, behavioral</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Respiratory pattern</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduced</td>
<td>Similar to wake, variable</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Reduced</td>
<td>Similar to wake, variable</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Reduced</td>
<td>Similar to wake, variable</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>Reduced</td>
<td>Similar to wake, variable</td>
</tr>
</tbody>
</table>
Heart rate and blood pressure were significantly lower during all stages of non-REM sleep than during wakefulness, and sympathetic activity was significantly lower during stages 3 and 4 (the asterisk denotes P<0.001). During REM sleep, sympathetic activity increased significantly (P<0.001), but the values for blood pressure and heart rate were similar to those recorded during wakefulness. Values are means ±SE.
As non-REM sleep deepens (stages 2 through 4), sympathetic-nerve activity gradually decreases and blood pressure (measured in millimeters of mercury) and variability in blood pressure are gradually reduced. Arousal stimuli elicited K complexes on the electroencephalogram (not shown), which were accompanied by increases in sympathetic-nerve activity and blood pressure (indicated by the arrows, stage 2 sleep). In contrast to the changes during non-REM sleep, heart rate, blood pressure, and blood-pressure variability increased during REM sleep, together with a profound increase in both the frequency and the amplitude of sympathetic-nerve activity. There was a frequent association between REM twitches (momentary periods of restoration of muscle tone, denoted by T on the tracing) and abrupt inhibition of sympathetic-nerve discharge and increases in blood pressure.
MORTALITY ASSOCIATED WITH OSA

Studies done several years ago found that OSA seemed to be associated with an increase in morbidity and mortality. He J, Kryger MH, Zorick FJ. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest.* 1988;94:9-14.
Assess for Major Cardiovascular Disease (CVD)
Risk Factors
Cardiovascular Consequences

- Systemic hypertension
- Pulmonary hypertension
- Cor pulmonale
- Brady-tachycardia
- Sinus arrest
- Complete heart block
- Atrial and ventricular arrhythmias
- Myocardial infarction
- Sudden death
<table>
<thead>
<tr>
<th>Table 1. Cardiovascular Conditions Associated with Obstructive Sleep Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
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<tr>
<td>Atrioventricular block</td>
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<tr>
<td>Tachydysrhythmia</td>
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<tr>
<td>Supraventricular tachycardia</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Ventricular tachycardia</td>
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<tr>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Stroke</td>
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<tr>
<td>Coronary heart disease</td>
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<tr>
<td>Pulmonary hypertension</td>
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</tbody>
</table>
The incidence of a cardiovascular disease (CVD) was explored in 182 middle-aged men with or without obstructive sleep apnea (OSA). All subjects were free of cardiovascular disease at baseline.

At 7 year follow-up compared with baseline, OSA patients developed more CVD than controls and the incompletely treated patients for OSA had more CVD than effectively treated patients.

Treatment of OSA reduces the risk of the development of cardiovascular disease.
Systemic Hypertension

33% of OSA patients have systemic hypertension

33% of Hypertensive patients have OSA

MEDLINE Search. 26 recent references on hypertension and sleep apnea syndrome. July 2002.

1: Curr Opin Nephrol Hypertens 2002 Mar;11(2):201-14

Sleep apnoea and hypertension.


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This review article provides an update on two major issues. First, the most recent evidence supporting the occurrence of an association between obstructive sleep apnoea syndrome, or more generally sleep-disordered breathing, and arterial hypertension in humans is summarized and discussed. This includes an evaluation of both cross-sectional and longitudinal studies. Second, new insights into the mechanisms responsible for the appearance of chronic hypertension in individuals suffering from recurrent nocturnal apnoeic episodes are provided, based both on experimental studies in animals and on clinical
83% of patients with drug-resistant hypertension have obstructive sleep apnea syndrome. 96% of the male patients had OSA compared with 65% of the female patients.
Data indicate that sympathetic-nerve activity, blood pressure, and heart rate are lower in normal subjects while they are in deep non-REM sleep than while they are awake. Arousal stimuli during non-REM sleep elicit K complexes, which are accompanied by bursts of sympathetic-nerve activity and transient increases in blood pressure. During REM sleep, sympathetic-nerve activity increases above the levels recorded during wakefulness, and the values for blood pressure and heart rate return to those recorded during wakefulness. Momentary restoration of muscle tone during REM sleep (REM twitch) is frequently associated with cessation of sympathetic-nerve discharge and increases in blood pressure.
• POSSIBLE MECHANISMS OF CARDIOVASCULAR DISEASE IN OSA
<table>
<thead>
<tr>
<th>Parameters Altered During Recurrent Apneas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td>Central venous pressure</td>
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<tr>
<td>Pulmonary artery pressure</td>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Stroke volume</td>
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<td>Cerebral perfusion pressure</td>
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<table>
<thead>
<tr>
<th>Potential Acute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
</tr>
<tr>
<td>Nocturnal pulmonary edema</td>
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</tbody>
</table>
Figure 1. A 9-min polysomnographic segment from a patient with SDB. Note the elevations in systemic blood pressure following apnea termination as well as the transient decreases in systolic blood pressure (arrows) when inspiratory efforts were made during the obstructive portion of the mixed apnea. Reprinted with permission from Shepard.13
<table>
<thead>
<tr>
<th>Potential Mechanisms</th>
</tr>
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<tbody>
<tr>
<td>Increased daytime sympathetic activity</td>
</tr>
<tr>
<td>Increased resting heart rates</td>
</tr>
<tr>
<td>Decreased R-R interval variability</td>
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<tr>
<td>Increased blood pressure variability</td>
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<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Increased endothelin-1 activity</td>
</tr>
<tr>
<td>Blunted vasodilation to cholinergic stimulation</td>
</tr>
<tr>
<td>Increased intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin</td>
</tr>
<tr>
<td>Increased adhesion of leukocytes to vascular endothelium</td>
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<tr>
<td>Increases in inflammatory mediators</td>
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<tr>
<td>C-reactive protein</td>
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<tr>
<td>Interleukin 6</td>
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<tr>
<td>Oxidative stress by oxygen free radicals</td>
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<tr>
<td>Increases in prothrombotic factors</td>
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<td>-----------------------------------</td>
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<tr>
<td>Plasminogen activator inhibitor</td>
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<tr>
<td>What else?</td>
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</table>
Figure 2. A representative recording from a patient with SDB, showing repetitive changes in airflow, effort, and oxygen saturation associated with cyclic variability in muscle sympathetic nerve activity, blood pressure, and heart rate. Reprinted with permission from Hedner et al.25
### Table 3—Findings in SDB and Potential Effects That May Link SDB to Cardiovascular Disease

<table>
<thead>
<tr>
<th>Findings in SDB</th>
<th>Potential Effects</th>
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<tbody>
<tr>
<td><strong>Neural factors</strong></td>
<td>HTN + Vascular injury + Insulin resistance</td>
</tr>
<tr>
<td>† Sympathetic activation</td>
<td></td>
</tr>
<tr>
<td>† Chemoreflex activation</td>
<td></td>
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<tr>
<td>† Baroreflex sensitivity</td>
<td></td>
</tr>
<tr>
<td><strong>Circulating factors</strong></td>
<td>HTN</td>
</tr>
<tr>
<td>† Atrial natriuretic peptide</td>
<td>? Protective effect</td>
</tr>
<tr>
<td>† Renin-angiotensin-aldosterone</td>
<td></td>
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<tr>
<td><strong>Local vascular factors</strong></td>
<td>HTN + Vascular injury</td>
</tr>
<tr>
<td>† Endothelin</td>
<td></td>
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<tr>
<td>† Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>† Endothelium-dependent vascular relaxation</td>
<td></td>
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<tr>
<td>† α and β₂ vascular responses</td>
<td></td>
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<tr>
<td><strong>Inflammation/oxidant injury</strong></td>
<td>Vascular injury</td>
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<tr>
<td>Intermittent hypoxia</td>
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<tr>
<td>† Increased superoxide anion</td>
<td></td>
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<tr>
<td>† C⁻ reactive protein</td>
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<tr>
<td>† Interleukin-6</td>
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<tr>
<td>† Tumor necrosis factor-α</td>
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<tr>
<td>† Soluble adhesion molecules</td>
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<tr>
<td><strong>Hypercoagulability</strong></td>
<td>Vascular injury + Thrombosis</td>
</tr>
<tr>
<td>† Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>† Platelet aggregability</td>
<td></td>
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<tr>
<td>Polycythemia</td>
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<tr>
<td><strong>“Syndrome Z”</strong></td>
<td>Metabolic syndrome (syndrome X):</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>† Leptin</td>
<td>Glucose intolerance</td>
</tr>
<tr>
<td><strong>Sleep deprivation</strong></td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Arousals</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>Central obesity</td>
</tr>
<tr>
<td>HTN</td>
<td>HTN</td>
</tr>
<tr>
<td>Glucose intolerance</td>
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</tbody>
</table>
The proposed pathophysiologic mechanisms for the acute cardiovascular changes that accompany the apnea-recovery-apnea cycle include:

1. negative intrathoracic pressure,
2. hypoxia,
3. arousals.
Occlusion of the upper airway results in a decrease in alveolar oxygen tension, followed by a reduction in arterial oxyhemoglobin saturation. Also, during obstructive apneas, repetitive, progressively vigorous efforts at inspiration against the occluded airway result in progressively acute decreases in intrathoracic pressure.

Intrathoracic pressure during an apnea can be as low as –80 cm H$_2$O.

The negative intrathoracic pressure results in
1-an increased transmyocardial pressure gradient, which effectively acts to increase cardiac afterload.
2- Decreased intrathoracic pressure also leads to:
  - increased venous return
  - leftward shift of the intraventricular septum,
  -- reduced LV compliance, and decreased LV end-diastolic volume.
- The combination of increased afterload and decreased end-diastolic volume results in decreased stroke volume and cardiac output.
The negative intrathoracic pressure results in

1. an increased transmyocardial pressure gradient, which effectively acts to increase cardiac afterload.

2. Decreased intrathoracic pressure also leads to:
   - increased venous return = leftward shift of the intraventricular septum,
   - reduced LV compliance, and decreased LV end-diastolic volume.
   - The combination of increased afterload and decreased end-diastolic volume results in decreased stroke volume and cardiac output.
Aortic baroreceptors are activated by the increased transmural intrathoracic aortic pressure, but carotid baroreceptors are inhibited because of the fall in blood pressure related to the decreased cardiac output. Sympathetic nerve activity is initially suppressed because the effect of aortic baroreceptors predominates. As the apnea continues, hypoxia may occur, with or without hypercapnia, and this, in turn, stimulates sympathetic output via peripheral chemoreceptors.\textsuperscript{23,24} Sympathetic activity increases peripheral vascular resistance through α-adrenergic receptors in the peripheral vasculature and increases heart rate and cardiac output through cardiac receptors. Thus, as shown in Figure 2, cyclic changes in blood pressure and heart rate mirror the changes in sympathetic tone.\textsuperscript{25} Arousals also contribute to the sympathetic activation at the termination of the apnea.\textsuperscript{26}
• Sympathetic activity increases peripheral vascular resistance through a-adrenergic
• cyclic changes in blood pressure and heart rate mirror the changes in sympathetic tone. Arousals also contribute to the sympathetic activation at the termination of the apnea
The acute effect of SDB on blood pressure was studied in middle-aged patients participating in the Wisconsin Sleep Cohort Study. Predictors of an acute pressor response to respiratory events included, in decreasing order of importance, change in minute ventilation, respiratory event duration, changes in heart rate and oxygen saturation, and arousal. An important finding from this study was that even the "nontraditional" hypopneas (defined as a 50% reduction in the amplitude of the respiratory inductance signal accompanied by a 1 to 3% oxygen desaturation), with or without EEG evidence of arousal, were associated with significant increases in blood pressure at termination of the event. The magnitude of the pressor response was greater for those nontraditional events with arousal than for those without arousal.
FIGURE 1. Recordings of sympathetic nerve activity, respiration, and intra-arterial blood pressure in an otherwise healthy patient with obstructive sleep apnea (OSA) during wakefulness (top left), during recurrent obstructive apneas (bottom panel), and during treatment with continuous positive airway pressure (CPAP) (top right). Even during wakefulness and normoxia, patients with OSA have high levels of resting sympathetic nerve activity. During obstructive apneas, chemoreflex activation by hypoxemia and hypercapnia causes even further increases in sympathetic activity, with recurrent surges in blood pressure most notable at the end of apnea events. Blood pressure increases up to 250/130 mm Hg even though the patient is normotensive during wakefulness. Treatment with CPAP lowers both sympathetic activity and blood pressure. REM = rapid eye movement. Reproduced from Somers et al. 24 with permission from the American Society for Clinical Investigation.
An association between OSA and hypertension has been observed. However, the association of OSA as an independent risk factor for hypertension has always been controversial because of multiple confounding variables for hypertension that are usually also characteristic of patients with OSA, such as age, sex, body mass index (BMI), alcohol use, and smoking. In many studies of the association between hypertension and OSA, these variables have not been controlled adequately. Because of the difficulty in accounting for multiple confounding factors, the association between OSA and hypertension has remained controversial with conflicting findings in multiple studies.

HYPERTENSION AND OSA

- Large recently published population-based prospective studies provide strong evidence that OSA is indeed an independent risk factor for hypertension, although the effect is small to moderate. The Wisconsin Sleep Cohort Study analyzed the development of hypertension as a function of the severity of OSA. Initially, 1189 subjects were enrolled, and the presence of OSA was determined by polysomnography. Of the original group, 709 subjects were followed up for 4 years, and 184 were followed up for 8 years.

HYPERTENSION AND OSA

• The unadjusted odds ratio for developing hypertension was 4.5 in the group with an AHI greater than 15 compared with the group without sleep apnea. When adjusted for age, sex, body habitus, smoking, and alcohol intake, the odds ratio for the development of hypertension was 2.9, providing strong evidence that OSA is an independent risk factor for hypertension.
HYPERTENSION AND OSA

• To avoid the confounding variables encountered in observational or case-control studies, an animal model of OSA was created by Phillipson et al. Experimentally induced OSA in dogs resulted in a 15% increase in both nocturnal and daytime blood pressure within 5 weeks, and blood pressure returned to baseline after cessation of the experiment. A similar number of noise-induced arousals resulted in a small increase in nocturnal blood pressure but not in daytime blood pressure.

Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea
HYPERTENSION AND OSA

- Although the general consensus is that CPAP treatment reduces nocturnal blood pressure in patients with OSA, the effect on daytime blood pressure is less clear. Recently, 3 major studies assessed the effect of CPAP on daytime blood pressure in patients with OSA. These studies found small to moderate decreases in blood pressure with CPAP. The most consistent finding was a significant decrease in diastolic blood pressure after 24 hours of CPAP. Additionally, the effect seemed greatest in patients with more severe OSA compared with those with mild OSA.

HYPERTENSION AND OSA

• Obstructive sleep apnea results in recurrent episodes of airway collapse, vigorous inspiratory effort, negative swings in intrathoracic pressure, hypoxemia, hypercapnia, and arousal from sleep at termination of the apnea. Both increased nocturnal and daytime sympathetic nervous system activity have been shown in untreated patients with OSA.
HYPERTENSION AND OSA

- Increased sympathetic activity leads to increased heart rate, cardiac output, peripheral vascular resistance, and increased tubular sodium reabsorption in the kidney, which may lead to elevated blood pressure. Patients with OSA, compared with those without OSA, have faster heart rates, decreased heart rate variability, and increased blood pressure variability. These changes in cardiovascular autonomic variability are associated with increased cardiovascular risk.
• Additionally, OSA is associated with an increase in C-reactive protein (CRP), impaired vascular endothelial function, elevated leptin levels, and a possible predisposition to weight gain.
The most recent set of guidelines (JNC VII) identified OSA as first on the list of identifiable causes of hypertension.
EVALUATION

CLASSIFICATION OF BLOOD PRESSURE (BP)*

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
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<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
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<tr>
<td>Hypertension, Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension, Stage 2</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

* See Blood Pressure Measurement Techniques (reverse side)
Key: SBP = systolic blood pressure  DBP = diastolic blood pressure

DIAGNOSTIC WORKUP OF HYPERTENSION
- Assess risk factors and comorbidities.
- Reveal identifiable causes of hypertension.
- Assess presence of target organ damage.
- Conduct history and physical examination.

- Obtain laboratory tests: urinalysis, blood glucose, hematocrit and lipid panel, serum potassium, creatinine, and calcium. Optional: urinary albumin/creatinine ratio.
- Obtain electrocardiogram.

ASSESS FOR MAJOR CARDIOVASCULAR DISEASE (CVD) RISK FACTORS
- Hypertension
- Obesity
  (body mass index ≥30 kg/m²)
- Dyslipidemia
- Diabetes mellitus
- Cigarette smoking
- Physical inactivity
- Microalbuminuria, estimated glomerular filtration rate <60 mL/min
- Age (>55 for men, >65 for women)
- Family history of premature CVD
  (men age <55, women age <65)

ASSESS FOR IDENTIFIABLE CAUSES OF HYPERTENSION
- Sleep apnea
- Drug induced/related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing’s syndrome or steroid therapy
- Pheochromocytoma
- Coarctation of aorta
- Thyroid/parathyroid disease
Day-Night Pattern of Sudden Death in Obstructive Sleep Apnea

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Study Overview

- The risk of sudden death from cardiac causes is highest between the hours of 6 a.m.
- and noon and is lowest from midnight to 6 a.m.
- This study found that in patients with obstructive sleep apnea, this pattern is altered -- the risk of sudden death from cardiac causes was much higher from midnight to 6 a.m.
- than during the other hours of the day.
- The increase in risk may be due to a higher incidence of episodes of apnea and hypopnea during these hours.
Conclusions

- People with obstructive sleep apnea have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in people without obstructive sleep apnea and in the general population.
Day–Night Pattern of Sudden Death in Obstructive Sleep Apnea
Volume 352:1206-1214
March 24, 2005 Number 12

• Apoor S. Gami, M.D., Daniel E. Howard, B.S., Eric J. Olson, M.D., and Virend K. Somers, M.D., Ph.D.

• **Background** The risk of sudden death from cardiac causes in the general population peaks from 6 a.m. to noon and has a nadir from midnight to 6 a.m. Obstructive sleep apnea is highly prevalent and associated with neurohormonal and electrophysiological abnormalities that may increase the risk of sudden death from cardiac causes, especially during sleep.
Day–Night Pattern of Sudden Death in Obstructive Sleep Apnea

- **Methods** We reviewed polysomnograms and the death certificates of 112 Minnesota residents who had undergone polysomnography and had died suddenly from cardiac causes between July 1987 and July 2003. For four intervals of the day, we compared the rates of sudden death from cardiac causes among people with obstructive sleep apnea and the following: the rates among people without obstructive sleep apnea, the rates in the general population, and the expectations according to chance. For each interval, we assessed the median apnea–hypopnea index and the relative risk of sudden death from cardiac causes. We similarly analyzed sudden death from cardiac causes during three time intervals that correlate with usual sleep–wake cycles.
Results From midnight to 6 a.m., sudden death from cardiac causes occurred in 46 percent of people with obstructive sleep apnea, as compared with 21 percent of people without obstructive sleep apnea (P=0.01), 16 percent of the general population (P<0.001), and the 25 percent expected by chance (P<0.001). People with sudden death from cardiac causes from midnight to 6 a.m. had a significantly higher apnea–hypopnea index than those with sudden death from cardiac causes during other intervals, and the apnea–hypopnea index correlated directly with the relative risk of sudden death from cardiac causes from midnight to 6 a.m. For people with obstructive sleep apnea, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 (95 percent confidence interval, 1.87 to 3.52). The analysis of usual sleep–wake cycles showed similar results.
• **Conclusions** People with obstructive sleep apnea have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in people without obstructive sleep apnea and in the general population.
Day-Night Pattern of Sudden Death from Cardiac Causes in 78 Persons with and 34 Persons without Obstructive Sleep Apnea (OSA) and in the General Population

Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

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N Engl J Med
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Study Overview

- Obstructive sleep apnea is a form of sleep-disordered breathing in which the upper airway closes repeatedly during sleep.
- In an observational cohort study, the risk of stroke or death from any cause was significantly increased among patients with sleep apnea, independent of other cardiovascular risk factors.
- More severe sleep apnea was associated with greater risk.
Study Overview

- Obstructive sleep apnea is a form of sleep-disordered breathing in which the upper airway closes repeatedly during sleep.
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- More severe sleep apnea was associated with greater risk.
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)

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).*  

<table>
<thead>
<tr>
<th>Severity of Syndrome</th>
<th>Stroke or Death</th>
<th>Mean Follow-up Period</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Patients</td>
<td>yr</td>
</tr>
<tr>
<td>AHI ≤3 (reference score)</td>
<td>13</td>
<td>271</td>
<td>3.08</td>
</tr>
<tr>
<td>AHI 4–12</td>
<td>21</td>
<td>258</td>
<td>3.06</td>
</tr>
<tr>
<td>AHI 13–36</td>
<td>20</td>
<td>243</td>
<td>3.09</td>
</tr>
<tr>
<td>AHI &gt;36</td>
<td>34</td>
<td>250</td>
<td>2.78</td>
</tr>
</tbody>
</table>

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

Conclusion

- The obstructive sleep apnea syndrome significantly increases the risk of stroke or death from any cause, and the increase is independent of other risk factors, including hypertension.
Sleep Apnea and Insulin Resistance

OSA patients have higher levels of fasting insulin.

The fasting insulin levels correlate with sleep variables such as RDI and lowest oxygen saturation. AHI is associated with insulin mediated glucose uptake.

OSA subjects are insulin resistant.

Plasma Leptin is increased in OSA.

Insulin resistant cytokines tumor necrosis factor-alpha and interleukin-6 are increased in OSA.
Cardiac Arrhythmias

Bradyarrhythmias:
- Bradycardia
- Bradytachycardia
- Sinus arrest
- Heart block - Mobitz type I
  Secondary heart block

Tachyarrhythmias:
- Ventricular ectopy
- Supraventricular tachycardia
- Ventricular tachycardia
CARDIAC ARRHYTHMIAS

- An increased incidence of both bradyarrhythmias and tachydysrhythmias has been associated with OSA and is likely related to the severity of OSA and degree of hypoxemia associated with apneic events.
- In patients who undergo cardioversion for atrial fibrillation, the recurrence rate in patients with OSA who are not receiving effective treatment is 2-fold higher (80%) than in patients with OSA who are receiving effective CPAP therapy.

What probing deep
Has ever solved the
mystery of sleep?

Thomas Aldrich (1836 -1907),
Human ignorance
ORE than a SNIOR

Assumption of breathing briefly at night as a result of sleep apnea can lead to serious health complications if left untreated, including high blood pressure, heart attack, abnormal heart rhythm, stroke, impotence, sleep deprivation, poor concentration, depression, and amnesia.
Elevated Levels of Neopterin in Sleep-Disordered Breathing*
Background: Sleep-disordered breathing (SDB) is increasingly being recognized as an independent risk factor for hypertension and cardiovascular disease. Recent evidence suggests that the maladaptive physiologic response to SDB, particularly cardiovascular effects, may result in part from systemic inflammation. Although abnormal cytokine levels have been documented in SDB, data on whether SDB is associated with cellular activation are limited. Thus, this investigation sought to determine whether neopterin, a marker released by activated macrophages, is increased in SDB.
Methods and results: Fifty-five men, free of medical comorbidity, undergoing polysomnography had fasting serum tested for neopterin levels. Multivariable regression methods were used to quantify the association between neopterin and quartiles of the apnea hypopnea index (AHI) while accounting for body mass index, waist circumference, and percentage of body fat.

Quartiles of AHI (I: < 3.83 events per hour; II: 3.83 to 11.98 events per hour; III: 11.99 to 36.82 events per hour; IV > 36.82 events per hour) indicated a range from no SDB through severe SDB.

Compared to the subjects in the first AHI quartile, serum neopterin levels were higher by 3.0%, 10.9%, and 26.5% in the second, third, and fourth AHI quartiles, respectively (p < 0.001 for linear trend).

Neopterin levels also were higher in those with greater degree of sleep-related hypoxemia, more stage 1 sleep, and less stage 2 sleep.
Conclusion: The results of this study indicate that severity of SDB independently associates with serum levels of neopterin, a marker for macrophage activation that may play an important role in the pathogenesis of SDB-related cardiovascular disease.