Uploaded to VFC Website

November 2012

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

Veterans-For-Change is a 501(c)(3) Non-Profit Corporation
Tax ID #27-3820181

If Veteran's don't help Veteran's, who will?

We appreciate all donations to continue to provide information and services to Veterans and their families.

https://www.paypal.com/cgi-bin/webscr?cmd=_s-xclick&hosted_button_id=WGT2M5UTB9A78

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members.

Inflammatory Aspects of Sleep Apnea and Their Cardiovascular Consequences

E. Kasasbeh, MD, David S. Chi, PHD, and G. Krishnaswamy, MD

Abstract: Obstructive sleep apnea (OSA) is a common medical condition that occurs in a considerable percentage of the population. Substantial evidence shows that patients with OSA have an increased incidence of hypertension compared with individuals without OSA, and that OSA is a risk factor for the development of hypertension. It is established that OSA may be implicated in stroke and transient ischemic attacks. OSA is associated with coronary heart disease, heart failure, and cardiac arrhythmias. Pulmonary hypertension may be associated with OSA, especially in patients with pre-existing pulmonary disease. Although the exact cause that links OSA with cardiovascular disease is unknown, there is evidence that OSA is associated with a group of proinflammatory and prothrombotic factors that have been identified as important in the development of atherosclerosis. OSA is associated with increased daytime and nocturnal sympathetic activity. Autonomic abnormalities seen in patients with OSA include increased resting heart rate, decreased R-R interval variability, and increased blood pressure variability. Both atherosclerosis and OSA are associated with endothelial dysfunction, increased C-reactive protein, interleukin 6, fibrinogen, plasminogen activator inhibitor, and reduced fibrinolytic activity. OSA has been associated with enhanced platelet activity and aggregation. Leukocyte adhesion and accumulation on endothelial cells are common in both OSA and atherosclerosis. Clinicians should be aware that OSA may be a risk factor for the development of cardiovascular disease.

Key Words: sleep apnea, obstructive sleep apnea, atherosclerosis, platelets, cardiovascular diseases, cytokines, inflammation

Obstructive sleep apnea (OSA) has evolved as a disease affecting multiple organs. Obstructive sleed apnea is a common disorder that is associated with a plethora of cardiovascular complications, including hypertension, pulmonary hypertension, coronary artery disease, strokes and arrhythmia. Cardiovascular complications represent a large portion of the complications caused by OSA. Over the past few years, several studies have discussed the many mechanisms through which sleep apnea contributes to the pathophysiology of cardiovascular disease. Patients with OSA experience repetitive hemodynamic oscillations during the night that differ from those seen in normal sleep. Certain changes in systemic arterial blood pressure, pulmonary arterial blood pressure, heart rate, and cardiac function occur in association with alterations in sleep state and in respiration.[1] The objective of this work is to review the cardiovascular complications that occur secondary to sleep apnea, and to assess the degree to which they affect the development of chronic cardiovascular pathology and disease.

Overview of Sleep Stages

The transition from wakefulness to sleep is accompanied by many changes in respiratory and cardiovascular regulation. Regarding respiratory changes, upon shift from wakefulness to nonrapid eye movement sleep (NREM), initially a small decrease in minute ventilation with an increase in arterial CO_2 pressure (Pa_{CO2}) is observed. As NREM sleep progresses from stages 1 to 4, minute ventilation decreases further, secondary to a reduction in respiratory drive, which causes a further increase in Pa_{CO2}.[2] Changes in cardiovascu-

Key Points

- Activation of neurohumoral, immunological, coagulation and inflammatory pathyways (including cytokines such as interleukin-6) can lead to vascular endothelial dysfunction, leukocyte recruitment and/or vascular injury. this could culminate in vascular complications.
- It is likely that aggressive treatment of obesity and sleep apnea could halt progression of complicating vascular disease. A better understanding of the inflammatory pathways could lead to better design of therapeutic approaches to a common and potentially serious disorder.

From the Division of Allergy and Immunology and the Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, Johnson City, TN.

Reprint requests to Guha Krishnaswamy, MD, Department of Medicine, Box 70622, East Tennessee State University, Johnson City, TN 37614. Email: krishnas@etsu.edu

The authors have no financial disclosures to declare.

Accepted October 14, 2005.

0038-4348/0−2000/9900-0058

lar autonomic regulation during sleep mirror these changes in respiratory control. As the metabolic rate drops to a relatively constant lower level during stages 1 to 4 of NREM sleep, parasympathetic nervous system tone increases, and sympathetic nervous system activity (SNA), heart rate (HR), blood pressure (BP), stroke volume, cardiac output, and systemic vascular resistance all decrease.[3] Thus, during NREM sleep, the cardiovascular and respiratory systems are dormant.

Upon transition from NREM to rapid eye movement (REM) sleep, there are further changes in respiratory and cardiovascular activity. These changes result in a decrease in ventilation and an increase in Pa_{CO2}.[4] This is accompanied by an irregular pattern of breathing which is probably related to dream content. In contrast, BP and HR increase to levels similar to those of relaxed wakefulness.[5] These changes may play a role in the OSA-related pathologies.

Effects of OSA on the Cardiovascular System

OSA has many effects on the cardiovascular system. Table 1 summarizes the recognized cardiovascular complications of OSA and resultant pathologies that develop in consequence.

Hypertension

Sleep apnea has been shown to result in hypertension. Respiratory disturbances during sleep have been observed in 22 to 48% of patients with essential hypertension, and the prevalence of hypertension in patients with sleep apnea is around 50%.[6] Surges in HR and BP typically occur 5 to 7 seconds after apnea termination,[6] coinciding with arousal from sleep, peak ventilation, and the nadir of Sa_{O2} (arterial saturation of oxygen). It is on the termination of the apnea, when the hyperventilation induces increased venous return and consequently increased output, that the greater cardiac output and peripheral vasoconstriction result in the highest levels of BP.[7] These repetitive surges counteract the usual fall in HR and BP that accompany normal sleep and are thought to contribute to the adverse cardiovascular consequences of OSA, particularly hypertension. It is also possible that OSA contributes to the nocturnal nondipping pattern of hypertension since hypoxemia during sleep apnea causes chemoreceptor-mediated stimulation of sympathetic drive during consequent nocturnal surges of BP.[8] Interestingly, the hypoxia that occurs during these apneic spells alone does not explain blood pressure elevations after obstructive apneas,[6] but is only one of the factors that, when added together, lead to hypertension in patients with OSA.

The most compelling evidence that OSA can elevate systemic pressure comes from population studies. The Wisconsin Sleep Cohort Study, a prospective investigation of apparently healthy state workers without a previous diagnosis of OSA, studied subjects with an apnea index of five or more events per hour of sleep.[9] These subjects had significantly higher blood pressures than did subjects with snoring but without apnea or subjects with neither snoring nor apnea.[9]

These data have been confirmed by a number of large population studies.[10–14] In the multicenter Sleep Heart Health Study a clear independent association between OSA and hypertension was observed in which the prevalence of hypertension increased with increasing apnea-hypopnea index (AHI).[13] In 1997, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure first acknowledged the importance of sleep apnea by recommending that OSA be ruled out as a contributor to resistant hypertension.[15]

Acute therapy of OSA, either with tracheostomy or nasal continuous positive airway pressure (nCPAP), results in a significant decrease in systemic blood pressure.[16] When OSA is eliminated by CPAP, sympathetic vasoconstrictor activity falls both acutely at night[5] and chronically during wakefulness[17] in association with reductions in BP. These data would imply that a substantial proportion of what is generally considered to be essential hypertension may in fact be hypertension secondary to undiagnosed and untreated OSA.

In the controversy about whether OSA can lead to daytime hypertension, one point that is frequently overlooked is that OSA causes elevations in BP during sleep. Considering that humans typically spend one-third of their lives sleeping, it is necessary to consider the possibility that these nocturnal increases in BP might contribute to hypertensive cardiovascular complications,[7] even if daytime hypertension secondary to OSA is not strongly proven. Furthermore, treatment of OSA may facilitate management of hypertension in patients whose blood pressure is difficult to control.

Table 1. Recognized cardiovascular complications of OSA and resultant pathology

Recognized cardiovascular complications of OSA	Resultant cardiac pathology
Arterial stiffness	ASHD
Hypertension	LV dysfunction, stroke
Atherosclerotic cardiovascular disease	Angina, AMI
Cerebrovascular disease	Stroke, cognitive decline
Cardiac arrhythmia	Sudden death, stroke
Ventricular dysfunction	Pulmonary edema, CHF
Pulmonary hypertension	Cor pulmonale

ASHD, atherosclerotic heart disease; LV, left ventricle; AMI, acute myocardial infarction; CHF, congestive heart failure.

Atherosclerotic Cardiovascular Disease

In the Sleep Heart Health Study cohort, OSA emerged as an independent risk factor for coronary artery disease (CAD).[18] One study showed that in patients with the combi-

nation of ischemic heart disease (IHD) and OSA, homocysteine levels were elevated.[12] Nocturnal ST-segment changes consistent with myocardial ischemia are quite common among patients with OSA and coexisting CAD.[19] Various studies have reported the prevalence of such ischemic changes ranging from 20 to 100%.[20,21] Ischemic episodes have been related both to O_2 desaturation and to the postapneic surges in HR and BP,[21–23] and can provoke awakening with complaints of angina.[22] Treatment with CPAP significantly reduces the total duration of ST-segment depression in persons with sleep apnea.[21] However, in uncontrolled studies, treatment of OSA with CPAP in patients with nocturnal angina was associated acutely with reduced frequency of ST-segment depression and chronically with relief of nocturnal angina.[21–23] In a multiple logistic regression model, current smoking, diabetes mellitus and OSA all remained independently associated with CAD.[24]

OSA is common in patients with prior MI.[25] The post-MI changes of cardiac function may predispose to the development of OSA, or may affect OSA severity. OSA in patients with CAD also may be a prognostic indicator. Five-year follow-up of 62 patients with established CAD suggested a significantly higher mortality (38%) in those with OSA compared with those without OSA (9%), after adjusting for other confounding factors.[26]

There is little direct evidence to conclusively support the hypothesis that untreated OSA contributes to vascular morbidity. One recent study looked into spontaneous nocturnal hypoxemia on myocardial ischemia in patients with severe coronary artery disease. It showed that hypoxemic and ischemic episodes apparently occurred at random; no causal relationship could be shown between hypoxemia and ischemia.[27] Nevertheless, further clinical outcome studies are awaited.

Cerebrovascular Disease

The association between stroke and OSA is based upon the same pathogenesis that would cause other cardiovascular complications. The hemodynamic, vascular, inflammatory, and thrombotic disease mechanisms activated by OSA may contribute to enhanced risk for cerebrovascular disease. Ischemic effects of repetitive episodes of nocturnal apnea would be potentiated by the associated hypoxemia and any preexisting impairment of cerebrovascular autoregulation and impaired vasodilator reserve. Acute apneic events are accompanied by dramatic reductions in cerebral blood flow.[28]

In the Sleep Heart Health Study, the presence of OSA was associated with a clear, but modestly increased prevalence of stroke.[18] Among subjects who have suffered a stroke, sleep apnea is extremely common and is reported to occur in 43 to 91% of patients.[29] Bassetti and Aldrich[30] argued that OSA most likely preceded stroke, based on the observation that the frequency and severity of sleep apnea did not differ between patients with stroke and those with transient ischemic attacks.

Moreover, sleep apnea is highly prevalent in patients with stroke.[29,31] It remains unclear whether sleep apnea is an independent risk factor for cerebrovascular disease. However, sleep-disordered breathing in patients with coronary artery disease is associated with a worse long-term prognosis and has an independent association with cerebrovascular events.[32]

Cardiac Arrhythmia

Nocturnal disturbances of cardiac rhythm have been reported in patients with OSA.[33–36] Arrhythmia occurred mainly during sleep stages I/II[37] and REM.[38] Cardiac dysrhythmias occurred more frequently during and immediately after than before OSA episodes, demonstrating their causal relations.[39] Some studies correlate arrhythmias to oxygen desaturation,[34] with more frequent arrhythmias (PVCs) with more pronounced oxygen desaturation,[37] while others showed no correlation.[38] The most common arrhythmias that have been described in correlation with OSA are severe sinus bradycardia and atrioventricular block, representing in part the diving reflex response to apnea and hypoxia.[40] These include extreme bradycardia and ventricular asystole lasting longer than 10 seconds.[41] These bradyarrhythmias occur even in the absence of any disease of the cardiac conduction system and often are eliminated by effective treatment of the OSA.[40]

Other arrhythmias have been described as well and include heart block,[34] atrial fibrillation,[42] and ventricular ectopy.[43] The correlation between these arrhythmias and cardiovascular sequelae, however, hasn't been proven. Despite the greater incidence of some types of cardiac arrhythmias during an acute myocardial infarction in OSA, these patients have the same clinical course in hospital and mortality rate as non-OSA patients.[44]

There is also a correlation between OSA severity and the severity of rhythm disturbance.[33] On the other hand, one study conducted on unselected patients with mild to moderate sleep-disordered breathing with coronary artery disease showed that these patients had premature ventricular contractions and higher heart rates but failed to show a correlation with serious ventricular arrhythmias.[45]

Therapy with nasal CPAP abolishes all episodes of ventricular asystole in most such patients.[46,47] CPAP has been shown to abolish arrhythmias in patients with sleep apnea in a number of studies.[48]

A recent study has, however, added a new perspective to pacemaker placement in patients with OSA. In fifteen patients with OSA and permanent pacemakers (placed previously for symptomatic bradycardia), atrial overdrive pacing at a rate of fifteen beats per minute faster than the patient's average nocturnal heart rate resulted in dramatic improvements in the hypopnea index (9 versus 3, $P < 0.001$).[49] This study suggested that atrial overdrive pacing significantly reduces the number of episodes of central or OSA without reducing the total sleep time. The mechanisms of any pacing-

induced amelioration of sleep apnea and the implications for future therapeutic strategies are presently uncertain, but intriguing. Any therapeutic strategy that would incorporate long-term atrial pacing would need to recognize the potential interactions between OSA and atrial fibrillation. In patients cardioverted for atrial fibrillation, the presence of untreated sleep apnea doubles the likelihood of recurrence of atrial fibrillation within 12 months, compared with patients with OSA receiving CPAP therapy.[50] The recurrence rate of AF at twelve months was significantly higher for patients with untreated OSA than for treated OSA or control patients. However, the preliminary findings may be therapeutically relevant in the future; OSA is not currently considered an indication for permanent pacemaker placement.

Ventricular Dysfunction and Congestive Heart Failure

Hypertension is the single most important predisposing factor for the development of left ventricular (LV) hypertrophy and systolic and diastolic LV failure.[51] Accordingly, the most obvious mechanism through which OSA could lead to the development or progression of LV failure is systemic hypertension. However, ischemia and reduced contractility due to hypoxia,[52] as well as cardiac myocyte injury or necrosis due to increased catecholamine stimulation[53] could also contribute to this. Regardless of the precise mechanisms involved, there is now direct experimental evidence that OSA can lead to interstitial pulmonary edema as well as LV hypertrophy and dysfunction. It is not clear whether OSA can lead to LV hypertrophy in humans; whereas one study reported greater LV wall thickness in normotensive OSA patients than in normotensive control subjects,[54] another did not.[55]

Observations from epidemiologic studies suggest an association between both OSA and congestive heart failure.[56–58] Patients with congestive heart failure and with diastolic dysfunction may have an especially high likelihood of OSA[59]; about half of a small sample of patients with diastolic dysfunction had an apnea-hypopnea index greater than 10.[59] In another study, Mueller maneuvers, which simulated the effects of obstructive apneas, caused more pronounced reductions in LV ejection fraction (LVEF) in patients with CAD than in those without.[60] These findings emphasize that the diseased myocardium is more susceptible to the adverse effects of obstructive apneas than is the normal myocardium.

In the Sleep Heart Health Study, the presence of OSA was associated with a 2.38 relative odds for CHF independent of other known risk factors.[18] This risk exceeded that for all other cardiovascular diseases examined including hypertension, CAD, and stroke. In the two largest series of patients with CHF with systolic dysfunction evaluated for sleep-disordered breathing, 11% of 81 patients[56] and 37% of 450 patients[58] had OSA. This prevalence exceeds the approximate 5 to 10% prevalence of OSA reported in otherwise healthy adults.[61]

OSA did not elicit acute overnight changes in brain-type natriuretic peptide (BNP), either in normal subjects or in patients with coexisting cardiovascular disease (including chronic heart failure).[62]

The activation of adrenergic, inflammatory, and other mechanisms in sleep apnea would reasonably be expected to worsen prognosis in heart failure. Indeed, preliminary data suggest that treatment of both OSA and CSA in patients with heart failure may have important beneficial effects. In small groups of patients with heart failure and OSA, there was modest improvement in both ejection fraction and functional class after treatment with CPAP.[63] A recent randomized controlled clinical trial showed that treatment of OSA among patients with CHF leads to improvement in cardiac function, sympathetic activity, and quality of life.[64] Withdrawal of treatment in some of these patients resulted in a deterioration in both of these measurements.

Pulmonary Hypertension

As clinical descriptions of OSA were disseminated, an association between OSA and cor pulmonale became widely accepted and was fostered by the obvious exposure of these patients to nocturnal hypoxia. It seemed likely that nocturnal hypoxia caused hypoxic pulmonary vasoconstriction, eventually leading to sustained pulmonary hypertension. This causal connection of OSA to right heart failure was questioned in a report in which all patients with OSA who had clinical features of cor pulmonale also had daytime (presumably awake) hypoxemia.[65] The authors suggested that OSA alone was inadequate to cause pressure overload of the right ventricle, and proposed that coexisting chronic obstructive lung disease was necessary.

Subsequent studies have examined the relationship between OSA and pulmonary hypertension. They have confirmed that daytime hypoxia is required in addition to (or instead of) OSA to cause sustained pulmonary hypertension. This daytime hypoxia may be a consequence of obstructive lung disease or, in some patients, obesity. Other reports have attempted to isolate the effect of OSA on pulmonary artery pressure by investigating only patients without coexisting lung disease. In one study in which pulmonary pressures were determined noninvasively, 11 of 27 patients (41%) had pulmonary hypertension.[66] However, the magnitude of the effect was quite small (mean pulmonary arterial pressure <26 mm Hg in all patients), making it unlikely that OSA is a common occult cause of pulmonary hypertension. Similar results were noted in the Sleep Heart Health Study when the echocardiographic findings of patients with and without OSA underwent blinded comparison.[67]

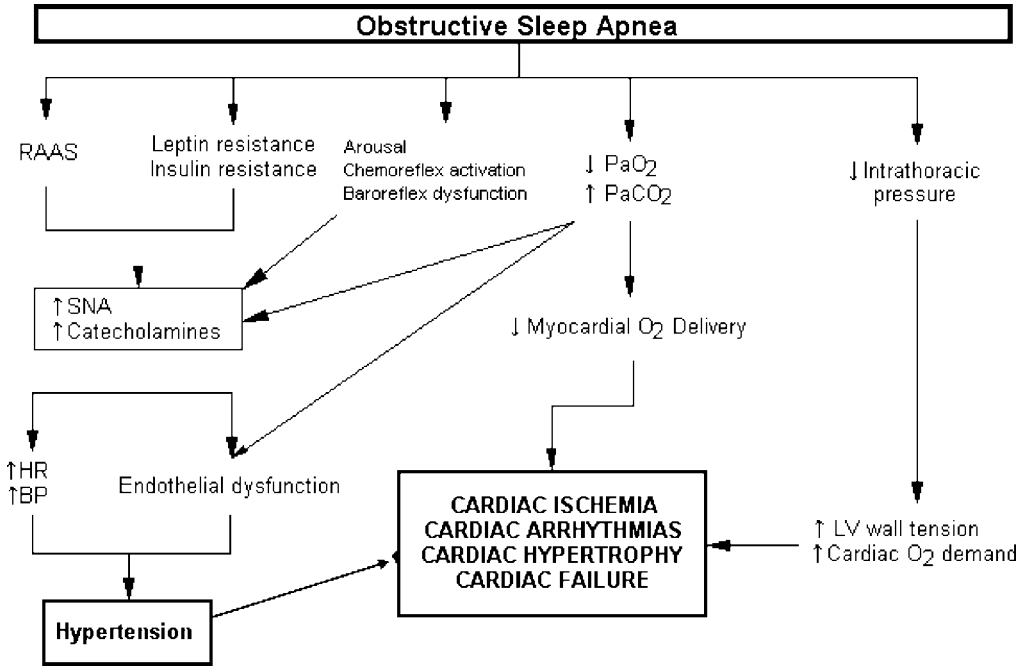

Fig. **Pathophysiology of cardiovascular disease in obstructive sleep apnea.**

Mechanisms for Vascular Disease in OSA: Role of Inflammation

There are a number of different mechanisms through which OSA causes diseases of the cardiovascular system. The Figure describes these various proposed mechanisms and links them together. Table 2 also details these mechanisms, mediators and their relationship to cardiovascular disease. Various inflammatory pathways may be activated in OSA leading to cardiovascular disease. These are summarized below.

Role of the Renin-angiotensin System

Angiotensin II levels positively correlate with higher daytime BP and may be higher in OSA patients.[68] Also, primary hyperaldosteronism may contribute to resistant hypertension in OSA patients. This was examined by Calhoun et al. in a study that proved that patients with hypertension that were at high risk for sleep apnea are twice as likely to have primary aldosteronism. This was demonstrated by lower plasma renin activity and greater 24-hour urinary aldosterone excretion, when compared with subjects at low risk for sleep apnea.[69]

Role for Oxidative Stress

In OSA, repetitive episodes of nocturnal apnea lead to intermittent hypoxia and recurrent reoxygenation secondary to reperfusion.[70] Low oxygen tension is a trigger for activation of polymorphonuclear neutrophils, which adhere to the endothelium and release free oxygen radicals.[71] Recent studies have implicated oxidative stress in blood vessels and the kidney in the pathogenesis of hypertension. Oxidative stress, through inactivation of nitric oxide[72] and activation of angio-

Table 2. Mechanisms, mediators and their relationship to cardiovascular disease

Central Mechanism	Mediators	Cardiovascular effect
Activation of RAS	Neurohumoral mediators	Hypertension Vasoconstriction
Oxidative stress	Hypoxemia	Vasoconstriction
	Superoxide radicals	Vascular remodeling
	Nuclear factor kappa-B	Inflammation
	Inflammatory responses	Inflammation/CRP
Inflammation	Cytokines (IL-6)	Vascular inflammation
	CRP	Atherosclerosis
	TNF	Inflammation
Endothelial	Adhesion molecules	Atherosclerosis
Dysfunction	Cytokines	Atherosclerosis
	Nitric oxide	Atherosclerosis
	Endothelin	Atherosclerosis
Coagulation	Platelet aggregation	Atherothrombosis
	Fibrinogen	Atherothrombosis
	Viscosity of blood	Atherothrombosis
Metabolic	Elevated leptin	Atherosclerosis/ obesity
Dysfunction	Hyperglycemia	Atherosclerosis
	Insulin resistance	Atherosclerosis

RAS, renin angiotensin system; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.

tensin II and thromboxane receptors, increases the generation of endothelin-1 and can subsequently cause vasoconstriction and endothelial dysfunction.[73] Also, OSA patients exhibit decreased vasodilatation in response to acetylcholine in comparison with matched controls, whereas responses to sodium nitroprusside (a direct donor of nitrous oxide [NO]) and verapamil did not vary between groups.[74] This phenomenon, which occurs frequently during each hour of sleep, every night, and over several decades in untreated patients with OSA could result in increased risk for atherosclerosis.[75] Thus, oxidative stress elicited by sleep apnea may be a factor in the pathogenesis of hypertension and vascular disease in OSA. Treatment of OSA by continuous positive airway pressure (CPAP) reduces superoxide, reverses suppression of NO,[72] and thus theoretically decreases the cardiovascular complications.

Cytokine & Acute Phase Responses in OSA

Hypoxemia and sleep deprivation may lead to increased levels of inflammation and inflammatory markers.[76–78] Patients with sleep apnea have increased interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP).[77,79] Inflammation is an important component in the pathogenesis of cardiovascular disease,[80] and elevated CRP may play a role in atherosclerosis as well as endothelial dysfunction.[81] Serum amyloid A (SAA), another inflammatory marker, which has been linked to the pathogenesis of atherosclerosis, is elevated in acute phase response.[82] SAA is an acute-phase protein in humans that is upregulated by inflammatory cytokines,[76] including IL-1 and IL-6.[83]

One study concluded that neutralizing TNF-alpha using etanercept, which is a TNF-alpha antagonist, is associated with a significant reduction of objective sleepiness in obese patients with OSA.[84] A recent report also showed that in OSA patients, circulating levels of IL-6 and TNF-alpha levels are significantly elevated, independent of body mass index. The levels of these mentioned cytokines were also related to the severity of OSA. This demonstrates the significance of inflammatory mediators, namely IL-6 and TNF-alpha, in the cardiovascular complications of OSA.[85] Erythropoietin levels have been shown to be elevated in untreated OSA patients with reduction after CPAP, also illustrating a potential association between OSA and cardiovascular disease.[86] A recent study attempted to establish the role of resistin, a white adipose tissue hormone, in OSA with findings showing no change in relation to CPAP therapy.[87] This finding was consistent with previous studies in this regard. However, this study did show that changes of inflammatory markers under CPAP treatment were related to resistin changes, suggesting a possible link to subclinical inflammation.

Multifactorial Endothelial Dysfunction

The hypoxia, hypercapnia, and pressor surges accompanying obstructive apneic events may serve as potent stimuli for the release of vasoactive substances and for the impairment of endothelial function. Increased levels of endothelin,[88] presumably in response to the hypoxemia of sleep apnea, may contribute to sustained vasoconstriction and other cardiac and vascular changes. Patients with OSA who are free of any other overt cardiac or vascular disease also have impaired endothelial function.[74] Endothelial dysfunction is often seen in patients with hypertension,[89] hyperlipidemia,[90] diabetes,[91] smoking,[92] and obesity,[74] and has been linked to increased risk of cardiovascular events.[93] Data are also present that show endothelial dysfunction in OSA independent of obesity and other risk factors.[74] While the comorbidities associated with sleep apnea may result in endothelial dysfunction, OSA itself may be an independent risk factor for the development of impaired endothelial function. Obstructive sleep apnea and hypopnea have a significant adverse effect on serum soluble cell adhesion molecule-1 levels that may be reduced by nasal CPAP treatment.[94] Also, plasma nitric oxide levels are reduced in OSA and can be increased by short- and long-term CPAP therapy. Although the precise mechanism underlying this observation remains to be clarified, it may have important implications for the development of cardiovascular disease in patients with OSA and for the life-saving effect of CPAP.[95]

Alterations in the Coagulation System

Hypercoagulability in OSA is mediated by comorbid hypertension and may account for high cardiovascular morbidity in OSA in general. Hypercoagulability (as measured by elevated thrombin/antithrombin III complex, fibrin D-dimer, and von Willebrand factor antigen) persisted even after controlling for gender, age, body mass index, mean SaO_2, and hematocrit.[96] A number of hypotheses have been tested to prove this. Platelet aggregability increases in patients with OSA,[97] and in part may be secondary to elevated nocturnal levels of catecholamines.[98] Abolition of OSA by CPAP therapy reduces platelet aggregability in association with reductions in nocturnal levels of catecholamines.[99] Increases in hematocrit,[100] nocturnal and daytime levels of fibrinogen[31] and blood viscosity[101] may also contribute to a predisposition to clot formation and atherosclerosis in patients with OSA. The observations that CPAP therapy can alleviate some of these abnormalities and can reduce factor VII clotting activity[102] and morning increases in the plasma fibrinogen concentration and whole blood viscosity,[102] suggest that OSA may be causally related to increased coagulability.

Metabolic Dysregulation in OSA: Neurohumoral-immune Axis Activation

OSA may be associated with abnormalities in metabolism that could predispose both weight gain and cardiovas-

cular risk. Leptin is an adipocyte-derived hormone that suppresses appetite and promotes satiety.[103] Leptin levels are elevated in obese individuals,[104] suggesting resistance to the metabolic effects of leptin. Leptin may predispose to platelet aggregation[105] and has been implicated as an independent marker of increased cardiovascular risk.[106] Men with OSA have higher leptin levels than similarly obese individuals without sleep apnea,[107] suggesting even greater resistance to leptin than is observed in obese individuals. Treatment with CPAP reduces leptin levels and also may be associated with decreased visceral fat accumulation.[108]

Also, OSA increases the risk of coronary artery disease by increasing plasma levels of glucose, triglycerides, and insulin, independent of obesity.[109] Other investigators have demonstrated that OSA may impair glucose tolerance and have shown that patients with OSA have higher levels of fasting blood glucose, insulin, and glycosylated hemoglobin, independent of body weight.[110] The severity of sleep apnea appears to correlate with the degree of insulin resistance.[111] Severe OSA is accompanied by a fivefold increase in the risk of overt diabetes mellitus.[110] Impaired glucose tolerance in patients with OSA, independent of the effects of obesity per se, may be linked to sleep deprivation.[112] However, treatment with CPAP does not show any consistent improvement in glucose tolerance.[113]

These data suggest that sleep apnea in itself may lead to obesity and thus induce the cardiovascular complications linked to obesity. Obesity also provides a certain body habitus that leaves patients more prone to developing sleep apnea, thus producing a vicious circle.

Summary

The increasing prevalence of obesity and obstructive sleep apnea has led investigators to begin studying this syndrome more actively. Studies from various laboratories and clinical environments suggest that OSA is an inflammatory disorder, with resultant cardiovascular consequences. Some of these are studies in evolution and further data, doubtlessly, will appear fairly soon. Nevertheless, the relationship of sleep apnea to vascular inflammation, cardiovascular morbidity (including hypertension, coronary artery disease and stroke) as well as mortality (arrhythmias and sudden cardiac death) as reviewed recently[114] suggest that these relationships merit further aggressive study. Since C-reactive protein is rapidly becoming a risk factor for cardiac pathology, and is elevated in patients with obesity and OSA, this might turn out to be a relevant marker worthy of further study. It is also likely that in selected individuals with OSA and concomitant vascular disease, aggressive treatment of the disorder can lead to amelioration or even retard progression of the vascular disease state.

References

1. Podszus T, Mayer J, Penzel T, Peter JH, vonWichert P. Nocturnal hemodynamics in patients with sleep apnea. *Eur.J Respir Dis Suppl* 1986;146:435–442.
2. Phillipson EA. Control of breathing during sleep. *Am Rev Respir Dis* 1978;118 (5):909–939.
3. White DP, Weil JV, Zwillich CW. Metabolic rate and breathing during sleep. *J Appl Physiol* 1985;59 (2):384–391.
4. Chandler SH, Nakamura Y, Chase MH. Intracellular analysis of synaptic potentials induced in trigeminal jaw-closer motoneurons by pontomesencephalic reticular stimulation during sleep and wakefulness. *J Neurophysiol* 1980;44 (2):372–382.
5. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* 1993;328 (5): 303–307.
6. Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, et al. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol* 1990;69 (6):2143–2148.
7. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988;2 (8607):397.
8. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax* 2000;55 (9):736–740.
9. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342 (19):1378–1384.
10. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med* 2000;160 (15):2289–2295.
11. Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. *Am J Respir Crit Care Med* 1999;160 (6):1875–1882.
12. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ* 2000;320 (7233): 479–482.
13. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000;283 (14):1829–1836.
14. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* 1997;157 (15):1746–1752.
15. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157 (21):2413–2446.
16. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003;107 (1):68–73.
17. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 1999;100 (23):2332–2335.
18. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier NF, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163 (1):19–25.
19. Hanly P, Sasson Z, Zuberi N, Lunn K. ST-segment depression during sleep in obstructive sleep apnea. *Am J Cardiol* 1993;71 (15):1341–1345.

20. Goldman MD, Reeder MK, Muir AD, Loh L, Young JD, Gitlin DA, et al. Repetitive nocturnal arterial oxygen desaturation and silent myocardial ischemia in patients presenting for vascular surgery. *J Am Geriatr Soc* 1993;41 (7):703–709.
21. Peled N, Abinader EG, Pillar G, Sharif D, Lavie P. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment. *J Am Coll Cardiol* 1999;34 (6):1744–1749.
22. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep apnoea and nocturnal angina. *Lancet* 1995;345 (8957):1085–1087.
23. Philip P, Guilleminault C. ST segment abnormality, angina during sleep and obstructive sleep apnea. *Sleep* 1993;16 (6):558–559.
24. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J* 1999;14 (1):179–184.
25. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990;336 (8710): 261–264.
26. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000;162 (1):81–86.
27. Smith HL, Sapsford DJ, Delaney ME, Jones JG. The effect on the heart of hypoxaemia in patients with severe coronary artery disease. *Anaesthesia* 1996;51 (3):211–218.
28. Netzer N, Werner P, Jochums I, Lehmann M, Strohl KP. Blood flow of the middle cerebral artery with sleep-disordered breathing: correlation with obstructive hypopneas. *Stroke* 1998;29 (1):87–93.
29. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke* 1996;27 (2):252–259.
30. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep* 1999;22 (2):217–223.
31. Wessendorf TE, Thilmann AF, Wang YM, Schreiber A, Konietzko N, Teschler H. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. *Am J Respir Crit Care Med* 2000;162 (6):2039–2042.
32. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med.* 2001;164 (10 Pt 1):1910–1913.
33. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *Chest* 2000;118 (3):591–595.
34. Koehler U, Fus E, Grimm W, Pankow W, Schafer H, Stammnitz A, et al. Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment. *Eur Respir J* 1998;11 (2):434–439.
35. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;79 (12):1645–1650.
36. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension* 1998;32 (2):293–297.
37. Koehler U, Glaremin T, Cassel W, Feuring M, Pomykaj T, Schafer H, et al. [Nocturnal ventricular arrhythmia in patients with sleep apnea and suspected coronary heart disease]. *Med Klin (Munich)* 1993;88 (12): 684–690.
38. Koehler U, Becker HF, Grimm W, Heitmann J, Peter JH, Schafer H. Relations among hypoxemia, sleep stage, and bradyarrhythmia during obstructive sleep apnea. *Am Heart J.* 2000;139 (1 Pt 1):142–148.
39. Szaboova E, Donic V, Albertova D, Turciansky M, Tomori Z. [Nocturnal cardiac dysrhythmias associated with obstructive sleep apnea]. *Sb Lek* 2002;103 (1):79–83.
40. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest* 1982;69 (6):1286–1292.
41. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, et al. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. *Eur Heart J* 2004;25 (12):1070–1076.
42. Coccagna G, Capucci A, Bauleo S, Boriani G, Santarelli A. Paroxysmal atrial fibrillation in sleep. *Sleep* 1997;20 (6):396–398.
43. Shepard JW, Jr., Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. *Chest* 1985;88 (3):335–340.
44. Marin JM, Carrizo SJ, Kogan I. Obstructive sleep apnea and acute myocardial infarction: clinical implications of the association. *Sleep* 1998;21 (8):809–815.
45. Mooe T, Franklin KA, Wiklund U, Rabben T, Holmstrom K. Cardiac rhythm in patients with sleep-disordered breathing and coronary artery disease. *Scand Cardiovasc J* 2000;34 (3):272–276.
46. Grimm W, Hoffmann J, Menz V, Kohler U, Heitmann J, Peter JH, et al. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea. *Am J Cardiol* 1996;77 (15):1310–1314.
47. Becker H, Brandenburg U, Conradt R, Kohler U, Peter JH, Ploch T, et al. [Influence of nCPAP therapy on bradycardic arrhythmias in sleep apnea]. *Pneumologie* 1993;47 Suppl 4:706–710.
48. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. *Circulation* 2000;101 (4):392–397.
49. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* 2002; 346 (6):404–412.
50. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;107 (20):2589–2594.
51. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275 (20): 1557–1562.
52. Kusuoka H, Weisfeldt ML, Zweier JL, Jacobus WE, Marban E. Mechanism of early contractile failure during hypoxia in intact ferret heart: evidence for modulation of maximal Ca2+-activated force by inorganic phosphate. *Circ Res* 1986;59 (3):270–282.
53. Daly PA, Sole MJ. Myocardial catecholamines and the pathophysiology of heart failure. *Circulation.* 1990;82(2 Suppl):I35–I43.
54. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens* 1990;8 (10):941–946.
55. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. *Am J Respir Crit Care Med* 2001;163 (7):1632–1636.
56. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998;97 (21):2154–2159.
57. Laaban JP, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. *Chest* 2002;122 (4):1133–1138.
58. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999;160 (4):1101–1106.

59. Chan J, Sanderson J, Chan W, Lai C, Choy D, Ho A, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. *Chest* 1997;111 (6):1488–1493.
60. Scharf SM, Bianco JA, Tow DE, Brown R. The effects of large negative intrathoracic pressure on left ventricular function in patients with coronary artery disease. *Circulation* 1981;63 (4):871–875.
61. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328 (17):1230–1235.
62. Svatikova A, Shamsuzzaman AS, Wolk R, Phillips BG, Olson LJ, Somers VK. Plasma brain natriuretic peptide in obstructive sleep apnea. *Am J Cardiol* 2004;94 (4):529–532.
63. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000;102 (1):61–66.
64. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med* 2004;169 (3):361–366.
65. Bradley TD, Rutherford R, Grossman RF, Lue F, Zamel N, Moldofsky H, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1985;131 (6):835–839.
66. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med.* 1994;149(2 Pt 1):416–422.
67. Guidry UC, Mendes LA, Evans JC, Levy D, O'Connor GT, Larson MG, et al. Echocardiographic features of the right heart in sleep-disordered breathing: the Framingham Heart Study. *Am J Respir Crit Care Med* 2001;164 (6):933–938.
68. Li Y, Zhang W, Wang T, Lu H, Wang X, Wang Y. [Study on the polymorphism of angiotensin converting enzyme genes and serum angiotensin II level in patients with obstructive sleep apnea hypopnea syndrome accompanied hypertension]. *Lin Chuang Er Bi Yan Hou Ke Za Zhi* 2004;18 (8):456–459.
69. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM. Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. *Chest* 2004;125 (1):112–117.
70. Prabhakar NR. Sleep apneas: an oxidative stress? *Am J Respir Crit Care Med* 2002;165 (7):859–860.
71. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med.* 2000;162(2 Pt 1):566-570.
72. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2000;162 (6):2166–2171.
73. Wilcox CS. Reactive oxygen species: roles in blood pressure and kidney function. *Curr Hypertens Rep* 2002;4 (2):160–166.
74. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000;102 (21):2607–2610.
75. Dean RT, Wilcox I. Possible atherogenic effects of hypoxia during obstructive sleep apnea. *Sleep.* 1993;16(8 Suppl):S15–S21.
76. Hartmann G, Tschop M, Fischer R, Bidlingmaier C, Riepl R, Tschop K, et al. High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. *Cytokine* 2000;12 (3):246–252.
77. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997;82 (5):1313–1316.
78. Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* 1999;84 (8):2603–2607.
79. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002;105 (21):2462–2464.
80. Lavie P. Pro: Sleep apnea causes cardiovascular disease. *Am J Respir Crit Care Med* 2004;169 (2):147–148.
81. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation* 2002;106 (12):1439–1441.
82. Svatikova A, Wolk R, Shamsuzzaman AS, Kara T, Olson EJ, Somers VK. Serum amyloid a in obstructive sleep apnea. *Circulation* 2003;108 (12):1451–1454.
83. Kisilevsky R, Tam SP. Acute phase serum amyloid A, cholesterol metabolism, and cardiovascular disease. *Pediatr Pathol Mol Med* 2002;21 (3):291–305.
84. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. *J Clin Endocrinol Metab* 2004;89 (9):4409–4413.
85. Ciftci TU, Kokturk O, Bukan N, Bilgihan A. The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine* 2004;28 (2):87–91.
86. Winnicki M, Shamsuzzaman A, Lanfranchi P, Accurso V, Olson E, Davison D, et al. Erythropoietin and obstructive sleep apnea. *Am J Hypertens* 2004;17 (9):783–786.
87. Harsch IA, Koebnick C, Wallaschofski H, Schahin SP, Hahn EG, Ficker JH, et al . Resistin levels in patients with obstructive sleep apnoea syndrome–the link to subclinical inflammation? *Med Sci Monit* 2004;10 (9):CR510–CR515.
88. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens* 1999;17 (1):61–66.
89. Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Chayama K, Oshima T. Effect of obesity on endothelium-dependent, nitric oxide-mediated vasodilation in normotensive individuals and patients with essential hypertension. *Am J Hypertens* 2001;14 (10):1038–1045.
90. Lee IK, Kim HS, Bae JH. Endothelial dysfunction: its relationship with acute hyperglycaemia and hyperlipidemia. *Int J Clin Pract Suppl* 2002; (129):59–64.
91. Ciarla MV, Bocciarelli A, Di Gregorio S, Tordi A, Cotroneo P, Marra G, et al. Autoantibodies and endothelial dysfunction in well-controlled, uncomplicated insulin-dependent diabetes mellitus patients. *Atherosclerosis* 2001;158 (1):241–246.
92. Milionis HJ, Jeremy JY, Mikhailidis DP. Regarding ″smoking is associated with dose-related increase of intima-media thickness and endothelial dysfunction″. *Angiology* 1999;50 (11):959–961.
93. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003;23 (2): 168–175.
94. Chin K, Nakamura T, Shimizu K, Mishima M, Nakamura T, Miyasaka M, et al. Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. *Am J Med* 2000;109 (7):562–567.
95. Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lucke C, Mayer K, et al. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. *Thorax* 2000;55 (12):1046–1051.

96. von Kanel R, Le DT, Nelesen RA, Mills PJ, Ancoli-Israel S, Dimsdale JE. The hypercoagulable state in sleep apnea is related to comorbid hypertension. *J Hypertens* 2001;19 (8):1445–1451.

97. Sanner BM, Konermann M, Tepel M, Groetz J, Mummenhoff C, Zidek W. Platelet function in patients with obstructive sleep apnoea syndrome. *Eur Respir J* 2000;16 (4):648–652.

98. Eisensehr I, Ehrenberg BL, Noachtar S, Korbett K, Byrne A, McAuley A, et al. Platelet activation, epinephrine, and blood pressure in obstructive sleep apnea syndrome. *Neurology* 1998;51 (1):188–195.

99. Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure. A preliminary investigation. *Chest* 1995;108 (3):625–630.

100. Hoffstein V, Herridge M, Mateika S, Redline S, Strohl KP. Hematocrit levels in sleep apnea. *Chest* 1994;106 (3):787–791.

101. Nobili L, Schiavi G, Bozano E, De Carli F, Ferrillo F, Nobili F. Morning increase of whole blood viscosity in obstructive sleep apnea syndrome. *Clin Hemorheol Microcirc* 2000;22 (1):21–27.

102. Chin K, Ohi M, Kita H, Noguchi T, Otsuka N, Tsuboi T, et al. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med.* 1996;153 (6 Pt 1):1972–1976.

103. Caro JF, Sinha MK, Kolaczynski JW, Zhang PL, Considine RV. Leptin: the tale of an obesity gene. *Diabetes* 1996;45 (11):1455–1462.

104. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al . Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334 (5):292–295.

105. Davi G, Guagnano MT, Ciabattoni G, Basili S, Falco A, Marinopiccoli M, et al. Platelet activation in obese women: role of inflammation and oxidant stress. *JAMA* 2002;288 (16):2008–2014.

106. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation* 2001; 104 (25):3052–3056.

107. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000;279 (1):H234–H237.

108. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999;100 (7): 706–712.

109. Zgierska A, Gorecka D, Radzikowska M, Baranowska B, Plywaczewski R, Bednarek M, et al. [Obstructive sleep apnea and risk factors for coronary artery disease]. *Pneumonol Alergol Pol.* 2000;68 (5-6):238–246.

110. Elmasry A, Lindberg E, Berne C, Janson C, Gislason T, Awad TM, et al. Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study. *J Intern Med* 2001;249 (2):153–161.

111. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002;165 (5):670–676.

112. Spiegel K, Leproult R, VanCauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354 (9188):1435–1439.

113. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002;165 (5):677–682.

114. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med* 2005;352 (12): 1206–1214.

Be a yardstick of quality. Some people aren't used to an enviroment where excellence is expected.

—Steve Jobs