

Inflammatory Aspects of Sleep Apnea and Their Cardiovascular Consequences

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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 sleep apnea is a common disorder that is associated with a plethora of cardio-

vascular 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 CO₂ 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 pathways (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.

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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 PaCO_2 .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 SaO_2 (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 night⁵ and chronically during wakefulness¹⁷ 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.

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-

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.

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 O₂ 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 pre-existing 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 Aldrich³⁰ 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/II³⁷ 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 stimulation⁵³ 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 OSA⁵⁹; 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 patients⁵⁶ and 37% of 450

patients⁵⁸ 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

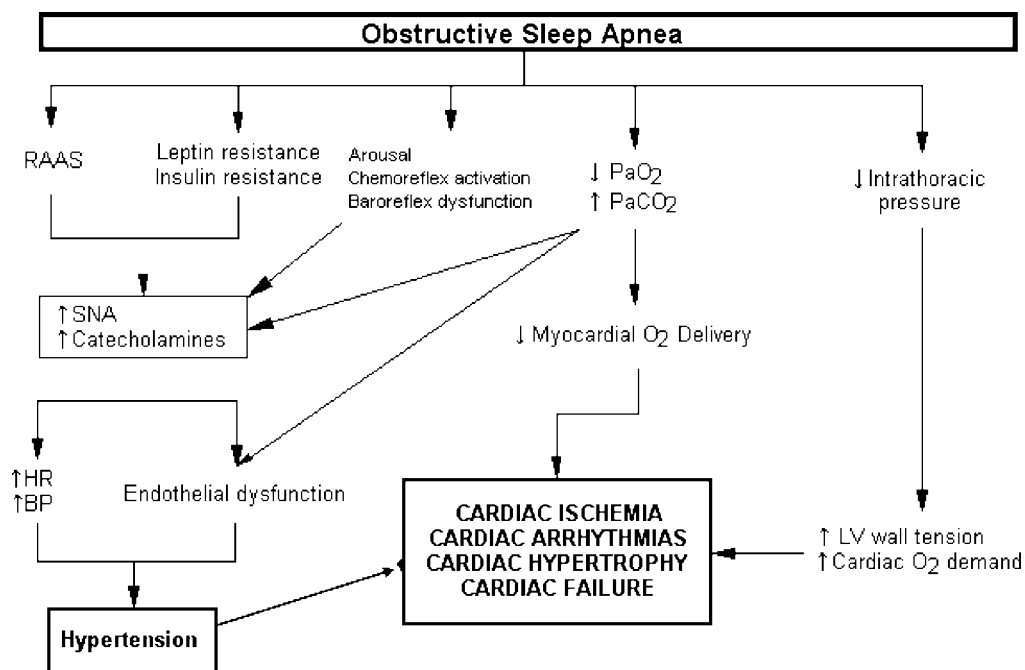


Fig. Pathophysiology of cardiovascular disease in obstructive sleep apnea.

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 day-time 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 oxide⁷² 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
Oxidative stress	Hypoxemia	Vasoconstriction
	Superoxide radicals	Vasoconstriction
	Nuclear factor kappa-B	Inflammation
	Inflammatory responses	Inflammation/CRP
Inflammation	Cytokines (IL-6)	Vascular inflammation
	CRP	Atherosclerosis
	TNF	Inflammation
Endothelial Dysfunction	Adhesion molecules	Atherosclerosis
	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- α (TNF- α), 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- α using etanercept, which is a TNF- α 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- α 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- α , 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 SaO₂, 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 fibrinogen³¹ and blood viscosity¹⁰¹ 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 activity¹⁰² 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 aggregation¹⁰⁵ 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 recently¹¹⁴ 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.

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

—Steve Jobs