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Cardiovascular disease and obstructive sleep apnea: implications for physicians

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Obstructive sleep apnea (OSA) has been strongly associated with several cardiovascular disorders during the past decade, and studies suggested that there might be a causal relationship. Recent studies have described several pathophysiologic mechanisms that are active in OSA and may participate in the development of cardiovascular disorders. Primarily, the repetitive respiratory events that occur in OSA cause hypoxia, hypercapnea, arousals, or disrupted sleep singly or in combination. These abnormal physiologic events result in increased sympathetic outflow, alterations in blood pressure control mechanisms, dysfunctional ventilatory regulation, and vascular alterations. As a consequence of the relative impact and the genetic predisposition, these pathophysiologic alterations may lead to or complicate a wide variety of cardiovascular disorders. Frequently, patients who have OSA present with complaints of excessive daytime sleepiness, chronic fatigue, snoring, morning headache, and nocturnal arousals. Difficult-to-control hypertension, recurrent exacerbations of congestive heart failure, and nocturnal angina are common cardiovascular manifestations of undiagnosed OSA. This article reviews the major cardiovascular disorders associated with OSA and the pathophysiologic mechanisms associated with their development.

(Key words: obstructive sleep apnea syndrome, cardiovascular disease)

Sleep-related breathing disorders (SRBD), the best-known being obstructive sleep apnea (OSA), were not investigated until the late 1960s, and little was truly known about these disorders until the mid-1970s. Commensurate with these advances was the first diagnostic classification for sleep disorders, an increasing number of physicians practicing sleep medicine, and the growth of sleep disorder centers. The major therapeutic options for treating SRBD were limited to oxygen administration and tracheostomies. The first commercially available continuous positive airway pressure (CPAP) machine became available in 1985.

In the 1990s, major advances in diagnostic methods and criteria heralded a broader and more comprehensive understanding of OSA. In 1993, Young and colleagues[1] reported the first large-scale trial documenting the extent of sleep-related breathing disorders in adults. That study demonstrated that the prevalence of well-established disease ranged from 2% to 3% in women and 4% to 5% in men. These data also suggested that more than 10% of the adult population may have a milder form of the disease that may become progressively worse with time and lead to OSA. By the mid-1990s, the association between cardiovascular disease and OSA was sufficiently strong to necessitate a multicenter trial to determine if OSA is an independent risk factor for cardiovascular disease, the Sleep Heart Health Study. Early data from the first 2 years of this trial suggested that OSA is an independent risk factor for cardiovascular disease; the risk increases with the severity of OSA.

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Sleep-related breathing disorders

The major categories of SRBD are OSA, central sleep apnea syndrome, and obesity-hypoventilation (*Table 1*). Of these categories, OSA is the most common. The primary mechanism leading to OSA is a repetitive narrowing of the upper airway during sleep, followed by an increase in upper airway resistance or complete cessation of ventilation for 10 to 120 seconds. In the milder forms of OSA, the sleeping individual may maintain airflow at the expense of increased work of breathing and frequent arousals. As OSA progresses, the respiratory events become more severe; hypoxia, hypercarbia, and dramatic disruptions of sleep occur.

Central sleep apnea syndrome is a disorder in which apneas or hypopneas result from a reduction in central respiratory drive. The clinical factors contributing to the reduction in central respiratory drive are cardiovascular disease, a central nervous system (CNS) pathologic process, or use of narcotic and sedative medication. Although this disorder is well known, its true occurrence is infrequent. In some instances, central sleep apnea may occur as a result of the physiologic adaptations to severe OSA.

Hypoventilation results from depression of the ventilatory drive (for example,

sedating medications, some CNS disorders), a significant mechanical disadvantage that cannot be overcome by the respiratory muscles (such as kyphoscoliosis, obesity), or neuromuscular disease (such as muscular dystrophy, amyotrophic lateral sclerosis). Typically, hypoventilation during sleep results from the mechanical disadvantage afforded by the recumbent position, changes in central respiratory drive, or the reductions in muscle tone associated with sleep. Nocturnal hypoventilation does not have the episodic nature of OSA or central sleep apnea syndrome.

Diagnostic criteria for respiratory disturbances

In 1979, the diagnosis of OSA required the presence of

☐ five or more respiratory disturbances (in the form of apneic episodes) per hour of sleep;

☐ desaturations of greater than 3%; and

☐ associated symptoms.

Individuals with these findings had an increased mortality and significant morbidity that improved with treatment. During the next decade, researchers began characterizing the anatomic derangements associated with these respiratory events and their pathophysiologic consequences. Several groups found that hypopneic episodes caused similar pathophysiologic events and clinical findings, albeit less severe. This resulted in the clinical criteria allowing apnea or hypopnea to be included as respiratory disturbances and the use of the respiratory disturbance index (RDI), or apnea-hypopnea index (AHI), to quantitate these events.[2] This shift in the diagnostic criteria identified individuals with previously undiagnosed OSA and provided a possible explanation for negative or equivocal studies relating OSA with cardiovascular disease that used the earlier criteria to define the OSA syndrome.

In the late 1980s, several investigators demonstrated that increased airway resistance and changes in lung mechanics could contribute to arousals[3,4] and sleep deprivation[5,6] and might be part of the spectrum of OSA.[7-9] This postulate was investigated in 15 patients with the diagnosis of idiopathic hypersomnia,[10] a patient population that had excessive sleepiness, but without the respiratory events characteristic of OSA. Monitoring of esophageal pressure in these individuals revealed crescendo increases in negative intrathoracic pressure that ended with arousals. The application of nasal continuous positive airway pressure (CPAP) in this group apparently relieved the upper airway resistance and symptomatically improved a majority of patients. Following those studies, several studies presented convincing evidence that increased upper airway resistance, without reductions in airflow, may represent the early presentation of OSA.[4,6,11,12]

Several studies have attempted to characterize the impact of increased airway resistance on respiratory control, ventilatory timing, and arousals in milder forms of OSA. Resistive loading of ventilation during sleep adversely affects pharyngeal size[13] and ventilatory control[14] in healthy volunteers, whether this occurs during sleep or is instituted before the onset of sleep. Stoohs and Guilleminault[6] studied eight men with chronic snoring and found that an increase in airway resistance associated with snoring resulted in increased respiratory effort, altered inspiratory timing, and a significant reduction in ventilation. A subgroup analysis demonstrated two different patterns of esophageal pressure development: one group in which the esophageal pressures became progressively more negative until an arousal resulted, and another in which the esophageal pressures plateaued and no arousal occurred.

These data suggest that there may be a progression from increased airway resistance to well-established sleep apnea and that clearly defining clinically significant sleep apnea is an important issue.[8] The impact of such determinations is underscored by the number of individuals affected by the disorder[1] and the number who have OSA that remains undiagnosed.[15] Also, the careful reader should consider that the results and interpretations of previous studies can be significantly affected by the OSA diagnostic criteria applied[1] and the technical definitions used in scoring polysomnograms.[2] The changes in the definitions of respiratory events and hypopnea[2] that have occurred during the past 15 years make comparing studies from different laboratories difficult.

Pathophysiology of upper airway closure

The upper airway comprises two major functional muscle groups. One muscle group functions to constrict the airway as part of swallowing (that is, pharyngeal constrictor mechanism) and the other muscle group dilates the airway to maintain luminal patency (that is, pharyngeal dilators).[16,17] During a normal respiration, the pharyngeal dilator mechanism increases pharyngeal motor tone before the fall in intraluminal pressure and prevents airway collapse. In OSA, the situation becomes more complex. The normal response (that is, pharyngeal dilation or increase in pharyngeal muscle tone) is either defective or ineffectual, thereby allowing or facilitating pharyngeal closure[18-20] once the intraluminal pressure exceeds the critical closing pressure (Pcrit).[21] Pharyngeal closure can occur in the posterior nasopharynx, the oropharynx, or the velopharynx, but often occurs in two or more locations. The return of patency occurs on arousal.

The closure of the airway may be either partial or complete, but the degree necessary to develop pathologic changes has been the source of much debate and investigation. Complete airway closure causes apnea and can lead to elevation of the arterial carbon dioxide level and hypoxia. However, when airway closure is incomplete, respiratory effort increases to maintain airflow and ventilation. The minimal response is an increase in effort and a more negative intrathoracic pressure. Under these circumstances, the intrathoracic pressure changes are transient or plateau and do not result in arousal or activation of the sympathetic nervous system.

Further closure of the airway or a decline in muscular effort will result in a decrease in airflow, often detectable during polysomnography. Decreases in air-

Table 1
Sleep-Related Breathing Disorders

Disorder	Symptoms and presentations	Polysomnographic findings
■ **Obstructive sleep apnea (OSA), a common disorder**	Typical complaints of excessive sleepiness or insomnia along with "heroic" snoring. May also be morning headaches, weight gain, decreased libido, witnessed occurrences of apnea,and frequent nocturnal arousals.	Frequent episodes of obstructed breathing during sleep (>5 per hour sleep) often associated with arterial desaturation.
■ **Central sleep apnea syndrome, a less common disorder**	Characterized by disrupted sleep, fatigue or excessive daytime sleepiness, and periodic respiration. Sleep is typically nonrestorative and snoring is less common than in OSA. Frequently, patients with this disorder have underlying congestive heart failure (CHF) or neurologic disease as a cause of the sleep apnea.	Demonstrates frequent occurrences of apnea or hypopnea (>10 seconds) that occur during sleep and have no evidence of obstruction. Two major patterns of ventilation occur: — Cheyne-Stokes pattern is most commonly associated with CHF. — Periodic respirations,which do not have the periodicity of Cheyne-Stokes, are more commonly associated with underlying neurologic disease.
■ **Central alveolar hypoventilation syndrome (rare)** ☐ Congenital ☐ Acquired, often referred to as Ondine's curse, is the most common form in adults	Patients typically have symptoms similar to those of patients with OSA, but snoring and witnessed occurrences of apnea are less frequent. Patients often have cyanosis, peripheral edema, and carbon dioxide retention, possibly due to underlying neurologic disease, chronic obstructive respiratory disorders, or sedative drugs.	No significant obstructive pathologic process, relatively frequent arousals, and prolonged episodes of arterial desaturation.

flow (that is, hypopnea) or complete cessation (that is, apnea), typically lasting more than 10 seconds, are associated with sympathetic excitation, hypoxia, hypercarbia, or arousals, either singly or in combination. Such instances meet the minimum operational criteria for a respiratory event. As mentioned previously, some individuals have the ability to maintain ventilation during airway narrowing by increasing effort. Under pathologic conditions, the negative intrathoracic pressure becomes progressively more negative until a crescendo occurs, followed by an arousal and recovery of pharyngeal patency. When sufficiently severe, these events may be associated with electroencephalographic evidence of arousal, transient increases in blood pressure, bursts of sympathetic activity, and hypoxia.

The importance of arousals as part of the pathophysiologic mechanisms relates to the fragmentation of sleep[4] and increased sympathetic activity. Under most circumstances, arousals are a protective mechanism with regard to ventilation and may be caused by upper airway resistance in otherwise healthy individuals. However, arousals may lead to sleep deprivation[5] by fragmenting sleep and increased sympathetic activity.[7] When sleep disruption or sleep deprivation ensues, the resulting depression of ventilatory responses is analogous to that seen in OSA.[8,9,13,22-24]

Common mechanical factors adversely affecting the airway during sleep include the supine position, obesity, and rapid eye movement (REM) sleep. Supine positioning allows the tongue, soft palate, and the anterior portion of the velopharynx to move posteriorly, flattening the airway and predisposing to closure. Obesity increases the amount of soft tissue

in the oropharynx and indirectly increases the work of breathing mediated by the chest wall and hemidiaphragms. During REM sleep, the physiologic muscle atonia that accompanies the stage decreases the tone to most skeletal muscles, including most muscles of respiration.

Until recently, the consequences of partial airway closure were not recognized as being associated with significant cardiovascular pathologic processes unless accompanied by hypoxia and arousals. The progress in recognizing the significance of these events has improved our understanding of sleep-related breathing disorders and the interrelationship with cardiovascular disease.

Cardiovascular risk in obstructive sleep apnea

Early studies demonstrated an increased risk of cardiovascular disease associated with habitual snoring. Frequent snoring (that which occurs 6 to 7 nights of each week) carried an increase in the age-adjusted risk of ischemic heart disease (range, 1.9 to 2.35), cerebral vascular accidents (range, 2.8 to 10.3), and cardiovascular-related early-morning death (relative risk, 4.1).[25-27] Similar individuals with habitual snoring were noted to have hypertension at an accelerated rate (range, 10.5% to 15.5%).[28] Despite these relationships, snoring alone is unlikely to be the culpable mechanism. Several authors have suggested that the underlying pathologic process relates to undiagnosed sleep apnea or the development of cardiovascular disease through as yet unknown mechanisms.

Relatively few studies have directly investigated the morbidity and mortality associated with OSA. He and colleagues[29] evaluated the all-cause mortality of patients with OSA. Those with an apnea index (AI) greater than 20 had an 8-year accumulative mortality rate of 37% compared with 4% for those with an AI of less than 20. In the same year, Partinen and colleagues[30] assessed the value of intervention in patients with OSA. The 5-year mortality for OSA was significantly improved with treatment (1% versus 11%, $P<.05$).[30] The use of the AI rather than the AHI clearly biases the studies in favor of more severe disease, but it does not negate the validity of the results. Individuals with OSA have a higher short-term mortality, and effective treatment with tracheostomies can alter these outcomes. Unfortunately, few comprehensive studies have been completed using the more recent diagnostic criteria to establish the true risk of morbidity and mortality with OSA so that our use of therapeutic interventions may be assessed more rigorously. These data may be forthcoming from the ongoing Sleep Heart Health Study.[31]

Prevalence of obstructive sleep apnea in selected cardiovascular conditions

Koehler and Schafer[32] studied 74 male patients who had documented stenotic lesions of one or more coronary arteries that exceeded 70%. In this study group, 68% of the cohort had an AHI greater than 10, while 35% had OSA diagnosed. They found no relationship between AHI, risk factors, coronary vessel involvement, or ejection fraction. However, the results may not be applicable to all patients with coronary artery disease and are not applicable to women. In another study using a random sample of patients with coronary artery disease, Andreas and colleagues[33] found that 50% qualified for the diagnosis of OSA using an AI of greater than 10. Mooe and colleagues studied two cohorts, one male[34] and one female,[35] in an attempt to determine if OSA is a predictor of coronary artery disease. Using an AHI greater than 10 as the threshold, they found that 37% of men and 30% of women would qualify for the diagnosis of OSA, results remarkably similar to those of Koehler and Schafer.[32] Both studies suggested that sleep apnea was a significant predictor for coronary artery disease after adjusting for age, body mass index (BMI), hypertension, smoking habits, and diabetes. This is important in that prior studies had failed to show such an association.

Isolated diastolic dysfunction accounts for up to one third of all reported cases of congestive heart failure (CHF). In an attempt to define the correlation between sleep-disordered breathing and isolated heart failure, Chan and colleagues[36] studied 20 subjects with New York Heart Association class II or III. In this group, 55% of subjects were identified as having sleep-disordered breathing, principally OSA. Body mass index and hypertension were similar between the groups. Echocardiographic findings demonstrated a significant, albeit mild, prolongation of deceleration time, an index of diastolic dysfunction, in the patients with OSA. Other investigators have shown that treatment with nasal CPAP increases the left ventricular ejection fractions significantly, and that these improvements are lost after the withdrawal of nasal CPAP.[37] Because the studies were performed during waking hours, the findings cannot be attributed to the mechanical effect of airway obstruction and suggest that the effect is due to more prolonged functions.

In stable patients with CHF, the incidence of sleep-disordered breathing has been reported in more than 50% of stable patients. In those with an AHI greater than 20, the ejection fraction was lower (22% ± 9% vs 30% ± 10%), time spent with saturations less than 90% was longer (23% ± 24% vs 2% ± 4% of total sleep time), and the lowest saturation was less (74% ± 13% vs 87% ± 4%).[38] The distinction between OSA and central apnea was addressed in two subsequent studies.[39,40] In patients with CHF, central sleep apnea appears to be more frequent than OSA (40% vs 11%, respectively).[40] However, recent studies have shown that occurrences of central apnea (and presumably occurrences of hypopnea) may be part of the pathophysiologic progression active in OSA, thereby clouding the distinction between central sleep apnea and OSA in patients with CHF.

Before 1994, studies evaluating the relationship between OSA and hypertension found that approximately 50% to 90% of patients with OSA had hypertension, whereas only 22% to 62% of patients with hypertension had OSA.[41,42] In one of the more extensive studies from this era, Hla and colleagues[42] studied a

cross-section of men and women (N=147), and found hypertension in 36% of persons with sleep apnea, 13% of individuals with chronic snoring, and 7% of nonsnorers. When they controlled for age, gender, and BMI, they found that OSA was independently associated with hypertension (odds ratio of 2.0 for an AHI >5, and 5.0 for a respiratory disturbance index >25). This finding contrasts with those of prior studies that did not show an independent relationship with OSA. However, using an elegant animal model, Fletcher and coworkers[43,44] have provided evidence that this is a causal relationship potentiated by arousals and alterations in oxygenation. Others have shown similar relationships in human studies.[45] Recent preliminary data from the Sleep Heart Health Study strongly suggest that OSA is an independent risk factor for cardiovascular disease after adjusting for BMI, gender, age, and hypertension. Whether treatment modifies the risk is, as yet, unknown.

Mechanisms in the development of cardiovascular disease

Review of the literature indicates that the disparity between clinical trials is evident and has detracted from the development of focused investigations into the pathophysiologic mechanisms involved in the development of cardiovascular disease. These differences probably relate to confounding medical disorders, changes in diagnostic methods, and modifications in diagnostic criteria.[2] With the refinement of our diagnostic methods, stronger associations between OSA and the development of cardiovascular disorders have become evident. Recent studies have identified several potential pathophysiologic mechanisms that could contribute to the development of cardiovascular disease (*Table 2*). The majority of these mechanisms, directly or indirectly, affect neurally mediated sympathetic activity and alter end-organ responses to cardiovascular regulation.[46-48] In some instances, the reflex responses involved with OSA and obstructive events also function in a protective role (*Table 3*).

Chemoreceptor stimulation

Acute reductions in the arterial P_{O_2} or increases in P_{CO_2} result in the direct stimulation of peripheral chemoreceptors in the aortic and carotid bodies and of central chemoreceptors in the ventral medulla.[49] Under most physiologic conditions, hypoxic stimulation causes an increase in ventilation, augments sympathetic activity to peripheral blood vessels, and an increase in vagal stimulation. Animal studies suggest that the primary reflex response to hypoxia is bradycardia that becomes evident only when ventilation is prevented. However, at low levels of hypoxia (P_{O_2}<40 mm Hg), a central pressor reflex response occurs that increases systemic arterial pressure. In contrast, the majority of hypercapnic stimulation occurs via central chemoreceptors, with approximately 12% of the ventilatory response arising from the peripheral chemoreceptors.[49]

The primary response to chemoreceptor stimulation is increased ventilation. The increased ventilation attenuates chemoreceptor-mediated reflex sympathetic responses to hypoxia and hypercapnea, and the reflex parasympathetic (vagal) response to hypoxia. Eliminating or reducing ventilation, as occurs with OSA, reduces this inhibitory influence on the sympathetic responses to hypoxia and, to a lesser extent, those due to hypercapnea. Thus, the reflexes mediated through the peripheral chemoreceptors are affected more by mechanical inhibi-tion than by the central chemoreceptors.

When hypercapnea and hypoxia occur together, the ventilatory and sympathetic responses are more than the sum of the individual effects and may be potentiated by acidosis; however, increases in blood pressure caused by the sympathetic activation inhibit the ventilatory and vasoconstrictor responses, mediated by peripheral chemoreceptor activation, through reflex activation of the baroreflexes. Similar inhibition may occur for the bradycardic response to hypoxia. These interactions are minimal or absent for the central chemoreflexes.

The sympathetic activation that occurs with hypoxia and hypercapnea may lead to the development of sympathetic excess that may persist into the waking state. Previous studies had shown that the diurnal variation in catecholamine secretion was absent in untreated OSA and suggested that this variation was due to repetitive episodes of asphyxia.[50] A more recent study evaluated the combined effect of hypoxia with hypercapnea.[51] They found that significant increases in sympathetic tone due to hypoxic and hypercapnic chemoreceptor stimulation persist up to an hour after the stimulus is removed in healthy individuals. This demonstrated that intermittent chemoreceptor stimulation could lead to prolonged sympathetic stimulation. To determine if chronic chemoreceptor activity in patients with OSA contributed to these effects, Narkiewicz and colleagues[52] studied a cohort of untreated patients with OSA and a cohort of age-matched control subjects. After excluding the presence of OSA in the control population, the investigators applied 100% oxygen to the subjects and measured muscle sympathetic nerve activity (MSNA). The MSNA in the control subjects declined, whereas the elevated MSNA in the patients with OSA remained unchanged after the administration of oxygen. These data suggest that tonic afferent activity of peripheral chemoreceptors contributes to the increased MSNA and thus sympathetic excess in OSA.

Muscle chemoreflex stimulation

Chemoreceptors provide neural input to feedback mechanisms regarding the metabolic status of a tissue bed. Some authors have postulated that there are chemoreceptors located in the muscle that provide immediate information regarding acute metabolic changes in the muscle that affect ventilation. These receptors may provide information that increases the sympathetic responses associated with hypoxia. This is an area of study for future investigations.

Altered baroreflex responsiveness

Baroreflexes incorporate the inputs from the aortic, carotid, and cardiopulmonary baroreceptors in responding to changes in blood pressure and cardiac filling. In

Table 2
Development of Cardiovascular Disease in Obstructive Sleep Apnea (OSA)—Potential Mechanisms

Potential mechanism	Explanation
■ **Tissue-dependent responses to hypoxia**	The response to hypoxia is dependent on the organ system involved. Tissue beds may adapt to hypoxia (hypoxic preconditioning), vasoconstrict to optimize oxygenation (pulmonary vasculature), vasodilate to increase delivery (skeletal muscle), increase oxygen extraction (heart), and/or sustain injury if unable to adapt adequately.
■ **Chemoreceptor stimulation**	Chemoreceptor stimulation primarily involves the activation of peripheral chemoreceptors to changes in carbon dioxide and oxygen tensions. This most commonly involves the receptors located in the aortic or carotid bodies.
■ **Muscle chemoreflex stimulation**	Muscle chemoreflex stimulation occurs in the major skeletal muscles and is stimulated by the accumulation of local metabolites. Reflex stimulation increases muscle sympathetic nerve activity and blood pressure.
■ **Altered baroreflex responsiveness**	Baroreflexes attempt to maintain blood pressure within a homeostatic range. Acute blood pressure shifts cause reflex alterations in autonomic tone to the heart and vasculature that attempt to return the blood pressure to its previous level. These alterations are most commonly disrupted by the presence of recurrent hypoxia.
■ **Coagulation and vasoactive substances**	The coagulation system and vasoactive substances typically interact locally to optimize blood flow or prevent blood loss. Abnormal or excessive activation may predispose to thrombosis and the development of cardiovascular disease.
■ **Sympathetic excess or altered autonomic balance**	Acute sympathetic excess occurs through reflex mechanisms and may increase neural or humoral mediators. Recurrent acute sympathetic stimulation will frequently result in prolonged sympathetic activity and increases in blood pressure that are unresponsive to reflex modulation by baroreflexes.
■ **Vascular remodeling**	Endothelium-dependent and independent vasoregulation aid in optimizing blood flow to organ systems, especially in the setting of hypoxia. Diminished vasodilation would increase blood pressure and predispose to the development of hypertension.
■ **Diminished adrenergic responsiveness**	Chronic sympathetic stimulation can down-regulate adrenergic responsiveness in OSA, this may protect against excessive cardiac stimulation, but it could limit appropriate increases in cardiac contractility and predispose to heart failure.
■ **Alterations in ventilatory control**	Increased ventilation induced by chemoreflex stimulation attenuates the associated sympathetic increases. A reduction in ventilation, either through airway obstruction or decreased central drive, allows the sympathetic increases to occur unabated.

one study, baroreflex responsiveness was assessed using nitroprusside to develop a transient hypotension.[53] Both cardiac baroreflex responsiveness, as assessed using changes in the R-wave–to–R-wave interval, and sympathetic baroreflex responsiveness, using the mean MSNA, were found to be depressed by 43% ($P<.05$) and 63% ($P<.05$), respectively. The baroreflex changes correlated with MSNA and remained statistically significant even after adjusting for age, BMI, and, to some degree, blood pressure. These data suggest that the response was due to OSA and was not as a result of hypertension. In another study, Ziegler and colleagues[54] studied the baroreflex responsiveness to a hypertensive stimulus during normoxia (fraction of inspired oxygen 0.21) and while breathing a 15% oxygen mixture. All subjects demonstrated decreased baroreflex responsiveness when exposed to hypoxia, a response that was slightly exaggerated in those with apnea, and apneic subjects demonstrated an enhanced pressor response to phenylephrine infusion. These data suggest that there is an interaction between baroreflexes and chemoreceptor activation[55] that results in suppressed sympathetic nerve activity resulting from hypoxia. Overall, baroreflex responses to hy- potensive stimuli are impaired in patients with OSA, whereas the baroreflex responses to hypertensive stimuli are reduced only during hypoxia. These

reflex alterations may contribute to the development of hypertension in this patient population.

Vascular remodeling and responsiveness

The mechanisms regulating vascular tone include myogenic, neurogenic, humoral, endothelial, and local factors. As noted previously, the neurogenic component of vascular control mediating vasoconstriction is increased. This neural component is most evident in the increases noted with MSNA,[56] improvements that resolve with adequate treatment,[57] and assessments of circulating catecholamines.[58,59] These responses may be potentiated by concomitant chemoreceptor activation resulting from hypoxemia. However, only a weak correlation exists between these measures and the presence of hypertension that may be attributable to counterregulatory mechanisms or adaptations that occur with prolonged activation.

Release of the atrial natriuretic peptide (ANP), a vasodilator, increases during obstructive events, presumably as the result of the mechanical effects on the atria that promote myocardial stretch[60] and could give rise to a state of pseudohypervolemia.[61] Additionally, hypoxia facilitates the de novo synthesis and release of ANP. These findings are also consistent with plasma renin, angiotensin II, and aldosterone measurements that are suppressed in patients with OSA. Such reductions would protect against the development of hypertension and vascular remodeling. In this setting, central hypervolemia would also be a major stimulus to suppress sympathetic activity through baroreflex mechanisms. Of clinical interest is whether angiotensin II inhibitors would be effective in the treatment of hypertension in OSA.

Table 3
Potential Mechanisms That May Decrease Adverse Responses in Obstructive Sleep Apnea (OSA)

Potential mechanism	Explanation
■ **Hypoxic preconditioning**	Brief exposure to hypoxia will increase the tolerance to subsequent hypoxia and ischemia. The improved tolerance will limit tissue damage and complications such as arrhythmias. These mechanisms have been clearly documented in the heart and the brain.
■ **Hypoxia**	Although hypoxia stimulates chemoreceptors, it causes vasodilation in cardiac and skeletal muscle beds. This functions to improve delivery of oxygen and removal of waste products
■ **Increased ventilation**	Increased ventilation suppresses sympathetic outflow and modulates activation of the sympathetic nervous system mediated by chemoreceptors.
■ **Sleep deprivation**	Sleep deprivation decreases the tendency to arouse and reduces chemoreceptor sensitivity. Both effects will limit the increases in sympathetic activity that occur during apneas
■ **Baroreflex stimulation**	Increased stimulation of arterial baroreceptors causing a reflex decrease in sympathetic stimulation. This protects against the acute increases in blood pressure associated with sympathetic activity during apneas and hypopneas.
■ **Pseudohypervolemia**	The apparent increase in venous return and central blood volume increases the stimulation of cardiopulmonary baroreceptors, decreasing sympathetic activity. This factor also reduces the activity of the renin-angiotensin-aldosterone axis and results in low levels of angiotensin II, a potent vasoconstrictor

Coagulation and vasoactive substances

Vasoactive substances have also been proposed as a mechanism by which cardiovascular disease could be initiated by OSA. One of the most studied and potent vasoconstrictors is endothelin. This peptide may be increased in OSA.[61] Mechanisms that could account for this finding include an increase in endothelin gene expression[62] and an increased release associated with hypoxia.[63] Another mechanism that may be active in promoting vasoconstriction is shifts in eicosanoid production.[64]

Recent investigations have focused on the role of endothelium-derived nitric oxide (NO) and changes in local vascular control mechanisms.[65] Infusions of acetylcholine and sodium nitroprusside were used to assess NO-dependent vasodilation.[66] Acetylcholine stimulates the release of NO, whereas nitroprusside functions as a direct NO donor. When these agents were infused in patients with OSA, endothelium-dependent vasodilation was reduced by approximately 25%, independent of the presence or absence of hypertension. However, the endothelium-independent vasodilation was 35% lower in the hypertensive patients with OSA as compared with that in all other groups. Altogether, these data suggest that a vascular mech-

anism plays a role either in angiogenesis or the development of hypertension (or both).

Although an association exists between intravascular thrombosis and some forms of cardiovascular disease, the presence of predisposing factors for thrombosis have not been well studied in OSA. In one study, patients with OSA with an RDI greater than 20 demonstrated a significant increase in fibrinogen and serum viscosity that decreased with treatment.[67] Platelet activation, a risk factor for acute coronary or cerebrovascular thrombosis, was shown by Eisensehr and colleagues[58] to be increased in OSA. In their study, the marker for platelet activation correlated with the RDI, suggesting that as severity of OSA increases, so does the risk of thrombosis.

Myocardial contractility and adrenergic responsiveness

With chronic sympathetic outflow, adrenergic receptors will down-regulate and physiologic responsiveness will be impaired. Such changes are consistent with the sympathetic increases associated with OSA and could contribute to decrements in cardiac responsiveness previously noted in OSA.[46] Nelesen and colleagues[68] attempted to verify this postulate using echocardiographic measures in patients with OSA and matched control subjects. In their study, the patients with OSA had increased cardiac contractility at baseline and did not have an increase with a laboratory stressor. In contrast, myocardial contractility increased in control subjects.

Ventilatory control

Ventilation directly affects the neural output of sympathetic and parasympathetic limbs of the autonomic nervous system. Changes in ventilation have direct effects on P_{CO_2} and P_{O_2} that may then indirectly affect neural sympathetic outflow mediated by peripheral and central chemoreceptors. Under circumstances in which sympathetic tone would be increased as the result of hypoxia, there is a commensurate inhibition of the sympathetic tone resulting from the compensatory hyperventilation. During occurrences of apnea, the inhibitory influence of hyperventilation is no longer present and the chemoreceptor stimulation results in a significant increase in sympathetic outflow. Sleep stage changes or arousals occur and facilitate the resumption of ventilation with the secondary effect of an additional increase in sympathetic tone.[45,69,70]

Resources

- **Sleep Heart Health Study (SHHS) WebPage**
  A Web site updated regularly with information pertinent to the progress and publications related to the SHHS. This may be accessed through *http://140.142.220.3/shhs/default.asp*
- **National Institutes of Health (NIH)**
  The NIH develops plans for research, education, and technology that span the time well into the 21st century. They are also actively involved in disseminating this information to the public and professionals alike. This plan includes aspects of a broad range of health topics. A good starting point is at their Web site: *http://www.nih.gov*. Osteopathic research opportunities also exist through the NIH and may be found through the funding opportunities page. One such listing may be found at *http://www.nih.gov/grants/guide/pa-files/PA-99-013.html*
- **American Academy of Sleep Medicine (Formerly the American Sleep Disorders Association)**
  This association is dedicated to the study and treatment of sleep and circadian rhythm disorders. Part of its mission is to disseminate information regarding sleep disorders and to provide practice standards. Some of this information may be obtained by visiting *http://www.asda.org*

Figure. *Internet sources for additional information.*

The degree of ventilatory response to metabolic stimuli may change in sleep apnea.[69] During normal sleep, the P_{CO_2} rises and the P_{O_2} falls by 2 torr to 3 torr as the result of central mechanisms. On awakening, the alterations in the blood gases are reversed and respiratory control normalizes. However, with as little as 27 hours of sleep deprivation, the ventilatory response to hypoxia and hypercarbia is depressed during waking hours and may be accentuated during sleep.[71] Based on some CPAP intervention studies, the abnormal response is corrected by adequate therapy.

Comment

Current data have shown that at least 2% to 5% of the general adult population has OSA, while 40% to 75% of those with selected cardiovascular disorders have OSA as a comorbid condition. The strength of this association suggests that there is a causal link between these disorders, and the pathophysiologic mechanisms active in OSA form a strong basis on which to base this assumption. Given the frequency of OSA in both the general population and in patients with cardiovascular disease, there is sound justification for primary care practitioners to consider OSA, especially when treating patients with cardiovascular disease.

The *Figure* provides a list of resources for additional information.

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