AHA/ACCF Scientific Statement

Sleep Apnea and Cardiovascular Disease

An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing

In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)

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Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease. Obstructive sleep apnea (OSA) affects an estimated 15 million adult Americans and is present in a large proportion of patients with hypertension and in those with other cardiovascular disorders, including coronary artery disease, stroke, and atrial fibrillation.[1–14] In contrast, central sleep apnea (CSA) occurs mainly in patients with heart failure.[15–19] The purpose of this Scientific Statement is to describe the types and prevalence of sleep apnea and its relevance to individuals who either are at risk for or already have established cardiovascular disease. Special emphasis is given to recognizing the patient with cardiovascular disease who has coexisting sleep apnea, to understanding the mechanisms by which sleep apnea may contribute to the progression of the cardiovascular condition, and to identifying strategies for treatment. This document is not intended as a systematic review but rather seeks to highlight concepts and evidence important to understanding the interactions between sleep apnea and cardiovascular disease, with particular attention to more recent advances in patient-oriented research. Implicit in this first American Heart Association/American College of Cardiology Scientific Statement on Sleep Apnea and Cardiovascular Disease is the recognition that, although holding great promise, this general area is in need of a substantially expanded knowledge base. Specific questions include whether sleep apnea is important in initiating the development of cardiac and vascular disease, whether sleep apnea in patients with established

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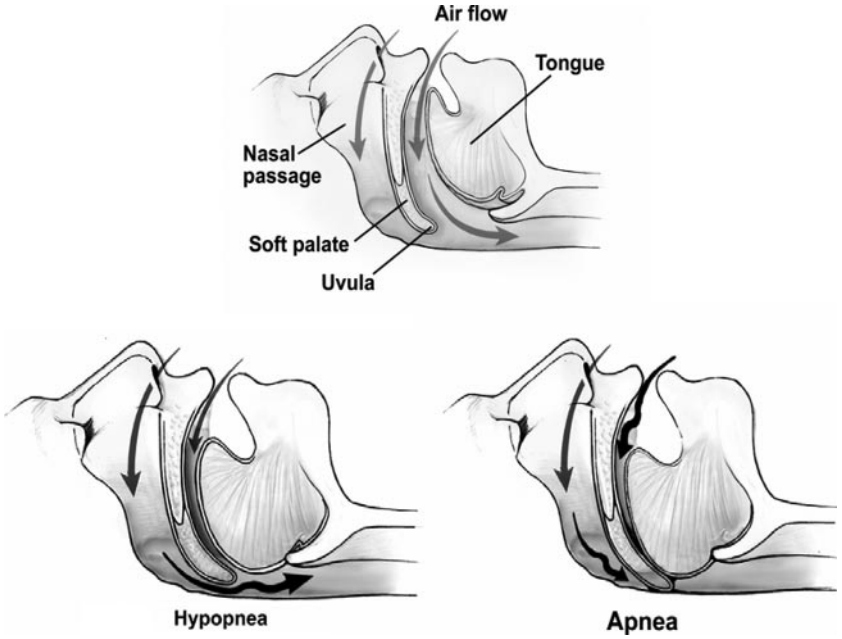

Figure 1. Partial and complete airway obstruction resulting in hypopnea and apnea, respectively. Reprinted from Hahn PY, Somers VK. Sleep apnea and hypertension. In: Lip GYH, Hall JE, eds. *Comprehensive Hypertension*. St. Louis, Mo: Mosby; 2007:201–207. Copyright Elsevier 2007. Used with permission.

cardiovascular disease accelerates disease progression, and whether treatment of sleep apnea results in clinical improvement, fewer cardiovascular events, and reduced mortality.

Experimental approaches directed at addressing these issues are limited by several considerations. First, the close association between obesity and OSA often obscures differentiation between the effects of obesity, the effects of OSA, and the effects of synergies between these conditions. Second, multiple comorbidities, including cardiovascular disease, metabolic syndrome, and diabetes, often are present in patients with sleep apnea. Hence, it becomes unclear whether abnormalities evident in the sleep apnea patient with cardiovascular disease are secondary to the sleep apnea, the cardiovascular condition, or both. The third consideration relates to randomization of sleep apnea patients to active or no treatment. Although this is a reasonable strategy for identifying the mechanistic and prognostic consequences of sleep apnea per se, it is limited by the difficulties inherent in any placebo-controlled treatment study of sleep apnea and the need to consider treatment in patients with severe daytime somnolence, even in the absence of associated cardiovascular disease.

Definitions, Classifications, Diagnosis, and Pathophysiology

Obstructive Sleep Apnea

OSA is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. An obstructive apnea is a ≥10-second pause in respiration associated with ongoing ventilatory effort. Obstructive hypopneas are decreases in, but not complete cessation of, ventilation, with an associated fall in oxygen saturation or arousal. A diagnosis of OSA syndrome is accepted when a patient has an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) >5 and symptoms of excessive daytime sleepiness[20] (Figure 1 and Table 1; see Table 2[5] for definitions of terms).

Although hypopneas constitute the majority of disordered breathing events, there is some controversy regarding the optimal criteria for definition of hypopneas. A recent analysis of data from >6000 adults participating in the Sleep Heart Health Study noted that hypopneas accompanied by oxyhemoglobin desaturation of ≥4% were associated with prevalent cardiovascular disease independently of confounding covariates.[21] In contrast, no association was observed be-

Table 1. Obstructive Sleep Apnea

Signs, symptoms, and risk factors
Disruptive snoring
Witnessed apnea or gasping
Obesity and/or enlarged neck size
Hypersomnolence (not common in children or in heart failure)
Other signs and symptoms include male gender, crowded-appearing pharyngeal airway, increased blood pressure, morning headache, sexual dysfunction, behavioral changes (especially in children)
Screening and diagnostic tests
Questionnaires
Holter monitoring
Overnight oximetry
Home-based/ambulatory unattended polysomnography
In-hospital attended overnight polysomnography
Treatment options
Positional therapy
Weight loss
Avoidance of alcohol and sedatives
Positive airway pressure
Oral appliances
Surgery
Uvulopalatopharyngoplasty
Tonsillectomy
Tracheostomy

Table 2. Definitions of Terms[5]

Term	Definition
Apnea	Cessation of airflow for >10 s
Hypopnea	A reduction in but not complete cessation of airflow to <50% of normal, usually in association with a reduction in oxyhemoglobin saturation
AHI	The frequency of apneas and hypopneas per hour of sleep; a measure of the severity of sleep apnea
OSA and hypopnea	Apnea or hypopnea resulting from complete or partial collapse, respectively, of the pharynx during sleep
CSA and hypopnea	Apnea or hypopnea resulting from complete or partial withdrawal of central respiratory drive, respectively, to the muscles of respiration during sleep
Oxygen desaturation	Reduction in oxyhemoglobin saturation, usually as a result of an apnea or hypopnea
Sleep apnea syndrome	At least 10 to 15 apneas and hypopneas per hour of sleep associated with symptoms of sleep apnea, including loud snoring, restless sleep, nocturnal dyspnea, headaches in the morning, and excessive daytime sleepiness
Polysomnography	Multichannel electrophysiological recording of electroencephalographic, electroculographic, electromyographic, ECG, and respiratory activity to detect disturbance of breathing during sleep
NREM sleep	Non–rapid eye movement or quiet sleep
REM sleep	Rapid eye movement or active sleep; associated with skeletal muscle atonia, rapid movements of the eyes, and dreaming
Arousal	Transient awakening from sleep lasting <10 s

Reprinted from Bradley et al,[5] with permission from Lippincott Wiliams & Wilkins. Copyright 2003, American Heart Association.

tween cardiovascular disease and hypopneas associated with milder desaturation or arousals. The investigators noted several limitations of their data, including the facts that causality cannot be inferred from their cross-sectional analysis and that additional cross-sectional and longitudinal studies are needed to compare interactions between event definitions and other sleep-disordered breathing (SDB)–related consequences.

Pharyngeal collapse in patients with OSA generally occurs posterior to the tongue, uvula, and soft palate or some combination of these structures. This portion of the pharyngeal airway (from the posterior nasal septum to the epiglottis) has relatively little bony or rigid support and is therefore largely dependent on muscle activity to maintain patency. The primary abnormality in patients with OSA is an anatomically small pharyngeal airway resulting from obesity, bone and soft tissue structures, or, in children, tonsils and adenoids.[22] During wakefulness, this leads to increased airflow resistance and greater intrapharyngeal negative pressure during inspiration. Mechanoreceptors located primarily in the larynx respond reflexively to this negative pressure and increase the activity of a number of pharyngeal dilator muscles, thereby maintaining airway patency while awake.[22,23] However, during sleep, the reflex pharyngeal muscle activity that drives this neuromuscular compensation is reduced or lost, leading to reduced dilator muscle activity and ultimately to pharyngeal narrowing and intermittent complete collapse.[24] During the subsequent apnea or hypopnea, hypoxia and hypercapnia stimulate ventilatory effort and ultimately arousal from sleep to terminate the apneic event. Thus, an upper airway that requires reflex-driven muscle activation to maintain patency during wakefulness may be vulnerable to collapse during sleep.

The pathophysiology of obstructive apneas is complex and varies between patients. Although deficient pharyngeal anatomy and variable upper airway dilator muscle control awake and asleep are likely the predominant causes of pharyngeal collapse in most patients with OSA, other mechanisms also likely contribute.[25–28] Loss of lung volume during sleep reduces longitudinal traction on the upper airway, rendering it more collapsible. In addition, ventilatory control system instability is associated with cycling respiratory output to ventilatory pump muscles and upper airway dilator muscles. As a result, at the nadir of such cycling, the pharyngeal airway may collapse completely or partially, yielding obstructive apneas or hypopneas. Accordingly, in the individual with ventilatory control instability, apneas/hypopneas may be central or obstructive, depending on the collapsibility of the upper airway. Finally, mechanisms such as variable surface tension in the pharyngeal airway, arousal threshold, and asynchronous timing of activation of upper airway versus pump muscles may contribute to apnea pathogenesis.

Screening of patients for SDB can be accomplished by several different methods, although the sensitivity and specificity of these have not been well documented, particularly in cardiovascular patients, and may be expected to be affected by pretest probability. Some of these options include the Epworth Sleepiness Scale,[29] the Berlin questionnaire,[30] overnight oximetry, and devices combining limited respiratory assessment, ECG, and oximetry.[31] Specialized analysis of 24-hour ECG recordings also has been proposed as a possible screening tool.[32] The available options have many shortcomings. The most often used in clinical practice is overnight oximetry.

In patients with suspected OSA, a definitive diagnosis often requires spending a night in a sleep laboratory during which multiple physiological variables are continuously recorded (polysomnography). These variables generally include sleep staging using the electroencephalogram, electromyogram, electrooculogram, respiration (flow, effort, oxygen saturation), and snoring. With these signals, disordered breathing, in addition to its effect on sleep and oxygenation, can be precisely quantified. The importance of the cardiovascular response to sleep has been recognized in the recently revised Sleep Scoring Manual from the American Association of Sleep Medicine (AASM),[33] which now includes scoring of a continuous-lead ECG as a recommended component of polysomnography.[34]

There is controversy as to whether disordered breathing during sleep can be adequately assessed using fewer signals recorded in the home. Most of these systems are limited to monitoring the respiratory channels listed above and do not include sleep staging or other nonrespiratory signals. After

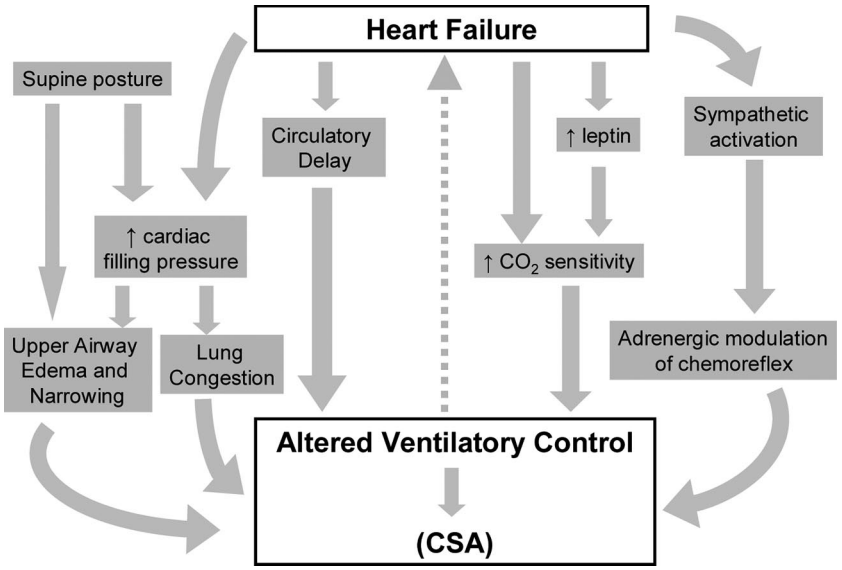

Figure 2. Schematic outlining possible mechanisms underlying development of CSA and the possible feedback from CSA resulting in exacerbation of heart failure.[16] Reproduced with permission.

careful assessment, the American Academy of Sleep Medicine concluded that certain home diagnostic methodologies probably do have a role in the diagnosis of obstructive sleep apnea if used by an experienced clinician.[35] Although this remains controversial, the Center for Medicare Services recently decided to pay for CPAP when the diagnosis of OSA was made with portable systems in the home. Thus, the use of such methodologies will likely increase in the future.

Central Sleep Apnea

CSA is characterized by repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive. A central apnea is a ≥10-second pause in ventilation with no associated respiratory effort. Generally, >5 such events per hour are considered abnormal. CSA syndrome is present when a patient has >5 central apneas per hour of sleep and the associated symptoms of disrupted sleep (frequent arousals) and/or hypersomnolence during the day.[20] Because central apneas also may occur in an individual with obstructive apneas, care must be exercised in deciding that CSA rather than OSA is the principal problem. Although there is no absolute standard in this regard, studies of patients with CSA require that >50% of all events be central, with >80% central events often being required.

CSA does not have any single cause (Figure 2). As a result, a number of syndromes have emerged, each of which may have somewhat different underlying pathophysiological mechanisms. Cheyne-Stokes respiration (CSR) generally occurs in patients with heart failure, although it has been described in association with neurological disorders, including neurovascular disorders and dementia. It is characterized by a crescendo-decrescendo pattern of breathing with a central apnea or hypopnea at the nadir of ventilatory effort. In patients with heart failure, CSR is believed to result from a high-gain ventilatory control system (increased hypercapnic responsiveness) combined with a prolonged circulation time.[15,36] This combination leads to unstable ventilatory control and this particular pattern of periodic breathing. Idiopathic CSA[37] also is characterized by unstable ventilation, which is due to a very steep ventilatory response to hypercapnia. Unstable ventilatory control in patients with both CSR and idiopathic CSA can promote obstructive events (apneas and hypopneas) in an individual with a collapsible pharyngeal airway resulting from diminished upper airway muscle activation at the nadir of the cycling respiration. Thus, both central and obstructive events are commonly seen in these patients, as discussed later.

The diagnosis of CSA may not be readily recognized by the clinician and currently requires a full-night polysomnogram to determine the frequency and pattern of central apnea (Table 3). Simplified monitoring systems or oximetry alone in the diagnosis of CSA has not been broadly accepted; full-night polysomnography remains the standard. Some patients with heart failure will demonstrate a periodic breathing pattern even during wakefulness and exercise.[38,39] In this case, a polysomnogram is often helpful to exclude concurrent obstructive apnea and to guide treatment for the nocturnal periodic breathing.

Table 3. Central Sleep Apnea

Signs, symptoms, and risk factors
Congestive heart failure
Paroxysmal nocturnal dyspnea
Witnessed apnea
Fatigue/hypersomnolence
Other signs and symptoms include male gender, older age, mitral regurgitation, atrial fibrillation, CSR while awake, periodic breathing during exercise, hyperventilation with hypocapnia
Screening and diagnostic tests
Overnight oximetry
Ambulatory (unattended) polysomnography
In-hospital (attended) polysomnography
Treatment options
Optimize treatment of heart failure
Positive airway pressure
Supplemental oxygen

Obstructive Sleep Apnea

Epidemiology

The high prevalence and wide spectrum of severity of OSA in adults have been well documented by several population-based cohort studies conducted in the United States, Europe, Australia, and Asia. Although measurement techniques and definitions have varied, most of these studies have shown that ≈1 in 5 adults has at least mild OSA (eg, AHI ≥5) and 1 in 15 has moderate or severe OSA (eg, AHI ≥15). Two population studies with AHI measured longitudinally have shown significant progression in OSA over time. In the Wisconsin Sleep Cohort,[40] the mean 8-year increase in AHI was greatest for habitual snorers compared with nonhabitual snorers, those with body mass index (BMI) ≥30 versus <30 kg/m^2, and those 45 to 60 versus 30 to 45 years of age at baseline. In the Cleveland Family Study, the change in median AHI was similarly highest for those 41 to 54 versus 11 to 40 and >54 years of age and BMI ≥31 versus <31 kg/m^2.[41]

However, >85% of patients with clinically significant and treatable OSA have never been diagnosed, and referral populations of OSA patients represent only the "tip of the iceberg" of OSA prevalence.[42,43] In addition to emphasizing the large burden of untreated OSA in the general population, the low level of medical detection demands caution in generalizing observations of OSA patients diagnosed in sleep clinics to cardiovascular disease patients with occult OSA. Understanding predictors of OSA free from sleep clinic referral bias is necessary to recognize cardiovascular disease patients likely to have OSA. When OSA was initially being documented as a diagnosable condition, patients were collectively described as "Pickwickian": morbidly obese, sleepy, middle aged, and male. This stereotype has undoubtedly influenced case finding and led to an overrepresentation of these characteristics in OSA patient populations. Large studies of OSA detected in population-based screening have shown that although male sex and obesity are clearly risk factors for OSA (associated with 2- and 4-fold-higher prevalences, respectively), clinically significant OSA is not rare in women or in nonobese persons and is even more common in older age compared with middle age. Furthermore, in contrast to the high prevalence of pathological sleepiness in OSA patient populations, excessive daytime sleepiness and OSA are not strongly correlated in general population studies.[40,44,45]

Few studies characterizing OSA in cardiovascular patients have been conducted. Available data indicate that OSA prevalence is 2 to 3 times higher than in reference populations without cardiovascular disease.[11,46] Risk factors for undiagnosed OSA in heart failure patients may differ from those based on observations of other OSA patients. In 450 heart failure patients referred for polysomnography, the odds ratio (OR) for OSA with male gender (OR, 2.8) was similar to that seen in population studies.[47] However, for men, only obesity was significantly related to OSA, and for women, age but not obesity was related to OSA. Of particular importance, and for reasons that are not well understood, OSA may not manifest with sleepiness in heart failure patients.[48,49]

Population-based epidemiology studies and observations of OSA patients have consistently shown the prevalence of hypertension, type II diabetes, cardiovascular disease, and stroke to be higher in people with OSA.[7,10,46,50–57] Because all these conditions are chronic, have multifactorial and overlapping origins, and have long latent periods before symptoms appear, identifying a causal role of OSA is difficult. In cross-sectional studies that rely on a diagnosis of cardiovascular disease as the end point, subjects with preclinical and asymptomatic disease will be missed. Risk factors or causes common to both conditions, including male sex, age, overweight, central body fat deposition, alcohol, smoking, and lack of exercise, explain some but not all of the correlation between OSA and cardiovascular disease. In addition to concern about these as "confounding" factors in investigating the independent role of OSA in promotion of cardiovascular disease, there also is interest in the concurrent presence of the constellation of OSA, cardiovascular disease, and their common risk factors.[10,51,58]

Before widespread use of continuous positive airway pressure (CPAP) as a standard of care,[59,60] patients with OSA treated conservatively had increased mortality compared with OSA patients who had undergone tracheostomy, even though the latter group had a higher BMI (34 versus 31 kg/m^2) and more severe OSA (AHI, 69 versus 43).[61] Most deaths were cardiovascular. Similarly, another study showed that mortality in OSA patients with an AHI >20 was 0% over 8 years in those treated with tracheostomy or nasal CPAP, significantly lower than those treated with uvulopalatopharyngoplasty or those left untreated.[62] Population-based longitudinal studies with objective measurement of OSA, initiated over the past 15 years, have begun to clarify the nature of the OSA–cardiovascular disease link. An 11-year follow-up of older residents in San Diego (Calif) showed the mortality rate for cardiovascular disease to be higher for those with OSA (35% for AHI <15, 56% for AHI ≥15).[46] Prospective analyses of the Wisconsin Sleep Cohort Study indicate that OSA increases the risk of incident hypertension.[56] Snoring, as a marker of OSA, predicted hypertension, cardiovascular disease, and type II diabetes in the Nurses Health Study,[50,53,54] as did short sleep duration.[63] In 1995, the Sleep Heart Health Study was initiated to investigate the role of OSA in cardiovascular disease using in-home polysomnography; baseline and follow-up data have been collected on a sample of ≈3000 adults, and longitudinal analyses are now underway.[64]

Clinical Presentation

OSA affects male individuals more commonly than female individuals and may present with a number of signs and symptoms suggestive of the disorder (Table 1) or with no symptoms whatsoever. However, clinical judgment ultimately must be used in deciding which patients deserve further evaluation. For example, virtually all patients with OSA snore, but not all snorers have sleep apnea.

Signs and symptoms apply to large patient cohorts that include patients with and without cardiovascular disease, raising the question of whether there are specific indications for apnea evaluation in patients with cardiac or vascular disease. The answer is likely "yes," given the high prevalence of OSA in hypertension, including resistant hypertension (requiring ≥3 medications), atrial fibrillation, and nocturnal angina. Both OSA and CSA occur commonly in patients with

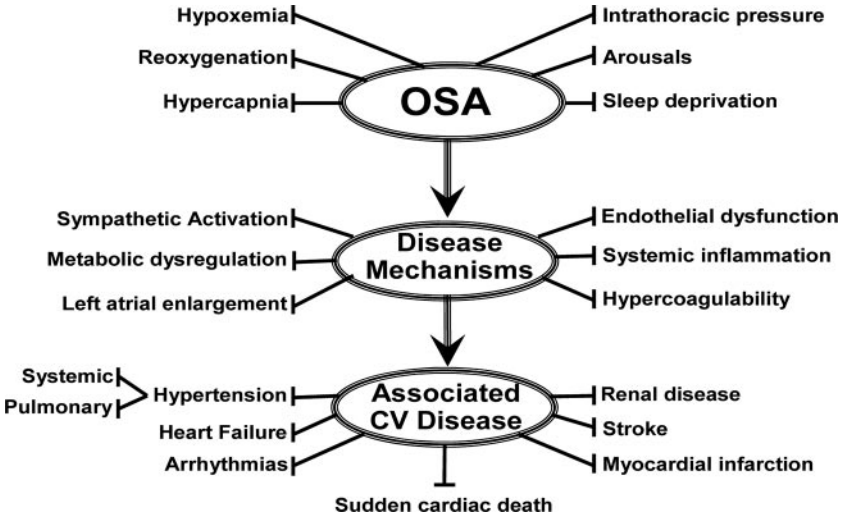

Figure 3. Schematic outlining proposed pathophysiological components of OSA, activation of cardiovascular disease mechanisms, and consequent development of established cardiovascular disease.

heart failure and may contribute to disease progression. Treating sleep apnea may be particularly relevant in these patients, and the diagnosis should be carefully considered. However, this does not imply that all patients with hypertension, atrial fibrillation, nocturnal angina, or heart failure should undergo formal testing for sleep apnea. If other indicators also are present (witnessed apneas, disruptive snoring, obesity, waking hypersomnolence) or if the cardiovascular condition is refractory to standard therapy, there should be a low threshold for pursuing this diagnosis.

Early studies suggested the interesting and clinically relevant possibility that OSA may have more deleterious cardiovascular consequences in subjects <50 years of age.[62] This concept has found support in more recent data showing that younger people with OSA may be more likely to have hypertension[65] and atrial fibrillation[66] and to suffer greater all-cause mortality.[67] These data may argue in favor of a more aggressive diagnostic and therapeutic strategy in younger and middle-aged subjects with OSA. Differential effects of race, gender, and other demographics also merit consideration and require further investigation.

Mechanisms of Disease and Associated Cardiovascular Risk

Obstructive apneas may induce severe intermittent hypoxemia and CO_2 retention during sleep, with oxygen saturation sometimes dropping to ≤60%, disrupting the normal structured autonomic and hemodynamic responses to sleep.[68] Apneas can occur repetitively through the night and are accompanied by chemoreflex-mediated increases in sympathetic activity to peripheral blood vessels and consequent vasoconstriction.[69,70] Toward the end of apneic episodes, blood pressure (BP) can reach levels as high as 240/130 mm Hg.[71] This level of hemodynamic stress occurs at a time of severe hypoxemia, hypercapnia, and adrenergic activation. Nocturnal apneas initiate a range of pathophysiological mechanisms outlined below, which may act to promote cardiac and vascular disease (Figure 3).

Sympathetic Activation

Heightened sympathetic drive elicited by recurrent apneas during sleep persists into normoxic daytime wakefulness.[71] Sympathetic traffic to peripheral blood vessels is increased even in people with OSA who are otherwise healthy independently of obesity.[72] Patients with OSA also have faster heart rates during resting wakefulness, suggesting that there also is increased cardiac sympathetic drive.[73] The mechanisms for this heightened sympathetic activation are not known. One possibility is that increased chemoreflex gain in OSA results in tonic chemoreflex activation even during normoxia, with consequent increased sympathetic activity. Administration of 100% oxygen (to eliminate tonic chemoreflex drive) significantly lowers sympathetic activity, heart rate, and BP in OSA patients during daytime wakefulness.[74]

Cardiovascular Variability

Compared with similarly obese control subjects, resting awake OSA patients have diminished heart rate variability and increased BP variability.[73] In patients with cardiovascular disease, reduced heart rate variability is associated with poorer outcomes.[75–77] The Framingham Heart Study has implicated lower heart rate variability as a precursor to the development of future hypertension,[78] and increased BP variability has been implicated in increased risk of end-organ damage in patients with hypertension.[79]

Vasoactive Substances

Recurrent hypoxemic stress induces increased release of vasoactive and trophic substances that may elicit vasoconstriction persisting for hours. Endothelin is released in cell culture during hypoxia.[80] In patients with OSA, untreated severe sleep apnea lasting several hours results in increased endothelin levels, which fall after 4 hours of treatment with CPAP.[81] More recent data support a role for endothelin in raising BP in OSA patients.[82] A positive correlation also has been reported between aldosterone and OSA severity, but this correlation was true only for patients with resistant hypertension and was not evident in normotensive controls.[83]

Inflammation

Hypoxemia appears to be an important mechanism for triggering systemic inflammation. Healthy subjects at altitude manifest increased levels of inflammatory molecules such as interleukin-6 and C-reactive protein.[84] Sleep deprivation also may trigger

systemic inflammation.[85,86] The combination of repetitive hypoxemia and sleep deprivation in OSA patients may be associated with increased levels of plasma cytokines, adhesion molecules,[87,88] serum amyloid A,[89] and C-reactive protein.[88,90–92] Although the increase in C-reactive protein in OSA appears to be independent of adiposity,[92] this question remains controversial.[93] There also is evidence for enhanced leukocyte activation in OSA.[94,95] Monocytes from OSA patients bind more actively to cultured endothelial cells than do monocytes from control subjects, and treatment by CPAP attenuates this monocyte binding.[94] Ryan et al[96] reported that in vitro, intermittent hypoxia and reoxygenation selectively activated the proinflammatory transcription factor nuclear factor-κB, whereas the adaptive regulator hypoxia-inducible factor-1α was not activated. Related studies in OSA patients also noted increased circulating tumor necrosis factor-α levels (which decreased after 6 weeks of CPAP) but not in erythropoietin and concluded that the intermittent hypoxia of OSA selectively activated inflammatory over adaptive pathways.

Oxidative Stress

The repetitive hypoxemia and reoxygenation that characterize sleep in OSA patients may be implicated in the triggering of oxidative stress mechanisms.[97–99] Some studies have reported increased levels of thiobarbituric acid reactive substances, isoprostanes, and oxidized low-density lipoprotein in OSA,[100] although these changes have not been confirmed in other studies.[101] Circulating free nitrotyrosine, a marker of nitrosative oxidative stress, is not elevated in OSA patients.[102] Microarray measures of gene transcription in OSA subjects before and after sleep suggest the activation of several mechanisms that may modulate and adapt to any increased reactive oxygen species developing in response to overnight hypoxemia.[103]

Endothelial Dysfunction

Systemic inflammation, sympathetic activation, pressor surges, and oxidative stress may all contribute to the development of endothelial dysfunction. However, evidence for endothelial dysfunction in OSA patients has not been consistent, and studies have been limited to relatively modest numbers of subjects. A selective impairment of resistance vessel (small vessel) endothelial function but not conduit vessel (brachial artery) endothelial function was reported in otherwise healthy OSA patients compared with similarly obese subjects proven to be free of sleep apnea.[81] However, other studies using correlative approaches in patients with comorbidities reported an inverse relationship between brachial artery flow-mediated dilation and sleep apnea severity.[104] Conflicting findings with regard to resistance vessel endothelial function in OSA[105,106] speak to the importance of careful exclusion of comorbidities in studies of OSA patients. Nevertheless, recent data suggest not only that conduit vessel endothelial function may be impaired in OSA but also that the impairment may be related to endothelial cell apoptosis and that treatment with CPAP may improve endothelial function.[107,108]

Insulin Resistance

Increased catecholamines, sleep deprivation,[109] and other pathophysiological characteristics of OSA may be associated with insulin resistance. Indeed, data from several studies suggest an association between OSA and glucose intolerance independently of BMI.[110–112] Vascular and other adverse effects of insulin resistance may contribute to cardiovascular disease in OSA. However, although some studies suggest that CPAP therapy may reduce insulin resistance in OSA,[113] a systematic review of 24 earlier reports, while confirming a probable independent link between SDB, glucose intolerance, and insulin resistance, also concluded that studies on the treatment of SDB with CPAP yielded inconsistent results and did not reveal an improvement in the metabolic disturbance after treatment.[114] Finally, related metabolic dysregulation such as leptin resistance and the metabolic syndrome also have been linked to OSA.[51,115]

Thrombosis

OSA also been associated with increased platelet activation, increased fibrinogen, and other potential markers of thrombotic risk.[116] However, additional studies are needed to more definitively evaluate the role of hemostatic mechanisms and to confirm any hypercoagulable state in OSA.[117]

Intrathoracic Pressure Changes

Obstructive apnea causes repetitive forced inspiration against a closed upper airway (the Mueller maneuver), which generates very substantial negative pressures in the chest cavity, to levels approaching −65 mm Hg. This negative intrathoracic pressure increases transmural gradients across the atria, ventricles, and aorta[118,119] and disrupts ventricular function[118] and autonomic and hemodynamic stability.[120] Consequences may include increased wall stress, increased afterload, increased atrial size,[121,122] impaired diastolic function,[121,123] thoracic aortic dilation, and propensity toward dissection.[124] Whether repetitive nocturnal increases in transmural gradients may contribute in the longer term to ventricular hypertrophy and remodeling and associated clinical consequences remains to be established.

Cardiovascular Diseases and OSA

Hypertension

The Prevalence of OSA in Hypertension

Both OSA and hypertension are common, and many individuals have both conditions. About 50% of OSA patients are hypertensive,[125] and an estimated 30% of hypertensive patients also have OSA, often undiagnosed.[126–130] In the Wisconsin Sleep Cohort Study, Hla et al[131] and Young et al[132] found a linear relationship between 24-hour BP and AHI that was independent of confounding factors such as BMI. Those patients with an attenuated nocturnal BP decline (nondippers) may be more likely to have coexisting OSA.[133] Nocturnal sympathetic activation and consequent higher sleep-related BPs[71] may attenuate the nocturnal dipping of BP. A blunted nocturnal BP decline has been associated with greater leukoaraiosis (white matter disease).[134] Recent data in almost 4000 subjects show an increase in all-cause mortality in those with a blunted (hazard ratio, 1.30; 95% CI, 1.00 to 1.69) or absent (hazard ratio, 1.96; 95% CI, 1.43 to 2.96) nocturnal BP fall.[135]

OSA and the Origin and Progression of Hypertension

Animal studies in rats and dogs have identified possible mechanisms by which OSA might lead to hypertension such as intermittent hypoxemia, chemoreceptor stimulation,[136]

sympathetic activation,[136,137] and the renin-angiotensin system. In dogs, obstructing a tracheostomy to simulate apnea causes an acute increase in BP of ≈20 mm Hg, which persists for several hours and is exacerbated by prior sleep deprivation.[138] The BP increase can be attenuated by pharmacological blockade of the autonomic nervous system with hexamethonium, indicating that it is mediated by the sympathetic nervous system rather than by mechanical factors related to changes in intrathoracic pressure. Longer-term (1 to 3 months) maintenance of repetitive nocturnal airway occlusion to mimic OSA more closely resulted in daytime hypertension in a dog model of OSA. Repetitive nocturnal arousal resulting from an acoustic stimulus delivered without airway occlusion did not elicit daytime hypertension, underscoring the importance of the hypoxemic stress.[139]

OSA has been proposed as an independent risk factor for the development of essential hypertension because it can precede and predict the onset of hypertension. This has been demonstrated by the Wisconsin Sleep Cohort Study, which noted a consistent OSA-BP dose-response relationship, even after controlling for age, sex, BMI, and antihypertensive medications.[56] Effects of OSA on hypertension may be especially evident in middle-aged compared with older subjects, and OSA may predominantly raise systolic BP.[65] Although OSA has also been implicated in pregnancy-associated hypertension,[140–142] the etiologic interactions need to be more clearly defined. In the third trimester of pregnancy, snoring is increased and the upper airway diameter is narrow compared with postpartum.[143] The severity of sleep apnea and the associated BP responses measured in the third trimester improve significantly ($P=0.03$) after parturition, further supporting the concept that pregnancy may exacerbate sleep apnea.[144]

To determine the interaction between OSA in patients with drug-resistant hypertension, defined as a clinic BP of ≥140/90 mm Hg while taking a combination of ≥3 antihypertensive drugs titrated to maximally recommended doses, Logan et al[145] noted that the prevalence of OSA, defined as an AHI of ≥10, was 83%. In another study,[146] sleep apnea was found to be an independent predictor of uncontrolled hypertension in patients <50 years of age. Increased aldosterone has been suggested as a possible contributor to resistant hypertension in sleep apnea.[83,147,148]

The weight of evidence has led the most recent Joint National Committee on the Detection and Management of Hypertension to identify OSA as an important identifiable cause of hypertension.[149]

Treatment of OSA: Effects on Hypertension

Effective treatment of OSA by CPAP has been shown to markedly and acutely decrease BP and sympathetic traffic during sleep.[71] Chronic effects of CPAP treatment are less clear because of the relative lack of robust longitudinal controlled studies. Many of the early studies had no control group or did not include 24-hour ambulatory BP recording. In an observational study of CPAP-treated versus CPAP-intolerant patients, no significant differences were evident in the development of new cases of hypertension in the treated versus untreated group.[150] In addition, short-term CPAP treatment in patients with well-controlled hypertension did not elicit any BP improvement.[151]

Recent studies have more often been placebo controlled,[152–154] comparing CPAP with either placebo pills or with sham CPAP. BP reduction is either modest or absent in normotensive subjects but may be more evident in hypertensives. Three studies reporting a fall in BP used subtherapeutic (sham) CPAP in the control arm. The largest of all the studies (118 patients)[155] reported a reduction of 3.4/3.3 mm Hg (slightly larger during the day than during the night). In patients taking antihypertensive drugs, the 24-hour mean BP fall was about twice as large (6.7 versus 3.3 mm Hg), and the benefit was greater in patients with more severe OSA. The second study[156] found that both placebo CPAP and real CPAP reduced daytime BP equally well but that only real CPAP lowered the nighttime pressure. The third study found that therapeutic CPAP lowered daytime BP by 10.3/11.2 mm Hg more than subtherapeutic CPAP and nighttime pressure by 12.6/11.4 mm Hg.[157] However, in another study comparing the effects of CPAP in hypertensives with and without OSA, CPAP lowered the nighttime pressure in those with OSA but had no effect on the daytime pressure.[158] A randomized placebo-controlled study of 1 month of therapeutic CPAP versus subtherapeutic CPAP on ambulatory BP showed no significant changes in systolic, diastolic, daytime, or nighttime BP.[159]

Finally, 3 meta-analyses of the effect of treating OSA with CPAP on BP have been published recently. One was restricted to trials involving ambulatory BP recordings,[160] the other to trials with treatment duration of >2 weeks. The second included OSA patients with heart failure and OSA patients with normal systolic function.[161] Overall, the net reduction in BP (≈2 mm Hg) was significant but modest. A third meta-analysis[162] included randomized controlled trials that reported systolic and diastolic BPs before and after CPAP/control and noted modest (≈1.5 mm Hg) decreases in both systolic BP ($P=0.23$) and diastolic BP ($P=0.06$). In 6 trials that evaluated more severe OSA (AHI >30), CPAP reduced systolic BP by ≈3 mm Hg ($P=0.10$) and diastolic BP by 2 mm Hg ($P=0.05$).

Considered together, these studies suggest that there are moderate and variable effects of CPAP on BP in patients with OSA. Patients with more severe OSA, difficult-to-control hypertension, and better CPAP compliance may have more substantial BP reduction with CPAP. The greater changes in BP seen in 1 study[157] may have a number of explanations: The duration of CPAP use was longer, the subjects were more hypertensive, and the device used to record BP may have caused less interference with sleep. CPAP also may improve BP control in patients with refractory hypertension.[163] In those hypertensive patients who cannot tolerate CPAP, oral appliances that effectively attenuate OSA also may lower BP.[164,165]

Treatment of Hypertension: Effects on OSA

It is likely that antihypertensive drugs will have different effects in patients with OSA, but there are few systematic data. Clonidine has been reported to suppress rapid eye movement (REM) sleep and hence to suppress the apneas occurring during REM, which resulted in lessened nocturnal hypoxemia.[166] Cilazapril, an angiotensin-converting enzyme

inhibitor, had no effect on the AHI but lowered BP during sleep,[167] whereas celiprolol, a β-blocker, decreased daytime BP but had relatively little effect during the night.[168] A comparison of the effects of 5 commonly used antihypertensive drugs (atenolol, amlodipine, enalapril, losartan, and hydrochlorothiazide) on BP and sleep architecture[169] showed no effect on the severity of the sleep apnea. The drugs had similar effects on daytime BP, although atenolol reduced the nocturnal pressure slightly more than the other drugs. Thus, there is no current evidence that any specific antihypertensive drug has direct effects on attenuating sleep apnea severity. Conversely, a recent report suggests that cough and rhinopharyngeal inflammation induced by angiotensin-converting enzyme inhibitors may worsen the AHI, which decreases after discontinuation of the drug.[170]

Heart Failure

Prevalence of OSA in Heart Failure

In 2 large case series, OSA was detected in 37% of 450[47] and 11% of 81[48] patients with heart failure resulting from systolic dysfunction who were referred for polysomnography. Only a minority of such patients complain of excessive daytime sleepiness.[48,49] The prevalence of OSA in heart failure was greater in men (38% versus 31%; $P<0.005$).[47] In men, the main risk factor for OSA was obesity, whereas in women, it was older age.[47]

However, these prior descriptions of disease frequency are limited by referral bias. To address this concern, Wang et al[171] performed a prospective study in which polysomnography was performed on all consenting patients newly referred to a tertiary hospital heart failure clinic for assessment and management. Of the 218 patients studied, OSA with an AHI ≥15 was detected in 26%. OSA also has been noted in >50% of heart failure patients with preserved systolic function.[172] Three months of CPAP was reported to attenuate abnormalities in diastolic function,[123] suggesting a potential etiologic role of OSA in diastolic heart failure.

OSA and the Origin and Progression of Heart Failure

The most direct mechanism by which long-standing OSA might induce left ventricular systolic dysfunction is by raising BP. Hypertension is the most common risk factor for ventricular hypertrophy and failure.[173] Nocturnal oxygen desaturation is an independent predictor of impaired ventricular relaxation during diastole.[174] In the Framingham study, increased BMI, an important predisposing factor for OSA, also was associated with greater risk of developing heart failure.[175]

It has been suggested that left ventricular hypertrophy is more closely linked to hypertension during sleep than during wakefulness.[176] Thus, the higher nocturnal BP in hypertensive patients with OSA than in those without[133] may place such individuals at greater risk in the long term for left ventricular hypertrophy and failure. In patients with heart failure, the coexistence of OSA may be associated with higher sympathetic nerve activity and higher systolic BP during wakefulness, despite more intense antihypertensive therapy.[177] Responses to cytokines, catecholamines, endothelin, and other growth factors produced in OSA also may contribute to ventricular hypertrophy independently of hypertension. Indeed, there is evidence to suggest that OSA is associated with altered cardiac structure and function[121,123,178,179] and that some of these changes may be reversible with effective CPAP treatment.

OSA could potentially contribute to the progression of heart failure through several pathological mechanisms: (1) by eliciting greater sympathetic outflow to the heart, kidney, and resistance vessels during wakefulness and sleep; (2) by increasing left ventricular afterload both acutely and chronically; (3) by inducing hypoxia and secondary increases in right ventricular afterload; and (4) by increasing the risk of myocardial infarction.[180] Recent studies using tissue Doppler imaging during dobutamine stress echocardiography have also raised the possibility that patients with OSA have depressed myocardial contractile reserve.[181] Finally, data obtained in heart failure patients with OSA, using cardiac C-11 acetate positron emission tomography, suggest a potential role for CPAP therapy in modulating myocardial energetics and metabolic efficiency in the failing heart.[182,183]

Heart failure patients with coexisting OSA are exposed to adrenergic activation during sleep[5] and when awake. BP rises above, rather than descends below, waking values.[184] Thus, myocardial oxygen demand increases at times of recurrent hypoxia. Consequent metabolic mismatch could directly reduce myocardial contractility.[185] These stresses may place the patient with OSA and heart failure at greater risk of myocardial ischemia,[186] worsening ventricular function, arrhythmias, and death.

The repetitive generation of up to −65 mm Hg intrathoracic pressure against the occluded pharynx induces striking hemodynamic and autonomic responses[120] and is a cardiac load unique to OSA.[187] When subjected to such abrupt increases in left ventricular transmural pressure (ie, afterload) and therefore myocardial oxygen demand, patients with systolic heart failure experience more profound and prolonged reductions in stroke volume[188] and greater reflex increases in central sympathetic outflow[189] than control subjects with normal left ventricular function. Because these obstructive events may occur hundreds of times over the course of the night, these abrupt increases in left ventricular transmural pressure could play an important role in the development of myocardial ischemia, myocyte slippage, contractile dysfunction, and ventricular dilation.[190]

However, yet to be established is whether OSA can cause heart failure. In addition, whether the presence of OSA in heart failure accelerates mortality remains unclear. In 78 patients with congestive heart failure being evaluated for possible heart transplantation, the presence of OSA did not affect long-term (52 months) survival.[191] On the other hand, more recent data suggest that the presence of untreated OSA (AHI >15) in patients with heart failure is associated with an increased risk of death compared with patients with an AHI <15 independently of confounding factors.[171]

Treatment of OSA: Effects on Heart Failure

OSA patients are advised to reduce weight and to abstain from alcohol and sedatives that predispose to pharyngeal collapse during sleep; these general measures may reduce the severity of heart failure and the severity of OSA.[192,193] There have been no

controlled studies of mandibular advancement devices or upper airway surgery involving OSA patients with heart failure. To date, randomized trials in heart failure have evaluated the impact of treating OSA on surrogate cardiovascular end points such as left ventricular ejection fraction rather than on hospitalization rates and mortality. Acutely, treatment of coexisting OSA by CPAP can eliminate recurrent hypoxia and reduce nocturnal BP and heart rate.[184] The first study to examine the effects of CPAP on left ventricular function during the awake state was uncontrolled. Eight patients with idiopathic dilated cardiomyopathy and coexisting OSA were studied. After 1 month of CPAP, mean left ventricular ejection fraction increased from 37% to 49% and dyspnea was reduced significantly,[187] but these responses dissipated within a week of withdrawal of CPAP. In the first randomized trial involving 24 patients with heart failure (mean left ventricular ejection fraction ≤45%) and moderate to severe OSA (mean AHI ≥20), 30 days of CPAP lowered daytime heart rate and systolic BP and increased ejection fraction by 9%. In contrast, there was no change in any of these variables in the 12 patients in the control group.[194] In a second larger randomized cohort with heart failure (mean left ventricular ejection fraction ≤55%) and OSA (mean AHI >5), there was a more modest 5% increase in ejection fraction after 3 months of CPAP treatment in the 71% of randomized patients who completed this trial.[195] Mean BP did not fall. It is notable, however, that a third randomized study, and the only one that used a crossover design, showed no effects of autotitrating CPAP compared with subtherapeutic CPAP on peak $\dot{V}O_2$, 6-minute walk distance, plasma catecholamines, or left ventricular ejection fraction, although there was a decrease in daytime sleepiness.[196] Differences in methodology and in patient characteristics may help explain some of the inconsistent findings from studies evaluating OSA treatment in congestive heart failure patients.[197] Recent observational data suggest a trend ($P=0.07$) to a lower mortality rate in heart failure patients with CPAP-treated OSA compared with untreated OSA.[171] However, whether CPAP treatment of patients with OSA and heart failure leads to mortality benefit has yet to be tested in a randomized clinical trial.[198]

Treatment of Heart Failure: Effects on OSA

Fluid retention in heart failure would be expected to potentiate airway obstruction. Prolonged recumbent posture, as occurs during sleep, would predispose to congestion of upper airway soft tissue structures. Consequent airway narrowing and increased airway resistance would require increased generation of negative intrathoracic pressures to maintain flow, thus theoretically predisposing to upper airway occlusion.[199] Indeed, in healthy volunteers, rapid displacement of ≈340 mL of fluid from the legs to the upper body, elicited by lower-body positive pressure, increased neck circumference and pharyngeal resistance to airflow, and reduced upper airway cross-sectional area.[200,201] Hence, decreased intravascular volume and attenuated venous congestion resulting from heart failure treatment could potentially reduce OSA severity. However, there is no systematic evidence that specific drugs used to treat heart failure have any direct influence on the severity of OSA,[169] apart from an increase in AHI reported in the setting of cough and airway inflammation with angiotensin-converting enzyme inhibitors.[170]

Stroke

The Prevalence of OSA in Stroke

Studies evaluating the prevalence of OSA in patients with stroke are inherently biased in terms of studying only stroke survivors. Other limitations include selection criteria such as evaluation only of those transferred to a rehabilitation unit. Furthermore, because vascular injury to the respiratory and other centers may precipitate CSA and/or OSA, poststroke sleep apnea characteristics cannot be assumed to have been present before stroke. Sleep breathing characteristics also may change significantly in the poststroke period.

Several studies have noted a high prevalence of sleep apnea in subjects studied shortly after stroke.[202,203] However, a recent study from Sweden noted that of 132 patients admitted for in-hospital rehabilitation who underwent overnight cardiorespiratory sleep monitoring, only 23 patients had OSA, 28 had CSA, and 2 patients had mixed apnea.[204] Body position is important in interpreting polysomnographic findings after stroke because poststroke AHI often is highest when patients are maintained in the recumbent position, especially within the first 24 hours of stroke.[205,206] Bassetti and Aldrich[206] found an AHI ≥10 in 62% of transient ischemic attack patients compared with 12% of control subjects, suggesting that SDB may precede the onset of stroke. This was not confirmed in a case-control study of 86 transient ischemic attack patients, in whom the likelihood of sleep apnea was similar to that in control subjects.[207]

OSA and the Origin and Progression of Stroke

The concept of sleep apnea as a risk factor for primary ischemic stroke is mostly inferential and derives from evidence implicating sleep apnea in hypertension and heart disease, both of which are risk factors for stroke. Mechanisms that have been implicated in any increased risk of stroke in OSA include BP swings, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, and prothrombotic and proinflammatory states. For example, blunted cerebral blood flow in response to hypoxia in patients with OSA has been described and has been reported to normalize after 4 to 6 weeks of CPAP therapy.[208] Epidemiological studies suggest that habitual snoring, a possible marker for OSA, is a risk factor for brain infarction independently of confounding factors such as obesity and age.[209] Similarly, excessive daytime sleepiness identified with the Epworth Sleepiness Score was significantly associated with stroke (OR, 3.07; 95% CI, 1.65 to 6.08) in a case-control study of 181 patients.[210] The authors suggested that daytime sleepiness was possibly the consequence of OSA. Some studies[211] noted a high prevalence of leukoaraiosis in those stroke patients who had sleep apnea, suggesting that OSA may lead to leukoaraiosis and consequently to stroke. In a cross-sectional study of Japanese men, brain magnetic resonance imaging revealed silent brain infarction in 25% of patients with moderate to severe OSA but in only 8% of patients with mild OSA and in 6% of control subjects, suggesting that OSA may

elicit early and asymptomatic cerebrovascular damage.[88] Available data often are limited by the use of oximetry rather than complete polysomnographic studies and by the relatively small numbers of subjects studied. Furthermore, the broad spectrum of comorbidities and pharmacological intervention in poststroke patients constrains identification of any independent premorbid etiologic role of sleep apnea.

In a cross-sectional analysis of >6000 subjects from the Sleep Heart Health Study, the OR of prevalent stroke was modestly greater (1.58) among those subjects with sleep apnea with an AHI ≥11.[57] More recent data obtained in large population samples have provided newer insights into sleep apnea as a potential cause of stroke. SDB with an AHI of ≥20 was associated with an increased risk of suffering a first-ever stroke over a 4-year follow-up in a cross-sectional analysis. However, in the prospective longitudinal analysis of these data, after adjustment for age, sex, and BMI, the OR was still elevated but no longer statistically significant (OR, 3.08; 95% CI, 0.74 to 12.81; $P=0.12$).[212]

Recent 10-year follow-up data of patients with stroke show an increased risk of death in those patients with OSA (adjusted hazard ratio, 1.76; 95% CI: 1.05 to 2.95; $P=0.03$) that is independent of age, sex, BMI, smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination Score, and Barthel Index of Activities of Daily Living. In contrast, CSA was not accompanied by increased poststroke mortality compared with control subjects (adjusted hazard ratio, 1.07; 95% CI: 0.65 to 1.76; $P=0.80$).[204] In an analysis of the effects of OSA on the composite outcome of stroke or death,[213] another study reported that increasing severity of sleep apnea was associated with an increased risk of stroke or death independently of age, sex, race, smoking, alcohol, BMI, diabetes, hyperlipidemia, atrial fibrillation, and hypertension. Although many patients were receiving some type of treatment for sleep apnea over the course of this observational study, the hazard ratio for those with severe OSA (AHI >36) was 3.3 (95% CI, 1.74 to 6.26).[213] This high risk of stroke or death even in the setting of apparent treatment for OSA suggests that the risk would have been even greater in the absence of treatment; an alternative that has to be considered is that treatment of OSA may have had only modest, if any, beneficial effects on the prevention of stroke or death.[214]

Treatment of OSA: Effects on Stroke

The application of noninvasive positive airway pressure ventilation offers patients with sleep apnea a window of opportunity to increase the rehabilitation potential after stroke. Unfortunately, CPAP compliance has not been good in patients recovering from stroke, and beneficial effects have not been confirmed.[215] Tolerability and compliance with CPAP after stroke may be limited compared with patients without stroke.[216] In a prospective study of patients after acute ischemic stroke, Bassetti et al[203] found that only 15% of those with sleep apnea continued CPAP chronically. On the other hand, Wessendorf et al[217] prospectively studied 105 stroke patients with OSA to evaluate the effectiveness and acceptance of treatment with CPAP. They found that 70% of patients continued treatment at home. The authors concluded that stroke patients with OSA can be treated effectively with CPAP and show improvement and acceptance similar to those of OSA patients without stroke. Whether patients with stroke and OSA benefit from treatment with CPAP remains to be determined.

Several studies suggest that OSA in the poststroke patient reduces motivation, decreases cognitive capacity, and may increase the risk of recurrent stroke and death. Dyken et al[218] noted that patients after stroke have a high prevalence of OSA and that those stroke patients with OSA had a markedly diminished poststroke survival. Similar findings regarding survival and limited rehabilitation success[219,220] have been reported by other investigators. Direct studies of the interaction between sleep apnea and rehabilitation outcome after stroke that used overnight pulse oximetry to evaluate the respiratory disturbance index suggested that hypoxic events during sleep predicted poorer recovery, especially in patients with poor function at admission. In polysomnographic studies of stroke patients in a rehabilitation unit, a high prevalence of sleep apnea, predominantly OSA, was accompanied by worse functional impairment and a longer time spent in hospital and rehabilitation.[221]

Effects of Stroke on Sleep Apnea

Immediately after an acute stroke, CSA may be more common than OSA[222] and may influence stroke outcome, whereas in the postacute recovery phase and during rehabilitation, OSA predominates.[220] The site of brain lesion, magnitude of injury, effects on upper airway tone, effects of supine posture during polysomnography, consequences of transient mental obtundation, and medications may have striking effects on the presence and severity of sleep apnea. The prevalence of sleep apnea several months after stroke, although still high, is less than that evident in the acute poststroke phase.[203]

Arrhythmias

Prevalence of Arrhythmias in Sleep Apnea

Cardiac arrhythmias are reportedly more frequent in persons with OSA and increase with the number of apneic episodes and the severity of the associated hypoxemia.[223–225] Nocturnal arrhythmias have been shown to occur in up to 50% of OSA patients. The most common arrhythmias during sleep include nonsustained ventricular tachycardia, sinus arrest, second-degree atrioventricular conduction block, and frequent (>2 bpm) premature ventricular contractions.[226–230] A tracheostomy can suppress these arrhythmias, except for premature ventricular complexes.[230] Controversy remains as to whether OSA is a primary etiologic factor for tachyarrhythmias because of the high incidence of cardiovascular comorbidities in persons diagnosed with OSA. However, recent data from the Sleep Heart Health Study, comparing 228 subjects with SDB and 338 subjects without SDB, suggested that those with severe SDB had a 2- to 4-fold-higher risk of nocturnal complex arrhythmias. Even after adjustment for age, sex, BMI, and prevalent coronary artery disease, patients with SDB had increased likelihoods of atrial fibrillation (OR, 4.02; 95% CI, 1.03 to 15.74), nonsustained ventricular tachycardia (OR, 3.40; 95% CI, 1.03 to 11.20), and complex ventricular ectopy (OR, 1.74; 95% CI, 1.11 to 2.74).[231]

Bradyarrhythmias. Prolonged apnea and hypoxemia in OSA elicit the diving reflex, which results in cardiac vagal activa-

tion, with simultaneous sympathetic activation to the peripheral blood vessels, including muscle, renal, and splanchnic but not cerebral vasculature.[232–234] Although the vagal response often will elicit a discernible bradycardia, in a minority of OSA patients (perhaps ≈10%), bradyarrhythmias such as atrioventricular block and asystole may develop, even in the absence of cardiac conduction disease. These are most likely to occur during REM sleep and with a drop in oxygen saturation of at least 4%.[226,235] Electrophysiological characteristics of the sinus node and atrial conduction system in OSA subjects with nocturnal bradyarrhythmias were normal or nearly normal while awake, and CPAP reversed the bradyarrhythmias, suggesting that OSA may have induced the arrhythmias.[234,236,237] First-line treatment of bradyarrhythmias in the setting of obstructive apneas and normal conduction would consist of treatment of OSA. Data emerging from the European Multi-Center Polysomnographic Study show a remarkably high prevalence (59%) of sleep apnea syndrome in patients with pacemakers.[238] Pacemakers were reprogrammed 12 to 24 hours before polysomnography to promote spontaneous atrial and ventricular rhythm with respect to individual indications for pacing. Sleep apnea syndrome was evident in 68% of patients with atrioventricular block. The authors raised the question of whether primary treatment of sleep apnea would have changed the need for pacing in some of these patients, noted that their patients were less symptomatic than typical sleep apnea syndrome patients, and suggested that paced patients should be systematically evaluated for sleep apnea because of its potential detrimental cardiovascular effects.

Atrial Fibrillation. Hypoxemia, sympathetic activation, pressor surges, transmural pressure changes, and systemic inflammation that occur in OSA also may be mechanisms that predispose to the development of atrial fibrillation. Data from Framingham[239] and from the Danish Diet, Cancer and Health Study[240] examining independent predictors of atrial fibrillation found obesity to be an important marker. Sleep apnea was not accounted for in either of these studies. However, after adjustment for left atrial enlargement in the Framingham data, the effects of obesity were no longer significant.[239] Sleep apnea has been associated with left atrial enlargement.[121,122] That OSA leads to atrial fibrillation is an appealing but presently unproven hypothesis. In a retrospective cohort study of >3500 adults without past or current atrial fibrillation who underwent complete overnight polysomnography, both obesity and nocturnal oxygen desaturation were independent predictors of incident atrial fibrillation, but only in subjects ≤65 years of age.[66]

Continuous cardiac monitoring with an implanted atrial defibrillator showed that episodes of persistent atrial tachyarrhythmias in OSA patients are more likely to occur at night.[241] Postoperative atrial fibrillation also may be more likely to occur in patients with OSA.[242] An estimated 50% of atrial fibrillation patients presenting for cardioversion are likely to have OSA compared with an ≈30% likelihood of OSA in a general cardiology clinic population.[243] The role of atrial fibrillation in any increased risk of stroke in patients with OSA remains to be determined.[214]

Ventricular Arrhythmias. Ventricular arrhythmias, primarily premature ventricular contractions, have been reported in up to 66% of patients with sleep apnea, which is significantly higher than the rates reported in persons without sleep apnea (0% to 12%).[226,227] However, there are no conclusive data demonstrating a primary etiologic role for OSA in ventricular arrhythmias.

In most OSA patients, ventricular arrhythmias appear most often during sleep, with the greatest frequency occurring during apneic periods.[244–246] This is a very different pattern of ventricular arrhythmia distribution compared with individuals without OSA. Recent data suggest that in heart failure patients with OSA and in normal sinus rhythm, ventricular ectopic beats occur more frequently during the apneic phases than during hyperpnea.[247] This is in contrast to those patients with CSA, in whom ventricular ectopy was noted to occur more frequently during hyperpneas than apneas. Although investigators may disagree on whether OSA patients without coexisting cardiovascular disease are more susceptible to ventricular arrhythmias compared with the non-OSA patient population, there is a perception that ventricular arrhythmias are most likely to occur in persons with the more severe forms of OSA and comorbid cardiovascular diagnoses.[248] In the Sleep Heart Health Study, a significant relationship was noted between SDB and nocturnal ventricular ectopy ($P<0.0003$) when it was considered a continuous outcome.[231]

The mechanisms by which OSA induces ventricular arrhythmias are uncertain. However, hypoxemia, bradyarrhythmias, and sympathetic activation induced by apneic events may play important roles. In one of the few studies to identify a specific hypoxemia level and link it to ventricular ectopy, Shepard et al[246] found an increase in the frequency of premature ventricular beats when oxygen saturations fell intermittently below 60%.

Treatment of Sleep Apnea: Effects on Arrhythmias

There are no conclusive epidemiologic or longitudinal intervention studies relating specifically to prevalence, severity, and consequences of cardiac arrhythmias and effects of OSA treatment. For bradyarrhythmias certainly, apneic events may be a primary cause in the absence of other coexisting pathology. Note, however, that bradyarrhythmias have been reported in REM sleep even in healthy young subjects.[249] If the underlying cardiac conduction system is normal and there is no significant thyroid dysfunction, bradyarrhythmias or heart block, both of which occur during apneic periods, may be treated effectively with CPAP or, if necessary, with tracheostomy.[230,244,245,250] Observational data suggest that the presence of untreated OSA in patients after successful cardioversion for atrial fibrillation is associated with an 82% risk for recurrence of atrial fibrillation within 1 year, about double the risk seen in effectively treated OSA patients after cardioversion.[251] Treatment of OSA may decrease the incidence and severity of ventricular arrhythmias.[244,245] In a randomized controlled trial of 1-month duration involving patients with OSA and systolic dysfunction, abolition of OSA by CPAP resulted in a 58% reduction in the frequency of ventricular premature complexes during sleep and a parallel reduction in nocturnal urinary norepinephrine concentrations.[252]

Treatment of Arrhythmias: Effects on Sleep Apnea

An initial report of atrial overdrive pacing in patients with pacemaker implantation[253] for bradyarrhythmia demonstrated a 50% reduction in obstructive apneas (from 6 to 3 per hour) and generated considerable interest in the concept of overdrive pacing for the treatment of OSA. However, this finding has not been replicated in subsequent investigations involving somewhat different patient populations.[254–256] In a study comparing atrial overdrive pacing with CPAP, at both 24 hours and 1 month after initiation of treatment in patients with OSA, atrial overdrive pacing had no significant effect on OSA severity, whereas CPAP was highly effective in treating OSA.[257] A prospective, single-blinded, randomized crossover trial of overnight temporary atrial pacing at 75 bpm in patients with moderate to severe OSA also showed that pacing did not significantly affect the AHI or the minimum nocturnal oxygen saturation.[258] Recent data confirm that despite a mild effect of atrial overdrive pacing on respiratory events in some heart failure patients with OSA, compared with CPAP, atrial overdrive pacing was not therapeutically effective in improving SDB.[259] There is currently no definitive evidence to support atrial overdrive pacing as a treatment option for OSA.

Myocardial Ischemia and Infarction

Prevalence of Sleep Apnea in Coronary Artery Disease

The prevalence of SDB in coronary artery disease patients has been shown to be up to 2-fold greater than in non–coronary artery disease subjects.[260–263]

Evidence That OSA Contributes to the Origin and Progression of Coronary Artery Disease

Severe intermittent hypoxemia, acidosis, increased BP, and sympathetic vasoconstriction, in conjunction with simultaneous changes in intrathoracic and cardiac transmural pressures, all argue compellingly for obstructive apneas as a potential trigger for cardiac ischemia. In the longer term, the cardiac and vascular disease mechanisms described earlier, including endothelial dysfunction and systemic inflammation, may promote structural coronary artery damage. In a study of >200 consecutive patients without a history of coronary artery disease who underwent electron-beam computed tomography within 3 years of polysomnography, the median coronary artery calcification score (Agatston units) was 9 in OSA patients and 0 in non-OSA patients ($P<0.001$).[264] Median calcification score increased as OSA severity worsened (P for trend by AHI quartile <0.001). Multivariate analysis confirmed an independent association between OSA and subclinical coronary artery disease, as measurable by coronary artery calcification.

Sleep apnea has been implicated in patients with nocturnal angina pectoris. Nocturnal angina and ST depression are diminished during treatment of sleep apnea by CPAP.[186,265] Similarly, Hanly et al[266] noted the ST depression occurred in about a third of patients with severe OSA. ST depression was markedly attenuated during nasal CPAP. However, these patients did not have proven coronary artery disease, and artifactual ST changes related to breathing patterns may have contributed. In patients with established coronary artery disease and moderate or severe OSA (AHI >15), there was no evidence of nocturnal myocardial injury detectable by measurements of cardiac troponin T.[267]

In longer-term studies, SDB in patients with coronary artery disease was associated with a significant increase in the composite end point of death, myocardial infarction, and cerebrovascular events at a 5-year median follow-up interval.[268] This composite end point occurred in 28% of men with SDB and in 16% of men without SDB. The corresponding percentages for women were 20% and 14%. However, neither oxygen desaturation index nor AHI was independently predictive of single end points of myocardial infarction or death.[268] In a case-control study, there was a graded increase in the odds of acute myocardial infarction with increased sleep apnea severity, even after adjustment for possible confounding factors.[269] A recent study of >500 subjects reported that people with OSA are more likely than those without OSA to have a family history of premature death from coronary artery disease independently of gender, BMI, and personal history of coronary artery disease (OR, 2.13; 95% CI, 1.04 to 4.66; $P=0.046$).[270]

Although much is known about the association between sleep apnea and stroke, arrhythmias, coronary artery disease, and myocardial ischemia and infarction, the data provide mostly observational, albeit valuable, insights. Although longitudinal data regarding independent effects of sleep apnea on stroke, cardiac ischemia, and lethal ventricular arrhythmias are limited, recent evidence suggests that in patients experiencing sudden cardiac death, those proven to be free of OSA have the greatest likelihood of death between 6 and 11 AM, the traditional window of cardiovascular vulnerability.[271] In striking contrast, more than half of sudden cardiac deaths in patients with proven OSA occur during the sleeping hours, between 10 PM and 6 AM. Thus, OSA appears to affect the timing of sudden cardiac death; however, it is not yet known whether OSA increases the overall risk of sudden cardiac death.

Treatment of OSA: Effects on Myocardial Ischemia and Infarction

An observational study suggested that in patients with combined OSA and coronary artery disease, treatment of OSA was associated with a decrease in the occurrence of new cardiovascular events.[272] A second prospective observational study assessed the incidence of fatal and nonfatal cardiovascular events in healthy men, snorers, and patients with treated and untreated OSA. In men with severe untreated OSA (AHI >30), both fatal and nonfatal cardiovascular events were markedly increased. In contrast, fatal and nonfatal cardiovascular events in treated OSA patients approached levels seen in simple snorers.[180] In a third observational study comparing cardiovascular outcomes in 107 CPAP-treated and 61 CPAP-intolerant patients, total cardiovascular deaths were more common in the untreated group ($P=0.0009$).[150] Several mechanisms and even benefits from intervention have been inferred from the available observational data.[273] However, there are no randomized trials of the effects of treatment of OSA on risk of developing coronary artery disease, risk of myocardial infarction, or risk of cardiovascular death.

Treatment of Coronary Artery Disease: Effects on Sleep Apnea

Although anecdotal reports from patients' spouses describe marked changes in sleep patterns, snoring severity, and witnessed apneas after bypass surgery and sometimes even after angioplasty, this phenomenon awaits more comprehensive study. Any improvement in left ventricular function from relief of cardiac ischemia could potentially attenuate airway obstruction and CSA, as discussed earlier.

Pulmonary Arterial Hypertension

The Prevalence of OSA in Pulmonary Arterial Hypertension

There are frequent episodes of increased pulmonary artery pressure during sleep in patients with OSA. It is less certain whether daytime pulmonary arterial hypertension also occurs in patients who do not have coexisting pulmonary or heart disease. Most of the studies that have addressed this question have used echocardiography to estimate pulmonary artery pressure, but some have used more precise right heart catheterization. In 1 series of 220 consecutive patients with OSA and an AHI >20, pulmonary arterial hypertension (mean arterial pressure >20 mm Hg) was found in 17% of patients.[274] However, it was relatively mild (only 2 of 37 patients had a pulmonary artery pressure >35 mm Hg). These patients also tended to be more obese and to have hypoxemia and hypercapnia while awake, and some may have had underlying chronic obstructive pulmonary disorder. Other smaller series of patients with OSA but no clinical history of chronic obstructive pulmonary disorder have reported daytime pulmonary arterial hypertension in 20% to 42% of cases.[275–277]

OSA and the Origin and Progression of Pulmonary Arterial Hypertension

The most likely primary mechanism for any OSA-related pulmonary arterial hypertension is hypoxemia, which is known to reflexively induce an acute increase in pulmonary arterial pressure.[278,279] However, there is debate as to whether OSA can be a primary cause of sustained pulmonary arterial hypertension. The most direct evidence comes from observations that treatment of OSA with CPAP may lower daytime pulmonary artery pressure.[280] The pulmonary arterial hypertension seen in association with OSA is generally mild and can be attributed to an elevated pulmonary vascular resistance because cardiac output and capillary wedge pressure are normal, at least at rest.[274] Pulmonary hypertensive OSA patients appear to have increased pulmonary vascular reactivity to hypoxia compared with patients without pulmonary arterial hypertension,[281] and CPAP has been reported to decrease pulmonary vascular reactivity to hypoxia.[280] An unresolved issue is whether nocturnal hypoxemia can lead to daytime pulmonary arterial hypertension or whether daytime hypoxemia, which is commonly observed in these patients, also is required. Two confounding factors that may contribute to daytime hypoxemia are severe obesity (obesity-hypoventilation syndrome) and chronic obstructive pulmonary disorder in association with OSA (the so-called overlap syndrome).[281] Thus, despite acute nocturnal increases in pulmonary artery pressure associated with obstructive apneas, proof that OSA causes pulmonary arterial hypertension has been limited by obesity, technical concerns regarding noninvasive measurements of pulmonary artery pressure in obese OSA patients, comorbidities and medication use in this population, and difficulties in identifying suitable control subjects.[6] Nevertheless, the most recent clinical classification of pulmonary hypertension identifies SDB in the category of respiratory disorders associated with pulmonary hypertension.[282]

Treatment of OSA: Effects on Pulmonary Arterial Hypertension

Sleep studies are probably an appropriate part of the evaluation of the patient with pulmonary arterial hypertension.[283] When elevated in patients with OSA, pulmonary artery pressures have been reported to fall after treatment with CPAP.[280,284,285] In an early study of 6 patients with OSA, tracheostomy was associated with marked declines in pulmonary artery pressure measured during sleep.[286] However, other studies have found less consistent changes, but in many patients, the pulmonary artery pressure was normal before CPAP was begun.[287] In a recent randomized crossover study of 12 weeks of effective versus sham CPAP in 23 patients with OSA, effective CPAP was associated with decreases in echocardiographic measurements of pulmonary artery systolic pressure.[288] Two patients who could not tolerate therapeutic CPAP were excluded from analysis. Pulmonary artery pressures were especially reduced in those patients with pulmonary hypertension or left ventricular diastolic dysfunction at baseline. Larger randomized studies are needed to identify more definitively any sustained effects of CPAP therapy on pulmonary hypertension and right heart function and to better establish any role for CPAP as one of the rapidly evolving therapeutic options for pulmonary hypertension.

End-Stage Renal Disease

Prevalence of OSA in End-Stage Renal Disease

Excessive daytime sleepiness is reported by most patients with end-stage renal disease (ESRD). The general area of sleep disorders in ESRD has been reviewed recently by Perl and colleagues.[289] ESRD patients often exhibit a mixed SDB pattern with both obstructive and central components.[290–292] When studied by polysomnography in a few small series of selected subjects, the prevalence of OSA in ESRD ranged from 40% to 60%.[290–292]

OSA and the Origin and Progression of ESRD

The most direct mechanism by which long-standing OSA might contribute to the origin of ESRD is by inducing chronic elevations in BP. OSA could further contribute to the progression of ESRD by acutely increasing sympathetic nerve discharge directed at the kidney and other vascular beds, raising BP during episodes of upper airway occlusion, and chronically accelerating the progression of renal damage,[293,294] with sustained elevations in BP during the awake state.[295,296] OSA has also been linked to glomerular hyperfiltration.[297] Whether OSA is an independent predictor of proteinuria is controversial.[298,299]

Importantly, coexisting OSA may increase the likelihood of cardiovascular complications, which are the principal

cause of morbidity and mortality in ESRD patients.[295,300] For example, in the ESRD population, systemic hypertension,[301] increased sympathetic activity,[302] nocturnal hypoxemia,[303] and left ventricular hypertrophy[304] may independently increase the risk of subsequent cardiovascular events. Furthermore, the frequency of arousal from sleep resulting from periodic limb movements also may be associated with premature mortality.[305]

Treatment of OSA: Effects on ESRD

Whether treatment of OSA affects the progression of renal disease is not known.

Treatment of ESRD: Effects on OSA

Although ESRD patients have a high prevalence of OSA, uremia itself may contribute independently to the pathophysiology of OSA by destabilizing central ventilatory control and causing edematous upper airway narrowing,[290] and increased pharyngeal resistance to airflow.[200,201] Although there are case reports of resolution of sleep apnea after renal transplantation,[306,307] the prevalence of OSA in ESRD patients remains similar before and after the introduction of peritoneal or conventional hemodialysis.[308] However, it would appear that the severity of OSA can be attenuated with nocturnal[309] or more aggressive dialysis. When 14 ESRD patients were studied before and after conversion to nocturnal home hemodialysis, which increases both the dose and frequency of dialysis by performing this procedure 6 nights per week for 6 to 8 hours per night, there was a marked reduction in the average AHI from 25±25 to 8±8. Seven of these patients were found to have OSA, with an AHI >15 while on conventional dialysis. Institution of nocturnal home hemodialysis led to significant increases in minimum and mean O_2 saturation during sleep. Nocturnal heart rate also fell.[310] A reduction in the volume of extracellular fluid in the upper airway was proposed as a mechanism to explain the alleviation of OSA.[309] Recent data support the concept that nocturnal peritoneal dialysis is superior to chronic ambulatory peritoneal dialysis in attenuating sleep apnea as a result of better fluid clearance during sleep.[311]

Treatment Options in OSA

Obesity is the single most important cause of OSA. Weight loss can lead to a decrease in AHI, improved sleep efficiency, decreased snoring, and improved oxygenation. The most dramatic results have been reported with surgical weight loss.[312–314] In addition, apnea often is worse in the supine posture, with some patients having OSA only in that position.[315,316] For patients with "positional apnea," behavioral techniques aimed at keeping the patient in the lateral posture during sleep (an uncomfortable object sewn into the back of the nightshirt or positional alarms) may offer benefit.

CPAP, applied via a nasal mask, continues to be the primary therapy for patients with OSA.[59,60] The device consists of a mask connected to a blower that maintains positive airway pressure at the desired level, acting as a pneumatic splint for the pharyngeal airway.[317,318] The prescribed CPAP pressure is generally determined in the sleep laboratory as that pressure required to eliminate all snoring, apneas, and hypopneas during all sleep stages and in all body positions. There is evidence supporting improvements in measures of OSA, daytime sleepiness, and neurocognitive function with nasal CPAP.[319–324]

Despite the effectiveness of CPAP in treating OSA, adherence to therapy continues to be a major problem.[325,326] This relates primarily to the facial interface (mask) and the pressure required to prevent airway collapse, with some patients finding CPAP intolerable. Most evidence suggests that proper introduction of and education regarding CPAP, in both the sleep laboratory and the physician's office, are important. Proper humidification of the inspired air, careful selection of the appropriate mask, and the addition of a pressure ramp all may improve compliance. In addition, the use of bilevel positive airway pressure (higher pressure on inspiration than expiration) or a constantly adjusting, autotitrating device may improve patient acceptance.

When CPAP proves unacceptable, oral appliances should be considered. Most such appliances lead to anterior mandibular repositioning, which acts by pulling the lower jaw (and thus the tongue) forward, thereby enlarging the pharyngeal airway.[327,328] With the adjustable devices, anterior displacement is minimal at first but is increased slowly over weeks until snoring and OSA are relieved or until side effects (primarily temporal mandibular joint pain) occur. Most need to be custom prepared by a dentist with considerable experience in the use of these devices. A recent analysis by the American Academy of Sleep Medicine reported oral appliances to be preferred over CPAP by many patients and to be successful in improving snoring, but only 52% were successful at relieving OSA (AHI <10).[329]

Surgery continues to be a viable approach to apnea therapy in some patients, with most procedures designed to enlarge the pharyngeal airway or bypass the obstruction.[330] Tracheostomy was the first surgical procedure used in the treatment of apnea and, although effective, is rarely performed now because of its social stigma and discomfort.[62] Uvulopalatopharyngoplasty was the first procedure introduced to enlarge the posterior pharyngeal airspace and to prevent airway collapse during sleep. However, efficacy has been somewhat limited.[331] A modified uvulopalatopharyngoplasty procedure using a CO_2 laser in the outpatient setting, called laser-assisted uvuloplasty, appears also to be of limited efficacy in the treatment of apnea.[332]

There are currently no widely applicable, effective medical therapies for OSA, except the treatment of predisposing factors such as hypothyroidism and acromegaly; treating the underlying condition can significantly improve the AHI.[333] No therapy for sleep apnea is easily accomplished and acceptable to all patients. Nevertheless, OSA should be considered a treatable condition. Therapy must be individualized on the basis of the severity of the disease, patient preferences, and anatomy of the upper airway.

Central Sleep Apnea

Epidemiology

The cause of CSA, apart from its occurrence as a prevalent comorbid condition of heart failure, stroke, and late-life aging,[15,334] is not completely understood. The prevalence of

CSA in the general population has been estimated in 2 population cohorts. In a southern Pennsylvania cohort, CSA at a severity level of ≥20 apneas per hour (central apnea index [CAI] ≥20) was not seen in men <65 years of age or women of any age.[44,45] In men >65 years of age, the prevalence was 5%. For CAI ≥2.5, the prevalence estimates for men in groups 20 to 44, 45 to 64, and 65 to 100 years of age were 0%, 1.7%, and 12%, respectively. The steep rise in CSA with older age was accompanied by a decrease in severity of OSA. In the Sleep Heart Health Study, in which age ranged from 40 to 97 years, the prevalence of CAI ≥1 was 9%.[335] Regardless of the threshold used, prevalence was higher in those with diabetes compared with those without diabetes; eg, for CAI ≥4, prevalence was 2.5% and 1.6%, respectively.[336] The demographics and other correlates of CSA in the general population have not been characterized.

A high frequency of CSA in heart failure, left ventricular dysfunction (even in the absence of overt heart failure), and stroke has been widely noted.[11,46,334,337] For reasons yet to be elucidated, fewer women with heart failure have CSA.[47,49,338,339] CSA defined by a CAI ≥15 was found in 40% of a sample of 81 male heart failure patients unselected for sleep apnea symptoms,[48] in 29% of 450 patients referred for polysomnography from a heart failure clinic,[47] and in 21% of 218 patients referred subsequently from the same clinic in a prospective survey.[171] Compared with heart failure patients with OSA, those with CSA may be more likely to be male and older and to have a lower BMI[47,334] and a higher pulmonary capillary wedge pressure.[340] Little is known about risk factors for CSA in persons without heart failure, and data on the prevalence and characteristics of CSA in other types of cardiovascular disease are sparse.

Clinical Presentation

There are considerably fewer published reports on patients with CSA. Patients with heart failure and CSA may complain of paroxysmal nocturnal dyspnea and frequent nocturnal arousals and awakenings. CSA may manifest in the typical crescendo/decrescendo pattern of CSR. However, snoring, excessive daytime sleepiness, and obesity are less common than in patients with OSA. Compared with heart failure patients without CSA/CSR, heart failure patients with CSA/CSR were more likely to be older (>60 years of age) and male and to have atrial fibrillation, lower arterial P_{CO_2} (≤38 mm Hg),[47] and heightened sensitivity to CO_2.[36] Oscillatory breathing patterns evident in heart failure patients during wakefulness[341] and exercise[38,342] also may predict both the presence of CSA and poorer prognosis.[39] Thus, in patients with heart failure and ≥1 of these characteristics, a diagnosis of CSA/CSR should be strongly considered, and a careful sleep history should be obtained. If sleep apnea is suspected (frequent arousals and awakenings, witnessed apnea, or paroxysmal nocturnal dyspnea), diagnostic polysomnography should be considered.

Mechanisms of Disease and Associated Cardiovascular Risk

Patients with asymptomatic left ventricular dysfunction and CSA have evidence for greater cardiac electric instability compared with patients with asymptomatic left ventricular dysfunction without CSA.[337] In patients with heart failure, high levels of resting sympathetic drive increase even further during episodes of central apnea.[343] Urine and plasma norepinephrine levels and muscle sympathetic nerve traffic during wakefulness are greater in heart failure patients with CSA compared with those without CSA.[177,344] However, it has been proposed that heightened sympathetic drive in heart failure patients with CSA may simply be a consequence of more severe heart failure rather than a direct consequence of CSA.[345] The role of inflammatory and other mechanisms in CSA remains unclear, in contrast to OSA, in which hypoxemia is usually more severe. Clarification of these mechanisms is especially difficult because of the multiple other comorbidities and medications that may influence these measurements in heart failure patients.

CSA in Heart Failure

Although OSA has been identified as a possible independent risk factor for the development of heart and vascular disease, CSA more often is a consequence of such cardiovascular illness, although it can occur even in healthy subjects, especially at altitude. CSA/CSR is characterized by oscillation of tidal volumes resulting in P_{aCO_2} levels below the apneic threshold. Increases in the respiratory rate, or hyperventilation, seen in association with heart failure or stroke produce P_{aCO_2} levels below the threshold, leading to suppression of central nervous system stimulation to the respiratory muscles and hence to central apnea. The overall mechanisms underlying CSA are complex and include chemoreflexes, pulmonary congestion, increased cardiac filling pressures, and prolonged circulation time.[346–348]

It is not yet known whether CSA is an epiphenomenon in the setting of heart failure or whether it may itself lead to increased risk or progression of heart failure.[337,339,349,350] In a study from Lanfranchi and colleagues,[339] a variety of baseline patient characteristics, including New York Heart Association class, left ventricular ejection fraction, and exercise capacity (determined by metabolic exercise testing), predicted mortality in a group of heart failure patients. Left atrial area and the AHI emerged as the 2 most potent predictors of mortality. On average, nonsurvivors had an AHI that was 2-fold higher than survivors. In particular, an AHI of >30 was associated with very poor outcome, especially in the setting of left atrial enlargement. Thus, the structurally abnormal heart may be less able to tolerate repetitive nocturnal apneas. Other studies also suggest that the higher rates of death and cardiac transplantation seen in patients with heart failure are proportional to the frequency of central apneic events[349] and that, along with CSA, other variables predicting survival include low diastolic BP and severe right ventricular dysfunction.[351] OSA and CSA also may coexist in patients with heart failure. In 12 heart failure patients with primarily OSA at the onset of sleep, lung-to-ear circulation time rose, P_{CO_2} fell, and OSA converted to CSA over the course of a single night.[352] A similar progression from predominantly OSA to predominantly CSA has been observed over a 1-month time frame in conjunction with a decrease in nocturnal P_{CO_2} and an increase in periodic breathing cycle length.[353]

Treatment Options in CSA

Because no randomized trials of therapy for CSA in heart failure have established a significant benefit with respect to hospitalization or mortality, there is no consensus as to whether CSA should be treated and, if so, what the optimal therapeutic strategy may be. However, it seems clear that optimizing management of the heart failure can improve CSA. The introduction of angiotensin-converting enzyme inhibition can lower the AHI and reduce the nocturnal desaturation of patients with mild to moderate heart failure.[354] Diuresis with a reduction in cardiac filling pressure also has been shown to reduce the severity of CSA,[340] but in some patients, the resulting metabolic alkalosis may promote CSA by narrowing the difference between ambient $Paco_2$ and the $Paco_2$ threshold for apnea.[355,356] β-Adrenergic blockade, which counters excess sympathetic activation and may modulate ventilatory responses in heart failure,[18] has been reported to decrease AHI in patients with CSA.[357] However, the increasing use of such antagonists in heart failure appears not to have altered the prevalence of CSA in this condition.[171] Should CSA persist despite intensified heart failure therapy, other interventions may be considered.

Nocturnal supplemental O_2 has been shown to abolish apnea-related hypoxia, to alleviate CSA, to decrease nocturnal norepinephrine levels over periods of 1 night to 1 month,[291,358,359] and to increase maximum O_2 uptake during a graded exercise test.[360] However, when administered for 1 month, O_2 had no impact on cardiac function or quality of life.[359] Long-term effects on cardiovascular end points have not been evaluated.

In a 5-day trial, theophylline reduced the severity of CSA but did not cause any improvements in right or left ventricular ejection fraction, quality of life, or clinical variables.[361] The potential adverse consequences of this positive inotropic and proarrhythmic agent preclude recommending it at this time for long-term use in patients with advanced heart failure. In a recent randomized, placebo-controlled, double-blind crossover protocol, a single dose of acetazolamide before sleep reduced CSA and attenuated related daytime symptoms.[362] However, at present, there is no evidence to support the long-term use of acetazolamide to suppress CSA.

In randomized trials of 1 day's to 3 months' duration, several forms of noninvasive positive airway pressure, including CPAP, bilevel, and adaptive pressure support servoventilation, have been shown to alleviate CSA in heart failure patients.[363–365] In patients with CSA, short-term application of CPAP reduced the frequency of ventricular ectopic beats.[245] In randomized trials, nightly application of CPAP for 3 months increased left ventricular ejection fraction, reduced mitral regurgitation and nocturnal urinary and daytime plasma norepinephrine, and improved quality of life.[363,366] Of 29 patients with heart failure and CSA who participated in a randomized trial of CPAP, those who complied with this intervention experienced a significant reduction in the combined rate of mortality and cardiac transplantation over a 5-year period, although intention-to-treat analysis did not show significant benefit of CPAP treatment.[367] Another prospective study used a randomized parallel design in treating CSR in heart failure patients, comparing 1 month of therapeutic and subtherapeutic adaptive servoventilation.[368] Twenty-six patients completed the trial. Active treatment attenuated daytime sleepiness ($P=0.014$), the primary end point. Although significant decreases in secondary end points of plasma brain natriuretic peptide ($P=0.001$) and urine metadrenaline ($P=0.018$) were noted, urine metnoradrenaline did not fall ($P=0.19$).

In a multicenter, randomized trial involving 258 patients with heart failure and CSA (the Canadian Positive Airway Pressure Trial for Patients With Congestive Heart Failure and Central Sleep Apnea [CANPAP]),[338] the application of CPAP reduced nocturnal desaturation and caused a modest but significant improvement in ejection fraction. However, the primary results of CANPAP also raised the possibility of early harm from CPAP, with early divergence of transplantation-free survival (the primary end point) favoring the control group ($P=0.02$). After a mean follow-up period of 2 years, the primary outcome of combined mortality and cardiac transplantation was identical in the treated and control groups. Hospitalization rates also were unaffected by CPAP. Unfortunately, despite only a 15% dropout rate in both arms, this trial was severely underpowered owing to a marked decline in the annual event rate as advances in medical and device therapy of heart failure were incorporated into standard clinical practice. The concerns listed above contributed to early termination of CANPAP, and the role of CPAP in heart failure patients with CSA must now be questioned.

The potential implications of the CANPAP findings are addressed in a recent and informative debate.[369,370] Issues of compliance and efficacy may be relevant. At 1 year, CPAP was used for 3.6 hours per night and attenuated AHI by 50%, indicating only a partial reduction in "apnea burden." Better-tolerated and more effective treatment of CSA might have resulted in improved survival.[214,371,372] In any event, at this time, CPAP should not be routinely considered as standard therapy for CSA in heart failure patients. Furthermore, the results of the CANPAP study should not be extrapolated to heart failure patients with OSA, which is much more effectively suppressed by CPAP.[194,214]

The limited effects of atrial overdrive pacing on CSA, including in patients with heart failure, have been discussed earlier. Some data suggest a role for cardiac resynchronization therapy (CRT). In a small, nonrandomized trial of patients with a mean left ventricular ejection fraction of 24%, left bundle-branch block, and CSA, CRT lowered the AHI from 19.2 to 4.6,[373] reduced the desaturation index, and shortened the apnea-hyperpnea cycle length, a surrogate for improved cardiac output, by 25%. In another report of patients already on CRT, discontinuation of pacing resulted in increased CSA severity within 1 day, with attenuation of CSA on the following night when CRT was resumed.[374] Changes in CSA appeared to be associated with CRT-induced changes in mitral regurgitation. Further studies are required to confirm these early results, to determine the mechanism(s) by which CRT might improve CSA, and to identify which CSA patients with heart failure would benefit from such interventions.

In summary, although CSA has been associated with increased mortality in heart failure patients, a causal role for CSA in the morbidity and mortality of heart failure awaits

more definitive evidence. A number of treatment strategies for CSA have been tested, but presently none is ideal with respect to both efficacy and tolerance, nor has any available therapy been demonstrated to improve survival.

OSA in Children

Childhood SDB encompasses children with OSA syndrome, the syndromes of central hypoventilation, and disorders of respiratory muscles. Children with comorbid conditions such as those with genetic syndromes that may alter airway anatomy, central control of breathing, or respiratory muscle function represent a large percentage of children presenting to pediatric sleep centers with SDB. Most published reports on the cardiovascular morbidity of childhood SDB have included children with various forms of SDB and comorbid conditions. This descriptive literature helped establish a link between SDB and cardiovascular disease in children but has limited the ability to estimate in the general population the cardiovascular risk from each form of SDB.

OSA in children frequently is due to adenotonsillar hypertrophy with airway narrowing, with only a modest role for obesity. Adenotonsillectomy often is an effective treatment. In a recent longitudinal study of serial polysomnography in children after adenotonsillectomy (at 6 weeks, 6 months, and 1 year postoperatively), BMI, rapidity of increase in BMI, and black race each conferred increased risk of recurrence of SDB.[375] The epidemic of childhood obesity may be changing the epidemiology of OSA in children.[376] There is no clear consensus in the pediatric community regarding which patients deserve an evaluation in the sleep laboratory, and decisions are made on a patient-individualized basis. Therefore, the schematic outlined in Table 1 is not necessarily applicable to children. Here, we focus primarily on the available evidence linking OSA to cardiovascular disease in children.

Hypertension

The effect of simple snoring on BP was examined in a study that included children with snoring but without OSA. Compared with age-, gender-, and BMI-matched control subjects, children with simple snoring had higher daytime resting systolic and diastolic BPs.[377] Among 14 children with upper airway obstruction and heart failure, 3 children had severe hypertension, which improved after treatment of OSA.[378]

Nighttime BPs may be higher in children with OSA. BP recorded during polysomnography in 41 children with OSA syndrome and 26 children with primary snoring showed a significantly higher diastolic BP for sleep and wakefulness in the OSA group. Possibly because of the sample size, no difference in prevalence of hypertension between the 2 groups was found.[379] A study of 23 Japanese children showed that those with AHI >10 had higher systolic and diastolic BP indexes during REM sleep and during wakefulness compared with those with AHI <10. However, the effect of BMI on BP was not accounted for in this comparison.[380]

In a report on 239 children (51% Hispanic) from the Tucson Children's Assessment of Sleep Apnea study, 6% had hypertension.[381] Systolic and diastolic hypertension and sleep efficiency were independently associated with respiratory disturbance index. However, adjusted ORs for confounding variables were not reported. Ambulatory 24-hour BP recordings on 39 children with OSA and 21 with simple snoring showed increased BP variability during wakefulness and sleep and less nocturnal BP dipping in children with OSA compared with children with simple snoring.[382] In addition to BMI, the frequency of oxygen desaturation during sleep and AHI were significant predictors for daytime and nocturnal BP variability, respectively. However, compared with snoring children, those with OSA did not have higher daytime or nighttime BP. Finally, 24-hour ambulatory BP recordings of 96 snoring children demonstrated an independent association between sleep diastolic BP and frequency of nocturnal oxygen desaturation.[383]

A common observation among the cross-sectional studies published in the last 10 years is that BP elevation seen in association with childhood OSA syndrome rarely surpasses the 95th percentile. On the basis of the current literature, there is no definitive evidence that established hypertension is a common cardiovascular complication of OSA syndrome in children and adolescents. However, severe hypertension has been described in advanced stages of OSA in anecdotal reports.[378,380–382,384] Furthermore, a recent study examined ambulatory BPs in 140 children 7 to 13 years of age with nightly snoring and tonsillar hypertrophy. In these otherwise healthy children, an AHI >5 was associated with an increase in morning BP surge, heightened BP load (percentage of BP measurements exceeding the 95th percentile), and higher 24-hour BP.[385]

It is unlikely that mild OSA in children will lead to significant cardiac dysfunction in the pediatric age range. However, it is not known whether mild OSA during early childhood predisposes to vascular injury and/or BP dysregulation during adolescence and adulthood.[386] Whether OSA is an independent risk factor for systemic hypertension in children remains unanswered.

Endothelial Dysfunction

In a study of 30 children (mean age, 9.5 ± 2.8 years) with primary snoring, pulsed-wave velocity over the forearm was higher compared with control children (9.7 ± 1.6 versus 7.9 ± 2.0 m/s; $P=0.001$). Systolic and diastolic BPs also were found to be higher in the snoring children (112 ± 10 versus 105 ± 8 mm Hg, $P=0.001$, and 60 ± 7 versus 53 ± 9 mm Hg, $P=0.004$, respectively). Multiple regression analysis identified primary snoring as the only significant factor for increased pulsed-wave velocity.[377]

Mechanisms of endothelial dysfunction in children have not yet been investigated. However, pediatric studies have described upregulation of inflammatory mediators known to play an important role in vascular injury. P-selectin, C-reactive protein, fibrinogen, interleukin-8, and interferon-γ levels were found to be higher in children with snoring and/or OSA compared with control subjects.[387–391] In a study of 143 adolescents, mean C-reactive protein level demonstrated a dose-response increase with SDB that was independent of BMI and partially explained by the severity of nocturnal hypoxemia.[91] Whether these mediators predict cardiovascular risk in children and adolescents has yet to be demonstrated.

Left Ventricular Structure and Function

Evidence Linking OSA to Left Ventricular Changes

Left ventricular hypertrophy has been described in small case series.[384,392] A case-control study showed that left ventricular mass and relative wall thickness were significantly greater in normotensive children with polysomnography-proven OSA compared with children with primary snoring and that an AHI $\geq$10 increased 6-fold the risk for left ventricular hypertrophy.[393]

In 29 adolescents with SDB, compared with 11 control subjects, left ventricular posterior wall thickness correlated with respiratory disturbance index, but no difference in left ventricular mass was found between the 2 groups.[394] Another study further demonstrated a dose-dependent decrease in left ventricular diastolic function with increased severity of OSA.[395] In children with snoring, the overnight increase in brain natriuretic peptide, a hormone released by ventricular myocytes in response to pressure and volume overload, was found to correlate with severity of the disorder.[396] The severity of sleep apnea may thus determine the presence of cardiac functional and structural changes. In otherwise healthy children, those with more severe SDB (AHI >5) had higher activity-adjusted ambulatory BP and echocardiographic evidence of increased left ventricular wall thickness.[385]

Effects of Treatment of OSA on the Left Ventricle

Left ventricular end-diastolic dimension and thickness of interventricular septum were found to be significantly greater in children with adenotonsillar hypertrophy who were clinically diagnosed with OSA on the basis of history and level of oxygen saturation during sleep compared with control subjects.[397] Adenotonsillectomy was associated with a reduction in left ventricular dimension and posterior wall and septal thicknesses. However, no statistical analysis was reported for these data. Two other studies have described a trend toward an improvement of left ventricular ejection fraction after surgical treatment of OSA.[398,399]

The mechanism of left ventricular hypertrophy in children with OSA is not well understood. Similarly, the degree of reversibility of abnormal left ventricular geometry after treatment has not been comprehensively examined. Existing data are largely confounded by a lack of comprehensive evaluation of the presence and severity of OSA in children.

Pulmonary Hypertension

Evidence Linking OSA to Pulmonary Hypertension

Literature on the relationship between OSA and pulmonary hypertension in children consists of single case reports[400–405] and small case series.[406–411] To date, no controlled studies have examined the prevalence of pulmonary hypertension across the spectrum of severity of OSA. Case series of clinic-based populations of children with OSA described ECG and echocardiographic findings consistent with cor pulmonale. Polysomnography was used in 43% of the reports, whereas the remaining studies relied on the presence of tonsillar hypertrophy and history of snoring to make a diagnosis of OSA.

In a case series of 22 children with polysomnography-proven OSA, 55% had cor pulmonale diagnosed by ECG and chest radiography. Genetic syndromes were present in 27% of the cases, and 2 children had coexistent congenital heart disease.[406] In another case series, 16 children who presented with unexplained cor pulmonale were diagnosed with different forms of SDB. OSA was present in 68% and genetic syndromes were present in 45% of the children with OSA.[392]

The effect of OSA on the pulmonary circulation in children without comorbid conditions was examined in 4 studies.[408–411] Two of these studies, with a total of 64 children, found no evidence of pulmonary hypertension,[409,410] whereas another study found that all 17 children with adenotonsillar hypertrophy and symptoms of OSA had pulmonary hypertension.[411] The fourth study gave a clinical description of selected children with adenotonsillar hypertrophy and cor pulmonale.[408]

Direct measurements of pulmonary artery pressure by cardiac catheterization are limited to 2 case reports.[412,413] Pulmonary hypertension was diagnosed by cardiac catheterization in 3 children with symptoms of OSA, adenotonsillar hypertrophy, and cardiac failure. Complete reversibility of pulmonary hypertension was shown in 1 case after adenotonsillectomy.[412] A second report on 2 children with Down's syndrome and 1 child with Pierre Robin sequence showed evidence of pulmonary hypertension that partially decreased with oxygen supplementation.[413]

Effects of Treatment of OSA on Pulmonary Hypertension

Ten publications (of which 6 were case reports)[400–404] noted an improvement of pulmonary hypertension after treatment of OSA. In a study by Hunt and Brouillette,[392] treatment of 10 children with OSA was associated with complete resolution of cor pulmonale in 9 cases and partial improvement in 1 case. In a series by Brouillette et al,[406] 12 children with cor pulmonale improved after treatment. Levine and Simpser[414] described 4 children with trisomy 21 who improved after treatment of OSA. In these studies, the cardiovascular outcome after treatment of OSA was determined on the basis of improvement versus no improvement in clinical symptoms, right ventricular hypertrophy, and/or cardiomegaly and thus was descriptive in nature. A single study demonstrated in 17 children a decrease in pulmonary artery pressure measured by echocardiography after treatment of OSA.[411]

Summary

The current literature regarding pediatric SDB has a number of limitations. Many studies rely on clinical history alone, which does not discriminate between primary snoring and OSA. This precludes an accurate estimation of cardiovascular morbidity in children with OSA.[415] Most reports lack a uniform definition of pulmonary hypertension and used diverse methods of testing for the presence of cor pulmonale. Most studies that found a high prevalence of pulmonary hypertension described children with polysomnography-proven severe OSA or children with clinical signs of cardiac dysfunction. Thus, most cohorts are not representative of the general population. The inclusion in many of the reports of children with comorbid conditions such as those with genetic syndromes, developmental delay, encephalopathy, and coma leaves the literature with a relatively small number of children with uncomplicated OSA. These limitations contribute to the large discrepancy in the reported prevalence of pulmonary hypertension in children with OSA.

Hence, the prevalence of cor pulmonale in children with uncomplicated OSA cannot be estimated. The levels of

severity of OSA and/or intermittent hypoxia associated with any increased risk for cor pulmonale are not known. Whether the risk for pulmonary vascular disease or other adverse cardiovascular changes differs in various pediatric age groups also is unknown. Furthermore, the pathophysiology of cor pulmonale and the contribution of pulmonary venous hypertension to overall pulmonary artery pressure in children with OSA are not well understood.

Future Directions: A National Center on Sleep Disorders Research/National Heart, Lung, and Blood Institute Perspective

The National Center on Sleep Disorders Research (NCSDR) was established by Congress in 1993. Because of the emerging evidence of associations between untreated SDB and cardiovascular disease, the NCSDR was established as a center within the National Heart, Lung, and Blood Institute (NHLBI). National Institutes of Health (NIH) funding of new initiatives related to SDB and cardiovascular disease has progressively increased, stimulated in large part by release of the first National Sleep Disorders Research Plan in 1996. The updated and expanded National Sleep Disorders Research Plan includes prioritized recommendations for future research to address existing gaps in our knowledge regarding SDB and cardiovascular disease. These include the following:

- The interaction between cardiac dysfunction and the ventilatory control system in the pathogenesis of CSR.
- Adequately powered clinical trials, particularly in high-risk populations, to assess the impact of therapy of SDB on hypertension, cardiovascular disease, metabolic syndrome, cardiac dysfunction, quality of life, and survival.
- Longitudinal normative data on sleep and cardiorespiratory patterning in children.
- Genes and gene products that may contribute to the cardiovascular pathophysiology of SDB. Conducting these studies in pediatric populations may have distinct advantages because they are less likely to be "contaminated" by age-associated comorbidities present in adult populations.
- Longitudinal studies to assess the long-term impact of SDB during childhood and into adulthood, especially considering the increasing prevalence of obesity in children.
- New and improved modalities for the treatment of SDB, including pharmacological, surgical, oral appliance, behavioral, muscle stimulation, and alternate strategies to improve efficacy of and compliance with CPAP.
- Novel noninvasive screening/diagnostic methodologies that are less expensive and more widely applicable than standard full polysomnography.

The NCSDR, NHLBI, and Trans-NIH Sleep Research Coordinating Committee encourage clinical investigators to actively address existing gaps in knowledge regarding SDB and cardiovascular disease. In addition to the National Sleep Disorders Research Plan, potential investigators should consult the 2 recent NIH program announcements, Research on Sleep and Sleep Disorders (R01) (http://grants.nih.gov/grants/guide/pa-files/PA-07-140.html) and Research on Sleep and Sleep Disorders (R21) (http://grants.nih.gov/grants/guide/pa-files/PA-06-238.html).

Summary

In the context of the current epidemics of obesity, hypertension, atrial fibrillation, and heart failure, the prevalence and consequences of both OSA and CSA are likely to increase. Numerous hurdles face the cardiovascular community in the development of consensus regarding best practice. One objective of this document is to help develop the platform from which, in collaboration with specialists in sleep medicine and related disciplines, such consensus may emerge. Challenges to be met include (1) the general absence of any structured sleep medicine education in cardiovascular training programs; (2) the logistic and economic obstacles to diagnosing and treating sleep apnea; (3) widespread comorbidities, including obesity, that obscure clearer understanding of any independent cardiovascular consequence of sleep apnea per se; (4) treatment options that are varied, predominantly device based, and not easily tolerated, particularly in patients with CSA; and (5) the absence of robust longitudinal interventional studies addressing whether treating sleep apnea confers any tangible benefit in terms of cardiovascular events. We also remain uncertain about what in the apneic patient facilitates cardiovascular disease and its progression. There is no clear evidence as to the best measurement for quantifying the severity of sleep apnea. Is it the frequency of apneas, the severity of desaturation, the overall burden of nocturnal hypoxemia, the arousals, sleep deprivation, or a combination of these and perhaps other characteristics that are key in promoting heart and blood vessel damage? In addition, we do not know the threshold of severity of apnea that we should treat and whether the thresholds for therapy are different in people with cardiovascular disease compared with those who are otherwise healthy.

Recognition that a multidisciplinary strategy is critical to appropriate evaluation of sleep-related disease[416] and heightened interaction between specialists in cardiovascular and sleep medicine hold promise for future improved and integrated patient care. In the meantime, the relative lack of definitive outcomes data to guide clinical practice necessitates a highly individualized approach to evaluation and management of those patients with comorbid cardiovascular disease and sleep apnea.

There will likely be continued rapid evolution in interpretation, dissemination, and implementation of mechanistic, prognostic, and therapeutic data. Evidence of activation of cardiovascular disease mechanisms by sleep apnea and evidence of sleep apnea as an independent etiologic factor in cardiovascular disease should serve as catalysts for definitive intervention studies. Important next steps in understanding and treating SDB as a means of preventing and mitigating cardiac and vascular disease should include further characterizing fundamental disease mechanisms, identifying economical and better-tolerated therapeutic options, confirming whether therapy attenuates cardiovascular morbidity and mortality, and defining appropriate therapeutic targets and cost-effective benefits of such therapy.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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