Sleep-Disordered Breathing and Cardiovascular Risk

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Abstract: Sleep-disordered breathing, broadly characterized by obstructive sleep apnea (OSA) and central sleep apnea (CSA), is an increasingly recognized public health burden. OSA, consisting of apneas or hypopneas associated with respiratory efforts in the face of upper airway narrowing or collapse, is a common disorder that can be effectively treated with continuous positive airway pressure (CPAP).[1] OSA not only results in daytime sleepiness and impaired executive function, but also has been implicated as a possible cause of systemic disease, particularly of the cardiovascular system. CSA, which may coexist with OSA, has gained attention because of the association of Cheyne-Stokes respiration with an ever-increasing prevalence of heart failure in an aging population. This article reviews some of the extensive literature on pathophysiologic mechanisms as they may relate to the development of cardiac and vascular disease and examine the evidence suggesting OSA as a specific cause of certain cardiovascular conditions. Available evidence regarding the implications of CSA in the context of heart failure is discussed.

Keywords: Obstructive sleep apnea, central sleep apnea, cardiovascular disease, continuous positive airway pressure, hypertension

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Acute Pathophysiologic Mechanisms of OSA

REPETITIVE EPISODES OF UPPER AIRWAY NARROWING OR OCCLUSION THAT CHARACTERIZE OSA GIVE RISE TO ACUTE STRESSORS SUCH AS HYPOXEMIA, reoxygenation, occasionally marked negative intrathoracic pressure, and central nervous system arousals. There may be differential effects related to each stressor, and it is plausible that these effects are cumulative over time. Indeed, there is evidence that people with obstructive sleep apnea have chronic dysregulation of cardiovascular homeostasis, as demonstrated by daytime abnormalities in sympathetic nervous system function and heart rate variability.[2] Whether these result from the summation of acute effects or are part of an inherent phenotype is not clear.

Mechanisms underlying these characteristics, delineated by both animal and human models, originate from complex interactions among the respiratory, cardiovascular, and central nervous systems.

There is considerable evidence that hypoxemia drives some important aspects of the pathophysiology in OSA. Reduced blood oxygen tension stimulates peripheral arterial chemoreceptors, the most important of which are the carotid bodies. These sensors have at least two neural connections thought to be important in mediating the response to OSA-associated hypoxemia. First, afferent relays in the brain stem elicit reflex increases in sympathetic efferent traffic during hypoxemic stimulation, as demonstrated by direct peripheral intraneural electrode recordings.[3, 4] Second, the carotid body afferents also synapse with respiratory centers within the brainstem to normally increase respiratory muscle output and minute ventilation.[5] There is an important interplay between these sympathetic and ventilatory responses, whereby increases in ventilation attenuate sympathetic activity. Hence, the sympathetic response to hypoxemia is potentiated during apnea, when the neuroinhibitory influence of lung expansion is eliminated.[6]

There appears to be an exaggerated peripheral chemoreflex response to hypoxemia in sleep apneics, as demonstrated by an augmented ventilatory and autonomic drive compared with control subjects.[5] Whether this results from repetitive hypoxemic exposure is not entirely clear, with conflicting human[7] and animal data.[8] This increased chemoreflex sensitivity may be the primary mediator of enhanced sympathetic tone in OSA. Chemoreflex activation results in increased sympathetic traffic to the peripheral vasculature, with consequent acute increases in arterial blood pressure.[2, 5] Homeostatic mechanisms, which under normal conditions temper increased sympathetic drive, are disrupted in OSA. Lung inflation, normally sympatholytic on account of stimulation of lung and chest wall stretch receptors mediated by vagal afferents, is incomplete during apneas and hypopneas.[9, 10] Baroreflexes, originating in major blood vessels such as the carotid sinus and aorta, and mediated through the central nervous system, also serve to buffer ventilatory[11] and sympathetic[3] responses to peripheral chemoreflex excitation. Several disease states seen in association with OSA, such as hypertension and heart failure, may result in impaired baroreflex function and may, thus, contribute indirectly to augmentation of the chemoreflex-mediated sympathetic response.[12]

The independent sequelae of repetitive episodes of reoxygenation can be difficult to decipher from those related to the coupled hypoxemia. Animal and cellular experiments suggest that repetitive reoxygenation promotes oxidative stress through formation of reactive oxygen species, a cascade that may be associated with mitochondrial dysfunction.[13] This process has also been implicated in the selective activation of inflammation-promoting NF- κB.[14] It is conceivable that heightened inflammation[15] and oxidative stress,[16, 17] reported in some clinical studies of OSA, are mediated through these mechanisms.

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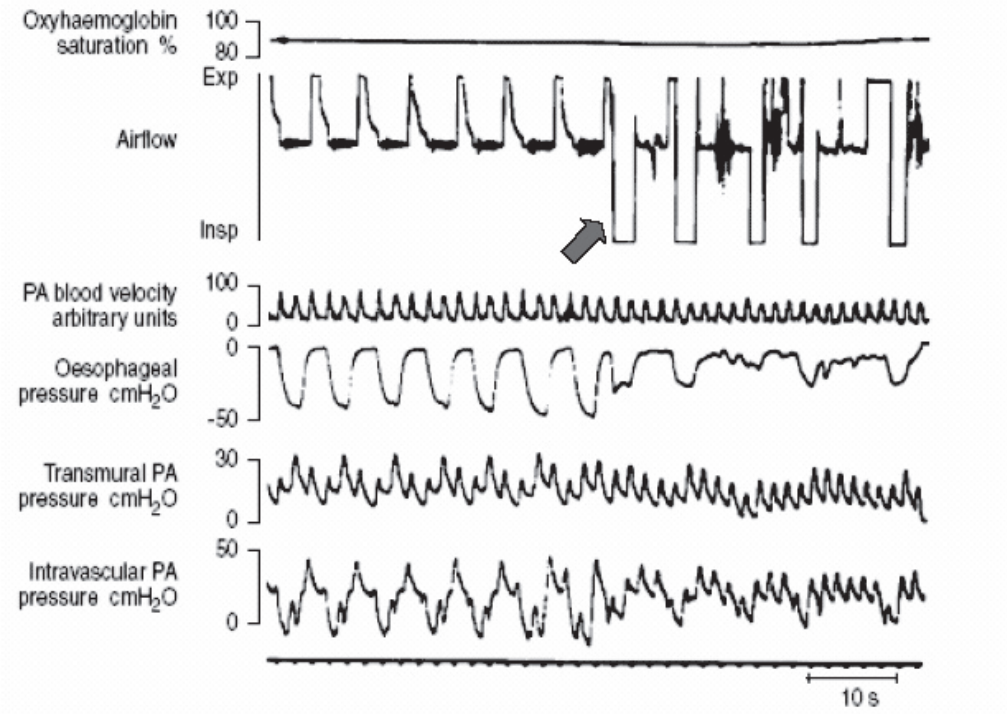

Figure 1—Inspiratory airflow limitation during snoring without oxyhemoglobin desaturation, associated with wide variation in esophageal pressure and pulmonary arterial (PA) pressure. Note pressure changes with relief of obstruction (arrow), as occurs with an arousal from sleep. Reproduced with permission reference 18.

The persistence of inspiratory efforts against an obstructed upper airway results in occasionally marked reductions in intrathoracic pressure, as measured by esophageal pressure, that have been associated with acute changes in pulmonary arterial pressures and blood flow[18] and increased cardiac afterload (Figure 1). Enhanced venous return that may occur with reduced intrathoracic pressure can result in acute leftward intraventricular septal shift[19] and alterations in transmural cardiac pressures,[20] with impedance of left ventricular (LV) filling[21] and increase in myocardial oxygen demand.

Central nervous system arousals, which usually coincide with, if not result in, termination of apneas and hypopneas,[22] appear to have independent effects on measured cardiovascular variables. In humans, arousals induced by acoustic stimuli have been found to result in abrupt increases in sympathetic tone, heart rate, and blood pressure.[23, 24] Superimposing upper airway obstruction seems to have additive effects, as demonstrated in an experimental model in which dogs subjected to repetitive airway occlusion superimposed upon acoustically induced arousals during sleep developed higher daytime blood pressure, compared with the group free of imposed apnea.[8]

Chronic Pathophysiology and Potential Markers of Cardiovascular Risk in OSA

It is important to recognize the inherent difficulties of research in this arena. Because OSA is more prevalent with aging[25] and is frequently accompanied by other comorbidities, particularly obesity and the metabolic syndrome, it can be difficult to disentangle its independent effects on the development of cardiovascular disease. Because the field of sleep medicine remains in its relative infancy, randomized interventional trials and longitudinal cohort studies, which may more powerfully assess a disorder's independent impact, have only recently begun to emerge. Thus, the OSA-cardiovascular disease literature has historically been dominated by case-control studies. While generating hypotheses on potentially novel and important physiologic processes, these studies are vulnerable to hidden biases and can promote conflicting results between studies. Finally, because OSA severity continues to be characterized by the apnea-hypopnea index (AHI), the relative effects of potentially important non–frequency-based parameters, such as duration and degree of hypoxemia, are probably under recognized. Figure 2 depicts the myriad of factors, many of which interact, that may be important in the evolution of cardiovascular disease in those with OSA.

Disturbed daytime neural circulatory control is evident in patients with OSA, even in the absence of overt cardiovascular disease. Enhanced sympathetic drive appears to be carried over into normal waking hours in some patients with OSA, even under conditions of normoxia, an effect that may be attributable in part to increased tonic chemoreflex drive.[2, 26] (Figure 3) Abnormalities in variability of both heart rate and blood pressure are present in OSA,[26] two findings that may act as markers for future cardiovascular disease.[27] The vascular system/endothelium, recognized to be a biologically active system, may be dysfunctional in OSA. Whether this results from OSA per se is not clear, but large population-based studies suggest that endothelial dysfunction may be an important marker of cardiovascular risk.[28] The small-vessel dilatory response to vasoactive substances such as acetylcholine, which represents resistance vessel endothelial function, is blunted in sleep apnea,[29, 30] although these findings are not evident in all studies.[31] Whether large- or conduit-vessel endothelial function is attenuated in OSA is unclear. There is evidence to support the role of reduced levels of the potent vasodilator nitric oxide in the mediation of vascular disease and blood pressure regulation in OSA. Ip and colleagues found significant correlations between reduced

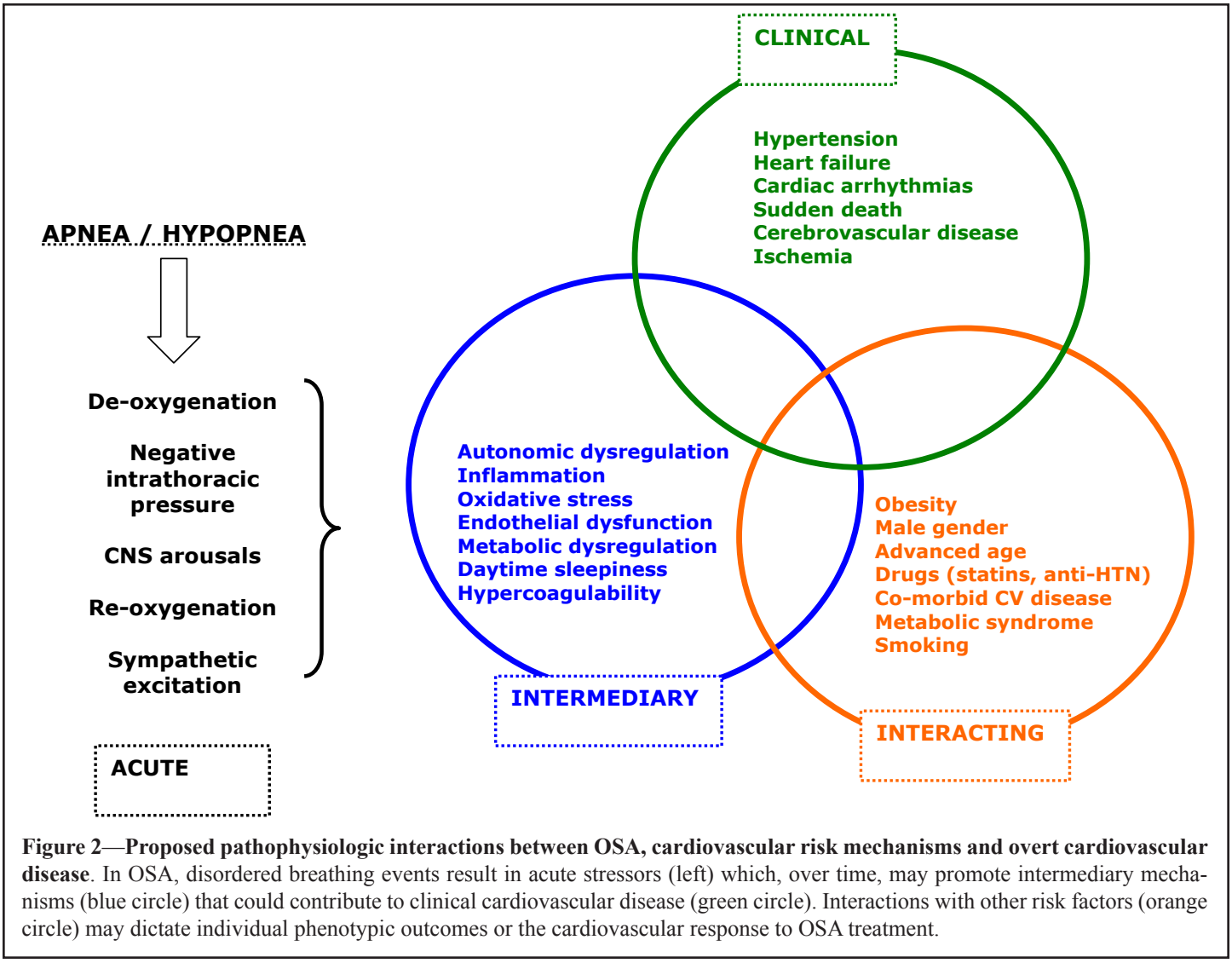

Figure 2—Proposed pathophysiologic interactions between OSA, cardiovascular risk mechanisms and overt cardiovascular disease. In OSA, disordered breathing events result in acute stressors (left) which, over time, may promote intermediary mechanisms (blue circle) that could contribute to clinical cardiovascular disease (green circle). Interactions with other risk factors (orange circle) may dictate individual phenotypic outcomes or the cardiovascular response to OSA treatment.

nitrite/nitrate levels and severity of OSA, with increases in these levels following overnight application of CPAP.[32] Levels of serum endothelin, a potent vasoconstrictor, may also be elevated in OSA patients compared with control subjects.[33]

Other features of OSA may indirectly increase the risk for cardiovascular disease. While the average individual with OSA is predisposed to glucose intolerance on the basis of excess body weight, other mechanisms that potentially contribute to hyperglycemia include increased sympathetic tone, repetitive hypoxemia, and sleep debt.[34] Both clinic and population-based studies[35, 36] support a relationship with glucose intolerance independent of obesity,[37] although these reports were dominated by male subjects with relatively severe sleep apnea. Disappointingly, a number of small studies have failed to demonstrate reversal of glucose intolerance by CPAP therapy after treatment ranging from 1 night to 6 months. In the largest trial published to date, Harsch and colleagues, studying subjects with an AHI greater than 20, showed improvement in insulin sensitivity over 2 nights of CPAP therapy, an effect that remained unchanged over the ensuing 3 months, suggesting a mechanism mediated in part through rapid attenuation of sympathetic drive.[38] That the effect of treatment was mitigated in those with a body mass index greater than 30 kg/m^2 suggests a greater role of obesity and a lesser, although potentially clinically important, independent role of OSA.

Inflammation is increasingly implicated in the pathogenesis of cardiovascular disease,[39] and the potential role of inflammation in the pathogenesis of OSA has garnered much attention.

C-reactive protein (CRP) is a sensitive marker of inflammation shown to be prognostic in prediction of cardiac events,[40] although its importance has recently been called into question by a large observational study.[41] Case-control studies in OSA have yielded conflicting results on the disposition of CRP. One group found CRP to be elevated in OSA patients compared with body mass index-matched controls,[15] whereas another found a stronger association with body weight than with AHI.[42] The disparity in findings may lie in the different adiposity between subjects in the 2 studies (mean case subject body mass index 36 kg/m^2 in the first study, compared with 29 kg/m^2 in the second), since CRP levels are known to correlate with body mass index.[43] A possible interaction with age has been suggested by a recent study of CRP in adolescents. After adjustment for a high rate of obesity, CRP levels showed a positive correlation with severity of sleep-disordered breathing.[44] Some studies suggest that treatment of OSA with CPAP may lower CRP levels,[45] but these findings and their clinical implications need further confirmation. Heightened inflammation in OSA is further supported by research at the cellular level. Up regulation of leukocyte adhesion factors in OSA,[46, 47] although not yet proven to translate to

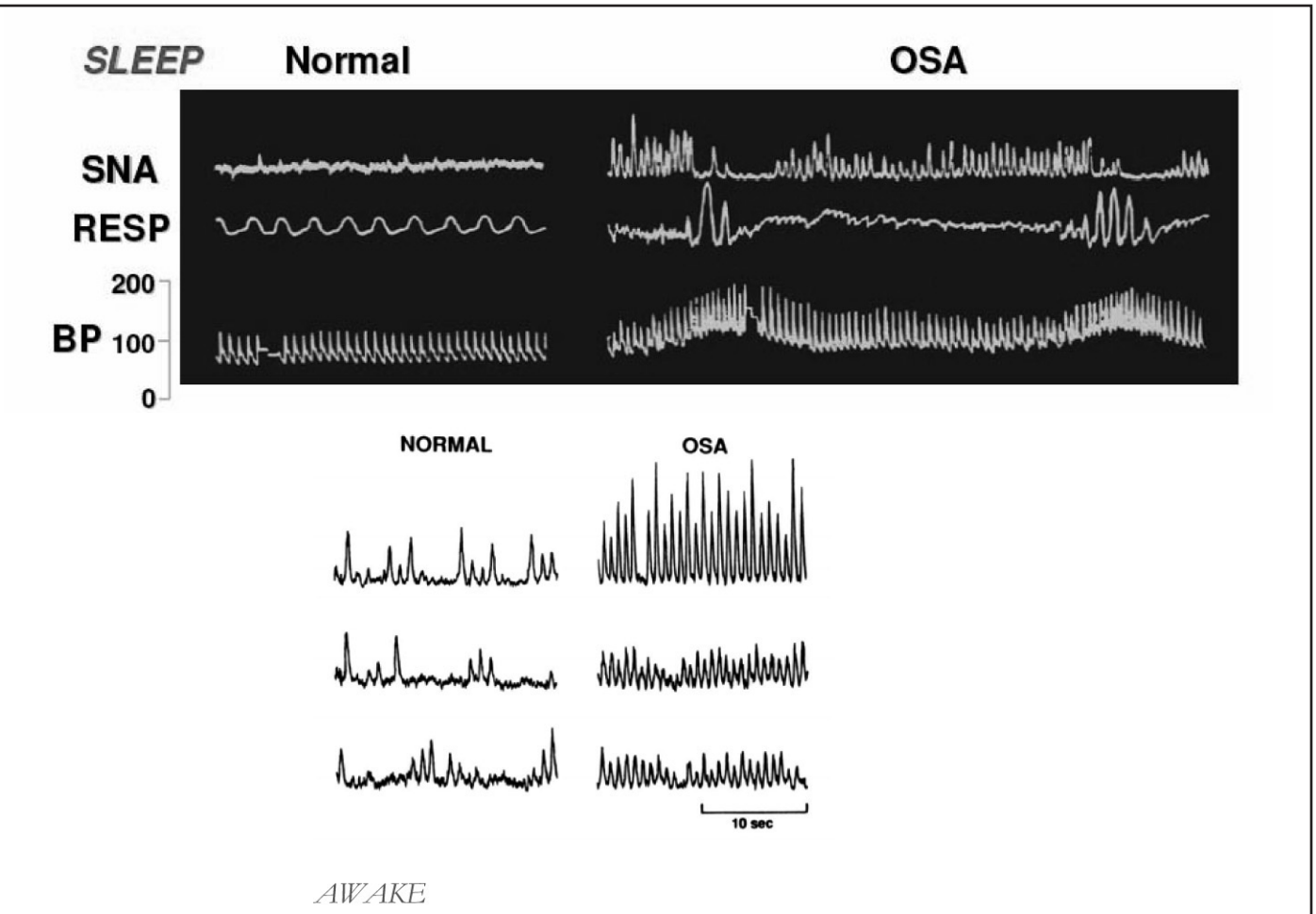

Figure 3—TOP: Peripheral muscle sympathetic neural activity SNA) during sleep in an individual without and with OSA. BOTTOM: Heightened SNA is carried over into normoxic wakefulness. Reproduced with permission reference 2.

clinical disease, could predispose to endothelial injury and vascular events. These pathways could be mediated through neutrophil-derived oxidative stress[16] and abnormalities in coagulation markers found in OSA.[48]

Hypoxia is known to stimulate vascular endothelial growth factors, which are found to be elevated in OSA.[49, 50] One year of CPAP use is associated with reductions in vascular endothelial growth factors levels, compared with no treatment.[50] Although direct evidence for stimulation of vascular growth via these proteins in OSA is currently lacking, it is conceivable that such neovascularization could represent an adaptive mechanism in OSA to protect against the deleterious end-organ effects of repetitive hypoxia. This hypothesis, if proven, has important implications for understanding the end-organ effects of repetitive hypoxia.

Not all markers of cardiovascular disease have been found to be altered in OSA. No acute changes in serum levels of brain natriuretic peptide were found between subjects with or without heart failure on whom single-night serial measurements were performed.[51]One could speculate that a predominance of hypopneas, with less-dramatic swings in intrathoracic pressure, compared with apneas, may result in more modest transmural pressure applied to the myocardium and limited elaboration of brain natriuretic peptide. Other negative case-control studies have been found with measurement of troponin T[52] and adiponectin,[53] the clinical ramifications of which need further clarification.

OSA and Clinical Cardiovascular Disease

Systemic Hypertension

Early cross-sectional reports linking OSA and systemic hypertension were limited by study design and potential confounding effects of comorbid variables, particularly obesity, but nevertheless provided an important basis for subsequent confirmation by more comprehensive population-based studies. Although demonstrating an association between OSA and hypertension,[54, 55] these prevalence data lack longitudinal observation to implicate causality. A prospective study from the Wisconsin Sleep Cohort was the first to provide persuasive evidence implicating OSA as a possible causal factor in hypertension.[56] Specifically, the presence of hypertension 4 years after initial assessment was found to be dependent upon the severity of OSA at baseline. It is notable that the study did not specifically identify subjects free of hypertension at baseline and could not determine the incident risk imparted by OSA. In fact, criticism was aimed at the 10% of patients at baseline and 17% at follow-up who were treated with antihypertensive medications. However, post-hoc analysis excluding those with hypertension or taking antihypertensives at baseline resulted in similar associations between AHI and hypertension at 4-year follow-up.[57] Collectively, the data are compelling to implicate OSA not only in acute increases in nocturnal blood pressure, but also in sustained daytime hypertension as well.

Although CPAP has been shown to acutely attenuate sympa-

Table 1—Potential Confounders of Placebo-Controlled Trials of Effects of CPAP on Blood Pressure

Baseline variation in

- Age
- Body mass index
- Measurement and severity of OSA (AHI, degree of oxyhemoglobin desaturation)
- Blood pressure—some normotensive and others hypertensive; differing methods for blood pressure measurement (ambulatory vs individual cuff)
- Drug therapy for hypertension
- Daytime sleepiness and method of measurement (subjective vs objective)
- Duration of treatment (2 to 12 weeks)
- Different control strategies (subtherapeutic CPAP, oral placebo)
- Variation in compliance with treatment among subjects
- Studies conducted predominantly in men
- Differential effects on daytime vs nighttime vs mean 24-h blood pressure

OSA refers to obstructive sleep apnea; AHI, apnea-hypopnea index; CPAP continuous positive airway pressure.

thetic drive and nocturnal blood pressure in patients with OSA,[2, 58, 59] data regarding effects on daytime blood pressure have been less clear cut. Numerous observational studies, often uncontrolled and from highly select populations, have suggested improvements in daytime blood pressure control with the use of CPAP. Subsequent randomized, placebo-controlled studies, however, have yielded variable results, due in large part to variations in population sample and methodology, as outlined in the Table, thus limiting the generalizability of the studies.

Some findings are worth noting. With the largest study to date, Pepperell and colleagues found a small but significant reduction in daytime blood pressure in a normotensive cohort after 4 weeks of therapy, an effect that appeared to be driven primarily by those with more frequent oxyhemoglobin desaturation episodes (Figure 4).[60] Becker et al carried out one of the longest trials (> 60 days) and found fairly dramatic reductions in mean blood pressure (9.9± 11.4 mm Hg) in a small cohort with severe OSA (mean AHI > 60 per hour), two thirds of whom were taking antihypertensive medications.[61] Offering some insight into the mechanisms of the systemic effects of OSA, a randomized controlled trial from Barbe et al suggests that normotensive subjects with severe OSA but without demonstrable daytime sleepiness are immune to the blood pressure-reducing effects of CPAP,[62] a finding also suggested by the Oxford group[63] (Figure 5) and other investigators.[64, 65]

Because a chronic condition such as OSA-associated hypertension could reasonably lead to vascular remodeling and other structural cardiovascular changes, it is entirely feasible that short-term controlled studies may fail to disclose the true effects of faithful CPAP therapy on hypertension. Furthermore, given the prevalence of hypertension and its effects on the development of other cardiovascular disease, including heart failure and stroke, the results of small changes in blood pressure, as noted above, may have far-reaching public health impact.[66]

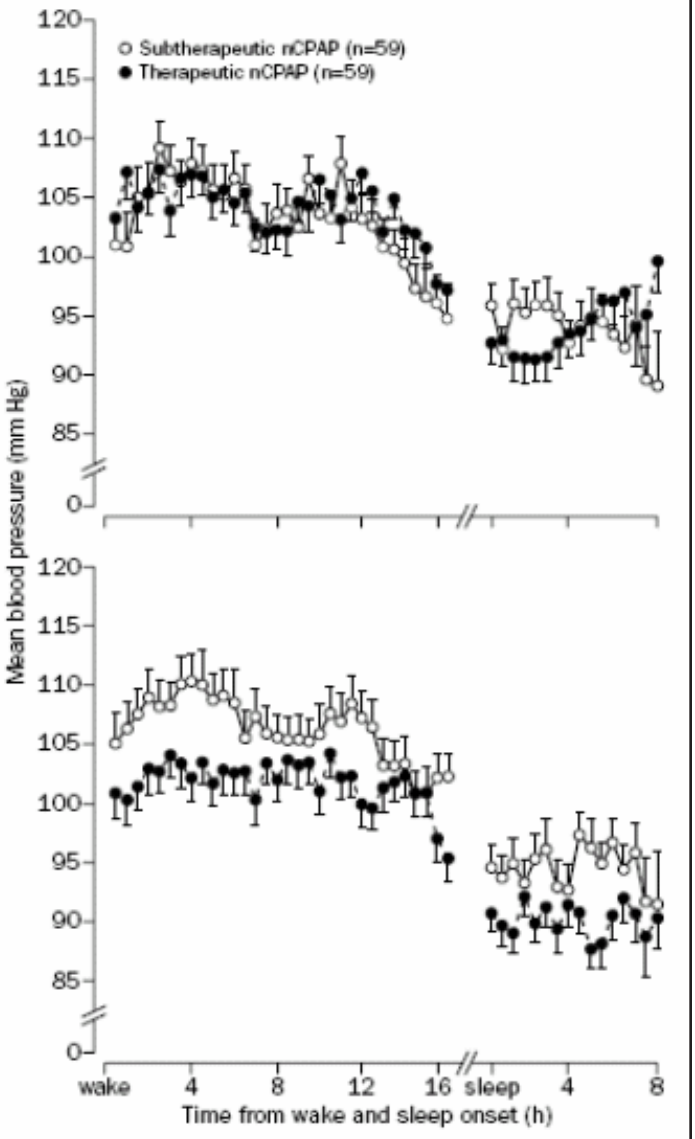

Figure 4—Changes in nocturnal and daytime blood pressure after one month of therapeutic (closed circles) vs. sub-therapeutic CPAP. Reproduced with permission from Reference 60.

Heart Failure-OSA

There is abundant physiologic evidence implicating OSA in perpetuating, if not inciting, heart failure. In addition to their association with systemic hypertension, OSA-related stressors, including hypoxemia, increased sympathetic drive, acute surges in blood pressure, and mechanical effects of intrathoracic pressure swings, have varying effects on myocardial oxygen supply and demand, particularly in the already compromised heart.

Neurohormonal activation, a key intermediary in the pathophysiology of heart failure, as evidenced by increased urinary catecholamine metabolites associated with repetitive obstructive events, may contribute to myocardial dysfunction.[67] The development of systolic dysfunction in OSA may also partially relate to elaboration of chemical mediators and cytokines, which have been found to be elevated in OSA[68] and are known to play a role in myocardial depression.[69, 70] A demonstrated shift in the predominance of sleep-disordered breathing in patients with heart failure from obstructive to central apneas over the course of a night's

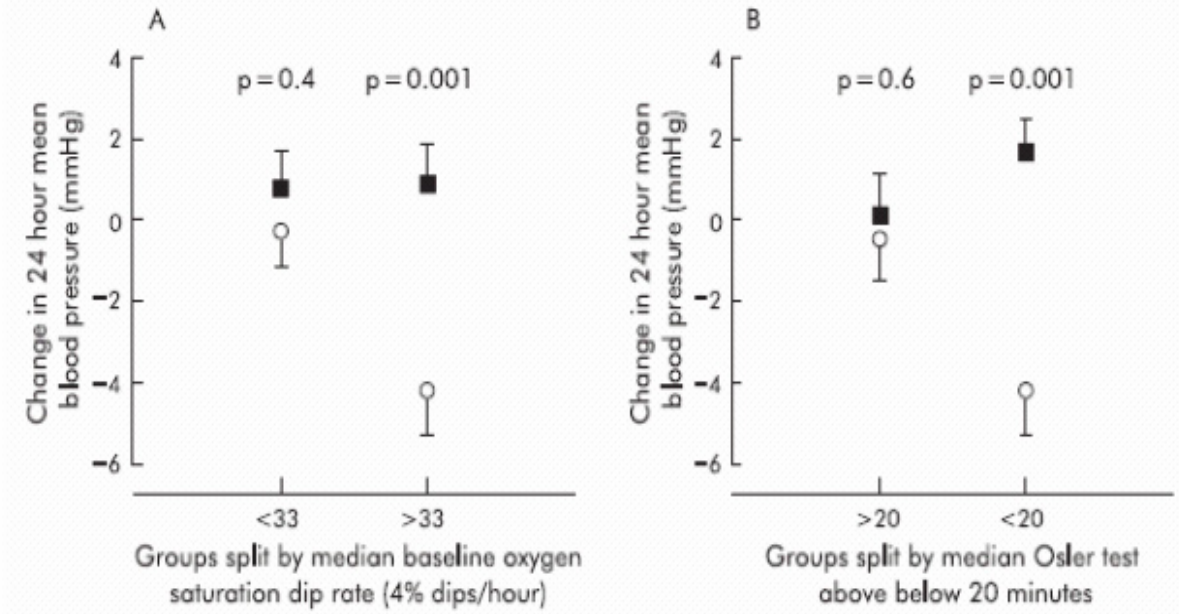

Figure 5—The blood pressure lowering effect of therapeutic CPAP in the Oxford trial was driven by those individuals with more frequent oxyhemoglobin desaturations and with objective evidence of excessive sleepiness as demonstrated by the Osler test. Reproduced with permission from Reference 63.

sleep, with prolongation of circulation time, suggests overnight deterioration in cardiac function.[71] Indeed, epidemiologic studies, although admittedly biased by referrals to sleep labs in the context of worsening symptoms, have suggested a strong association between heart failure and OSA.[72, 73]

In a canine model, experimentally induced acute upper airway occlusion has been shown to result in elevation of left ventricular transmural pressure with an associated abrupt fall in left ventricular stroke volume.[8] Using the same model, chronic intermittent upper airway occlusion over 3 months resulted in deterioration of left ventricular systolic function. In humans, inspiring against a closed glottis (reproduced experimentally as the Mueller maneuver) causes a more profound reduction in cardiac index in patients with heart failure, compared with those without heart failure, suggesting that obstructive events in those with concomitant OSA and left ventricular systolic dysfunction may lead to further impairment of nocturnal cardiac function.[74]

Diastolic dysfunction has been associated with OSA in some,[75, 76] but not all,[77] studies. Variable results could be due to a number of factors related to the uncontrolled design of these reports, including the presence of preexisting hypertension, effects of cardiac medications, and the inability to control for chronicity of OSA, an important factor in potentially irreversible cardiac remodeling. However, a randomized, controlled, crossover trial has demonstrated a high prevalence of abnormal left ventricular relaxation in patients with newly diagnosed OSA that was significantly improved after 12 weeks of CPAP therapy.[78]

Although a plethora of observational data in OSA and systolic heart failure exists, there have been few randomized controlled studies assessing outcome. A small study has shown significant improvement in left ventricular ejection fraction (LVEF) and functional status following CPAP therapy for OSA in patients with heart failure, compared with maximal medical therapy.[79] It is noteworthy, however, that, despite the presence of severe OSA (mean AHI > 30) and LVEF less than 30% in both the control and treatment groups, the subjects did not demonstrate significant daytime sleepiness by standard measurements. A larger study of randomized patients with heart failure and OSA comparing CPAP with usual care found a significant increase in LVEF but no change in mean blood pressure after 3 months.[80] Once again, subjective sleepiness was mild. Further research is needed to determine the exact therapeutic role of CPAP therapy in heart failure, particularly in the absence of daytime hypersomnia. Whether treatment of OSA in heart failure improves outcomes such as survival remains unknown.

There is evidence to suggest that established congestive heart failure may actually cause new-onset OSA, particularly in individuals with an anatomic predisposition to pharyngeal collapse, such as in obesity. The mechanism may relate to upper airway edema, which occurs with the recumbent position, and has been reproduced in humans via experimental alterations in central venous pressure.[81] Alternatively, CSA with Cheyne-Stokes respiration, to be discussed subsequently, may result in loss of the pharyngeal muscle dilator reflex normally present to maintain upper airway patency with inspiration, predisposing to collapse.[82]

Heart Failure-Central Sleep Apnea

CSA, in large part due to the association with heart failure, has been increasingly studied in recent years. CSA in heart failure often manifests as Cheyne-Stokes respiration, characterized by crescendo-decrescendo breathing terminating in an apnea without measurable ventilatory effort. In contrast to OSA, CSA is primarily a disorder of ventilatory control, and affected patients comprise a more heterogeneous group than those with OSA. For the purposes of this review, discussion will be limited to CSA (with Cheyne-Stokes respiration) first in the context of heart failure, in which this breathing disorder is most prevalent,[83] and second, in relation to cardiac arrhythmias.

There are a number of pathophysiologic mechanisms by which

patients with heart failure manifest CSA and Cheyne-Stokes respiration,[84] which has also been referred to as periodic breathing. First, heart failure is associated with increased ventilatory drive on account of at least two mechanisms: pulmonary vagal stimulation related to congestion, accentuated by the supine posture, plus enhanced central and peripheral chemoreflex responses compared to those without heart failure.[85-87] As a result, patients with heart failure have reduced arterial carbon dioxide levels ($Paco_2$) that often hover near the apneic threshold, which, when crossed, results in central apnea. Breathing instability is perpetuated on account of circulatory delay related to cardiac dysfunction, as the resultant hypocapnia suppresses central chemoreceptors while peripheral co_2 accumulates.[88, 89] Further importance of $Paco_2$ is demonstrated by the abolition of CSA with inhalation of co_2-enriched gas.[90] Although sleep is fragmented by frequent arousals, the stimulus appears to be hyperpnea rather than upper airway collapse, as is seen in OSA, with limited data showing that only a minority of patients report daytime symptoms of sleepiness.[73, 91]

Although CSA is, to a large degree, a marker of severity of underlying heart failure, multivariate analysis suggests that CSA is independently associated with increased mortality in heart failure.[92] This trend may be mechanistically explained in part by sympathetic overactivity and hemodynamic variability present in this population, which may also be more prone to cardiac arrhythmias.[91, 93]

The treatment of CSA currently lacks standardization, mainly due to a lack of long-term outcome data, but also because of the uncertainty over which metric best measures CSA severity. For example, it may well be that duration of hypoxemia rather than a central AHI has the greatest impact on outcomes in heart failure. Treatment of the underlying heart failure would be expected to improve CSA, as has been demonstrated by a limited number of studies.[94, 95] Reduction of pulmonary capillary wedge pressure has been found to attenuate CSA in patients with heart failure.[96] Further evidence for the effect of improving cardiac function on CSA comes from studies of heart failure patients with left bundle branch block treated with cardiac resynchronization therapy, resulting in significant reductions in the occurrence of central apneas and hypopneas.[97, 98] Further longitudinal studies will be needed to assess the impact, if any, on long-term outcomes. Especially provocative is the question of whether the mortality reduction that follows cardiac resynchronization therapy in patients with severe heart failure[99] is related in any way to improvement in CSA.

Supplemental nocturnal oxygen, probably on account of its effects on reducing ventilatory drive, has been shown to decrease the occurrence of central apneas,[100] consolidate sleep, and improve daytime exercise tolerance in heart failure.[101, 102] Limited randomized studies have suggested that CPAP may improve cardiac function and quality of life in CSA.[103, 104] However, a long-term, randomized, multicenter trial (CANPAP) recently reported the lack of mortality difference between heart failure patients with CSA treated with CPAP compared with no CPAP.[105] This finding may be explained by reduced mortality attributable to improvements in medical therapy for heart failure patients in recent years, as well as the limited efficacy of CPAP in treating CSA in heart failure, as has been demonstrated by the persistence of central apneas on follow-up sleep studies. Because results of CANPAP suggest that recent changes in the paradigm of medical therapy of heart failure (use of β-receptor and aldosterone antagonists) may effectively reduce attributable mortality, earlier reports on the prevalence of CSA in heart failure may now be overestimated.

Another form of positive airway pressure, adaptive servo-ventilation, recently approved for use in the United States, has been shown in short-term controlled trials to effectively suppress CSA and significantly improve daytime sleepiness in patients with stable heart failure and CSA.[106, 107] After 1 month of treatment with adaptive servo-ventilation, there were reductions in neurohormonal activity and brain natriuretic peptide levels, but no changes in LVEF.[106] Although there is some evidence of effect after 6 months of therapy,[108] long-term outcome studies are needed.

Pulmonary Hypertension

The role of OSA in pulmonary hypertension is controversial. It is known that alveolar hypoxia induces acute increases in pulmonary vascular resistance as an autoregulatory enhancement of the V/Q relationship.[109] Conceivably, hypoxic vasoconstriction over the long term could result in vascular remodeling and subsequent fixed changes in the pulmonary vessels, leading to chronic elevations in pulmonary arterial pressures, as may be seen in advanced chronic obstructive pulmonary disease. The specific effects on the pulmonary vasculature of long-term repetitive episodes of hypoxemia with intervening normoxia, such as occur with OSA, are not known.

For years, the prevailing sentiment was that OSA could not cause daytime pulmonary hypertension in the absence of clinical lung disease or daytime baseline hypoxemia. This was based partially on an early report, in which patients with right heart failure had significantly reduced daytime blood oxygen tensions and elevated carbon dioxide tensions attributed to chronic obstructive lung disease.[110] Another early study of pulmonary hypertensives with OSA included a skewed population largely with chronic obstructive pulmonary disease.[111] Although causality has not been proven, more recent data have shown an association between pulmonary hypertension and OSA in the absence of clinically evident lung or left heart disease.[112] However, pulmonary artery pressure elevations associated with OSA were mild and seemed to occur in those patients with lower resting daytime oxygenation. Follow-up studies by these investigators, while lacking a control group with which to compare, showed attenuation of heightened pulmonary vasculature pressure responses to hypoxia by 4 months of CPAP therapy, which also resulted in reductions in both elevated and normal pulmonary artery pressures upon follow-up.[113] Although the patients in this study with elevated pulmonary artery pressures at baseline responded more robustly to CPAP therapy, there has otherwise been little demonstrated correlation between severity of OSA, as measured by the AHI and degree of pulmonary hypertension, suggesting interindividual variation in response to hypoxemia. In cross-sectional analysis, statistically significant increases in right ventricular wall thickness in primarily obese patients with the most severe OSA (AHI > 90th percentile) have been demonstrated, although ventricular function and dimensions were no different.[114] This suggests that repetitive elevations of pulmonary artery pressure and pulmonary vascular resistance resulting from OSA may lead to compensatory changes in the right ventricle.

Notwithstanding technical issues related to adequate echocardiographic images in predominantly obese subjects, research into this aspect of OSA is confounded by other comorbidities, drug effects (including occult anorectic ingestion), and difficulties

with finding an appropriate control group with which to compare endpoints. Although OSA may contribute to pulmonary artery pressure elevations in conjunction with other risk factors, current information does not conclusively implicate OSA as a primary cause of severe pulmonary hypertension.

Cardiac Arrhythmias

A number of studies have reported on the association between OSA and various nocturnal arrhythmias. Recent data from the Sleep Heart Health Study, after adjusting for many confounders, showed that, compared with subjects with a respiratory disturbance index less than 5, those with severe OSA (respiratory disturbance index ≥ 30 or more) had a higher rate of atrial fibrillation, nonsustained ventricular tachycardia, and ectopic ventricular beats.[115] The cross-sectional study design limits the relationship to a compelling association, since this and other existing studies cannot confidently identify OSA as a cause of rhythm abnormalities.

In addition to the vascular sympathetic overdrive noted in many people with sleep apnea, heightened vagal output to the heart during apnea may occasionally manifest by peripheral vasoconstriction accompanied by occasionally profound bradycardia.[116] This response is referred to as the "diving reflex" because of its characterization in diving marine mammals. Although bradycardia may be marked in only a minority of patients with OSA, in whom it may correlate with the AHI, these bradyarrhythmias can occur in the absence of any structural heart disease and may respond to effective CPAP therapy.[117-119] The Sleep Heart Health Study found similar, though relatively common, rates of bradycardias and conduction delays between those with severe OSA and those without significant OSA.

Mounting data strengthen the association between OSA and atrial fibrillation. Within 12 months of successful electrical cardioversion, people with untreated sleep were found to have an arrhythmia recurrence rate double that of patients treated with CPAP.[120]

Continuous cardiac monitoring with an atrial defibrillator showed that the onset of nearly 75% of episodes of persistent atrial fibrillation occurred between 8 pm and 8 am,[121] which could partially be explained by the presence of OSA. Use of a validated questionnaire predicted the prevalence of OSA in a population of patients with atrial fibrillation to be 49%, compared with 32% in a control population of patients from a general cardiology clinic.[122] Further longitudinal and outcome-based interventional trials are needed to characterize the relationship between OSA and atrial arrhythmias. In particular, whether OSA is an independent cause of new onset atrial fibrillation remains unknown.

Perhaps on account of its association with heart failure, CSA has been implicated as possibly imparting an increased risk of arrhythmias. Patients with heart failure and CSA have been noted to have a higher prevalence of atrial fibrillation.[73, 97] In a comparison of asymptomatic subjects with left ventricular dysfunction with and without CSA, 24-hour ambulatory cardiac rhythm monitoring revealed a significantly increased incidence of nonsustained ventricular tachycardia in those with severe CSA (AHI > 30), compared with mild or no CSA.[123] Javaheri and colleagues found that arterial hypocapnia was highly predictive of CSA in subjects with left ventricular dysfunction and conferred a 20-fold higher risk of ventricular tachycardia, compared with normocapnia.[124] Although the groups in these studies were well-matched in regard to underlying cardiac systolic function, the exact role of CSA in arrhythmia risk, independent of cardiac disease, remains to be determined.

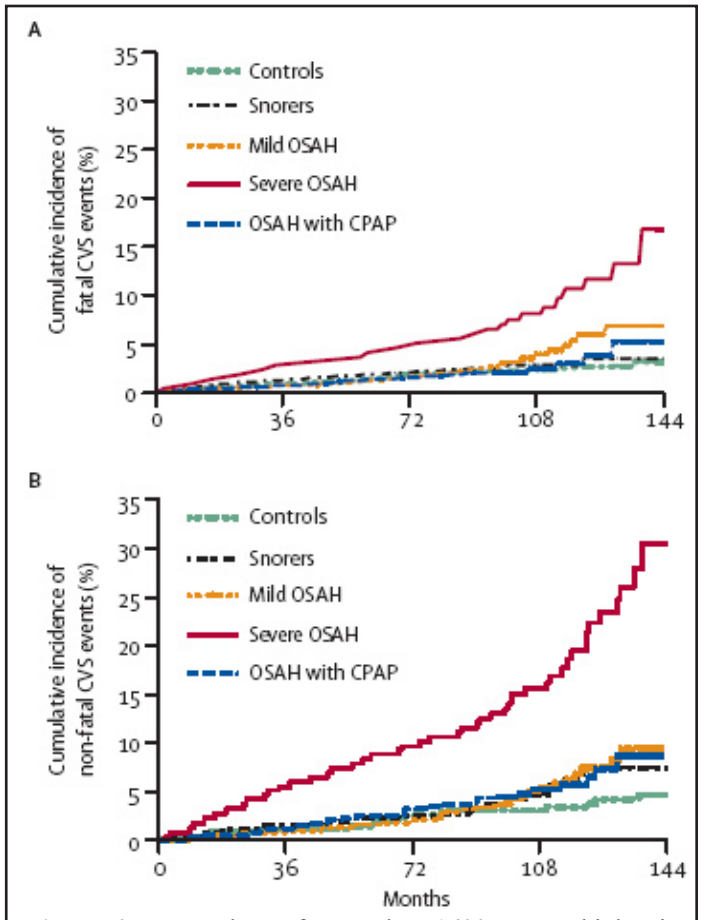

Figure 6—In a cohort of more than 1600 men, a higher incidence of fatal (top) and non-fatal (bottom) cardiovascular events was observed in the 36% with severe OSA who were noncompliant with CPAP treatment. Reproduced with permission from Reference 140.

Ventricular arrhythmias have been reported in patients with OSA,[115, 125] although a causative role for OSA in serious arrhythmias or sudden death has not been definitively proven. However, recent data provide further evidence suggesting such a link. Review of polysomnographic measures in 112 patients with sudden death suggested a markedly higher rate of lethal cardiac events between the hours of midnight and 6 am in those with OSA, compared to those without, along with a direct correlation between AHI and risk of death during the night.[126] Although the study suggests that OSA may influence time of sudden cardiac death, it does not clearly demonstrate that OSA heightens the risk of sudden death from cardiac causes.

The interaction between cardiac rhythm and sleep-disordered breathing is undoubtedly complex. Provocative results from Garrigue et al[127] showing improvement in central as well as obstructive apneas as a result of overdrive atrial pacing in bradycardic patients, have not been confirmed by multiple subsequent clinical trials.[128-130] It may be noteworthy, although of limited clinical importance, that a small reduction in obstructive hypopneas (13.4 to 10.9 per hour) occurred in 1 of the trials after atrial overdrive pacing.[128] Further research in this area may help elucidate hitherto unrecognized pathways in cardiopulmonary interaction, but, at present, there does not appear to be a role for overdrive pacing

in subjects with OSA, bradycardia, and normal systolic function.

Cardiac Ischemia and Vascular Disease

The repetitive insults related to hypoxemia, blood pressure surges, and enhanced sympathetic tone that occur in OSA can be considered a nightly stress test for the heart.[131] Nocturnal ST-segment changes have been reported in OSA patients without clinically significant coronary artery disease[132] but are more common in patients with preexisting angina in whom they tend to be associated with oxygen desaturation.[133, 134] These effects may be reversed by CPAP therapy in patients with sleep apnea.[135]

Several studies have reported a high prevalence of OSA in patients with atherosclerotic heart disease.[136, 137] There are also data that support the role of OSA as a possible prognostic factor in long-term outcomes in coronary artery disease and myocardial infarction.[138, 139]

Recently published 10-year longitudinal follow-up of a large cohort of male patients with severe untreated OSA (noncompliant with CPAP), compared with snorers, treated OSA, and healthy men, demonstrated a higher risk of both fatal and nonfatal cardiovascular events, including myocardial infarction, stroke, and coronary artery bypass grafting in the OSA group (Figure 6).[140] The findings are potentially biased by an OSA group that, at study entry, had a higher baseline prevalence of hypertension and increased serum glucose levels, as well as unmeasured effects attributable to patients who are noncompliant with medical therapy. However, the unprecedented duration of careful follow-up provides further evidence supporting an important relationship between OSA and cardiovascular events, both fatal and nonfatal.

OSA has been associated with a number of factors that could reasonably explain its role in coronary artery disease and subsequent ischemic heart disease. As mentioned previously, elevated levels of vasoactive and trophic substances, such as endothelin and vascular endothelial growth factors, are seen in people with sleep apnea. Endothelial function, found to be impaired in a group of patients with asleep apnea who were otherwise free of clinically evident cardiac or vascular disease, has been linked to an increased risk of cardiovascular events.[30] The hypoxemia-reoxygenation phenomenon occurring repetitively in apneics may act as an oxidative stress on the vasculature, analogous to ischemia-reperfusion injury seen in other disease states,[17] resulting in free radical-mediated damage to the endothelium and providing a subsequent nidus for atherosclerosis.[141] Elevated homocysteine levels have also been noted in a case-control study of patients with ischemic heart disease and OSA,[142] although levels were not increased in otherwise healthy subjects with OSA.[143] Ischemic cardiac disease may indeed be partially related to OSA but could also result indirectly from the association with obesity, glucose intolerance, and other cardiovascular risk factors comorbid with OSA.

Cerebrovascular Disease

Several studies have investigated the association between stroke and sleep-disordered breathing.[144-146] A large prospective study showed self-reported snoring to be an independent risk factor for stroke in women.[147] Until recently, associations with OSA have been reported primarily in cross-sectional and case-control studies, so it had been unclear if OSA is a direct contributor to stroke incidence because comorbidities and risk factors are commonly seen in both diseases. However, Yaggi and colleagues recently reported longitudinal data (mean follow-up 3.4 years) on mortality from stroke and other causes in more than 1000 patients with preexisting OSA, showing an increasing risk of events with OSA severity.[148] Although not powered to detect potential differences related to treatment of OSA, and in contrast to findings in the Marin cohort, there did not appear to be treatment effects in the more than half of patients who were treated with CPAP, lost weight, or underwent upper airway surgery.

It is feasible that stroke, particularly as represented in case-control studies, may itself predispose to sleep-disordered breathing. This may relate to disruption of central respiratory control mechanisms, leading to CSA, or brainstem-mediated upper airway reflexes that may cause obstructive apneas or hypopneas. Indeed, in a report of 161 inpatients with acute stroke or transient ischemic attack who underwent studies at baseline and 3 months later, more than 70% had an AHI greater than 10.[149] Nearly one third of apneas were central in origin during the acute phase. At 3 months, however, the central apneas were significantly reduced, whereas the obstructive events remained stable. This could suggest that obstructive sleep apnea preceded, and perhaps contributed to, stroke, whereas central apneas resulted from the acute neurologic event.

In addition to effects on atherogenesis and blood vessel function noted above, a number of other mechanisms may predispose to stroke in OSA. The strong association with atrial fibrillation may confer a heightened risk of embolic events. Furthermore, OSA has been

shown to promote thrombosis, as evidenced by enhanced platelet aggregation[150] and activation,[151] elevated fibrinogen levels,[152] and diminished fibrinolytic activity.[153] Lastly, Doppler measurements have suggested that apneic events are associated with reduced cerebral blood flow,[154, 155] which can result in cerebral hypoxia.[156] Although CPAP treatment has been shown to reverse some of these findings,[157, 158] the impact of treatment on the occurrence of stroke and death, as demonstrated by the Yaggi study, may be limited and needs further evaluation.

The presence of a patent foramen ovale (PFO) has been linked to stroke risk and has also been invoked as having increased prevalence in OSA, a finding that could conceivably be linked to persistent cardiac transmural pressure changes related to breathing efforts against upper airway obstruction. An initial small study evaluating the prevalence of PFO in subjects with diagnosed OSA found that 33 of the 48 OSA subjects had a PFO when screened with transesophageal echocardiography.[159] Additionally, OSA events have been shown to be able to provoke right-to-left shunting through a PFO, suggesting that OSA may give rise to a higher risk of paradoxical emboli.[160] However, any relationship between OSA and PFO, and any role for PFO as a mechanism increasing stroke risk in OSA, remains to be defined.

SUMMARY

Due to heightened recognition and perhaps a rising prevalence, OSA is increasingly associated with cardiovascular risk factors and disease. Bolstered by well-described pathophysiologic responses to apneas and hypopneas, there are mounting data suggesting a potentially important causative role of OSA in cardiovascular disease, particularly systemic hypertension. Recently published lon-

gitudinal cohort studies have strengthened previously recognized associations with stroke and mortality from cardiac events.

Further studies with rigorous methodologies and designs are needed to draw clearer conclusions about the role of OSA in arrhythmias and heart failure. Findings from the CANPAP trial suggest further exploration of the association between CSA and heart failure are needed, particularly with an increasingly aged population at risk for heart failure. Perhaps most importantly, studies designed to assess the impact of treatment of CSA and OSA, including positive airway pressure therapies, weight loss, and surgery, on cardiovascular disease prevention and outcomes are urgently needed.

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