

## STATE-OF-THE-ART PAPER

# Obstructive Sleep Apnea and Cardiovascular Disease

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Obstructive sleep apnea (OSA) is a common disorder associated with an increased risk of cardiovascular disease and stroke. As it is strongly associated with known cardiovascular risk factors, including obesity, insulin resistance, and dyslipidemia, OSA is an independent risk factor for hypertension and has also been implicated in the pathogenesis of congestive cardiac failure, pulmonary hypertension, arrhythmias, and atherosclerosis. Obesity is strongly linked to an increased risk of OSA, and weight loss can reduce the severity of OSA. The current standard treatment for OSA—nasal continuous positive airway pressure (CPAP)—eliminates apnea and the ensuing acute hemodynamic changes during sleep. Long-term CPAP treatment studies have shown a reduction in nocturnal cardiac ischemic episodes and improvements in daytime blood pressure levels and left ventricular function. Despite the availability of effective therapy, OSA remains an underdiagnosed and undertreated condition. A lack of physician awareness is one of the primary reasons for this deficit in diagnosis and treatment. (J Am Coll Cardiol 2003;41:1429–37) © 2003 by the American College of Cardiology Foundation

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, affecting thousands of patients each year in the U.S. alone (1,2). It is characterized by repetitive partial or complete closure of the upper airway during sleep. Acute physiologic stresses occur during these episodes of asphyxia, including arterial oxygen desaturation, surges in sympathetic activity, and acute hypertension. In a patient with moderate-to-severe OSA, these cycles may occur hundreds of times a night.

Descriptions of sleep-disordered breathing date back nearly 200 years (3), but only in the past 20 years have treatment options made diagnosis and intervention a priority (4). The association between OSA and cardiovascular disease was first raised by observational studies linking snoring, a surrogate for OSA, with increased cardiac events (5). Subsequent studies have demonstrated a clear relationship between the presence and severity of OSA and both systemic hypertension and increased cardiovascular disease (6–8). Currently, OSA is thought to play a role in the pathogenesis of systemic hypertension and congestive cardiac failure, as well as possibly acute coronary syndromes, pulmonary hypertension (PHT), arrhythmias, and cerebrovascular events (9). This review focuses on the epidemiology and diagnosis of sleep apnea, its potential role in the pathogenesis of cardiovascular disease, and the relationship between successful management and improved outcomes.

## EPIDEMIOLOGY AND DIAGNOSIS OF OSA

Obstructive sleep apnea is part of a spectrum of sleep-related breathing disorders that includes snoring, upper airway resistance syndrome (increased respiratory effort without apnea or hypopnea), and central sleep apnea (CSA) (apnea without respiratory effort). The OSA syndrome is the combination of obstructive apneas with daytime tiredness or recurrent awakenings or gasping episodes (10). Initial descriptions of OSA were of severe apnea in obese, middle-age male patients (11,12). It is now appreciated, however, that women account for one-third of OSA patients (13), and a normal body mass index (BMI) is common, particularly in subjects who are elderly (14) or from Southeast Asia (15).

Clinical suspicion of OSA is usually raised by complaints of snoring and daytime tiredness, despite an adequate duration of sleep. Mainly, OSA patients are managed clinically by sleep physicians with a background in respiratory medicine or neurology. Atypical presentations are not uncommon, however, and result in OSA patients presenting to a variety of medical specialists. Indeed, many OSA patients remain asymptomatic from their apneas, presenting instead with hypertension, arrhythmias, or congestive cardiac failure to a cardiologist (Table 1).

Polysomnography is the “gold standard” diagnostic tool for assessing sleep-disordered breathing. It requires an overnight stay at a sleep laboratory, with monitoring of oxygen saturation, heart rate, sleep stage by electroencephalography, nasal airflow, oral airflow, jaw muscle tone by electromyography, sleep position, and chest and abdominal movement. Measurement of these parameters allows diagnosis of the type of sleep-disordered breathing and its severity. The apnea-hypopnea index (AHI)—the number of obstructive events per hour—is the most commonly used

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**Abbreviations and Acronyms**

- AHI = apnea-hypopnea index
- BMI = body mass index
- CI = confidence interval
- CPAP = continuous positive airway pressure
- CSA = central sleep apnea
- OR = odds ratio
- OSA = obstructive sleep apnea
- PHT = pulmonary hypertension
- RR = relative risk

measurement to quantify OSA: mild OSA = 5 to 15 events/h; moderate = 15 to 30 events/h; and severe = >30 events/h (10). A “negative” polysomnographic study does not exclude mild OSA, however, because there is night-to-night variability in the frequency of obstructive events (Fig. 1).

Estimates of the prevalence of OSA have shown a wide variance depending on the methodology used. However, three large-scale studies using polysomnography have reported similar prevalence estimates for OSA (16–18). The Wisconsin Sleep Cohort Study showed that 25% of middle-age men and 10% of middle-age women had sleep-disordered breathing (AHI >5/h), with 4% of men and 2% of women also having hypersomnolence, fulfilling the current diagnostic criteria for the sleep apnea syndrome (16).

Recently, alternative methods of screening for OSA have become available, which allow for home-sleep assessments. The most advanced of these devices records respiratory effort, desaturation, airway obstruction, and sleep stage. Arterial oxygen saturation alone is not an effective screening tool, as the majority of patients with mild OSA have few desaturations (19). In the future, simpler and cheaper methods of diagnosis of sleep-disordered breathing will help improve diagnosis in this under-recognized condition.

**Table 1.** Clinical Evaluation

Symptoms
Loud snoring
Choking or gasping episodes
Tiredness on waking
Excessive daytime sleepiness
Poor concentration and short-term memory
Associated clinical findings
Increased body mass index
Increased neck circumference
Small erythematous oropharynx
Systemic hypertension
Congestive cardiac failure
Pulmonary hypertension
Cor pulmonale
Atypical presentations
Nocturnal palpitations
Morning headaches
Seizures
Gastroesophageal reflux
Nocturia

**VASCULAR DISEASE AND OSA**

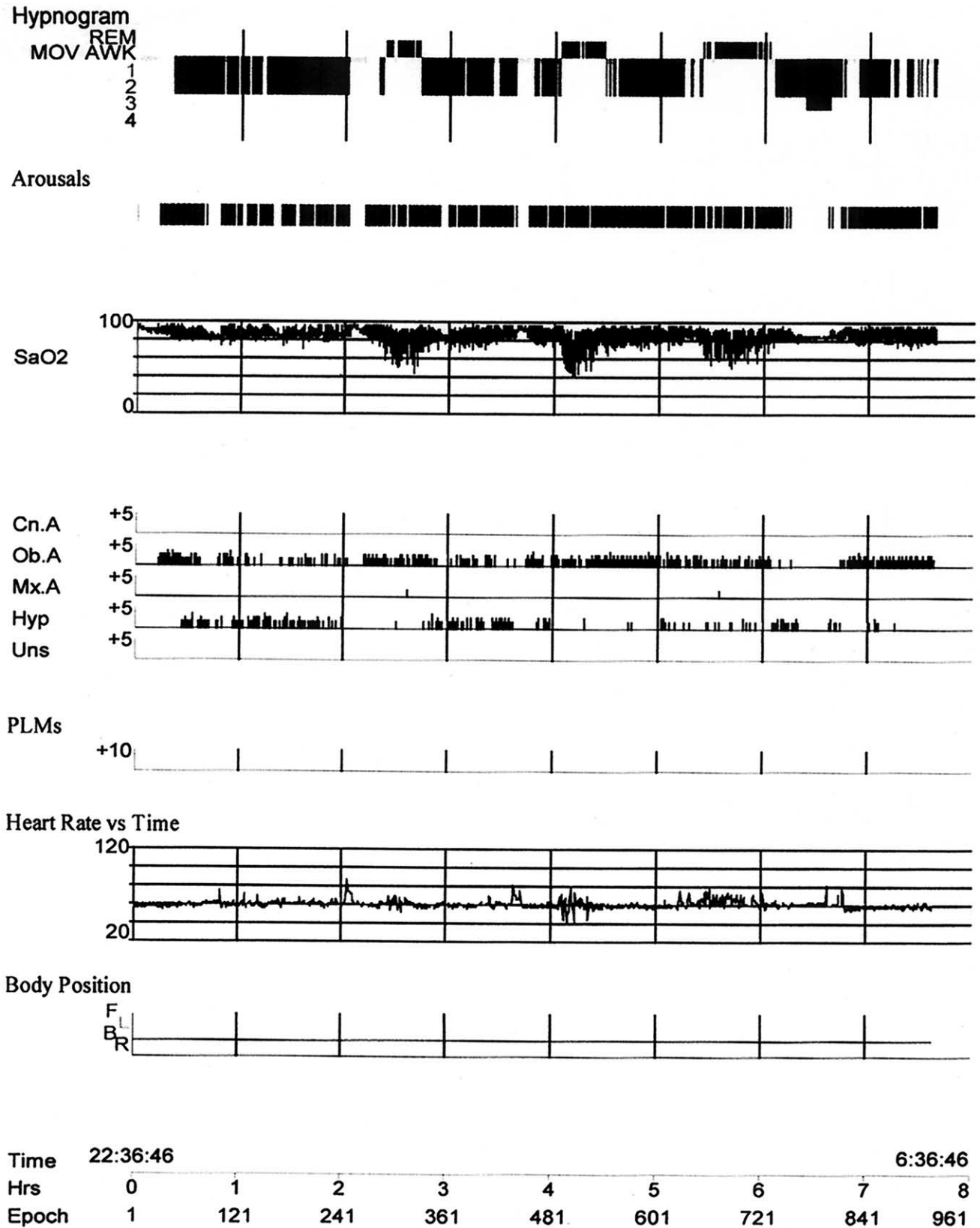
**Sleep apnea and hypertension.** Obstructive sleep apnea is now recognized to be an independent risk factor for daytime hypertension. An association between OSA and hypertension was suggested by a series of population and cohort studies, observational studies in patients attending hypertension clinics and sleep clinics (20,21). A recent sleep clinic study reported a linear relationship between hypertension and severity of OSA, with each extra apneic episode per hour increasing the odds of hypertension by 1% (22). Increased variability of blood pressure and loss of the nocturnal blood pressure dip were also reported (23). In the large Sleep Heart Health Study, 6,132 middle-age subjects had unattended (no technician was present) home, full polysomnographic studies; adjusting for confounders resulted in an odds ratio (OR) of 1.37 (95% confidence interval [CI] 1.03 to 1.83) for hypertension, between the highest and lowest categories of AHI (24).

Prospective confirmation of the association was reported by the Wisconsin Sleep Cohort Study, which measured the incidence of hypertension over a four- to eight-year follow-up in 709 subjects. The AHI was a significant independent predictor of daytime hypertension, with an OR of 2.89 (95% CI 1.46 to 5.64) for those with AHI >15/h and no evidence of a threshold below which the association did not hold (25). The implications of this study are profound, indicating that OSA is a new primary cause of hypertension (Fig. 2).

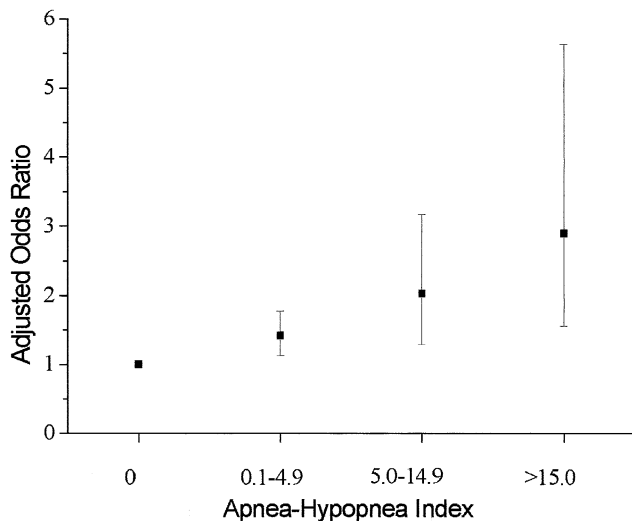
Treatment of OSA with nasal continuous positive airway pressure (CPAP) has led to falls in office, intra-arterial (26), and ambulatory blood pressure (27) in small, nonrandomized studies. Also, CPAP reduces the sympathetic nervous system activation associated with apneas (Fig. 3). A recent prospective, randomized, placebo-controlled comparison between therapeutic and subtherapeutic CPAP reported a reduction in blood pressure, particularly in those with more severe OSA (28).

**Sleep apnea and risk factors for atherosclerosis.** Patients with OSA have many features in common with the “metabolic syndrome,” including systemic hypertension, central obesity (29), and insulin resistance (30). The AHI correlates with BMI, waist-to-hip ratio, hypertension, and diabetes, whereas trends toward lower high-density lipoprotein and elevated triglycerides are reported for OSA subjects <65 years old (14). Although the association between OSA and the metabolic syndrome is, to a large extent, mediated by obesity, AHI remains an independent predictor of insulin resistance, even after correcting for BMI (31).

In a controlled study of patients with type II diabetes and OSA treated with nasal CPAP, Brooks et al. (32) showed improved insulin sensitivity, while weight and drug treatment remained stable. One possible mechanism by which OSA might increase insulin resistance is through increased sympathetic nerve activity, demonstrated to occur not only



**Figure 1.** Polysomnography: an overnight summary. The graphs from the top are: 1) hypnogram: the sleep stage report (MOV AWK = movement when awake; REM = rapid eye movement; 1 to 4 = non-rapid eye movement sleep); 2) arousals: each is a single mark; 3) SaO<sub>2</sub> = percentage oxygen saturation; 4) apnea score: each is a single mark (Cn.A = central apnea; Ob.A = obstructive apnea; Mx.A = mixed apnea; Hyp = hypopnea; Uns = unscored); 5) PLMs = paroxysmal limb movements; 6) heart rate versus time (beats/minute); 7) body position; this subject remained on his back throughout the study; and 8) time (h).



**Figure 2.** Dose-response relationship between the severity of obstructive sleep apnea based on apnea-hypopnea index and the adjusted odds ratio of hypertension, defined as blood pressure >140/90 mm Hg or current treatment with antihypertensive medications. Odds ratio was adjusted for baseline hypertension status, age, gender, habitus, and weekly alcohol and cigarette use.  $p = 0.002$  for linear trend of the logistic regression coefficients. Data from Peppard et al. (25).

at night but also during the day; such activity is reduced by CPAP treatment.

Although the association between OSA and the metabolic syndrome tends to confound studies of the independent effects of OSA on vascular disease, increased awareness of this association should enhance recognition of patients likely to have OSA (Fig. 4) (33).

### ACUTE CORONARY AND CEREBROVASCULAR SYNDROMES

**Sleep apnea and acute cardiovascular events.** The risk of experiencing angina or an acute coronary syndrome is increased in the hours after waking from sleep. In OSA, cyclical variations in heart rate and blood pressure are dramatic (26), more so than many hemodynamic stresses in daily life, and occur during sleep, a time when in normal subjects blood pressure and heart rate are the lowest and least variable. In OSA, increased peripheral sympathetic nerve activity during sleep persists during wakefulness at approximately twice the normal levels (34) and may affect acute coronary events in the early hours of the day.

Early epidemiologic studies suggested an association between snoring and myocardial infarction in men (35). In a subsequent community study when confounding variables were accounted for, the OR for increased coronary disease was reduced but remained significant at 1.4 (95% CI 0.4 to 4.5) (36).

A tightly matched case-control study of acute coronary care patients confirmed OSA as an independent predictor of coronary artery disease, with an OR of 3.1 (7). At long-term follow-up, subjects with coronary artery disease whose OSA remained untreated had worse mortality (37).

Whether there is a relationship between nocturnal OSA and ischemia remains controversial. A randomly selected group of 226 patients having coronary angiography investigated with an overnight sleep study and Holter monitoring demonstrated frequent episodes of nocturnal ischemia, but this had only limited correlation with sleep-disordered breathing (8). Previous smaller studies of patients with moderate-to-severe OSA reported relatively high incidences of nocturnal ischemia (38-40).

**Stroke.** Strong evidence of a link between snoring and stroke now exists from case-control studies and the Nurses Health Study (41-44); after eight-year follow-up, there was an age-adjusted relative risk (RR) of stroke of 1.6 (95% CI 1.21 to 2.12) for occasional snorers and 1.88 (95% CI 1.62 to 2.53) for regular snorers. The BMI and covariate corrections removed the significance of regular snoring, suggesting the effect is partly mediated by obesity, but statistical significance remained for occasional snorers (RR 1.42, 95% CI 1.07 to 1.89) (45).

Mechanisms by which OSA may precipitate stroke include hypertension, mechanical stress on carotid atheroma during the snoring phase of cyclical apneas, altered cerebral perfusion (46,47), increased coagulability (48,49), and/or induction of atrial arrhythmias with thrombus formation leading to embolism.

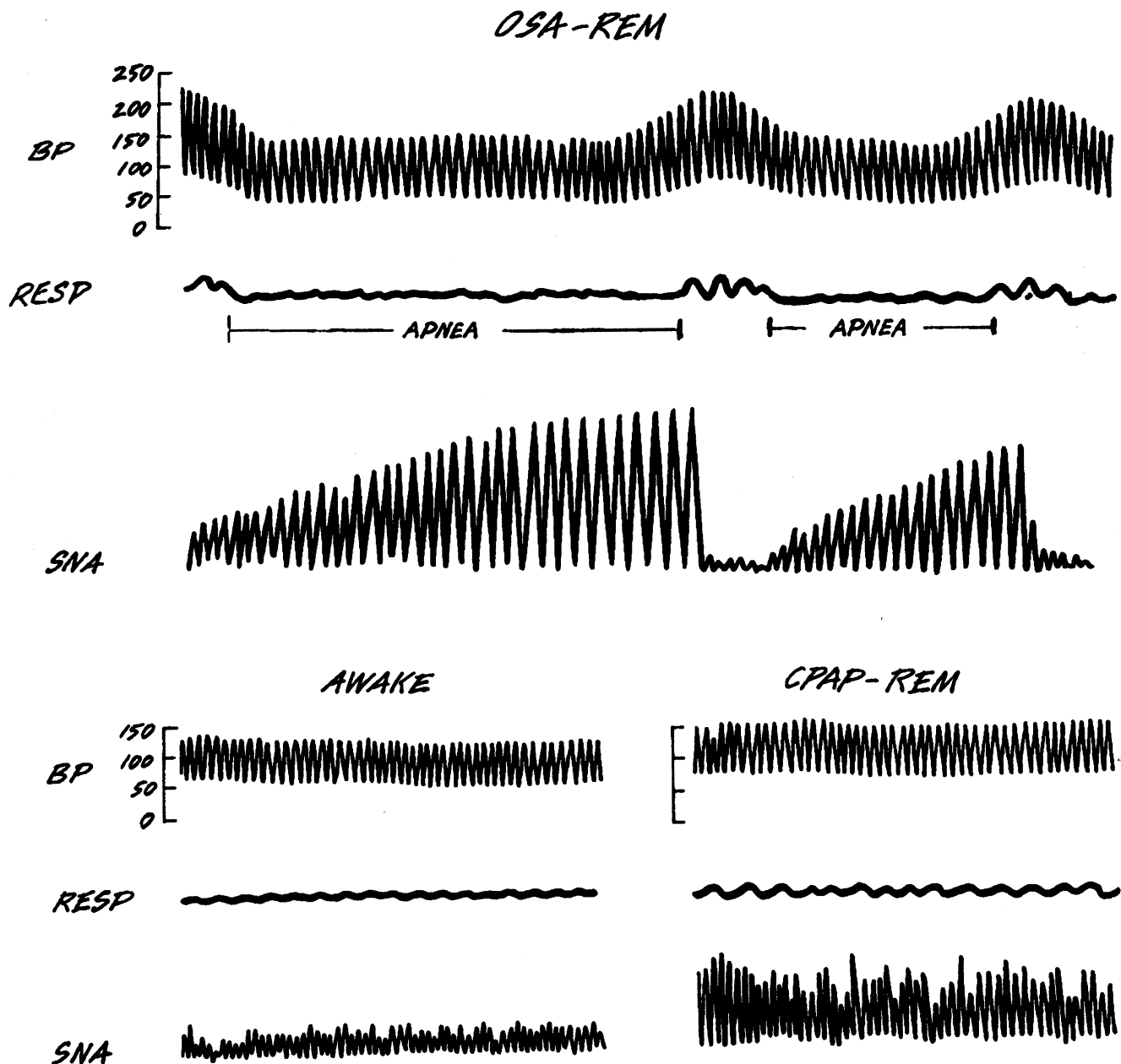
**Arrhythmias.** Both tachyarrhythmias and bradyarrhythmias have been implicated as possible causes of cardiovascular morbidity in OSA patients. The risk of arrhythmia with OSA appears to be related to sleep apnea severity. Analysis of electrocardiographic recordings in 458 patients having sleep studies showed a 58% prevalence of arrhythmias in patients with OSA, compared with 42% in nonapneics, most arrhythmias occurring in those with AHI >40/h (50).

The role of sleep-disordered breathing in arrhythmias in heart failure is still being defined. In a study of 81 males with stable heart failure, incidences of atrial fibrillation and ventricular tachycardia were significantly higher in sleep apnea subjects (AHI >10/h) than in those without apnea (51).

One small, prospective study showed that CPAP reduced premature ventricular contractions and couplets in OSA patients with normal left ventricular function (52). In a small but intriguing study (53), atrial pacing reduced the severity of OSA based on AHI. However, the mechanism by which this might have been achieved is unclear; reflex effects on upper airway tone represent one possible explanation.

### HEART FAILURE AND OSA

Obstructive sleep apnea is common in heart failure patients. Javaheri et al. (51) performed polysomnography on 81 males with stable heart failure, identifying 11% with OSA. Despite only one-quarter of this group reporting tiredness, over one-half had some form of sleep-disordered breathing, with



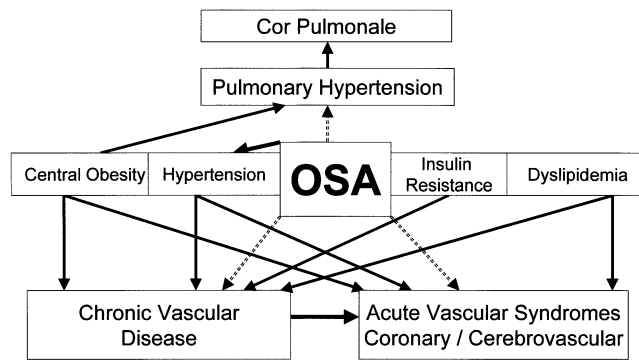
**Figure 3.** Sympathetic nerve activity increases through the obstructive apnea, resulting in marked vasoconstriction followed by increased systolic and diastolic blood pressure. Continuous positive airway pressure (CPAP) stabilizes both sympathetic activity and blood pressure surges. BP = blood pressure (mm Hg); OSA = obstructive sleep apnea; REM = rapid eye movement; RESP = respiration; SNA = sympathetic nerve activation. Adapted from Somers et al. (67) with permission.

CSA in 40%. Central sleep apnea differs from OSA in that there is periodic cessation of breathing with *no respiratory effort*, followed by hyperventilation. The key mechanisms of periodic breathing in heart failure patients are enhanced chemoreflex sensitivity, hypocapnia, and unstable breathing control, especially during sleep (54,55).

Patients with heart failure can have a combination of CSA and OSA, which can vary during sleep or over time. In one study, within-night changes were documented with progression from predominantly OSA early in the night to CSA, presumably due to the fall in the arterial pCO<sub>2</sub> level to below the apneic threshold (56).

A diagnosis of sleep-disordered breathing provides important prognostic information and potential therapeutic options for heart failure patients (57). The frequency of apnea is highly predictive of mortality, with AHI >30/h, providing prognostic information over and above New York Heart Association functional class and left ventricular ejection fraction (58). Treatment of OSA with CPAP improves quality of life, but no published study has been adequately powered to show a mortality benefit (59).

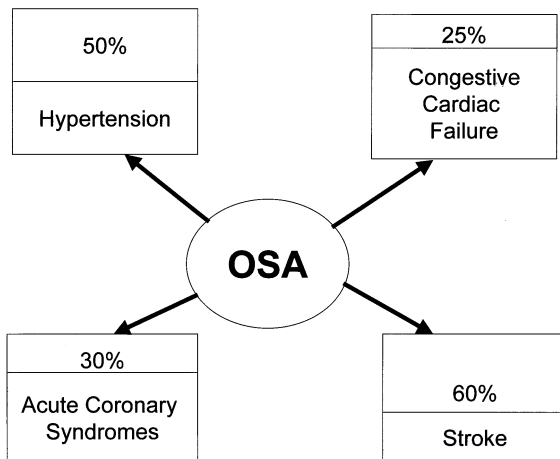
Echocardiographic studies have shown both systolic (60) and diastolic (61) dysfunction with increasing AHI. Possible mechanisms include the effects of hypoxia (62) and the



**Figure 4.** Schema illustrating the risk factor clustering of obstructive sleep apnea (OSA) and the proposed links to both acute and chronic vascular disease. **Solid line** = proven risk factor; **dashed line** = potential risk factor.

repetitive intrathoracic pressure changes that accompany obstructive apneas. Negative intrathoracic pressure increases left ventricular afterload (63), as well as impairs left ventricular relaxation (64). Cardiac contractility is also reduced and left ventricular volumes rise, both at end-systole and end-diastole (65). Hypoxia itself may directly impair the energy-dependent processes of myocyte contraction and relaxation (66). Activation of the sympathetic nervous system, by both hypoxia and arousal, may induce tachycardia and peripheral vasoconstriction, further increasing ventricular afterload (67).

**Pulmonary hypertension.** Acute pulmonary hemodynamic changes during obstructive apneas have been well defined, but the extent to which these translate into permanent



**Figure 5.** Prevalence of obstructive sleep apnea (OSA) in patients with cardiovascular and cerebrovascular disease. The figures used are approximations from published data and are unadjusted for baseline variables (1 to 4): 1. Parati G, Ongaro G, Bonsignore MR, Glavina F, Di Rienzo M, Mancia G. Sleep apnoea and hypertension. *Curr Opin Nephrol Hypertens* 2002;11:201–14; 2. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999;160:1101–6; 3. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep* 1999;22:217–23; and 4. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. *Eur Respir J* 1999;14:179–84.

**Table 2.** Epworth Sleepiness Scale

Situation	
Sitting and reading	
Watching TV	
Sitting in an inactive place (e.g., movie)	
As a passenger in a car without a break for an hour	
Lying down to rest in the afternoon when the circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, while stopped for a few minutes	
Scale	Score
No chance of dozing	0
Slight	1
Moderate	2
High	3
(Score for each situation is added to total)	
Total	
≤6 = Less tired than average	
7–8 = Average	
≥9 = Tiredness requiring investigation	

daytime PHT remains less certain than in the systemic circulation. Sustained daytime PHT in OSA subjects has been investigated in several studies, the majority of which have found an increased prevalence of PHT (68–70).

The largest confounding group, however, is patients with chronic obstructive pulmonary disease (“overlap” syndrome). Only three published studies have excluded patients with this disease; their PHT prevalence results are 20% (71), 41% (69), and 27% (72), respectively. No correlation was found in these studies between the severity of PHT and AHI. Nocturnal desaturation, however, was linked with daytime PHT.

### OSA SCREENING AND MANAGEMENT: A CARDIOLOGIST’S PERSPECTIVE

**Establishing the diagnosis.** The majority of individuals with OSA and vascular disease remain undiagnosed, largely due to limited physician awareness of this association (Fig. 5) (1). All patients with hypertension, obesity, or heart failure should be asked routinely about OSA and referred for a sleep study if they are symptomatic (Table 2). Simple screening questions such as “Do you snore?,” “Are you tired on waking?,” or “Do you fall asleep during the day?” will identify the majority of patients with significant OSA. The Epworth Sleep Scale standardizes these questions by providing a rapid, validated method of screening for tiredness and is useful in both clinical practice and research settings (Table 1) (10).

**Treatment.** For obese subjects, including those with the metabolic syndrome, weight loss is a cornerstone of therapy, not only by reducing AHI, though seldom to normal, but also by improving hypertension, lipid metabolism, and insulin resistance. Patients with a normal BMI, severe OSA at diagnosis, or those having difficulty losing weight require specific treatment of OSA, such as nasal CPAP or an oral appliance.

The mainstay of OSA therapy for the past 20 years has

been nasal CPAP (4). This treatment maintains a patent airway during sleep by splinting the airway with positive pressure applied through a nasal mask, eliminating apneas, sleep fragmentation, and consequent hemodynamic changes. Although CPAP is an effective treatment of OSA, compliance can be a problem, even in patients with severe symptomatic OSA. Some patients do not tolerate the therapy, and others find purchasing a machine financially prohibitive. Early follow-up when commencing CPAP therapy, therefore, is important. Common concerns raised when initiating CPAP therapy include nasal congestion or dryness, which can usually be overcome with a humidifier, and abrasions or mask leak, which respond to local measures. Nursing support and intensive education programs have also been shown to improve compliance (73). Follow-up studies indicate, on average, 4 h of effective CPAP is administered per night, and even this amount of CPAP treatment improves daytime tiredness (74).

The latest development in CPAP treatment is automated CPAP (75). These devices determine the pressure requirements for each breath. Improved tolerability is particularly noticeable in patients who wake frequently, those with body position-dependent and rapid eye movement-related OSA (76). Detailed data logging of compliance and air leak by these devices also allows monitoring of the effectiveness of treatment.

Alternative treatments for OSA in patients who cannot tolerate CPAP include mandibular advancement splints and surgical interventions. Caution is necessary when prescribing these therapies, as apneas are rarely completely averted and less information is available on their effectiveness, particularly in patients with cardiac failure. In extreme situations where OSA is severe and CPAP is not tolerated, tracheostomy will cure OSA (77).

**Who to treat?** Treatment of OSA to relieve symptoms of daytime tiredness and to avoid somnolence-induced motor vehicle and work-related accidents is an established practice (78). Recently there has been increased interest in the role of CPAP to prevent cardiovascular disease and aid in controlling hypertension. Evidence for a dose-response relationship between AHI and daytime hypertension is strong, and small studies have shown improvements in blood pressure (27,79), baroreceptor sensitivity (80), and nitric oxide derivative production (81), and a reduction in sympathetic nervous system activation (67,82,83) with treatment of OSA.

In heart failure patients, CPAP provides symptomatic relief and reduces the need for intubation during acute exacerbations (84). Small trials have demonstrated improved quality of life (85) and exercise capacity (86) with CPAP therapy. Improved left ventricular ejection fraction has also been reported, with deterioration in left ventricular ejection fraction on withdrawal of therapy (87). Mechanisms by which CPAP therapy exerts its beneficial effect may include reductions in left ventricular afterload (88) and sympathetic nerve activity (82). Currently, the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure

Patients with Central Sleep Apnea (CANPAP) is underway, with the aim of further defining the role of CPAP in heart failure therapy (89).

Arrhythmia reduction (52,90) and improved PHT (91) have also been reported with CPAP. For many cardiovascular events, including acute coronary syndromes and sudden death, however, no treatment studies are available, so treatment decisions must be made empirically.

## FUTURE DIRECTIONS

Much data suggest that OSA is a novel cardiovascular disease risk factor; however, it will take a series of carefully conducted pathophysiological and clinical studies to bridge these gaps in our knowledge in this area. Sleep apnea has clearly been demonstrated to be an independent risk factor for hypertension. More importantly, all published studies have shown that a large proportion (40% to 80%) of stroke patients have OSA, suggesting it may increase the stroke risk beyond direct effects on blood pressure level and variability.

We have also to review, and perhaps redefine, OSA from the perspective of heart disease. Established definitions of OSA are based simply on respiratory and neurophysiologic parameters, but if the cardiovascular consequences of this disease are the most important ones, then this disease may be better defined by parameters such as heart rate, rhythm, or blood pressure responses to these breathing events, rather than the events themselves.

Finally, cardiologists have adapted better than most physicians to the need to build an evidence base of efficacy and cost-effectiveness for newer therapies in medicine. Obstructive sleep apnea and the cardiovascular disorders associated with it are all extremely common and we need to establish cost-effective methods to screen for and treat patients with OSA.

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