Sleep-related Breathing Disorders and Cardiovascular Disease

Francoise Roux, MD, Carolyn D'Ambrosio, MD, Vahid Mohsenin, MD

Sleep-related breathing disorders, ranging from habitual snoring to the increased upper airway resistance syndrome to sleep apnea, are now recognized as major health problems. The majority of patients have excessive daytime sleepiness and tiredness. Neuropsychological dysfunction results in poor work performance, memory impairment, and even depression. Until recently, the coexistence of cardiovascular and cerebrovascular diseases with sleep-related breathing disorders was thought to be the result of shared risk factors, such as age, sex, and obesity. However, in the past 5 years several epidemiologic studies have demonstrated that sleep-related breathing disorders are an independent risk factor for hypertension, probably resulting from a combination of intermittent hypoxia and hypercapnia, arousals, increased sympathetic tone, and altered baroreflex control during sleep. Sleep apnea may lead to the development of cardiomyopathy and pulmonary hypertension. Early recognition and treatment of sleep-related breathing disorders may improve cardiovascular function. **Am J Med. 2000;108:396–402.**

Within the past 15 years, there have been important advances in understanding the pathophysiology of sleep-related breathing disorders, including habitual snoring, increased upper airway resistance syndrome, and sleep apnea. Sleep-related breathing disorders have been recognized as important causes of morbidity and mortality (1–11). Among adults, sleep apnea is more common than asthma. In the United States, approximately 12 million people 30 to 60 years of age have obstructive sleep apnea (2), and 38,000 die each year from cardiovascular disease attributed to sleep-related breathing disorders (3). Among the approximately 31 million US citizens aged 65 years and older, nearly 7.5 million have sleep apnea, including 46% with moderate or severe disease (12). Among nursing home residents, up to half have clinically important sleep apnea.

In two recent studies, approximately 40% to 50% of outpatients with asymptomatic or mildly symptomatic congestive heart failure had obstructive sleep apnea or Cheyne-Stokes respiration with central sleep apnea (13,14). Sleep-related breathing disorders may contribute to progression of heart failure and worsen its prognosis (15).

In this article, we review the cardiovascular consequences of sleep-related breathing disorders, including the acute effects of apnea on the cardiovascular system, and the associations between sleep-related breathing disorders and hypertension, cardiac arrhythmias, pulmonary hypertension, and congestive heart failure. We also discuss how congestive heart failure causes periodic breathing during sleep.

From the Yale Center for Sleep Disorders, Yale University School of Medicine, New Haven, Connecticut.

Requests for reprints should be addressed to Vahid Mohsenin, MD, Yale Center for Sleep Disorders, 333 Cedar Street, PO Box 208057, New Haven, Connecticut 06520–8057.

Manuscript submitted April 27, 1999, and accepted in revised form November 16, 1999.

DEFINITION AND METHODOLOGIC ASPECTS OF SLEEP-RELATED BREATHING DISORDERS

There are several types of sleep-related breathing disorders. Sleep apnea is defined as repetitive prolonged cessation of airflow associated with sleep arousal and at times with oxygen desaturation. Sleep apnea can be obstructive, in which respiratory effort persists despite occlusion of the oropharyngeal airway; central, in which both respiratory efforts and airflow cease; or a mixed central/obstructive pattern (16). Hypopnea is defined as a greater than 50% reduction in air flow with either an oxygen desaturation of greater than 3% or an arousal. A respiratory effort-related arousal event occurs when increasing effort leads to an arousal from sleep that does not meet the criteria for apnea or hypopnea. Increasing respiratory effort or out-of-phase breathing is the hallmark of increased upper airway resistance syndrome. However, the measurement of respiratory effort during sleep is difficult, because there are no noninvasive ways to measure increased resistance to breathing. Current techniques include respiratory inductance plethysmography and measurement of nasal pressure (17); change in pulse transit time is being evaluated as a measure of increased respiratory effort (18). Because there is night-to-night variability in the frequency of respiratory events in patients with milder forms of sleep-related breathing disorders, a "negative" polysomnogram does not rule out sleep-related breathing disorders in a symptomatic patient.

The usual daytime manifestations of sleep-related breathing disorders are excessive sleepiness, fatigue, unrefreshing sleep, and poor concentration. The constella-

0002-9343/00/$–see front matter
PII S0002-9343(00)00302-8

tion of obstructive sleep apnea, oxygen desaturation, and excessive sleepiness has been termed the obstructive sleep apnea syndrome.

A recent statement of the American Academy of Sleep Medicine and the American Thoracic Society outlined the diagnostic criteria for sleep-related breathing disorders (17). Obstructive sleep apnea-hypopnea syndrome requires excessive daytime sleepiness that is not better explained by other factors, as well as five or more obstructed breathing events (apnea, hypopnea, or respiratory effort-related arousals) per hour during sleep. The number of these events per hour of sleep determines the Respiratory Disturbance Index (RDI). The severity is rated as mild when there are 5 to 15 events per hour, moderate at 15 to 30 per hour, and severe at greater than 30 events per hour.

Apneic or hypopneic events are commonly associated with oxygen desaturation and are terminated by arousal. These repetitive events are associated with substantial changes in sympathetic discharge and in intrathoracic pressure that affect cardiovascular function.

ACUTE AND TRANSIENT EFFECTS OF SLEEP-RELATED BREATHING DISORDERS ON THE CARDIOVASCULAR SYSTEM

In normal subjects, systemic blood pressure decreases approximately 10% to 15% during sleep, with the greatest reductions occurring in nonrapid eye movement (non-REM) stages 3 and 4 (19). Cardiac output also decreases by approximately 10% during non-REM sleep (19,20). The decrease in cardiac output results from reductions in heart rate and stroke volume. Because systemic blood pressure decreases substantially in conjunction with a less pronounced decrease in cardiac output, systemic vascular resistance probably declines slightly during non-REM sleep.

In contrast with the normal physiologic effect of sleep on the cardiovascular system, the hemodynamic response to apneic stimuli is more complex. The acute hemodynamic consequences of obstructive sleep apnea include systemic and pulmonary hypertension, increased left ventricular afterload, and decreased cardiac output. These changes are primarily the result of sympathetic stimulation, alterations in intrathoracic pressure, and hypoxia and hypercapnia.

Neurohumoral Response to Apnea

Apneic events result in brief surges in sympathetic nervous system activity, vasoconstriction, and transient hypertension (21,22). Systemic blood pressure is usually lowest during the early to middle portion of most apneic episodes. A gradual increase in pressure is then observed, and a sudden elevation occurs after termination of apnea (Figure 1). During apneic episodes that are 35 to 40 seconds in duration, cardiac output decreases by approximately one-third (23). After termination of apnea, cardiac output increases by 10% to 15% above baseline. The combination of increasing systemic pressure and decreasing cardiac output indicates that systemic vascular resistance increases during apnea. Systemic vasoconstriction is believed to be mediated by alpha sympathetic neural activity, because patients with Shy-Drager syndrome, who are sympathetically denervated, have minimal changes in heart rate or systemic pressures in response to apnea (24). During hypoxia and at the termination of apnea, serum catecholamine levels increase, causing acute elevation in pulmonary and systemic blood pressures (25). Some of these alterations persist during wakefulness. The sympathetic neural response to apnea is, in large part, related to hypoxemia and hypercapnia (26,27), although cardiac sympathetic function and integrity, as assessed with radionuclide imaging, are impaired in sleep apnea (28). During the apneic period, heart rate slows in proportion to the duration of apnea and the degree of oxyhemoglobin desaturation (29). Increased vagal efferent activity partly mediates these reductions in heart rate, as atropine usually ameliorates apnea-related bradycardia (30). The resumption of ventilation is associated with a rapid increase in heart rate, presumably in response to a decrease in vagal tone.

Brady- and tachyarrhythmias are common during sleep in patients with obstructive sleep apnea syndrome (31). In addition, several other types of arrhythmias can occur, including sinus pauses of 2 to 13 seconds in duration, ventricular ectopy, and complete heart block. Whereas supraventricular bradyarrhythmias and tachyarrhythmias during sleep is mainly the result of an alteration in sympathetic nervous system tone, ventricular arrhythmias are related to marked hypoxia, because they usually occur when oxyhemoglobin saturation falls below 60% (32).

Effect of Intrathoracic Pressure

During obstructive sleep apnea, the intrathoracic pressure can be as low as -80 cm H_2O (33), which can substantially alter cardiac function (34,35). Increased venous return causes a leftward shift of the interventricular septum (ventricular interdependence), thereby reducing left ventricular compliance and decreasing left ventricular end-diastolic volume (33). Further, the decrease in intrathoracic pressure delays blood leaving the intrathoracic aorta, hence increasing left ventricular afterload (36). The combination of decreased left ventricular end-diastolic volume and increased left ventricular afterload results in decreased stroke volume and cardiac output. As a result of these hemodynamic changes and the surges in catecholamine levels, systemic blood pressure increases cyclically during sleep.

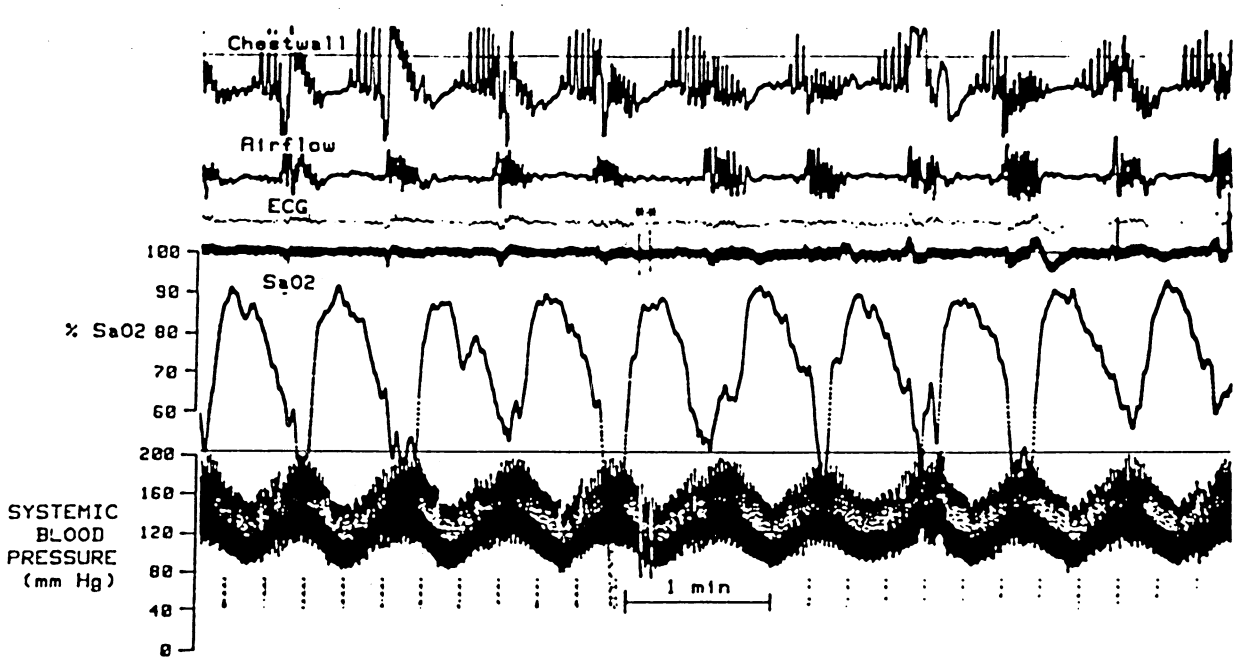

Figure 1. Intermittent increase in systolic and diastolic blood pressure during episodes of obstructive sleep apnea. ECG, electrocardiographic tracing; SaO_2, arterial oxyhemoglobin saturation. Reprinted with permission from (37).

Effect of Hypoxia

Changes in blood oxygen tension are sensed primarily by the carotid chemoreceptors, which, when activated, lead to bradycardia, arteriolar constriction in many vascular beds, and increased secretion of catecholamines. Hypoxia-induced systemic vasoconstriction occurs during apnea, especially when the oxyhemoglobin saturation falls below 65% (37). The resulting hypertension is transient.

Pulmonary vasoconstriction occurs in response to alveolar hypoxia in order to match lung perfusion with ventilation. In patients with obstructive sleep apnea, recurrent episodes of hypoxemia during sleep lead to repeated acute increases in pulmonary artery pressures (38,39). However, fewer than 20% of these patients develop sustained daytime pulmonary hypertension (mean pulmonary artery pressure greater than 20 mm Hg) (40). Right ventricular hypertrophy can occur in patients with more marked obstructive sleep apnea and oxygen desaturation (41–43). However, overt pulmonary hypertension with right ventricular failure is seen primarily in patients with obstructive sleep apnea who also have chronic alveolar hypoventilation and hypercapnia.

CHRONIC CARDIOVASCULAR EFFECTS OF SLEEP-RELATED BREATHING DISORDERS

Sleep-related breathing problems are associated with several cardiovascular diseases. Although a review by Wright et al (44) on the health effects of obstructive sleep apnea dismissed these effects, citing the lack of controlled prospective studies, several recent epidemiologic studies (45–47) and trials (48–51) have demonstrated a strong association between sleep-related breathing disorders and cardiovascular disease that is independent of shared risk factors, such as obesity, age, and male sex (Table).

Hypertension

More than half of patients with obstructive sleep apnea have systemic hypertension (45) compared with an expected prevalence of 20% in middle-aged obese men. Approximately 25% of patients with hypertension have obstructive sleep apnea (52–54). For example, one study found that 30% (14 of 46) of hypertensive men had sleep apnea, with an apnea index greater than 10, compared with only 9% (3 of 34) of controls (53).

A greater prevalence of cardiovascular complications is seen throughout the spectrum of sleep-related breathing disorders, from snoring to obstructive sleep apnea. A study of 3,323 Danish men found an association between self-reported snoring and blood pressure, but the association was lessened when other risk factors were taken into account (55). Lindberg et al (46) prospectively studied 2,668 men aged 30 to 69 years for the development of hypertension in relation to snoring, excessive daytime sleepiness, and other known cardiovascular risk factors during a 10-year follow-up period. Of the habitual snorers, 12.5% reported that they had developed hypertension, compared with 7.4% of the remaining subjects (*P*

Table. Cardiovascular and Cerebrovascular Complications of Sleep-related Breathing Disorders

Complication	Odds Ratio* (95% Confidence Interval)	Reference
Hypertension	1.5 (0.7–3.3)	(11)†
Simple snoring	3.3 (1.1–14)	(56)‡
RDI 5–15 (vs 0)	3.3 (1.0–14)	
RDI 15–30 (vs 0)	4.8 (1.1–23)	
RDI >30 (vs 0)	6.6 (1.1–38)	
Ischemic heart disease	1.9 (1.2–3.1)	(5)
	1.4 (0.4–4.5)	(11)†
Myocardial infarction	5.5 (1.7–18)	(6)
Sudden death	4.1 (1.5–12)	(9)
Stroke	3.1 (1.7–5.9)	(8)

* Unless otherwise indicated, the odds ratios refer to the increase in risk associated with any sleep-related breathing disorder.
† Adjusted for age, sex, body mass index, and smoking status.
‡Adjusted for age, sex, and obesity.
RDI = Respiratory Disturbance Index.

<0.001). After adjustment for age, body mass index, weight gain, smoking, alcohol consumption, and physical activity, habitual snoring was an independent predictor for the development of hypertension, with an odds ratio of 2.6 [95% confidence interval (CI), 1.5 to 4.5)]. In a cross-sectional study of 805 Wisconsin state employees aged 30 to 60 years, polysomnography data were analyzed in relation to blood pressure measurements made before bedtime and after rising (56). Compared with subjects who did not have sleep-related breathing disorders, and after adjustment for body mass index, age, and sex, sleep-related breathing disorders were associated with cardiovascular disease (Table). The dose–response relation between sleep-related breathing disorders, including snoring, and hypertension was independent of known confounders (57).

Sleep-related breathing disorders were risk factors for cardiovascular diseases in a 10-year prospective study in 3,100 men, in which the age-adjusted mortality was 2.9 (95% CI, 1.3 to 6.7) times greater in men with snoring and excessive daytime sleepiness compared with men who did not have these symptoms. Further adjustment for body mass index, hypertension, cardiac disease, and diabetes reduced the relative risk of cardiovascular mortality to 2.0 (95% CI, 0.8 to 4.7) (47). These studies suggest that snoring and the increased upper airway resistance syndrome may be associated with an increased risk of cardiovascular disease.

The evidence supporting a possible cause–effect relation between obstructive sleep apnea and hypertension comes primarily from intervention studies, which have often observed both acute and chronic reductions in blood pressure after treatment of the sleep disorder (49–51,58,59). The chronic application of nasal continuous positive airway pressure (CPAP) to patients with hypertension and obstructive sleep apnea results in reduction of hypertension while awake and during sleep (51,59–61). In one study, the blood pressure–lowering effect of CPAP was seen only in patients whose blood pressure did not decrease during sleep, "nondippers," with obstructive sleep apnea syndrome (62). Some of the effects of CPAP on blood pressure may have been in part the result of weight loss (60). In one study, patients with sleep apnea who were successfully treated had a substantial reduction in cardiovascular events compared with equally affected patients who refused treatment (6).

The mechanisms underlying the development of sustained hypertension in sleep-related breathing disorders are not known. Possibilities include hypoxemia (63,64), repeated arousals (65), sustained increases in catecholamine levels (25) and sympathetic tone (66), enhanced endothelin secretion, and altered eicosanoid activity (67). Furthermore, carotid chemoreceptors may maintain increased peripheral sympathetic activity and blood pressure after cessation of asphyxia or exposure to hypoxia. Increased ventilatory and pressor responsiveness to isocapnic hypoxia has been demonstrated in awake young subjects with mild hypertension (68). Brief exposure to hypoxia may result in sustained increases in peripheral sympathetic activity.

Coronary Artery Disease

A greater risk of coronary artery disease in sleep-related breathing disorders is suggested by several retrospective and cross-sectional studies (6,69,70). The prevalence of sleep-related breathing disorders (measured as RDI of 10 or more) was 37% among men (70) and 30% among women (71) with angiographically verified coronary artery disease. In another study, clinically important sleep apnea was found in 50% of patients with coronary artery disease (72). Nearly 30% of patients with coronary artery disease and concomitant sleep apnea experienced myocardial ischemia during apnea, primarily during REM sleep (73). Patients with coronary artery disease should be screened for sleep-related breathing disorders.

Idiopathic Cardiomyopathy and Congestive Heart Failure

Idiopathic cardiomyopathy and congestive heart failure have been reported in patients with obstructive sleep apnea (74–76). Left ventricular hypertrophy was more common in 30 normotensive patients with obstructive sleep apnea than in controls (77). In one study, all 8 patients with congestive cardiomyopathy of unknown origin had obstructive sleep apnea, and 4-week treatment with nasal CPAP increased the mean (±SD) left ventricular ejection fraction significantly from 37% ± 4% to 49% ± 5% (75).

Cheyne-Stokes respiration occurs in many patients with congestive heart failure (13,14,78), and these patients have a worse prognosis than those without Cheyne-

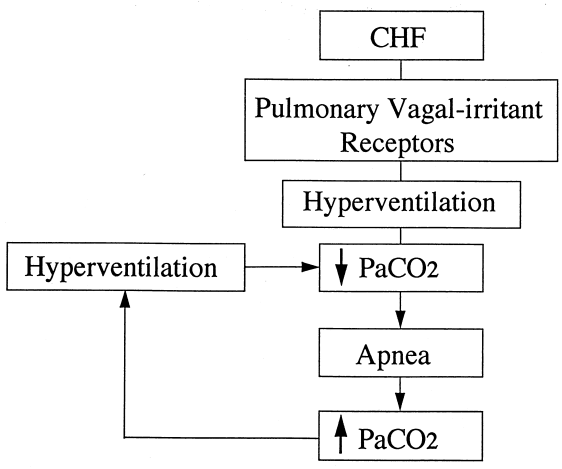

Figure 2. The proposed mechanism of Cheyne-Stokes respiration in congestive heart failure (CHF). Interstitial pulmonary edema stimulates the pulmonary J-receptors, which in turn causes rapid shallow breathing. The resultant hyperventilation lowers the arterial $PaCO_2$ below the apneic threshold. During apnea, the $PaCO_2$ gradually increases and stimulates respiration primarily by means of the central chemoreceptors. This self-perpetuating cycle results in periods of hyperpnea interspersed with apnea.

Stokes respiration (15,79). Cheyne-Stokes respiration appears to be the result of instability of the central control of respiration. Naughton et al (80) have proposed that central apnea in patients with congestive heart failure and Cheyne-Stokes respiration is triggered and propagated by hyperventilation and subsequent reduction in arterial carbon dioxide tension ($PaCO_2$) below the apneic threshold. During apnea or hypopnea, the $PaCO_2$ increases gradually, resulting in rapid breathing and hyperventilation until the $PaCO_2$ again decreases below the apnea threshold (Figure 2). The duration of apnea is proportional to the preceding minute ventilation and the decrease in $PaCO_2$ (80). The hyperventilation and periodic breathing may be the result of stimulation of pulmonary vagal-irritant receptors by pulmonary congestion (81). Patients with congestive heart failure and Cheyne-Stokes respiration have lower values for awake and nocturnal transcutaneous $PaCO_2$ than those without Cheyne-Stokes respiration (80).

Cerebrovascular Disease

Two studies found that about one-third of strokes apparently occurred during sleep (82,83). Among potential risk factors for stroke in one study, only snoring was significantly associated with stroke in sleep (82). In the other study (83), sleep-related breathing disorders were associated with a threefold increase in the risk of stroke (Table).

The hemodynamic changes associated with disordered breathing during sleep may stress the cerebral circulation. In several cross-sectional studies, patients with a history of transient ischemic attacks or stroke have had a greater prevalence of sleep-related breathing disorders than control subjects (8,10,84–86). However, it is not clear whether sleep-related breathing disorders were an independent risk factor for stroke or increased stroke risk because of associated hypertension.

Sleep-related breathing disorders affect cerebral hemodynamics (87,88), including a greater than 50% reduction in cerebral blood flow during apneic and hypopneic events (89). The reduction in blood flow is related to the duration of hypopneas and the degree of oxygen desaturations. In addition, there is also increased platelet activation and aggregation in the obstructive sleep apnea syndrome (90).

SUMMARY

Sleep-related breathing disorders are a group of conditions that range from simple snoring with sleep disruption, to the increased upper airway resistance syndrome, to sleep apnea. These disorders may be associated with substantial cardiovascular morbidity and mortality, and early recognition and treatment may be effective in reducing these complications.

REFERENCES

1. He J, Kryger MH, Zorick FJ, et al. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest*. 1988;94:9–14.
2. Young T, Palta M, Dempsey J, et al. The occurrence of sleep disordered breathing among middle-aged adults. *NEJM*. 1993;328: 1230–1235.
3. A report of the National Commission on Sleep Disorders Research. Wake up America. a national sleep alert. Washington, DC: US Government Printing Office, 1995.
4. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. *Clin Chest Med*. 1998;19:1–19.
5. Koskenvuo M, Kaprio J, Telakivi M, et al. Snoring as a risk factor for ischaemic heart disease and stroke in men. *BMJ*. 1987;294:16–19.
6. Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest*. 1990;97:27–32.
7. Parish M, Shepard J. Cardiovascular effects of sleep disorders. *Chest*. 1990;97:1220–1226.
8. Palomaki H. Snoring and the risk of ischemic brain infarction. *Stroke*. 1991;22:1021–1025.
9. Seppala T, Partinen M, Penttila A, et al. Sudden death and sleeping history among Finnish men. *J Intern Med*. 1991;229:23–28.
10. Mohsenin V, Valor R. Sleep apnea in patients with hemispheric stroke. *Arch Phys Med Rehabil*. 1995;76:71–76.
11. Olson LG, King MT, Hensley MJ, et al. A community study of snoring and sleep-disordered breathing. Health outcomes. *Am J Respir Crit Care Med*. 1995;152:717–720.
12. Ancoli-Israel S, Kripke DF, Klauber MR, et al. Morbidity, mortality, and sleep-disordered breathing in community dwelling elderly. *Sleep*.1996;19:277–282.
13. Blackshear JL, Kaplan J, Thompson RC, et al. Nocturnal dyspnea and atrial fibrillation predict Cheyne-Stokes respiration in patients

with congestive heart failure. *Arch Intern Med*. 1995;155:1297–1302.
14. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation*. 1998;97:2154–2159.
15. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med*. 1996;153:272–276.
16. Hudgel DW. Mechanisms of obstructive sleep apnea. *Chest*. 1992; 101:541–549.
17. The report of an American Academy of Sleep Medicine Task Force: sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999;22:667–689.
18. Argod J, Pepin J-L, Levy P. Differentiating obstructive and central sleep respiratory events through pulse transit time. *Am J Respir Crit Care Med*. 1999;158:1778–1783.
19. Khatri IM, Freis ED. Hemodynamic changes during sleep. *J Appl Physiol*. 1967;22:867–873.
20. Miller JC, Horvath SM. Cardiac output during human sleep. *Aviat Space Environ Med*. 1976;47:1046–1051.
21. Tilkain AG, Guilleminault CS, Schroeder JS, et al. Hemodynamics in sleep induced apnea. Studies during wakefulness and sleep. *Ann Int Med*. 1976;85:714–719.
22. Motta J, Guilleminault C, Schroeder JS, et al. Tracheostomy and hemodynamic changes in sleep-induced apnea. *Ann Intern Med*. 1978;89:454–458.
23. Guilleminault C, Motta J, Mihm F, et al. Obstructive sleep apnea and cardiac index. *Chest*. 1986;89:331–334.
24. Schroeder JS, Motta J, Guilleminault C. Hemodynamic studies in sleep apnea. In: Guilleminault C, Dement WC, eds. *Sleep Apnea Syndromes*. New York: Alan R Liss, 1978:177–196.
25. Ziegler MG, Nelesen R, Mills P, et al. Sleep apnea, norepinephrine-release rate, and daytime hypertension. *Sleep*. 1997;20:224–231.
26. Somers VK, Mark AL, Zavala DC, et al. Contrasting effect of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. *J Appl Physiol*. 1989;67:2101–2106.
27. Smith M, Neidermaier O, Hardy S, et al. Role of hypoxemia in sleep apnea-induced sympathoexcitation. *J Autonomic Nervous System*. 1996;56:184–190.
28. Otsuka N, Ohi M, Chin K, et al. Assessment of cardiac sympathetic function with iodine-123-MIBG imaging in obstructive sleep apnea syndrome. *J Nucl Med*. 1997;38:567–572.
29. Zwillich C, Devlin T, White D, et al. Bradycardia during sleep apnea, characteristic and mechanism. *J Clin Invest*. 1982;69:1286–1292.
30. Imaizumi T. Arrhythmias in sleep apnea. *Am Heart J*. 1980;100: 513–516.
31. Guilleminault C, Connoly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983;52:490–494.
32. Shepard JW, Garrison MW, Grither DA, et al. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. *Chest*. 1985;88:335–340.
33. Shiomi T, Guilleminault C, Stoohs R, et al. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. *Chest*. 1991;100:894–902.
34. Stoohs R, Guilleminault C. Cardiovascular changes associated with the obstructive sleep apnea syndrome. *J Appl Physiol*. 1992;75:583–589.
35. Virolainen J, Ventila M, Turto H, et al. Influence of negative intrathoracic pressure on right atrial and systemic venous dynamics. *Eur Heart J*. 1995;16:1293–1299.
36. Buda AJ, Pinsky MR, Ingels NB, et al. Effect of intrathoracic pressure on left ventricular performance. *NEJM*. 1979;301:453–459.
37. Shepard JW. Cardiopulmonary consequences of obstructive sleep apena. *Mayo Clin Proc*. 1990;65:1250–1259.
38. Sajkov D, Cowie RJ, Thornton AT. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 1994;149:416–422.
39. Laks L, Lehrhaft B, Grustein RR, et al. Pulmonary artery pressure response to hypoxia in sleep apnea. *Am J Respir Crit Care Med*. 1997;155:193–198.
40. Chaouat A, Weitzenblum E, Krieger J, et al. Pulmonary hemodynamics in obstructive sleep apnea syndrome. Results in 220 consecutive patients. *Chest*. 1996;109:380–386.
41. Berman EJ, DiBenedetto RJ, Causey DE, et al. Right ventricular hypertrophy detected by echography in patients with newly diagnosed obstructive sleep apnea. *Chest*. 1991;100:347–350.
42. Noda A, Okada T, Yasuma F, et al. Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest*. 1995;107:1538–1544.
43. Ahmed Q, Chung-Park M, Tomashefski JF. Cardiopulmonary pathology in patients with apnea/obesity hypoventilation syndrome. *Hum Pathol*. 1997;28:264–269.
44. Wright J, Johns R, Watt I, et al. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airway pressure: a systematic review of the research evidence. *BMJ*. 1997; 314:851–860.
45. Hla KM, Young TB, Bidwell T, et al. Sleep apnea and hypertension. A population based study. *Ann Intern Med*. 1994;120:382–388.
46. Lindberg E, Janson C, Gislason T, et al. Snoring and hypertension: a 10 year follow-up. *Eur Respir J*. 1998;11:884–889.
47. Lindberg E, Janson C, Svardsudd K, et al. Increased mortality among sleepy snorers: a prospective population based study. *Thorax*. 1998;53:631–637.
48. Guilleminault C, Eldridge FL, Simmons FB, et al. Sleep apnea syndrome: can it induce hemodynamic changes? *West J Med*. 1975; 123:7–16.
49. Davies RJO, Crosby J, Prothero A, et al. Ambulatory blood pressure and left ventricular hypertrophy in subjects with untreated obstructive sleep apnoea and snoring compared with matched control subjects and their response to treatment. *Clin Res*. 1994;86:417–424.
50. Suzuki M, Otsuka K, Guilleminault C. Long-term nasal continuous positive airway pressure administration can normalize hypertension in obstructive sleep apnea patients. *Sleep*. 1993;16:545–549.
51. Wilcox I, Grunstein RR, Hedner JA, et al. Effect of nasal continuous positive airway pressure during sleep on 24-hour blood pressure in obstructive sleep apnea. *Sleep*. 1993;16:539–544.
52. Kales A, Cadieux AJ, Shaw LC, et al. Sleep apnea in a hypertensive population. *Lancet*. 1984;3:1005–1008.
53. Fletcher EC, DeBehnke RD, Lovoi MS, et al. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med*. 1985;103:190–194.
54. Williams AJ, Houston D, Finbeg S, et al. Sleep apnea syndrome and essential hypertension. *Am J Cardiol*. 1985;55:1019–1022.
55. Jennum P, Hein HO, Suadicani P, et al. Cardiovascular risk factors in snorers. A cross-sectional study of 3,323 men aged 54 to 74 years: the Copenhagen Male Study. *Chest*. 1992;102:1371–1376.
56. Young T, Finn L, Hla KM, et al. Snoring as part of a dose-response relationship between sleep-disordered breathing and blood pressure. *Sleep*. 1996;19:S202–S205.
57. Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med*. 1997;157:1746–1752.
58. Lund-Johansen P, White WB. Central hemodynamics and 24-hour blood pressure in obstructive sleep apnea syndrome: effects of corrective surgery. *Am J Med*. 1990;88:678–682.
59. Mayer J, Backer H, Brandenburg U, et al. Blood pressure and sleep apnea: results of long-term nasal continuous positive airway pressure therapy. *Cardiology*. 1991;79:84–92.

60. Rauscher H, Formanek D, Popp W, et al. Nasal CPAP, and weight loss in hypertensive patients with obstructive apnoea. *Thorax*. 1993; 48:529–533.
61. Schotte DE, Stunkard AJ. The effects of weight reduction on blood pressure in 301 obese patients. *Arch Intern Med*. 1990;150:1701–1704.
62. Engleman HM, Gough K, Martin SE, et al. Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: effects in "non-dippers." *Sleep*. 1996;19:378–381.
63. Iwase N, Kikuchi Y, Hida W, et al. Effects of repetitive airway obstruction on O2 saturation and systemic and pulmonary arterial pressure in anesthetized dogs. *Am Rev Respir Dis*. 1992;146:1402–1410.
64. Garpestad E, Ringler J, Parker JA, et al. Sleep stage influences the hemodynamic response to obstructive sleep apneas. *Am J Crit Care Med*. 1995;152:199–203.
65. Ringler J, Bansner RC, Shannon R, et al. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol*. 1990;69:2143–2148.
66. Hedner J, Enjell H, Sellgreen J, et al. Is high and fluctuating muscle nerve sympathetic activity in the syndrome of sleep apnea of pathogenetic importance for the development of hypertension? *J Hypertension*. 1998;6:S529–S531.
67. Kourembanas S, Marsden PA, McQuillan LP, et al. Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. *J Clin Invest*. 1991;88:1054–1057.
68. Trzebski A, Tafil M, Zoltowski J, et al. Sensitivity of chemoreceptor drive in young men with mild hypertension. *Cardiovasc Res*. 1982; 16:163–172.
69. Hung J, Whitford EG, Parsons RW, et al. Association of sleep apnoea with myocardial infarction in men. *Lancet*. 1990;336:261–264.
70. Mooe T, Rabben T, Wiklund U, et al. Sleep-disordered breathing in men with coronary artery disease. *Chest* . 1996;109:659–663.
71. Mooe T, Rabben T, Wiklund U, et al. Sleep-disordered breathing in women. occurrence and association with coronary disease. *Am J Med*. 1996;101:251–256.
72. Andreas S, Schulz R, Werner G, et al. Prevalence of obstructive sleep apnoea in patients with coronary artery disease. *Cor Art Dis*. 1996; 7:541–545.
73. Schafer H, Koehler U, Ploch T, et al. Sleep-related myocardial ischemia, and sleep structure in patients with obstructive sleep apnea, and coronary artery disease. *Chest*. 1997;111:387–393.
74. Chaudhary BA, Nadini M, Chaudhary T, et al. Pulmonary edema due to obstructive sleep apnea. *South Med J*. 1984;77:499–501.
75. Malone S, Liu PP, Holloway R, et al. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet*. 1991;338:1480–1484.
76. Thomas R. The cardiomyopathy of obstructive sleep apnea. *Ann Intern Med*. 1996;125:425.
77. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnea. *J Hypertension*. 1990;8:941–946.
78. Lieber C, Mohsenin V. Cheyne-Stokes respiration in congestive heart failure. *Yale J Biol Med*. 1992;65:39–50.
79. Likoff MJ, Chandler S, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol*. 1987;59:634–638.
80. Naughton M, Benard D, Tam A, et al. Role of hyperventilation in the pathogenesis of central apnea in patients with congestive heart failure. *Am Rev Respir Dis*. 1993;148:330–338.
81. Churchill E, Cope E. The rapid shallow breathing resulting from pulmonary congestion and edema. *J Exp Med*. 1929;49:531–537.
82. Palomaki H, Partinen M, Juvela S, et al. Snoring as a risk factor for sleep-related brain infarction. *Stroke*. 1989;10:1311–1315.
83. Marler JR, Price TR, Clark GL. Morning increase in onset of ischemic stroke. *Stroke*. 1989;20:473–476.
84. Partinen M. Ischemic stroke, snoring and obstructive sleep apnea. *J Sleep Res*. 1995;4:156–159.
85. Dyken ME, Somers VK, Yamada T, et al. Investigating the relationship between stroke and obstructive sleep apnea. *Stroke*. 1996;27: 401–407.
86. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep*. 1999;22:217–223.
87. Hayakawa T, Terashima M, Hayakawa Y, et al. Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas. *Chest*. 1996;109:16–21.
88. Placidi F, Diomedi M, Cupini LM, et al. Impairment of daytime cerebrovascular reactivity in patients with obstructive sleep apnoea syndrome. *J Sleep Res*. 1998;7:288–292.
89. Netzer N, Werner P, Jochums I, et al. Blood flow of the middle cerebral artery with sleep-disordered breathing: correlation with obstructive hypopneas. *Stroke*. 1998;29:87–93.
90. Bokinsky G, Miller M, Ault K, et al. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy. *Chest*. 1995;108:625–30.