

Obstructive Sleep Apnea: Its Relevance in the Care of Diabetic Patients

Suzanne Boyer, MD, and Vishesh Kapur, MD, MPH

Diabetes and obstructive sleep apnea (OSA) are common disorders that often coexist. One explanation for this overlap is the presence of shared risk factors such as obesity. There may also be a more complex relationship between these conditions in which an underlying metabolic disorder predisposes to both or in which metabolic and autonomic abnormalities associated with one influence the development of the other. Because both diabetes and OSA are associated with increased cardiovascular morbidity and mortality, it is possible that the presence of both conditions results in additive or even synergistic health risks.

For these reasons, it is important to have heightened awareness of symptoms and signs of OSA in a diabetic patient population. This review discusses the pathophysiology, clinical significance, presentation, diagnosis, and treatment of OSA. It also examines associations between OSA and features of diabetes such as insulin resistance and autonomic neuropathy.

Epidemiology of OSA

Sleep-disordered breathing (SDB) refers to an abnormal breathing pattern during sleep that is often quantified as the apnea-hypopnea index (AHI). The clinical diagnosis of OSA requires the presence of both SDB and symptoms of sleep disruption. In other words, SDB refers to the physiological abnormality seen in patients with the clinical syndrome of OSA.

In the general population, SDB is estimated to occur in 9% of middle-aged women and 24% of middle-aged men. However, only 2% of women and 4% of

men also complain of daytime sleepiness and therefore meet strict criteria for OSA.¹ The prevalence is higher in older and more obese populations. It is estimated that up to 60% of community-residing elderly people have significant SDB,² and a recent study of mildly obese but otherwise healthy men (mean body mass index [BMI] = 30 kg/m²) found a 60% prevalence of SDB and a 27% prevalence of OSA.³

It remains unclear why such a large proportion of people with SDB appear to lack symptoms of sleep disruption and therefore do not meet criteria for the syndrome of OSA. However, even symptomatic disease remains widely unrecognized. One recent study estimated that 93% of women and 82% of men with moderate to severe OSA remain undiagnosed.⁴

Clinical Significance of OSA

The diagnosis of OSA has significant clinical implications (Table 1). The

adverse consequences are numerous and include impaired quality of life and increased cardiovascular morbidity and overall mortality.⁵

Impaired Quality of Life

OSA patients often suffer from significant daytime impairment because of excessive sleepiness. Many studies have reported an increased frequency of occupational⁶ and motor vehicle accidents.^{7,8} People with OSA also have impaired neuropsychological and cognitive functioning and reduced quality of life.⁹

Cardiovascular Disease

Because OSA often occurs in the presence of co-morbid conditions, it has been difficult to discern its individual contribution to other medical problems. However, growing evidence supports a link between SDB and adverse cardiovascular outcomes independent of other confounding factors. The most solid evidence comes from prospective and large cross-sectional studies that have revealed a strong link between SDB and the development of hypertension independent of age, sex, and obesity.¹⁰⁻¹²

Cross-sectional and case-control studies have suggested an increased risk for coronary artery disease/myocardial ischemia,^{13,14} cerebrovascular accidents,^{15,16} and cardiomyopathy.^{15,17} Brady- and tachyarrhythmias may occur with increased frequency in patients with SDB,^{18,19} and ventricular tachycardia has been reported in the setting of severe hypoxemia.²⁰

In patients with preexisting cardiovascular disease, the evidence for increased morbidity and mortality is

IN BRIEF

Obstructive sleep apnea (OSA) is a common and frequently unrecognized disorder. It is often found in patients with obesity, diabetes, and cardiovascular disease, and there is growing evidence that sleep apnea is independently associated with increased cardiovascular morbidity. This article reviews the presentation, diagnosis, and treatment of OSA and its related health risks. It also discusses the proposed associations between OSA and diabetes and insulin resistance.

Table 1. Adverse Outcomes Associated With OSA

- Excessive daytime sleepiness
- Impaired cognitive and neuropsychological functioning
- Reduced quality of life
- Occupational and motor vehicle accidents
- Hypertension
- Brady- and tachyarrhythmias
- Coronary artery disease and myocardial ischemia
- Cerebrovascular accidents
- Cardiomyopathy/congestive heart failure
- Pulmonary hypertension
- Increased overall mortality
- Insulin resistance

even stronger.^{21,22} The ongoing Sleep Heart Health Study, a large, prospective, multi-center study, will hopefully provide more definitive answers about these important cardiovascular outcomes.²³

SDB is also associated with mild increases in daytime pulmonary artery pressure. However, contrary to historic reports, it is unlikely to result in clinically significant pulmonary hypertension and cor pulmonale unless it occurs in the presence of coexisting lung disease or obesity hypoventilation syndrome (OHS).^{24,25} In OHS, a condition that may be associated with OSA, obese patients demonstrate both nocturnal and daytime hypoventilation characterized by chronic hypercarbia and hypoxemia.

Pathophysiology of OSA

The SDB seen in OSA is caused by recurrent partial or complete obstruction of the airway during sleep. Resistance to airflow is increased at areas of anatomic narrowing in the nasopharynx and oropharynx. These areas may be further compromised by a sleep-related reduction in muscle tone and the effects of gravity related to being in the supine position. As a result, ventilation may be decreased (hypopnea) or absent (apnea) for several seconds until upper airway

muscle tone increases, allowing the resumption of normal ventilation. This recovery is often associated with an arousal or shift to a lighter sleep stage. As deeper sleep resumes and muscle tone diminishes, the cycle may repeat itself. Hypopneas and apneas may also result in oxygen desaturation of variable degree.

The acute physiological changes that may be seen with SDB include systemic and pulmonary hypertension, dysrhythmia, reduced cerebral blood flow, increased left ventricular afterload, and decreased cardiac output. These changes may be the result of hypoxemia and hypercarbia, repeated arousals, increased catecholamine levels, increased sympathetic tone, and/or intrathoracic pressure swings.²⁶

Any condition that reduces the diameter of any portion of the upper airway may contribute to SDB. Tonsillar hypertrophy or abnormal oral/nasal anatomy may cause airway narrowing.²⁷ Obesity may contribute to obstruction in part because of fatty tissue infiltration of the pharynx.²⁸ Drinking alcoholic beverages or using sedatives at bedtime may exacerbate SDB by reducing muscle tone and by delaying arousal, thereby prolonging respiratory events.²⁹

SDB may vary on a nightly basis depending on sleeping position or sleep stages. It is often more severe in the supine position because of decreased airway stability. It is also more apparent during rapid-eye-movement (REM) sleep, because muscle tone is lowest and control of breathing is most variable during this phase of sleep.³⁰

Diabetes and OSA

Like OSA, diabetes is a common disorder. It is estimated that 8% of American adults have diabetes, 90% of which is classified as type 2 diabetes.³¹ Studies have shown that these patients have a significantly increased risk of atherosclerotic disease and cardiovascular mortality³² compared to those without diabetes. Much emphasis has been placed on the recognition and treatment

of modifiable cardiovascular risk factors such as tobacco abuse, dyslipidemia, and hypertension in this population.

Obesity as a Common Link

Obesity, particularly central obesity that results from increased visceral fat accumulation, is a major risk factor for development of type 2 diabetes.³³ As mentioned earlier, obesity is also a strong risk factor for development of OSA. In one study, an increase in BMI of one standard deviation was associated with a threefold increase in the risk of SDB.¹ Furthermore, central obesity, which is often measured as a waist-to-hip ratio, appears to be an even stronger predictor for SDB than is BMI.²⁸

Because obesity is a risk factor for development of both OSA and type 2 diabetes, it is not surprising that the two conditions often coexist. In one study of middle-aged men, the prevalence of SDB (AHI > 20) was 36% in patients with diabetes compared with 15% in normoglycemic subjects.³⁴ Obesity, measured as either the BMI or waist-to-hip ratio, accounted for most of this discrepancy. However, an independent relationship between diabetes and SDB remained after controlling for this confounder. It seems that in addition to the effects of shared risk factors such as obesity, there may be a more complex interaction between OSA and diabetes.

Syndrome X: Insulin Resistance and SDB

Syndrome X, also known as the metabolic syndrome or the insulin resistance syndrome, refers to a cluster of cardiovascular risk factors whose central feature is thought to be insulin resistance. Other major features of this syndrome include central obesity, hypertension, and dyslipidemia.

One effect of the co-occurrence of these conditions is that the independent risk for cardiovascular disease associated with one condition varies depending on the presence of the other factors. Prospective studies have shown that Syn-

drome X is associated with an increased risk of cardiovascular morbidity and mortality and that this risk is greater than that associated with the individual components of the syndrome.³⁵

Nearly 90% of people with type 2 diabetes demonstrate insulin resistance, and approximately 80% meet the criteria for Syndrome X.³⁵ Although the prevalence is not known, patients with OSA also appear to share many features with Syndrome X patients.

A growing body of epidemiological evidence supports a link between insulin resistance and SDB. Several large cross-sectional studies have demonstrated that SDB is associated with glucose intolerance and insulin resistance independent of confounders such as obesity.^{3,36-38} One study also noted a dose-response relationship between the severity of nocturnal hypoxemia caused by SDB and the degree of insulin resistance.³ Studies evaluating the effect of treatment of sleep apnea on insulin resistance have had conflicting and inconclusive results.^{39,40}

Other physiological findings support a link between OSA and insulin resistance. SDB is associated with increased sympathetic nerve activity and catecholamine release, which in turn may promote hyperinsulinemia by stimulating glycogenolysis and gluconeogenesis.⁴¹ Hypoxemia has also been linked with impaired glucose metabolism in studies of normal men at high altitude.⁴² Last of all, experimental sleep deprivation in healthy subjects appears to be associated with abnormal glucose tolerance.⁴³

As noted previously, OSA is strongly associated with hypertension and central obesity. In fact, with the exception of dyslipidemia, which has not been extensively studied in the OSA population, each feature of Syndrome X has been shown to have some degree of association with SDB independent of the effect of confounders. It has been suggested that OSA may represent an additional element in this metabolic syndrome.⁴⁴

Diabetic Autonomic Neuropathy and SDB

There may be other physiological explanations for an association between OSA and diabetes independent of metabolic dysfunction. Several studies have found an increased prevalence of SDB in patients with diabetes and autonomic neuropathy, including non-obese type 1 diabetic patients.^{45,46} During sleep, respiratory function is partially controlled by the autonomic nervous system. If this system is impaired, the airway may become less stable and control of breathing more variable, which can result in SDB.

Clinical Presentation of OSA

Patients with OSA typically complain of loud snoring and daytime sleepiness. In severe cases, patients fall asleep during stimulating activities, such as driving, or during conversation or meals. More frequently, they fall asleep during passive activities, such as watching TV or reading. Some patients deny sleepiness but note significant daytime fatigue or lack of energy.⁴⁷ They may also describe restless or unrefreshing sleep, episodes of nocturnal choking or gasping, awakening with dry mouth or headaches, frequent nighttime esophageal reflux, and nocturia (Table 2). Patients' bed-partners may report breathing irregularities, such as apnea, or complain of nocturnal kicking, which may be a secondary effect of frequent micro-arousals. Often, these patients are overweight, typically with central obesity, and many have a history of hypertension.

On physical exam, one of the most common findings is a crowded oropharynx. Often, there is hypertrophy of the tissues of the tongue, lateral pharynx/tonsils, soft palate, and/or uvula even to the point of totally obscuring the view of the posterior wall. Other physical findings, such as retrognathia, micrognathia, and a high arch to the hard palate, may also be markers for higher risk.²⁷ The nasopharynx may reveal a deviated septum, nasal polyps, hypertrophied turbinates, or other evidence of chronic rhinitis, all of which

may also contribute to airflow obstruction.⁴⁸ A neck circumference >17 inches in men and >16 inches in women has been found to be predictive of SDB.⁴⁹ The remainder of the exam may reveal secondary effects of OSA, such as an abnormal cardiac exam or lower extremity edema. However, these findings are nonspecific.

Regression models have found a combination of these factors to be the most useful in the diagnosis of OSA. These include hypertension, habitual snoring, witnessed apneas, nocturnal gasping/choking, increased neck circumference, BMI >25 kg/m², age >40 years, and male sex.⁵⁰ Still, neither exam nor history has adequate sensitivity and specificity to make the diagnosis without further studies.

Establishing an OSA Diagnosis

The gold standard for OSA diagnosis is overnight polysomnography in a sleep

Table 2. Clinical Features Associated With OSA

Demographics

- Age >45 years*
- Male sex*

Symptoms

- Loud and habitual snoring*
- Witnessed nocturnal apnea*
- Excessive daytime sleepiness
- Unrestful sleep or frequent awakenings
- Awakening choking or gasping*
- Awakening with headache
- Awakening with sore throat or dry mouth
- Nocturia
- Nocturnal gastroesophageal reflux
- Nocturnal kicking or twitching

Exam Findings

- Obesity, BMI >25 kg/m²*
- Neck circumference >17 inches in men, >16 inches in women*
- Crowded oropharynx
- Micrognathia, retrognathia, or other anatomic abnormality
- Evidence of chronic nasal obstruction

*strongest predictors based on epidemiological data

laboratory. This study typically includes monitoring of snoring, pulse oximetry, electrocardiogram (EKG), muscle tone, eye movement activity (to detect REM sleep), electroencephalogram (EEG, to detect sleep stage and presence of cortical arousals), nasal/oral airflow, and chest and abdominal wall movement (to detect respiratory effort). Obstructive hypopneas and apneas are seen as reduction or absence of airflow with persistent respiratory effort, i.e., chest or abdominal wall movement.

One measure of severity of OSA is the frequency of these respiratory events occurring per hour of sleep, which is usually reported as the AHI or the respiratory disturbance index (RDI). Recently, attempts have been made to standardize the measurement and classification of respiratory events, but in clinical practice there remains significant heterogeneity in the definition of hypopneas.⁵¹ The threshold for an abnormal AHI may range from 5 to 15 depending on the definition used to identify hypopneas. Other important measures of severity include the degree of oxygen desaturation, the amount of sleep disruption (usually interpreted from both an overall arousal index and how well typical sleep patterns are preserved), and the severity of symptoms.

There is continuing controversy over the use of portable, unattended monitoring systems, such as oximetry and limited cardiopulmonary studies, as screening or diagnostic tools for OSA.^{52,53} Oximetry studies are restricted to information on heart rate and saturation to indirectly measure SDB. Cardiopulmonary studies measure respiratory (chest/abdominal excursion, nasal/oral airflow, and oximetry) and cardiac (EKG) parameters but usually exclude sleep parameters (EEG, muscle tone, eye movements). The diagnostic sensitivity and specificity are highly variable depending on the parameters measured, the patient population studied, and the criteria used to indicate the presence of SDB.

The major disadvantage of these studies is the possibility of false-nega-

tive results. These studies are also dependent on participants using the equipment in a home setting without hands-on assistance, which may result in a significant failure rate for data acquisition. At this time, no well-controlled studies have validated the use of unattended limited studies to diagnose OSA, and their routine use is not supported by the American Academy of Sleep Medicine.⁵³

Treatment of OSA

Treatment options for OSA include behavior modification; medical management including devices such as dental appliances or continuous positive airway pressure (CPAP) therapy; and surgical interventions.

Behavioral Modification

Weight loss is probably the most effective lifestyle modification. Although it is clearly a difficult goal for people to accomplish, even modest weight loss may result in significant improvement.²⁸ Avoiding sleeping in the supine position,⁵⁴ sleep deprivation,⁵⁵ and alcohol, hypnotics, or narcotics before bedtime may be beneficial.²⁹

Pharmacotherapy

Pharmacotherapy has a limited role in the management of OSA. Treatment of chronic or seasonal nasal congestion with an appropriate regimen of antihistamines, decongestants, nasal steroids, and/or saline irrigation may improve SDB.⁴⁸

CPAP Via Mask

Lifestyle modifications and treatment of nasal congestion are worthwhile to recommend to all patients; however, except for in those with mild disease, they are usually only partially effective. Most patients require more aggressive treatment, and nasal CPAP is the usual first line of therapy.

Patients are fitted with a nasal or nasal/oral mask through which pressurized air is delivered. This pressurized air acts as a pneumatic splint and prevents

collapse of the airway regardless of the site of obstruction. Appropriately used, CPAP is highly effective at eradicating SDB and associated desaturation and sleep disruption.⁵⁶

CPAP therapy is initiated in a sleep laboratory because the amount of pressure required to eliminate apneas and hypopneas needs to be determined on an individual basis. This also allows the technician to assist patients in finding the best fitting and most comfortable mask and to trouble-shoot any problems that arise during the first night.

Despite the many benefits of CPAP therapy, it is a somewhat intrusive treatment, and it may take several weeks for patients to become comfortable with its nightly use. Fortunately, many patients note improvement in sleep quality and daytime functioning during this same window of time.

Side effects include dry mucus membranes and nasal congestion or rhinorrhea, which can usually be remedied with nasal steroid spray/saline irrigation or by adding a heated humidifier to the CPAP. Patients using nasal masks may be bothered by air escaping from the mouth, which also reduces efficacy of the treatment. Adding a chin strap or switching to an oral/nasal mask should resolve this complaint. The wide variety of available mask styles and sizes should minimize problems with poor fit, such as local skin irritation and air leak. Other side effects, such as claustrophobia and perceived inconvenience, are more difficult to remedy. Long-term compliance ranges from 65 to 80%, and some data suggest that patients with the most severe and symptomatic disease have the highest compliance rates.^{57,58}

Dental Appliances

Dental appliances that modify the position of the tongue or jaw have been used to treat OSA with varying degrees of success. These devices displace the lower jaw and/or tongue forward and relieve posterior airway obstruction during sleep.

A randomized, placebo-controlled

trial that included patients with all degrees of severity of OSA reported short-term normalization of the AHI in about 55% of patients using a mandibular advancement device.⁵⁹ A recent prospective trial reported that 63% of patients with mild to moderate OSA achieved a normal AHI and maintained it after 4 years. Unfortunately, as with CPAP, compliance remains an issue and, at 4 years, one-third of patients had discontinued using the device.⁶⁰

These devices remain a second line therapy, especially for patients with severe disease.

Surgical Intervention

Surgical procedures have a long history in the treatment of OSA. However, outcome data are somewhat limited.

Uvulopalatopharyngoplasty (UPPP) is the most common of these surgeries and involves removal of part of the soft palate, uvula, and redundant pharyngeal tissues. This procedure remedies only one possible area of obstruction, and as a result, the outcome is quite variable. In 1996, an American Academy of Sleep Medicine review of the literature reported that UPPP had a short-term success rate of 40% in patients with OSA.⁶¹ Unfortunately, some of the benefits of the surgery may be lost over time. A recent prospective study of patients with mild to moderate OSA treated with UPPP showed a 50% complete response rate at 1 year, but only 33% continued to have success after 4 years of follow-up. Furthermore, long-term side effects, such as difficulty swallowing and nasal regurgitation, have been reported in 8–10% of patients.⁶⁰

The combination of several surgical procedures addressing different areas of airway obstruction may improve success rates.⁶¹ Interventions may include nasal polypectomy, septoplasty, nasal turbinate reduction, radiofrequency ablation of tongue/soft palate/turbinates, genioglossal advancement, hyoid suspension, and maxillary/mandible surgery.

Tracheostomy is the definitive surgical procedure for OSA because it com-

pletely bypasses all possible areas of obstruction. However, it has significant associated medical and psychological morbidity and should be considered only in the most severe cases in which patients do not tolerate or respond to positive pressure therapy and other interventions.⁶¹

Response to Therapy

Treatment of OSA has been shown to improve symptoms and reduce the adverse medical consequences associated with the disorder. Several prospective, randomized, placebo-controlled trials have shown improvement in daytime sleepiness, cognitive functioning, psychological well-being, and quality of life with CPAP therapy.^{62–64} Prior observational studies are now supported by recent randomized, placebo-controlled trials showing that short-term CPAP therapy results in a small but statistically significant drop in blood pressure.^{65,66} Further studies are needed to establish whether this will correlate with a clinically significant improvement in control of hypertension over the long term. Data from retrospective studies suggest a reduction in motor vehicle accidents⁶⁷ and arrhythmia¹⁸ and improvement in pulmonary hemodynamics,⁶⁸ heart failure,¹⁷ and overall survival.⁵

Conclusion

In summary, diabetes and OSA are common disorders that often coexist in the setting of shared risk factors and perhaps a similar metabolic environment. Both disorders are associated with adverse cardiovascular morbidity and mortality. Although no studies have specifically evaluated cardiovascular outcomes when both conditions are present, it is likely that the risks are additive or perhaps even synergistic.

Currently, emphasis is being placed on identifying and treating modifiable cardiovascular risk factors, such as tobacco abuse, obesity, hyperglycemia, hypertension, and dyslipidemia. Today, there is growing evidence that OSA should be added to this list. Clinicians need to be

vigilant in screening and treating diabetic patients for OSA.

REFERENCES

- ¹Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 328:1230–1235, 1993
- ²Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O: Sleep-disordered breathing in community-dwelling elderly. *Sleep* 14:486–495, 1991
- ³Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartx AR, Smith PL: Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 165:677–682, 2002
- ⁴Young T, Evans L, Finn L, Palta M: Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20:705–706, 1997
- ⁵He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest* 94:9–14, 1988
- ⁶Lindberg E, Carter N, Gislason T, Janson C: Role of snoring and daytime sleepiness in occupational accidents. *Am J Respir Crit Care Med* 164:2031–2035, 2001
- ⁷Masa JF, Rubio M, Findley LJ: Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. *Am J Respir Crit Care Med* 162:1407–1412, 2000
- ⁸Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J: The association between sleep apnea and the risk of traffic accidents. *N Engl J Med* 340:847–851, 1999
- ⁹Baldwin CM, Griffith KA, Nieto FJ: The association of sleep-disordered breathing and sleep symptoms with quality of life in the sleep heart health study. *Sleep* 24:96–105, 2001
- ¹⁰Nieto FJ, Young TB, Lind BK, Shahar E: Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 283:1829–1836, 2000
- ¹¹Peppard PE, Young T, Palta M, Skatrud J: Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 342:1378–1384, 2000
- ¹²Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A: Association of hypertension and sleep-disordered breathing. *Arch Intern Med* 160:2289–2295, 2000
- ¹³Peker 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* 14:179–184, 1999
- ¹⁴Moore T, Rabben T, Wiklund U, Franklin KA, Eriksson P: Sleep-disordered breathing in men with coronary artery disease. *Chest* 109:659–663, 1996
- ¹⁵Shahar E, Whitney CW, Redline S, Lee ET, Newman AB: Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the

Sleep Heart Health Study. *Am J Respir Crit Care Med* 163:19–25, 2001

¹⁶Dyken ME, Somers VK, Yamada T: Investigating the relationship between stroke and obstructive sleep apnea. *Stroke* 27:401–407, 1996

¹⁷Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD: Obstructive sleep apnea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet* 338:1480–1484, 1991

¹⁸Harbison J, O'Reilly P, McNicholas WT: Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *Chest* 118:591–595, 2000

¹⁹Hoffstein V, Mateika S: Cardiac arrhythmias, snoring, and sleep apnea. *Chest* 106:466–471, 1994

²⁰Shepard JW, Garrison MW, Grither DA: Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. *Chest* 88:335–340, 1985

²¹Moore T, Franklin KA, Holmstrom K, Rabben T, Wiklund U: Sleep-disordered breathing and coronary artery disease. *Am J Respir Crit Care Med* 164:1910–1913, 2001

²²Peker Y, Hedner J, Kraiczi H: Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 162:81–86, 2000

²³Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW: The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 20:1077–1085, 1997

²⁴Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP: Pulmonary arterial hypertension in patients with sleep apnoea syndrome. *Thorax* 55:934–939, 2000

²⁵Kessler R, Chaouat A, Weitzenblum E, Oswald M, Ehrhart M, April M, Krieger J: Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. *Eur Respir J* 9:787–794, 1996

²⁶Roux F, D'Ambrosio C, Mohsenin V: Sleep-related breathing disorders and cardiovascular disease. *Am J Med* 108:396–402, 2000

²⁷Partinen M, Guilleminault C, Quera-Salva MA, Jamieson A: Obstructive sleep apnea and cephalometric roentgenograms: the role of anatomic upper airway abnormalities in the definition of abnormal breathing during sleep. *Chest* 93:1199–1205, 1988

²⁸Strobel RJ, Rosen RC: Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep* 19:104–115, 1996

²⁹Berry RB, Desa MM, Light RW: Effect of ethanol on the efficacy of nasal continuous positive airway pressure as a treatment for obstructive sleep apnea. *Chest* 99:339–343, 1991

³⁰Oksenberg A, Silverberg D, Arons E, Radwan H: The supine position has a major effect on optimal nasal continuous positive airway pressure: relationship with rapid eye movements and non-rapid eye movements sleep, body mass index, respiratory disturbance index and age. *Chest* 116:1000–1006, 1999

³¹Harris MI, Flegal KM, Cowie CC: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998

³²Saydah SH, Loria CM, Eberhardt MS, Brancati FL: Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care* 24:447–453, 2001

³³Haffner SM: Epidemiology of type 2 diabetes: risk factors. *Diabetes Care* 21:C3–C7, 1998

³⁴Elmasry A, Lindberg E, Berne C, Janson C, Gislason T, Tageldin MA, Boman G: Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study. *J Intern Med* 249:153–161, 2001

³⁵Isomma B, Almgren P, Tuomi T: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001

³⁶Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS: Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 165:670–676, 2002

³⁷Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Loutsikas A, Lin H, Kales A, Chrousos GP: Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance and hypercytokinemia. *J Clin Endocrinol Metab* 85:1151–1158, 2000

³⁸Strohl KP, Novak RD, Singer W: Insulin levels, blood pressure and sleep apnea. *Sleep* 17:614–618, 1994

³⁹Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grunstein RR, Sullivan CE, Yue DK: Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab* 79:1681–1685, 1994

⁴⁰Chin K, Shimizu K, Nakamura T, Narai N, Masuzake H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M: Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 100:706–712, 1999

⁴¹Dimsdale JE, Coy T, Ancoli-Israel S, Mills P, Clausen J, Ziegler MG: Sympathetic nervous system alterations in sleep apnea: the relative importance of respiratory disturbance, hypoxia, and sleep quality. *Chest* 111:639–642, 1997

⁴²Larsen JJ, Hansen JM, Olsen NV, Galbo H, Dela F: The effect of altitude hypoxia on glucose homeostasis in men. *J Physiol* 504:241–249, 1997

⁴³Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. *Lancet* 354:1435–1439, 1999

⁴⁴Wilcox I, McNamara S, Collins F, Grunstein RR, Sullivan CE: "Syndrome Z": the interaction of sleep apnoea, vascular risk factors, and heart disease. *Thorax* 53:S25–S28, 1998

⁴⁵Ficker JH, Dertinger SH, Siegfried W, Konig HJ, Pentz M, Sailer D, Katalinic A, Hahn EG: Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neu-

ropathy. *Eur Respir J* 11:14–19, 1998

⁴⁶Mondini S, Guilleminault C: Abnormal breathing patterns during sleep in diabetes. *Ann Neurol* 17:391–395, 1985

⁴⁷Chervin RD: Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest* 118:372–379, 2000

⁴⁸Mirza N, Lanza DC: The nasal airway and obstructed breathing during sleep. *Otolaryngol Clin North Am* 32:243–262, 1999

⁴⁹Davies RJ, Ali NJ, Stradling JR: Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. *Thorax* 47:101–105, 1992

⁵⁰Rowley JA, Aboussouan LS, Badr MS: The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. *Sleep* 23:929–938, 2000

⁵¹Redline S, Kapur V, Sanders M, Quan S, Gottlieb D: Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am J Respir Crit Care Med* 161:369–374, 2000

⁵²Netzer N, Eliasson AH, Netzer C, Kristo DA: Overnight pulse oximetry for sleep-disordered breathing in adults: a review. *Chest* 120:625–633, 2001

⁵³Chesson AL, Ferber RA, Fry JM, Grigg-Damberger M, Hartse KM, Hurwitz TD, ASDA Standards of Practice Committee: Practice parameters for the indications for polysomnography and related procedures. *Sleep* 20:406–422, 1997

⁵⁴Jokic R, Klimaszewski A, Crossley M, Sridhar G, Fitzpatrick M: Positional treatment vs. continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome. *Chest* 115:771–781, 1999

⁵⁵Neilly JB, Kribbs NB, Maislin G, Pack AI: Effects of selective sleep deprivation on ventilation during recovery sleep in normal humans. *J Appl Physiol* 72:100–109, 1992

⁵⁶Strollo PJ, Sanders MH, Atwood CW: Positive pressure therapy. *Clin Chest Med* 19:55–68, 1998

⁵⁷Popescu G, Latham M, Allgar V, Elliott MW: Continuous positive airway pressure for sleep apnoea/hypopnea syndrome: usefulness of a 2 week trial to identify factors associated with long term use. *Thorax* 56:727–733, 2001

⁵⁸McArdle N, Devereux G, Heidarnahad H: Long-term use of CPAP therapy for sleep apnoea/hypopnea syndrome. *Am J Respir Crit Care Med* 159:1108–1114, 1999

⁵⁹Mehta A, Qian J, Petocz P, Darendeliler M, Cistulli P: A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 163:1457–1461, 2001

⁶⁰Walker-Engstrom M, Tegellberg A, Wilhelmsson B, Ringqvist I: Four-year follow up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea. *Chest* 121:739–746, 2002

⁶¹Sher AE, Schechtman KB, Piccirillo JF: The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syn-

drome: an American Sleep Disorders Association review. *Sleep* 19:156-177, 1996

⁶²Montserrat JM, Ferrer M, Hernandez L, Farre R, Vilagut G, Navajas D, Badia JR, Carrasco E, De Pablo J, Ballester E: Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome. *Am J Respir Crit Care Med* 164:608-613, 2001

⁶³Jenkinson C, Davies RJ, Mullins R, Stradling JR: Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized prospective parallel trial. *Lancet* 353:2100-2105, 1999

⁶⁴Henke KG, Grady JJ, Kuna ST: Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypop-

nea syndrome. *Am J Respir Crit Care Med* 163:911-917, 2001

⁶⁵Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 359:204-210, 2002

⁶⁶Faccenda JF, Mackay TW, Boon NA, Douglas NJ: Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 163:344-348, 2001

⁶⁷George CFP: Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 56:508-512, 2001

⁶⁸Sajkov D, Wang T, Saunders NA, Bune AJ, McEvoy R: Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 165:152-158, 2002

Suzanne Boyer, MD, is a senior fellow and Vishesh Kapur, MD, MPH, is an assistant professor of medicine in the Department of Pulmonary and Critical Care Medicine and director of the Sleep Disorder Center at the University of Washington School of Medicine, in Seattle.