Sleep Apnea and the Heart: Diagnosis and Treatment

Dai Yumino, MD, Hiroshi Kasanuki, MD

Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan

Although sleep apnea is closely associated with cardiovascular disease, it remains underdiagnosed and undertreated. Obstructive sleep apnea elicits a cascade of harmful cardiovascular stimuli, and central sleep apnea is a prognostic factor for heart failure and may exert adverse effects on outcomes. The adverse effects of obstructive sleep apnea can promote the development of atherosclerosis and have also been implicated in the pathogenesis of cardiovascular disease. Sleep apnea characterized by variables of the autonomic nervous system may have a direct association with arrhythmia. Polysomnography with electroencephalography is the gold standard for assessing sleep apnea. Alternative methods of screening for OSA have recently become available. Continuous positive airway pressure for obstructive sleep apnea reduces cardiac risk and cardiovascular disease mortality. Targeting sleep apnea in the primary and/or secondary prevention of cardiovascular disease may lead to better outcomes.
[Rev Cardiovasc Med. *2008;9(3):159-167*]

Key words: Heart failure • Sleep apnea • Cardiovascular disease • Apnea-hypopnea index • Continuous positive airway pressure

Growing evidence from epidemiologic studies suggests that obstructive sleep apnea (OSA) may be a treatable risk factor for hypertension and cardiovascular disease (CVD),[1,2] and central sleep apnea (CSA) is a prognostic factor for heart failure (HF)[3] that may constitute a separate, additional adverse influence on outcomes.[4] Despite the overwhelming evidence showing a close association between sleep apnea and CVD, sleep apnea remains underdiagnosed and undertreated. After discussing the diagnosis of sleep apnea, this article will examine the association between OSA and CVD factors such as atherosclerosis,

hypertension, vascular disease, and pulmonary hypertension arrhythmias. It will also consider implications of OSA and CSA in patients with heart failure. Treatment options for OSA and CSA will be presented.

Diagnosis of Sleep Apnea

OSA is caused by upper airway collapse during inspiration and is accompanied by strenuous efforts to breathe. CSA is characterized by apneas secondary to diminution or cessation of thoracoabdominal respiratory movement due to decreased central respiratory drive. The apnea-hypopnea index (AHI) describes the number of apneas and hypopneas that occur per hour of sleep. OSA, defined as the presence of an AHI of 5 or more, is found in 24% of middle-aged men and 9% of middle-aged women.[5] CSA is primarily seen in patients with HF, although occasionally it may occur in healthy individuals.

Evidence that OSA is a treatable risk factor for CVD is accumulating, but physicians still pay little attention to patients' breathing patterns, partly due to the limitations of physical examinations and sleep studies. OSA patients generally snore and experience excessive daytime sleepiness. In contrast, most cardiovascular patients experience no significant difference in sleepiness with or without OSA.[6] Similarly, HF patients with CSA do not complain of significant sleepiness.[7] The symptoms may overlap with the fatigue characteristic of patients with severe HF. Therefore, patients with CVD may overlook sleep apnea, which could have adverse effects on their disease status. Table 1 shows clinical evaluations of patients with CVD and OSA. Polysomnography with electroencephalography is the gold standard for assessing sleep apnea. Recently, alternative methods of screening for OSA have become available, which allow for home assessments. In the future, simpler and less expensive methods for diagnosing sleep apnea will improve the diagnosis of this overlooked condition.

Table 1
Signs and Symptoms Suggestive of OSA With Cardiovascular Diseases

General Symptoms
Loud snoring
Choking or gasping episodes
Excessive daytime sleepiness
Nonrestorative sleep
Fatigue
Typical Presentations With Cardiovascular Disease
Nocturia
Nocturnal palpitations
Morning headaches
Gastroesophageal reflux
Paroxysmal nocturnal dyspnea
Peripheral edema
Difficult-to-control blood pressure
Cor pulmonale
Others
Witnessed apneas
Family history
Increasing body weight (especially neck circumference)

OSA, obstructive sleep apnea.

Cardiovascular Disease and Obstructive Sleep Apnea

OSA elicits a cascade of unfavorable cardiovascular stimuli during sleep that is characterized by repetitive apnea-induced hypoxia, generation of exaggerated negative intrathoracic pressure, arousals from sleep, sympathetic nervous system activation, and parasympathetic withdrawal, as well as the production of reactive oxygen species and inflammatory mediators.[8,9] Downstream, these stimuli promote trophic stimulation of the myocardium, vascular endothelial dysfunction, increased platelet aggregability, and insulin resistance. These adverse effects can promote the development of atherosclerosis and have also been implicated in the pathogenesis of CVD.[8] A recent prospective cohort study has shown that compared with healthy controls, untreated male patients with severe OSA have significantly greater risks of fatal and nonfatal cardiovascular events (odds ratios, 2.87 and 3.17, respectively).[10] Figure 1 shows the estimated correlation between the prevalence of OSA and CVD.

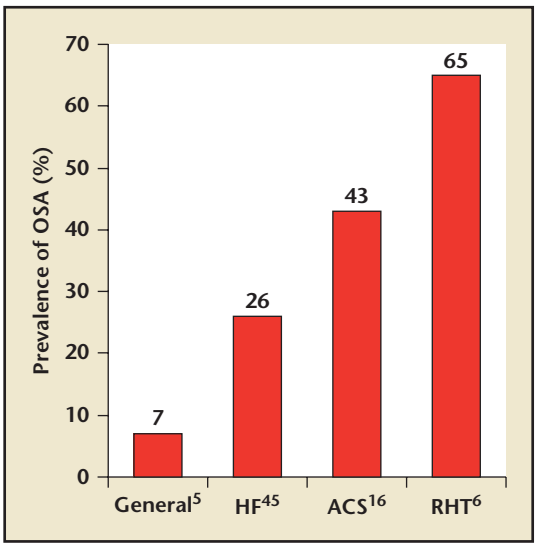


Figure 1. *Prevalence of OSA (apnea-hypopnea index ≥ 15/h) in patients with cardiovascular disease. OSA, obstructive sleep apnea; HF, heart failure; ACS, acute coronary syndrome; RHT, refractory hypertension.* www.medreviews.com

Atherosclerosis

There is a close correlation between markers of CVD and OSA. However, demonstration of an independent association between OSA and atherosclerosis has been difficult because the majority of patients with OSA share several traditional risk factors for atherosclerosis, including obesity, hypertension, and insulin resistance.[8] Previous studies demonstrated that compared with individuals without OSA matched for age, sex, body mass index, and blood pressure, those with OSA had more pronounced signs of early atherosclerosis as manifested by greater carotid artery intima-medial thickness and faster carotid to femoral artery pulse-wave velocity.[11] Furthermore, 4 months of continuous positive airway pressure (CPAP) treatment significantly improved markers of atherosclerosis in normotensive middle-aged men with severe OSA.[12] It is, however, premature to recommend screening for and treatment of OSA as a strategy for primary or secondary prevention of atherosclerosis and its consequences.

Hypertension

The evidence supporting a causal association between OSA and hypertension is compelling. Perhaps the most convincing prospective data were provided by the Wisconsin Sleep Cohort Study,[1] which demonstrated an independent association between OSA at baseline and the development of new hypertension within 4 years. The most recent guidelines placed OSA at the top of the list of causes of secondary hypertension.[13] Randomized, placebo-controlled studies demonstrated that several months of CPAP therapy resulted in a significant reduction in daytime blood pressure.[14] However, Barbé and colleagues[15] found that in 55 severe OSA patients without daytime sleepiness, 24-hour blood pressure monitoring did not show any variation from baseline to 6 weeks after initiation of CPAP treatment.

Resistant hypertension patients have a high incidence of cardiovascular events and thus represent an important healthcare problem. A recent study has demonstrated that 65% of resistant hypertension patients had OSA, and 3-month CPAP treatment significantly reduced systolic blood pressure (−5.2 mm Hg), especially nocturnal values (−6.1 mm Hg).[9] It is noteworthy that those patients generally presented a low pretest clinical probability of OSA. In that study, 55% of patients reported chronic snoring, and only 18% experienced daytime sleepiness.[9] This observation supports the need for sleep studies in all patients with resistant hypertension, regardless of the clinical characteristics of OSA.

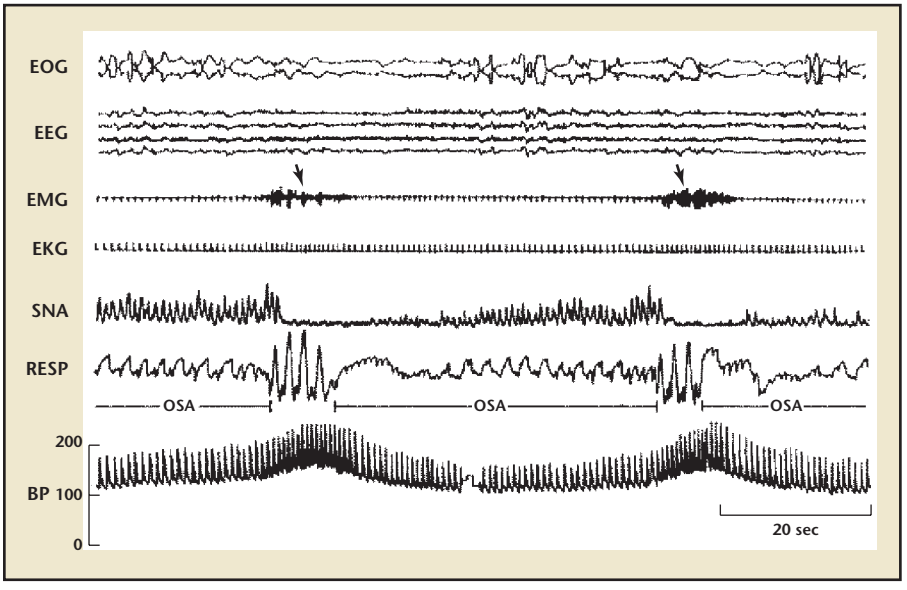
Sleep studies should be performed in all patients with resistant hypertension.

The mechanisms of the hypertensive effects of OSA are multifactorial because hypertension is a disease with other potential etiologies or factors, such as body fat distribution, age, sex, environment, and insulin resistance. Nevertheless, nocturnal chemoreflex activity (Figure 2) might carry over into excessive sympathetic activity and higher blood pressure even during the daytime.

Vascular Disease (Coronary Artery Disease, Aortic Disease)

In patients with coronary artery disease, the presence of OSA adversely affects prognosis and is an independent predictor of cardiovascular mortality.[16] Patients with both OSA and coronary artery disease also have a higher rate of nocturnal ischemic events compared with patients who have OSA alone, and treatment with CPAP significantly reduces the total duration of ST-segment depression in

Figure 2. *Recordings of the electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (EKG), sympathetic nerve activity (SNA), respiration (RESP), and blood pressure (BP) in a patient with obstructive sleep apnea (OSA) during rapid eye movement sleep. BP surges occurred at the end of the apneic periods. Reprinted with permission of the American Society for Clinical Investigation, from Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. Vol. 96, pages 1897-1904.[9] Copyright 1995; permission conveyed through Copyright Clearance Center, Inc.* www.medreviews.com



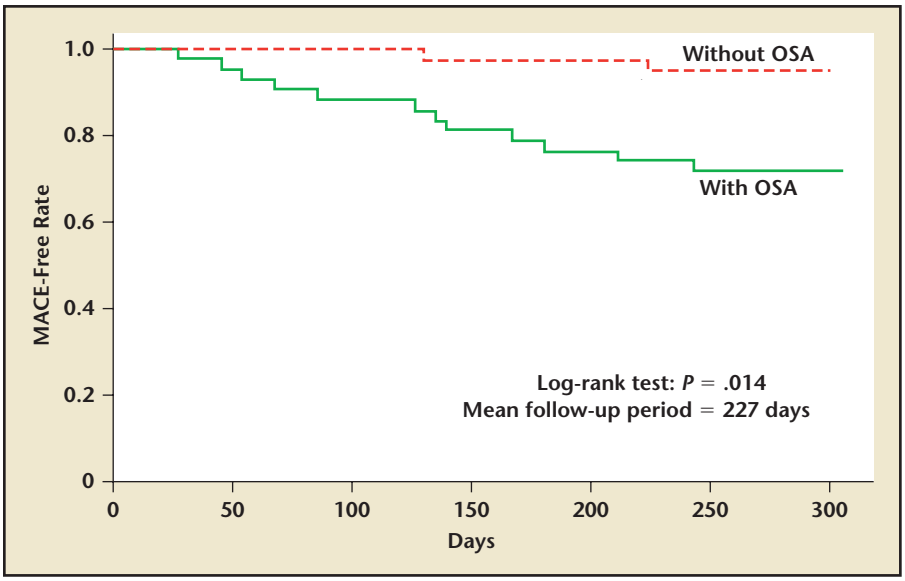


Figure 3. *Kaplan-Meier analysis of the rates of freedom from a major adverse cardiac event (MACE; cardiac death, reinfarction, and target vessel revascularization) in acute coronary syndrome patients with obstructive sleep apnea (OSA) (n = 51) (solid line) and without OSA (n = 38) (dotted line). Reprinted from the* American Journal of Cardiology, *Vol 99, Yumino D, Tsurumi Y, Takagi A, et al. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome, pages 26-30,*[16] *Copyright 2007, with permission from Elsevier.* www.medreviews.com

patients with sleep apnea.[17] Our observational study[16] showed that in patients with acute coronary syndrome, OSA appeared to be an independent predictor of clinical and angiographic outcomes after percutaneous coronary intervention (Figure 3). However, there is still no interventional study designed to determine whether treating OSA could be useful in the primary and secondary prevention of coronary artery disease.

OSA could be a contributing factor to thoracic aortic expansion in some patients[18] through the mechanical stress on the aorta wall caused by repeated exacerbation of negative intrathoracic pressure. Peters and colleagues[19] reported that a decrease in intrathoracic pressure confined to diastole can distend the intrathoracic aorta in rats. Thus, we speculated that the sudden rises and changes in the transmural pressure of the aortic wall, repeated hundreds of times nightly over years, could contribute to thoracic aortic expansion. Serizawa and colleagues[20] showed that OSA appeared to be an independent factor associated with thoracic aortic expansion, but not with hypertension.

Pulmonary Hypertension

Daytime pulmonary hypertension is present in 20% to 40% of OSA patients.[21,22] Pulmonary hypertension in OSA could have a precapillary component related to the combined effects of increased right ventricular preload (increased venous return due to apnea-induced negative intrathoracic pressure), afterload (increased pulmonary vasoconstriction), and vascular endothelial remodeling, but it could also have a postcapillary component related to permanent or episodic elevation of left ventricular (LV) afterload from increased systemic blood pressure and the presence of diastolic dysfunction. These stressors appear to contribute to the high prevalence of daytime hypertension in patients with OSA. In addition, CPAP therapy restores normal levels of vasoactive mediators, including circulating endothelin-1 and nitric oxide levels,[8] and improves LV diastolic dysfunction due to the elimination of nocturnal hypoxia, nocturnal sympathetic surges, and LV afterload. A previous study showed that in OSA patients with pulmonary hypertension, CPAP often lowers nocturnal and daytime pulmonary artery pressure.[22]

Arrhythmias

Sleep apnea characterized by variables of the autonomic nervous system may have a direct association with arrhythmia. Recent data from the Sleep Heart Health Study demonstrated an association between sleep apnea and nocturnal arrythmias.[23] One study showed an association between OSA and bradyarrhythmias,[24] particularly in patients exhibiting severe nocturnal oxygen desaturation, although bradycardia may be marked in only a minority of patients with OSA. The mechanism of these bradyarrhythmias is usually attributed to the reflex increase in vagal tone triggered by a combination of apnea-related severe hypoxia and stimuli of pulmonary mechanical receptors. The diagnosis of sleep apnea is crucial because CPAP reverses heart block in a significant percentage of patients with OSA.[24] Pacemaker guidelines from the American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology (ACC/AHA/NASPE) now recommend that the presence of sleep apnea be considered a cause of transient atrioventricular block during nocturnal sleep apnea and be treated with CPAP.[25]

In patients with cardioversion for atrial fibrillation, the presence of untreated sleep apnea doubles the likelihood of the recurrence of atrial fibrillation within 12 months, compared with patients with OSA receiving CPAP.[26] Continuous cardiac

monitoring with an atrial defibrillator showed that the onset of about 75% of episodes of persistent atrial fibrillation occurred between 8 PM and 8 AM, which could partially be explained by the presence of OSA.[27] However, whether OSA is an independent cause of new-onset atrial fibrillation remains unknown.

An excess of sudden deaths during sleep between midnight and 6 AM in patients with OSA[28] suggests that OSA may trigger lethal nocturnal ventricular arrhythmias. A randomized controlled clinical trial confirmed that alleviation of OSA by CPAP during sleep in patients with HF significantly reduces ventricular ectopy during sleep.[29] In addition, to investigate the mechanism of OSA and ventricular arrhythmias, Gomita and colleagues[30] described a case study that showed the relationship between OSA and the nocturnal profile of a signal-averaged electrocardiogram and QT interval. The researchers conducted simultaneous polysomnographic recording and continuous high-resolution Holter monitoring before and after CPAP treatment. Ventricular arrhythmia and the nocturnal profile of a signal-averaged electrocardiogram and QT interval were improved by CPAP treatment. OSA not only results in hypoxia and alteration of the autonomic nervous system as a modifier and in the generation of premature ventricular complex as a trigger, but it may also generate depolarization and repolarization abnormalities. OSA with all 3 elements may contribute to the arrhythmogenesis of ventricular arrhythmias.

Heart Failure

A large, population-based study identified OSA as an independent risk factor for HF.[2] In addition, OSA often coexists with HF,[7] and CPAP treatment reduces blood pressure and improves LV systolic function.[31] These observations suggest that OSA contributes to the pathogenesis of HF. The coexistence of OSA in patients with HF exerts unique nocturnal adrenergic stresses (repetitive surges of the sympathetic nervous system) and mechanical stresses (increased LV transmural pressure and LV and right ventricular afterload) that could result in greater adaptive LV and right ventricular remodeling than would occur in patients without OSA.[8] Dogs exposed to experimental OSA for several weeks develop nocturnal and diurnal hypertension, followed by LV hypertrophy and then systolic dysfunction.[32] This process mimics the natural history of hypertension, in which LV hypertrophy progresses to HF. HF patients with coexisting OSA were reported to have a higher prevalence of LV hypertrophy than patients without OSA.[33] This remodeling was the greatest in the septum; septal thickness was greater in those with OSA and correlated with the AHI. However, the difference in right heart function and morphology in HF patients with and without OSA is still uncertain. In some HF patients, there is a gradual shift from OSA to predominantly CSA.[34] These observations suggest that OSA causes overnight deterioration in LV function and an increase in LV filling pressure that lead to hyperventilation and hypocapnia. In contrast, if some of this fluid accumulates in the upper airway, the pharynx could narrow and become more susceptible to collapse.[8] However, there is as yet no direct evidence to support this hypothesis. Several cardiovascular responses to nocturnal CPAP persist into wakefulness. For example, in OSA patients, CPAP reduces awake sympathetic activity and oxidative stress, increases endothelial-derived nitric oxide, and augments endothelial-mediated vasodilation.[8] In the first randomized trial in this field of 24 HF patients with OSA (AHI $\geq$ 20/h), nightly CPAP for 1 month increased echocardiographically measured left ventricular ejection fraction (LVEF) by 9% ($P < .001$).[31] HF patients with OSA are often not hypersomnolent,[7] and there is no consensus as to whether these patients require treatment, although CPAP improves heart function as described above.

Heart Failure and Central Sleep Apnea

The pathophysiology of CSA in patients with HF is complex and remains controversial. The primary stimulation for ventilation during sleep is PCO_2.[35] We propose that narrowing ΔPCO_2 (the difference between the eupneic PCO_2 and apnea threshold PCO_2 levels) due to stimulation of pulmonary mechanical receptors, increased peripheral/central chemoresponsiveness, and passing from wakefulness to sleep predisposes to the development of CSA. Several additional factors, such as metabolic alkalosis, low functional residual capacity, cerebrovascular flow reduction, upper airway instability, and hypoxia, may further contribute to respiratory instability and continued CSA.[35]

The main clinical significance of CSA in HF is, first, whether CSA is associated with increasing morbidity and mortality, and, second, the causal relationship between CSA and HF. Evidence from univariate and multivariate analyses showed that CSA is a marker of poor prognosis in patients with HF.[3] In contrast, CSA may also be detrimental to the failing heart. In CSA, each pause in breathing elicits profound increases in muscle sympathetic nerve activity by deactivating pulmonary stretch receptors and causing hypoxia, arousal, and hypercapnia, which

stimulate peripheral and central chemoreceptors.[4] Overnight urinary norepinephrine concentrations and daytime plasma norepinephrine concentrations are markedly higher in HF patients with CSA than in those without, and they are directly related to the frequency of arousals from sleep and to the degree of apnea-related hypoxia, but not to LVEF. These data suggest that CSA can trigger sympathetic nerve activity in patients with HF.[4] However, the alternative view is that increased sympathetic nerve activity provides inotropic support in HF. In other words, CSA may function as an intermittent inotropic treatment for end-stage HF during sleep. A recent study has shown that the long-term survival benefit conferred by intermittent inotropy was greater in patients with nonischemic HF than in those with ischemic HF.[36] Therefore, CSA may be a form of compensation for HF when its etiology is taken into account.

Treatment

Obstructive Sleep Apnea

Obesity is the most important modifiable risk factor for OSA,[5] and OSA may predispose to weight gain and obesity. Patients with newly diagnosed OSA often have a history of excessive recent weight gain in the period preceding the diagnosis.[37] It is also known that obese patients with increased risk of OSA have difficulty in losing weight without treatment of OSA. CPAP is recommended for patients with symptomatic OSA even if the AHI is in the mild range (5 to 15 episodes per hour), although evidence-based criteria for the efficacy of CPAP are particularly strong for patients with 15 or more AHI episodes per hour.[38] Because of its ease of treatment and proven efficacy, CPAP is considered first-line therapy for severe OSA and for OSA with concomitant cardiovascular disorders. As shown above, CPAP treatment has been shown to modify nontraditional markers (eg, circulating inflammatory markers, endothelial function, carotid intima-medial thickness, and pulse-wave velocity), improve traditional markers of cardiac risk (eg, hypertension, insulin resistance), and reduce the morbidity and mortality of CVD. However, because those studies were only a few months in duration, it was not possible to determine whether these effects were long-lasting or whether they led to improvement in clinically important outcomes, such as morbidity and mortality. Other therapies, such as oral appliances, sleep positioning, and uvulopalatopharyngoplasty, should be considered when CPAP is unsuccessful. One study added a new perspective to pacemaker implantation in patients with OSA. Provocative evidence suggests that modulation of cardiac rhythm characteristics by atrial overdrive pacing may attenuate the severity of both OSA and CSA.[39] The mechanisms of any pacing-induced amelioration of sleep apnea and the implications for future therapeutic strategies are presently uncertain but intriguing.

Central Sleep Apnea

A primary objective of the treatment of CSA is to improve HF. However, there is still no consensus on whether CSA should be treated, and, if so, what the optimum therapy would be. First, we must consider optimal pharmacotherapy (eg, angiotensin-converting enzyme inhibitors and beta-blockers) and, if necessary, nonpharmacotherapy (eg, pacemakers, biventricular pacing, valvuloplasty) for HF. Several medications have also demonstrated efficacy in CSA. Theophylline[40] and acetazolamide[41] reduced the severity of CSA in short-term trials but did not yield improvements in LVEF, quality of life, or clinical outcome. A number of studies investigated the effects of supplemental oxygen in patients with HF and CSA.[42] Randomized, controlled trials have shown that short-term (1-week to 12-week) administration of nocturnal supplemental nasal oxygen reduced the total duration of CSA and improved maximum exercise capacity, decreased overnight urinary norepinephrine excretion, and improved cardiac function and quality of life. However, oxygen supplementation was not reported to improve clinical outcome.

Various forms of nasal positive pressure ventilation (NPPV) devices, including CPAP, bilevel positive airway pressure, and adaptive servoventilation, have been examined in randomized trials to alleviate CSA in patients with HF. However, thus far, only CPAP has been evaluated in terms of the effects on cardiovascular outcome. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial (the largest and longest-term multicenter trial)[43] showed that CPAP attenuated CSA but did not improve survival in patients with HF, although it improved nocturnal oxygenation, increased LVEF, lowered norepinephrine levels, and increased the 6-minute walk distance. One stratified analysis examined the effects of CPAP on LVEF and transplant-free survival in terms of the effects on CSA 3 months after randomization.[44] The major findings were that in the 57% of patients in whom CPAP reduced the AHI to less than 15, LVEF and transplant-free survival improved as compared with the control group, but it did not improve in the group with no CSA reduction. In addition, the group in whom CPAP suppressed CSA was younger, had less severe CSA, and

had slightly fewer central events than the group in whom CPAP did not suppress CSA.

The effects of CPAP mainly involve treatment of HF, including augmentation of cardiac output and O_2 delivery, decreased LV afterload by increasing intrathoracic pressure, and reduced cardiac sympathetic activity. CPAP also decreases preload by impeding venous return and reducing right ventricular and LV end-diastolic volume. In addition, CPAP may affect sleep apnea. Because most patients with CSA have coexisting OSA, CPAP suppresses the OSA component and reduces the severity of sleep apnea. CPAP has other effects that could dampen periodic breathing, such as lung inflation and stabilization of the upper airway, which may be an additional factor suppressing central apneas. The acute response of cardiac output to CPAP therapy in awake patients with HF is dependent on cardiac preload and rhythm. In patients with HF and with high LV filling pressure (> 12 mm Hg), CPAP of 5 to 10 cmH_2O generally augments cardiac output, but in patients with HF and low LV filling pressure or atrial fibrillation,[42] it generally reduces cardiac output. Suggested indications for HF patients who may benefit from CPAP treatment are given in Table 2.

Table 2
Proposed Indicators for Beneficial CPAP Treatment in Heart Failure Patients With CSA

Younger age
Presence of sinus rhythm
Less severe CSA and fewer central events
Left ventricular filling pressure not low (eg, ≥ 12 mm Hg)
CPAP suppressed AHI (eg, < 15/h for 3 months)

CPAP, continuous positive airway pressure; CSA, central sleep apnea; AHI, apnea-hypopnea index.

A problem is that patients with fewer symptoms have a lower acceptance of CPAP.[7] Good compliance is seen when CPAP improves cardiac function in CSA patients without airway obstruction, but the pressure setting must be appropriate. When patients were acclimatized to CPAP during a gradual 2- to 7-day titration period to higher pressures of 8 to 12.5 cmH_2O, the frequency of central apnea and hypopnea fell by 50% to 67% after 2 to 12 weeks.[42] Taking the results together, CPAP improves cardiovascular function in patients with HF and CSA, but only when it is titrated slowly to pressures of 10 cmH_2O and accompanied by reductions in the AHI.

Two other types of NPPV—bilevel positive airway pressure and adaptive servoventilation—have been evaluated in patients with HF. However, the effects on cardiovascular function were not assessed. These NPPV treatments for CSA may be useful in the management of HF. However, this is a developing medical field, and it remains unclear which patients may benefit and which treatments are indicated.

Future Directions and Conclusions

There is ample evidence that sleep apnea is a novel CVD risk factor. Targeting sleep apnea as primary and/or secondary prevention of CVD could lead to a possible breakthrough in treatment. Treatment of sleep apnea in tandem with established cardiovascular approaches could result in improvement of this increasingly common condition, despite its controversy. The link between sleep apnea and other risk factors for the development of heart disease should be clarified. Controversy exists on the cause-and-effect relationship between sleep apnea and CVD. It must be determined whether exacerbation of circulating markers (eg, inflammation), metabolic disease (eg, hypertension,

Main Points

- Obstructive sleep apnea (OSA) is caused by upper airway collapse during inspiration and is accompanied by strenuous efforts to breathe. Central sleep apnea (CSA) is characterized by apneas secondary to diminution or cessation of thoracoabdominal respiratory movement due to decreased central respiratory drive.
- The adverse effects of OSA can promote the development of atherosclerosis and have also been implicated in the pathogenesis of cardiovascular disease.
- Sleep apnea characterized by variables of the autonomic nervous system may have a direct association with arrhythmia.
- A large, population-based study identified OSA as an independent risk factor for heart failure.
- Continuous positive airway pressure is considered first-line therapy for severe OSA and for OSA with concomitant cardiovascular disorders. There is no consensus on whether CSA should be treated, and, if so, what the optimum therapy would be.

insulin resistance), and CVD (eg, coronary artery disease, HF) predispose to OSA and/or CSA. We need to identify subgroups (eg, age, sex, underlying disease, sleepiness) of patients with sleep apnea and target who should receive treatment. Finally, the sleep and cardiovascular research community must conduct large-scale, randomized trials that will determine whether treatment of sleep apnea prevents cardiovascular events. Sleep apnea could be a risk factor for CVD, but before it can be added to the list of traditional risk factors and be targeted for therapy, it must be investigated further. ■

References

1. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378-1384.
2. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001; 163:19-25.
3. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol*. 2007;49:2028-2034.
4. Yumino D, Bradley TD. Central sleep apnea and Cheyne-Stokes respiration. *Proc Am Thorac Soc*. 2008;5:226-236.
5. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328: 1230-1235.
6. Martinez-Garcia MA, Gomez-Aldaravi R, Soler-Cataluna JJ, et al. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. *Eur Respir J*. 2007;29:951-957.
7. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol*. 2006;106: 21-28.
8. Bradley TD, Floras JS. Sleep apnea and heart failure: part I: obstructive sleep apnea. *Circulation*. 2003;107:1671-1678.
9. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897-1904.
10. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365:1046-1053.
11. Drager LF, Bortolotto LA, Lorenzi MC, et al. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2005; 172:613-618.
12. Drager LF, Bortolotto LA, Figueiredo AC, et al. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2007; 176:706-712.
13. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.
14. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2002;359:204-210.
15. Barbé F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med*. 2001;134:1015-1023.
16. Yumino D, Tsurumi Y, Takagi A, et al. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol*. 2007;99: 26-30.
17. Peled N, Abinader EG, Pillar G, et al. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment. *J Am Coll Cardiol*. 1999;34:1744-1749.
18. Cistulli PA, Wilcox I, Jeremy R, Sullivan CE. Aortic root dilatation in Marfan's syndrome: a contribution from obstructive sleep apnea? *Chest*. 1997;111:1763-1766.
19. Peters J, Kindred MK, Robotham JL. Transient analysis of cardiopulmonary interactions. I. Diastolic events. *J Appl Physiol*. 1988;64:1506-1517.
20. Serizawa N, Yumino D, Takagi A, et al. Obstructive sleep apnea is associated with greater thoracic aortic size. *J Am Coll Cardiol*. 2008;52:885-886.
21. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis*. 1988;138:345-349.
22. Arias MA, Garcia-Rio F, Alonso-Fernandez A, et al. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. *Eur Heart J*. 2006;27:1106-1113.
23. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006;173:910-916.
24. Becker H, Brandenburg U, Peter JH, Von Wichert P. Reversal of sinus arrest and atrioventricular conduction block in patients with sleep apnea during nasal continuous positive airway pressure. *Am J Respir Crit Care Med*. 1995;151: 215-218.
25. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (ACC/AHA/NASPE committee to update the 1998 pacemaker guidelines). *Circulation*. 2002;106:2145-2161.
26. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. 2003;107:2589-2594.
27. Mitchell AR, Spurrell PA, Sulke N. Circadian variation of arrhythmia onset patterns in patients with persistent atrial fibrillation. *Am Heart J*. 2003;146:902-907.
28. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352:1206-1214.
29. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax*. 2005;60:781-785.
30. Gomita K, Yumino D, Ajiro Y, et al. Assessment of the fluctuation of late potential and QT interval during sleep in a patient with end-staged hypertrophic cardiomyopathy who has nocturnal ventricular tachycardia and obstructive sleep apnea. *Heart Rhythm*. 2006;3: S339-S340.
31. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003; 348:1233-1241.
32. Parker JD, Brooks D, Kozar LF, et al. Acute and chronic effects of airway obstruction on canine left ventricular performance. *Am J Respir Crit Care Med*. 1999;160:1888-1896.
33. Usui K, Parker JD, Newton GE, et al. Left ventricular structural adaptations to obstructive sleep apnea in dilated cardiomyopathy. *Am J Respir Crit Care Med*. 2006;173:1170-1175.
34. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO2 and circulatory delay. *Circulation*. 2001;103:238-243.
35. Dempsey JA, Smith CA, Przybylowski T, et al. The ventilatory responsiveness to CO_2 below eupnoea as a determinant of ventilatory stability in sleep. *J Physiol*. 2004;560:1-11.
36. Tsagalou EP, Anastasiou-Nana MI, Terrovitis JV, et al. The long-term survival benefit conferred by intermittent dobutamine infusions and oral amiodarone is greater in patients with idiopathic dilated cardiomyopathy than with ischemic heart disease. *Int J Cardiol*. 2006;108: 244-250.
37. Phillips BG, Hisel TM, Kato M, et al. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens*. 1999; 17:1297-1300.
38. Kushida CA, Littner MR, Hirshkowitz M, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep*. 2006;29:375-380.
39. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med*. 2002;346:404-412.
40. Javaheri S, Parker TJ, Wexler L, et al Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med*. 1996;335:562-567.
41. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind,

prospective study. *Am J Respir Crit Care Med*. 2006;173:234-237.
42. Arzt M, Bradley TD. Treatment of sleep apnea in heart failure. *Am J Respir Crit Care Med*. 2006; 173:1300-1308.
43. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353:2025-2033.
44. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation*. 2007;115: 3173-3180.
45. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol*. 2007;49: 1625-1631.