Sleep Apnea and Cardiovascular Disease
A Bidirectional Relationship

Takatoshi Kasai, MD, PhD; John S. Floras, MD, DPhil; T. Douglas Bradley, MD

Sleep apnea occurs in ≈5% to 10% of the general population, regardless of race and ethnicity. By contrast, in patients with cardiovascular diseases (CVDs), its prevalence, depending on the specific disorder surveyed, can range between 47% and 83%. One form, central sleep apnea (CSA), is rare in the general population, but is detected often in conditions characterized by sodium and water retention, such as heart failure (HF). Such epidemiological observations raise several important and as yet unresolved questions: What accounts for this remarkable concentration of sleep apnea among patients with CVD and its association with fluid retaining states? Does obstructive sleep apnea (OSA) predispose at-risk individuals to develop, over time, hypertension, coronary artery disease, stroke, or HF? Conversely, could mechanisms engaged by CVD, such as activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, with consequences including renal sodium retention, contribute over time to the development or exacerbation of sleep apnea? From the clinical perspective, is sleep apnea, when present in patients with CVD an epiphrenomenon, perhaps related to ageing, or a causal contributor to worse prognosis? And if so, are there now sufficient data to recommend randomized controlled trials to determine whether specific treatment of sleep apnea can reduce mortality or cardiovascular event rates? Our objectives, in this review, are to provide novel insight into each of these specific questions by integrating into our contemporary understanding of relationships between sleep apnea and CVD new epidemiological, observational, mechanistic, and trial data; to introduce a hypothetical model of bidirectional causality; and to consider directions for future research.

Normal Sleep

In healthy subjects, during non–rapid eye movement sleep (but comprising only 15% of total sleep time), and pathologically, whether because of fitful sleep or shorter overall sleep time, as evident in patients with HF or drug-resistant hypertension, or by coexisting sleep apnea, whether obstructive (OSA) or central (CSA).

Sleep Apnea: Epidemiology and Pathophysiology

Obstructive Sleep Apnea

Both in the general population and in those with CVD, OSA is 2 to 3 times more common in men than in women, and in older adults than in the young. Although obesity is associated with OSA in patients with coronary artery disease and hypertension among patients with HF and stroke, in comparison with the general population, a larger proportion with OSA patients are nonobese, and there is little or no relationship between body mass index and severity of OSA.

OSA arises when sleep-related withdrawal of respiratory drive to the upper airway (UA) dilator muscles is superimposed on an UA predisposed to collapse because it is narrow and highly compliant. The UA may be narrowed if surrounded by a small boney envelope, as with retrognathia, or if soft tissue mass within this boney envelope is increased, as with tonsillar hypertrophy or macroglossia. In obese individuals, pharyngeal fat deposition facilitates UA narrowing and collapse by increasing external peripharyngeal soft tissue pressure. Peripharyngeal fluid accumulation increases soft tissue mass, and it has been shown that fluid shifting from the legs during inflation of antishock trousers causes narrowing and increased UA resistance. The most likely mechanism for this is increased peripharyngeal tissue pressure. It may also be possible that fluid shifting into the peripharyngeal tissues might inhibit pharyngeal dilator muscle activity, thereby increasing UA collapsibility, but this seems less likely than an increase in tissue pressure. Nasal obstruction can also increase the risk for developing OSA, possibly by causing increased collapsibility of the UA owing to increased airway resistance upstream from the collapsible portion on inspiration. Hereditary factors and respiratory control system instability may also contribute to the pathogenesis of OSA, but these possibilities remain controversial.

UA
collapse during sleep can cause partial or complete cessation of airflow (hypopnea and apnea, respectively). Because the drive to breathe persists, inspiratory efforts against the now-occluded UA generate negative intrathoracic pressure, out-of-phase thoracoabdominal motions, distortion of the chest wall, and diminished airflow.

Central Sleep Apnea
CSA, in contrast, occurs when PaCO₂ during sleep falls below the apnea threshold, resulting in withdrawal of central drive to respiratory muscles. The UA remains for the most part patent. Respiratory movements are either absent (apnea) or attenuated in proportion to the decrease in respiratory drive (hypopnea), but are in-phase and are not accompanied by airflow limitation. In HF, CSA is manifest as Cheyne-Stokes respiration (CSR), a form of periodic breathing with a crescendo-decrescendo pattern of tidal volume accompanied by a long periodic cycle duration. Prolonged hyperpnea alternates with central apnea or hypopnea. In the context of the present review, CSA should be considered synonymous with CSR unless indicated otherwise.

Although CSA occurs in <1% of the general population, it is common in patients with HF, atrial fibrillation (AF), and stroke, where its prevalence ranges from 12% to 53%. In patients with HF, neither the presence nor severity of CSA relates to body mass index. Rather, its risk factors include male sex, older age, low PaCO₂, coexistence of AF, and use of diuretics. Central apneas occur in HF because of inherent respiratory control system instability. This arises from stimulation of pulmonary vagal irritant receptors by pulmonary congestion secondary to increased left ventricular (LV) volume and filling pressure that augments respiratory drive reflexively, and from increased central and peripheral chemosensitivity, as well as arousals from sleep. Each of these can elicit hyperventilation that causes PaCO₂ to fall below the apnea threshold, thereby abolishing central respiratory drive to the muscles of respiration. Airflow ceases until metabolic CO₂ production causes PaCO₂ to rise above the apnea threshold, triggering hyperventilation, which again causes PaCO₂ to fall below the apnea threshold. Raising pCO₂ above the apnea threshold either by inhalation of a CO₂-enriched gas or by application of increased dead space via a facemask abolishes CSA in patients with HF, demonstrating the fundamental role of hypocapnia in its pathogenesis. In AF, CSA probably arises through factors similar to those related to HF, that is, subtle degrees of nocturnal pulmonary congestion and a tendency to hyperventilate because of atrial dilation, elevated left atrial pressure, and reduced cardiac output. Following stroke, CSA with a CSR pattern is strongly associated with coexisting occult LV systolic dysfunction, rather than with the type, location, or severity of the stroke, suggesting that cardiac dysfunction, rather than the neurological lesion per se, is the major factor contributing to CSA in this setting.

Contribution of Fluid Retention to the Pathogenesis of Sleep Apnea
The high prevalence of OSA in nonobese patients with HF, in drug-resistant hypertension, and in renal failure, and the higher prevalence of CSA in HF patients than in general population led us to hypothesize that fluid retention and, more specifically, nocturnal shift of dependent fluid rostrally while recumbent during sleep, is intimately involved in the pathogenesis of both forms of apnea. Distention of neck veins or edema of the periphery could initiate CSA by provoking hyperventilation (Figure 1). Sodium and water retention in conditions such as obesity, hypertension, and HF may be dietary, neurogenic, as a consequence of increased renal sympathetic nerve discharge, which stimulates renin release and renal sodium retention, or hormonal, for example, secondary to activation of the renin-angiotensin-aldosterone axis.

As an initial test of this hypothesis, we demonstrated that in response to a 5-minute application of lower-body positive pressure, neck circumference increased, the pharyngeal cross-sectional area decreased, and pharyngeal resistance and collapsibility increased simultaneously with a reduction in leg fluid volume in healthy subjects. Such rapid changes in neck circumference and UA properties could only be caused by a change in fluid volume within the periphery. Redolfi et al identified, in 23 otherwise healthy nonobese men, direct relationships between the volume of fluid displaced gravitationally from the legs overnight and both the overnight increase in neck circumference and the severity of OSA as assessed by frequency of apneas and hypopneas per hour of sleep (ie, apnea-hypopnea index, AHI). These novel findings were replicated in men with HF (Figure 2) and renal failure, and in patients with hypertension. Fluid volume displaced from the legs overnight was in turn directly proportional to the time spent sitting during the day and the degree of leg edema, and inversely proportional to physical fitness. Thus, the volume of fluid available for displacement from the legs appears to be a function of sedentary living and leg edema. These observations strongly suggest that in CVD patients prone to fluid retention, overnight rostral fluid displacement from the legs could initiate or contribute to
the severity of OSA by causing fluid accumulation in the neck, narrowing the pharynx and increasing its propensity to collapse during sleep. In a recent study, the absence of any change in the severity of OSA from the first to the second half of the night was advanced as an argument against the role of overnight rostral fluid displacement in the pathogenesis of OSA. However, because overnight leg fluid volume changes were not assessed, no conclusions about the role of overnight fluid shifts in the pathogenesis of OSA could reasonably have been drawn from this observation.

More recent evidence that nocturnal rostral fluid shift can cause OSA was provided by the observation in both nonobese men with OSA and in patients with chronic venous insufficiency that the use of venous compression stockings reduced daytime-dependent fluid accumulation, the volume of nocturnal rostral fluid shift, and the AHI by \( \approx 35\% \). Further evidence favoring this concept comes from several observations. First, it has also been shown that the severity of OSA and CSA in HF patients is proportional to dietary sodium intake, likely as a consequence of salt and water retention. Second, in patients with OSA and drug resistant hypertension, antagonism of aldosterone by spironolactone, and blunting of renal sodium and water retention by radiofrequency sympathetic denervation reduce the AHI. Third, in two studies, Tang et al demonstrated that fluid removal at night by cycled peritoneal dialysis in patients with renal failure reduced the severity of OSA in comparison with removing the same amount of fluid over 24 hours and was associated with an increase in pharyngeal caliber. Similar observations were made by Hanly and Pierratos when patients with renal failure were transitioned from daytime to nocturnal hemodialysis. Finally, in patients with acute exacerbations of diastolic HF, diuretic therapy was associated with an increase in pharyngeal caliber accompanied by a modest reduction in the AHI.

The volume of fluid that leaves the legs overnight in HF patients with predominantly CSA also relates directly to the AHI. However, the amount that shifts is double that in HF patients with predominantly OSA, and, in contrast to OSA, there is an inverse relationship between the volume displaced and PaCO\(_2\) during sleep (Figure 2). A substantial portion of the fluid leaving the legs of HF patients with CSA likely accumulates in the lungs where it can cause pulmonary congestion and stimulate hyperventilation (Figure 1). It has been shown that a low PaCO\(_2\) in HF patients is related to elevated LV filling pressure, presumably by stimulation of pulmonary vasoconstriction. In addition, it is well known that paroxysmal nocturnal dyspnea and orthopnea are due to posturally dependent redistribution of fluid from the lower body to the lungs. These observations are consistent with the concept that fluid displaced from the legs can redistribute to the lungs while the patient is recumbent during sleep.

Importantly, this series of observations has stimulated three novel concepts: nocturnal rostral fluid shift contributes to the pathogenesis of both OSA and CSA; once sleep apnea develops, its severity, as assessed by the AHI, relates to the volume of fluid so displaced; and the magnitude of overnight rostral fluid movement contributes to the type of apnea that predominates. Based on these findings, it is reasonable to propose, first, that the prevalence of sleep apnea is increased in patients with CVD in comparison with the general population because the former are more likely to manifest sodium-retaining physiology, and second, that reports in HF patients of transformations, over time, from OSA to CSA and vice versa, can be explained by disease progression or therapy that alters daytime fluid retention and, as a consequence, the volume of fluid available to shift rostrally overnight.

What, then, of the opposite scenario: can OSA predispose at-risk individuals to develop, over time, hypertension, coronary artery disease, HF, or stroke?

Cardiovascular Effects of OSA
Repetitive obstructive apneas expose the heart and circulation to a cascade of noxious stimuli that, over time, may initiate or contribute to the progression of most cardiovascular disorders.

Negative Intrathoracic Pressure
A unique feature of OSA is the generation of exaggerated negative intrathoracic pressure during futile inspiratory efforts against the occluded pharynx. This will immediately increase LV transmural pressure (ie, intraventricular minus intrathoracic pressure), a key element of LV afterload. It also increases venous return, augmenting right ventricular preload, whereas OSA-induced hypoxic pulmonary vasoconstriction increases right ventricular afterload. Consequent right ventricular distension and leftward septal displacement during diastole impairs LV filling. The combination of increased LV afterload and diminished LV preload during obstructive apneas causes a progressive reduction in stroke volume and cardiac output that is more pronounced in patients with LV systolic dysfunction than in those with normal LV function. Increased LV transmural pressure also raises myocardial oxygen demand, while simultaneously...
triggering a fall in coronary blood flow, this at a time when apnea-related hypoxia reduces oxygen supply and increases efferent sympathetic nerve traffic (see below). Together, these mechanisms can precipitate myocardial ischemia in those with preexisting coronary disease and impair cardiac contractility and diastolic relaxation.6 Cerebral blood flow also declines significantly during obstructive apneas, probably secondary to the fall in cardiac output.50

Over months to years, these repetitive increases in wall tension can stimulate a range of processes involved in ventricular remodeling, resulting in asymmetrical septal or concentric LV hypertrophy51 or ventricular dilatation.52 The latter may be exacerbated at times that other adverse remodeling processes are active, such as after myocardial infarction.53

Negative intrathoracic pressure swings during obstructive events also increase atrial and intrathoracic aortic wall stress, thereby increasing the likelihood of nocturnal atrial arrhythmias and thoracic aortic dissection.54–57

**Autonomic Dysregulation**

OSA immediately elicits both sympathetic excess and parasympathetic withdrawal.58 The sympathetic nervous system is activated simultaneously by cycles of apnea-induced hypoxia and CO2 retention, which stimulate both central and peripheral chemoreceptors, apnea-induced cessation of pulmonary stretch receptor-mediated inhibition of central sympathetic outflow, and silencing of sympathoinhibitory input from carotid sinus baroreceptors by reductions in stroke volume and BP during obstructive apneas. When the apnea is interrupted by arousal from sleep, the latter process simultaneously augments SNA and reduces cardiac vagal activity. The result is a postapneic surge in both BP and HR.

These acute adverse effects of OSA on the autonomic nervous system are not confined to sleep. Elevations in sleep BP that arise if dogs are exposed chronically to experimental OSA are sustained into wakefulness.59 Patients with OSA and cardiac dysfunction also have elevated SNA and depressed cardiac vagal activity when awake.60 Reversal of OSA by continuous positive airway pressure (CPAP) lowers SNA and increases cardiac vagal modulation of high-frequency HR variability both at night and during wakefulness.61,62 The mechanisms for such daytime carryover effects remain unclear but may relate to the adaptation of chemoreceptor reflexes or central processes governing autonomic outflow.

Cardiac vagal withdrawal increases HR and reduces HR variability at high frequencies (i.e., respiratory sinus arrhythmia). The latter is a marker of adverse outcomes, including malignant arrhythmias.63 Sympathetic overactivation also acts to increase HR, itself an adverse, albeit nonspecific prognostic signal,64 and can worsen the prognosis of patients with CVD specifically by causing cardiac β-adrenoreceptor desensitization, arrhythmias, myocyte injury and necrosis, and peripheral vasoconstriction (leading to increased afterload and BP), and promoting renal sodium retention, both directly and via stimulation of the renin-angiotensin-aldosterone axis.58

**Oxidative Stress, Inflammation, and Endothelial Dysfunction**

Intermittent apnea-related hypoxia and postapneic reoxygenation can induce oxidative stress with production of reactive oxygen species, and activation of inflammatory mediators that are capable of impairing vascular endothelial function and promoting athrogenesis.65 Patients with OSA have low plasma nitrate and nitrite concentrations and high levels of oxidative stress markers, abnormalities reversible by CPAP.66 Intermittent hypoxia can also activate nuclear transcriptional factors, including nuclear factor-κB, which stimulates production of inflammatory mediators, and several intracellular and vascular cell adhesion molecules, as well.67 This could facilitate endothelial damage and atherogenesis. In subjects with OSA, but otherwise healthy, endothelium-dependent vasodilation is impaired.65 and, in randomized trials, treating OSA by CPAP improved both endothelium-dependent and/or -independent vasodilation without reducing plasma biomarkers of inflammation.65 Butt and colleagues recently reported that otherwise healthy patients with OSA had impaired myocardial perfusion that improved with CPAP. Enhanced apoptosis of endothelial cells and fewer circulating endothelial progenitor cells in OSA patients may contribute to these processes.69

In comparison with control subjects, patients with OSA display greater signs of early atherosclerosis, including increased carotid intima-media thickness and increased arterial stiffness.67 In a randomized trial involving such subjects, CPAP reduced both carotid intima-media thickness and arterial stiffness, supporting a causal relationship between OSA and atherosclerosis.70

**Platelet Activation and Hypercoagulability**

In OSA patients, platelet markers of thrombotic risk increase during sleep; in nonrandomized trials, these decreased in CPAP-treated subjects.71 Morning fibrinogen concentration and plasminogen activator inhibitor type-1 level also are increased in OSA patients.72,73 Mehra and colleagues showed, in an epidemiological study, that both fibrinogen and plasminogen activator inhibitor type-1 increase with increasing AHI even after adjustment for confounders. These indicate less fibrinolytic potential and a hypercoagulable state. In a nonrandomized study, morning fibrinogen concentration was shown to decrease after 1 night of CPAP.71 One randomized study showed that 2 weeks of CPAP therapy for OSA was associated with a significant decrease in plasminogen activator inhibitor type-1.73 Taken together, these observations suggest that increased platelet activation and hypercoagulability could play a role in the increased susceptibility of OSA patients to thromboembolic phenomena such as stroke.75

**Cardiovascular Effects of CSA**

CSA is more likely a consequence, rather than a cause, of HF. However, because it elicits many of the pathophysiologic mechanisms associated with OSA, with the notable exception of the extremes of negative intrathoracic pressure, CSA also has the capacity to initiate a vicious cycle that could cause further deterioration in cardiovascular function. Muscle SNA and cardiac SNA during wakefulness are higher in HF patients with CSA than in those without CSA, or those with OSA, possibly because of greater HF severity.20,60 Cycles of CSR entrain, rhythmically, low-frequency oscillations in BP and HR in patients in sinus rhythm,23 and the ventricular response to AF, as well.76 No studies have examined the
influence of CSA on oxidative stress, inflammatory mediators, or endothelial function.

**Relationships Between Sleep Apnea and Cardiovascular Disease**

Although capable of exacerbating certain CVDs, once present, is there evidence that OSA, in particular, can initiate one or more of these conditions in susceptible individuals? Current epidemiological evidence concerning hypertension, CVD, and cardiovascular mortality is summarized in Tables 1 to 3.77–88 Although most of them strongly suggested causal relationships between OSA and CVDs and cardiovascular mortality, these observations must be interpreted with caution. Because these studies were observational in nature, even after adjusting for known risk factors, other unknown confounders might have affected the outcomes. In addition, some studies focused on subgroups which were not prespecified, making associations difficult to interpret.

**Hypertension**

The prevalence of OSA in primary hypertension is ≈35%.89 However, whether OSA is truly an independent risk factor for the development of hypertension has yet to be definitively established. It is known that intermittent hypoxia or experimentally induced OSA can cause persistent daytime hypertension in rats and dogs, respectively.59,90 In rats, hypertensive population,96 and, in hypertensive mice, captopril prevented 17% reduction in adverse cardiovascular events in a hypertensive groupa5m m greduction in sleep-time systolic BP caused a 65% to 80%,4,91 was by far the most common secondary cause identified, and that its treatment may lower BP in such patients,92 does suggest that OSA plays a provocative role in hypertension.

It is now appreciated that nighttime systolic and diastolic BP confer greater long-term cardiovascular risk than daytime, 24-hour ambulatory, or conventional clinic BP.93,94 Because hypertensive patients whose BP does not fall normally at night (ie, nondippers) are at greater risk for LV hypertrophy and failure than normal dippers,95 and because OSA, as a consequence of nocturnal sympathetic activation, is an important cause of nondipping, it may be a particularly potent yet reversible stimulus to LV hypertrophy and failure. In 1 recent human study a 5 mm Hg reduction in sleep-time systolic BP caused a 17% reduction in adverse cardiovascular events in a hypertensive population,96 and, in hypertensive mice, captopril prevented cardiovascular remodeling only when administered before sleep.97

**Coronary Artery Disease**

The prevalence of OSA in patients with coronary artery disease (CAD) is ≈30%.98 A cross-sectional analysis of the SHHS reported that the risk of CAD was increased modestly in OSA subjects in the highest AHI quartile in comparison with those in the lowest (odds ratio, 1.27; 95% confidence interval, 0.99–1.62).99 However, a subsequent longitudinal analysis of data from the same cohort found that the presence of OSA at
baseline was not a significant predictor of incident CAD after adjustment for other risk factors. Of note, a subgroup analysis suggested that OSA conferred a slightly increased risk of developing CAD in men ≤70 years of age (Table 2).

However, if present in patients with CAD, OSA can provoke ischemic changes in the ECG, and nocturnal angina, as well, and increase the risk of major adverse cardiac events and restenoses following percutaneous coronary inter-

### Table 2. Summary of Cohort Studies Regarding Obstructive Sleep Apnea and Incidence of Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Male, %</th>
<th>Mean Age, y</th>
<th>Mean BMI, kg/m²</th>
<th>Diagnostic Technique for OSA</th>
<th>Duration, y</th>
<th>Findings</th>
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<td>AF</td>
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<tr>
<td>Mooe et al⁸⁰</td>
<td>Patients with CABG</td>
<td>121</td>
<td>79</td>
<td>62</td>
<td>...*</td>
<td>In-hospital cardiorespiratory monitoring†</td>
<td>...*</td>
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<tr>
<td>Gami et al⁸¹</td>
<td>Sleep-clinic patients</td>
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<td>In-lab PSG</td>
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<tr>
<td>Gottlieb et al⁸²</td>
<td>SHHS</td>
<td>4422</td>
<td>44</td>
<td>62</td>
<td>28</td>
<td>Home PSG</td>
<td>8.7 (mean)</td>
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<td>Stroke</td>
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<tr>
<td>Arzt et al⁸³</td>
<td>WSC</td>
<td>1475</td>
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<td>30</td>
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<td>Munoz et al⁸⁴</td>
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<tr>
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<td>45</td>
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<td>Home PSG</td>
<td>8.7 (median)</td>
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<td>Patients with CAD</td>
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<td>Home PSG</td>
<td>8.7 (mean)</td>
</tr>
</tbody>
</table>

AHI indicates apnea-hypopnea index; BMI, body mass index; CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea; SHHS, Sleep Heart Health Study; WSC, Wisconsin Sleep Cohort; PSG, polysomnography; AF, atrial fibrillation; CAD, coronary artery disease; CABG, coronary artery bypass graft; HF, heart failure; and 4% ODI, 4% oxygen desaturation index.

*Not reported.
†This system does not record sleep stages or arousals.
vention for acute coronary syndromes. Those who experience a myocardial infarction during the night are more likely than those whose infarct occurred during daytime hours to have OSA, suggesting that OSA can trigger plaque rupture or myocardial ischemia. After acute myocardial infarction, the coexistence of OSA is associated with an increased combined rate of death, myocardial infarction, and stroke and impaired recovery of LV systolic function.

Heart Failure

Over a period of years, the accumulated impact of recurrent nightly cycles of increased LV wall stress, hypoxia, and sympathetic activation in susceptible individuals may well lead to LV hypertrophy, dilatation, and a decline in systolic function. Cross-sectional data from the SHHS showed the presence of OSA with an AHI >11 to be associated with a 2.38 relative increase in the likelihood of having HF, independently of confounding factors. Longitudinal analysis of the same cohort demonstrated that, after adjustment for confounding factors, OSA severity was a significant predictor of incident HF in men but not in women (Table 2).

The prevalence of OSA in HF populations has been reported to range from 12% to 53%, again greater than in the general population. In 1 observational study, Wang et al reported that untreated OSA (defined as AHI >15) in HF patients was associated with increased mortality, in comparison with those with an AHI <15, even after adjustment for confounding risk factors. CSA, which is much more prevalent in HF (21%–37%) than in the general population, has been found in some HF studies to be a significant independent predictor of mortality. Sleep apnea, in general, has been shown to increase the mortality risk of patients with ischemic HF, principally because of an excess rate of sudden death. The implication of these findings is that the mechanical, autonomic, and oxidative stresses imposed by sleep apnea can aggravate myocardial ischemia and contribute to increased mortality, perhaps through the generation of malignant ventricular arrhythmias. These observations, in concert with those described above, that fluid retention related to the HF state can contribute to the pathogenesis of sleep apnea, suggest a bidirectional relationship between HF and sleep apnea as outlined in Figure 3. Adverse effects of OSA and CSA can contribute to the progression of HF, whereas sodium and fluid retention arising from HF can contribute to the pathogenesis of both OSA and CSA.

Arrhythmias

Several mechanisms elicited by OSA could initiate atrial or ventricular arrhythmias: wall stretch, secondary to abrupt decreases in intrathoracic pressure, with attenuation over time of normal cell to cell communication through remodeling; myocardial ischemia secondary to apnea-induced intermittent hypoxia and increased wall tension; and activation of cardiac inflammatory pathways. Although cross-sectional studies have not demonstrated an increased prevalence of bradyarrhythmias in OSA, apnea-induced hypoxia can provoke parasympathetically mediated atrioventricular block that is reversible by CPAP.

In dogs, pacing of the right atrium during UA occlusion increased the autonomic activity of the right pulmonary arterial ganglionic plexi, and more readily induced AF than the same stimulus without UA occlusion. Blockade of these ganglionic plexi, either pharmacologically or by neural ablation, AF induction during UA occlusion was inhibited, suggesting a causative link between OSA and AF mediated by autonomic neural factors.

Epidemiological data suggest significant associations between AF and both OSA and CSA. In a cross-sectional analysis of the SHHS, Mehra and colleagues found that subjects with OSA were 5 times as likely to have AF as those without OSA. Observational studies suggested that OSA predicts a greater risk for new-onset AF (Table 2) or its recurrence following cardioversion to sinus rhythm. In addition, recent meta-analyses showed that patients with OSA have a 25% greater risk of AF recurrence after catheter ablation than those without OSA. In one such study, OSA (mean AHI of 27) was present in 87% of patients with AF recurrence after pulmonary vein isolation. On the other hand, 2 studies have reported a strong relationship between AF and CSA, not OSA, in patients with and without HF. However, there may be differences between studies in patient populations and classification of respiratory events. Nevertheless, taken together, these data argue for investigation for sleep apnea as part of the evaluation and therapy of AF.

In the SHHS, the prevalence of nonsustained ventricular tachycardia, and ventricular bigeminy and trigeminy, was higher in subjects with OSA than in those without OSA. Ventricular ectopy is also more common in HF patients with CSA than those without sleep apnea; indeed, among those with CSA, ectopic beats occur more frequently during episodes of CSA, a time of increased SNA, than during episodes of normal breathing.
The widespread deployment of implantable cardioverter-defibrillators in patients with HF and ventricular systolic function has provided novel insight into the incidence of malignant ventricular arrhythmias in HF patients with and without sleep apnea. In 1 such analysis, involving 71 patients followed for 6 months after implantable cardioverter-defibrillator implantation, appropriate device discharge occurred 4-fold more frequently in those with than without sleep apnea, with events clustering between midnight and 6 AM. In a larger, more recent study, involving 283 patients followed for 54 months after implantation of an implantable cardioverter-defibrillator in conjunction with biventricular pacing, discharge risk doubled, and the time to first appropriate discharge was 25 months earlier in those with CSA, and 17 months earlier in those with OSA, in comparison with patients who did not have sleep apnea.

**Stroke**

Cross-sectional data from the SHHS revealed a 1.58 times greater odds for stroke in the highest AHI quartile than in the lowest quartile. Longitudinal analysis of data from this cohort reported, after adjustment for other risk factors, a significant association between severity of OSA and incident stroke in men but not in women. Several observational studies also concluded that OSA increases stroke prevalence and incident stroke risk. As noted in Table 2, the odds ratios for risk were not consistently significant once potential confounding variables were accounted for.

In patients who have had a stroke, the prevalence of OSA is ~60%, and of CSA ~12%. In this study, the presence of OSA, but not CSA, was associated with worse functional and motor, but not worse cognitive disability. Impaired neurological function related to OSA may result from reduced cerebral blood flow, intermittent hypoxia, and impaired cerebral autoregulation. A recent 10-year follow-up study of 132 stroke patients showed that, after adjustment for other risk factors, patients with OSA had 1.76 times greater mortality than controls. In this study, the coexistence of CSA was not associated with mortality. The reason for this remains unclear, but because CSA with CSR after stroke is usually a sign of occult LV dysfunction, unrelated to the location, size, or type of stroke, this breathing disorder is more likely a consequence of cardiac than of cerebrovascular disease per se.

**Cardiovascular Mortality**

Data from several community-based cohort studies demonstrate significant relationships between OSA and cardiovascular mortality (Table 3). Eighteen-year follow-up data from the Wisconsin Sleep Cohort showed that, in comparison with subjects without sleep apnea, the adjusted mortality risks of those with severe untreated OSA were significantly higher (3.8 times for all-cause and 5.2 times for cardiovascular mortality). A recent 10-year follow-up study of 132 stroke patients showed that, after adjustment for other risk factors, patients with OSA had 1.76 times greater mortality than controls. In this study, the coexistence of CSA was not associated with mortality. The reason for this remains unclear, but because CSA with CSR after stroke is usually a sign of occult LV dysfunction, unrelated to the location, size, or type of stroke, this breathing disorder is more likely a consequence of cardiac than of cerebrovascular disease per se.

Table 3. Summary of Community- or Population-Based Cohort Studies Regarding Obstructive Sleep Apnea and Cardiovascular Mortality

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<tr>
<th>Cohort</th>
<th>N</th>
<th>Men, %</th>
<th>Mean Age, y</th>
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<th>Diagnostic Technique for OSA</th>
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<td>Young et al</td>
<td>WSC</td>
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<td>48</td>
<td>29</td>
<td>In-lab PSG</td>
<td>13.8 (mean)</td>
</tr>
<tr>
<td>Punjabi et al</td>
<td>SHHS, without SA treatment</td>
<td>6294</td>
<td>47</td>
<td>63</td>
<td>28</td>
<td>Home PSG</td>
<td>8.2 (mean)</td>
</tr>
</tbody>
</table>

AHI indicates apnea-hypopnea index; BMI, body mass index; CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea; SHHS, Sleep Heart Health Study; SA, sleep apnea; WSC, Wisconsin Sleep Cohort; PSG, polysomnography; and CPAP, continuous positive airway pressure.
tive, do not establish a direct causal relation between OSA and an increased risk of sudden death during sleep.

In the largest clinic-based study, Marin and colleagues found that, in comparison with 264 healthy control men matched for age, sex, and weight, 235 men with severe untreated OSA (AHI > 30) had 3.5 times more fatal and 4.7 times more nonfatal cardiovascular events after a mean follow-up period of 10 years. However, event rates in the 372 men with moderate to severe OSA who accepted CPAP treatment did not differ significantly from the control group.

Treating Sleep Apnea

The principal clinical indication to treat OSA in the general population is excessive daytime sleepiness. However, most patients with OSA and CVD do not report excessive daytime sleepiness and report lower Epworth Sleepiness Scale scores for any given AHI in comparison with the general population. Thus, the majority of CVD patients lack this usual indication for treatment, and despite considerable observational, nonrandomized data, it remains uncertain whether OSA patients who do not report excessive daytime sleepiness require therapy at all. Similarly, most patients with CSA and CVD do not report excessive daytime sleepiness. Thus, indications for therapy of CSA in patients with CVD are equally unclear.

If there is an indication to treat OSA, general measures include weight reduction, avoidance of alcohol and sedative drugs in the evening, and, if OSA is specific to this posture, avoidance of supine sleep. In most, however, the treatment of choice is CPAP. Custom-made oral appliances that displace the mandible and tongue forward may benefit some, but are generally less effective than CPAP.

Hypertension

Suppression of OSA by CPAP immediately reduces nocturnal SNA and BP. Because BP oscillates considerably during cycles of apnea and hyperpnea, it is difficult to accurately quantify nocturnal BP by conventional or ambulatory measurements, and, thus, the true impact of CPAP on nocturnal BP can only be discerned by continuous noninvasive or invasive monitoring. The effects of chronic CPAP treatment have been assessed in several randomized trials; unfortunately, none of these trials measured nocturnal BP continuously. Moreover, many such trials were compromised, because most subjects who enrolled were either normotensive or had hypertension well controlled by medications. Considering only those trials in which most subjects had uncontrolled hypertension (Table 4), treatment of OSA with CPAP reduced BP during wakefulness, and was most effective in patients with increased BP and more severe OSA accompa-
nied by hypoxemia. Several meta-analyses have been performed on randomized trials that included subjects irrespective of baseline BP. Although one meta-analysis did not show a significant effect of CPAP on BP,2 others reported a modest effect size of CPAP of ≈2 mm Hg in mean BP reduction. However, these trials were heterogeneous in their patient populations (including, for example, HF patients) and means of measuring BP, with some using 24 hour ambulatory recordings, whereas others used only clinic BP measurements. Taken together, the data suggest nonetheless that treatment of OSA by CPAP can lower BP in patients who are hypertensive at baseline.

Coronary Artery Disease

CPAP can immediately alleviate ischemic changes in the ECG and nocturnal angina. In an observational study, patients with both CAD and OSA (AHI ≥15) who were treated had fewer cardiovascular events than those who were not treated. In another observational study, Cassar and colleagues reported similar findings in OSA patients (AHI ≥15) who underwent percutaneous coronary intervention: in comparison with untreated OSA patients, the cardiovascular death rate was reduced significantly (P = 0.027) and there was less all-cause mortality (P = 0.058). Data from randomized trials are needed to determine whether CPAP treatment should be recommended to such patients.

Heart Failure

Because fluid retention and overnight rostral fluid shift contribute to the pathogenesis of OSA, optimization of medical HF therapy should be the first line of OSA therapy for HF patients. Data from a nonrandomized trial in which the administration of furosemide and spironolactone was accompanied by an increase in UA caliber and a modest reduction in the AHI among patients with diastolic HF and severe OSA support this approach. Four months of exercise rehabilitation also lowered AHI modestly in HF patients with OSA. On the other hand, a recent meta-analysis of nonrandomized studies of OSA patients with HF reported no significant effect of cardiac resynchronization therapy on AHI.

If OSA in HF patients is immediately abolished by CPAP, negative intrathoracic pressure swings are attenuated and LV afterload, BP, and HR all fall. Several randomized controlled trials of CPAP involving HF patients with OSA have evaluated the effects of treatment on cardiovascular variables measured during wakefulness. Kaneko and colleagues showed that, after 1 month of CPAP treatment, daytime systolic BP and HR fell, and LV ejection fraction (LVEF) increased by 9%. Expansion of this trial demonstrated that this reduction in systolic BP was accompanied by a reduction in sympathetic vasoconstrictor nerve discharge, suggesting that the sympathoexcitation of OSA is superimposed on the background sympathoexcitation of HF. In another randomized trial of 3 months’ duration involving patients with less severe HF and milder OSA, Mansfield et al showed that LVEF increased significantly, by 5%. Daytime BP did not fall, but urinary norepinephrine excretion did. Taken together, these data demonstrate consistently that treatment of OSA by CPAP in patients with systolic HF can increase LVEF and reduce SNA. Although no randomized trials have determined the effects of CPAP on morbidity and mortality in such patients, 2 observational studies comparing CPAP-treated and untreated HF patients have been performed. Wang et al reported a trend, over a mean 2.9-year follow-up period, to a lower mortality rate in CPAP-treated patients (P = 0.07), and Kasai and colleagues found CPAP-treated patients to have significantly greater hospitalization-free survival after a mean of 2.1 years. These encouraging observations underscore the need for adequately powered randomized trials to assess the effects of treating OSA on morbidity and mortality in HF patients.

Because systemic and pulmonary congestion contribute to the initiation and perpetuation of CSA, optimization of HF therapy should be considered the cornerstone of its therapy. Several approaches have been used to treat CSA in HF, but none have demonstrated any benefit with respect to cardiovascular morbidity or mortality. Whether cardiac rehabilitation improves CSA is uncertain. One study reported a 64% reduction in the AHI after 6 months of exercise training, whereas another 4-month study found no significant change in the AHI. A recent meta-analysis of nonrandomized trials reported that, after cardiac resynchronization therapy, the AHI fell significantly (mean reduction of −13) as cardiac function improved. However, suppression of CSA may not be sustained over the longer term. Cardiac transplantation also has been reported to alleviate CSA.

Small randomized trials report that 1 night to 1 month of nocturnal oxygen can reduce the AHI of HF patients with CSA by ≈50%, and a more recent 13-month randomized trial reported that nocturnal supplemental oxygen improved quality-of-life, but there is no evidence as yet that supplemental oxygen can improve cardiovascular function or clinical outcomes. Recently, Ponikowski and colleagues, in a nonrandomized study, reported that 1 night application of unilateral temporary transvenous phrenic nerve stimulation reduced the AHI in patients with CSA by 49%. Whether such improvement can be sustained chronically, or whether permanent phrenic pacing would be accepted by HF patients, is unknown. Because increased LV filling pressure and volume are present in the majority of CSA patients with HF, short-term trials of CPAP evaluated the effects of increasing intrathoracic pressure (thereby reducing both cardiac preload and afterload) on venricular systolic function, mitral regurgitation, and urinary norepinephrine excretion. Findings that all of these factors improved led to the Canadian Continuous Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure (CNPAP) trial, which sought to determine whether CPAP would improve CSA, morbidity, mortality, and cardiovascular function in patients with CSA receiving optimal medical therapy for HF. In this trial, which enrolled 258 HF patients with CSA, CPAP attenuated CSA, improved LVEF, and lowered plasma norepinephrine concentration, but, after a mean follow-up of 2 years, there was no significant difference between the 2 groups with respect to the primary end point of heart transplant-free survival. Because reversal of CSA per se appears to be 1 means by which CPAP could improve cardiovascular event rates, a post hoc analysis of the CNPAP trial was conducted. Patients ran-
domly assigned to CPAP were divided into 1 group in whom the AHI was reduced below the entry threshold of 15 (CSA suppressed), and the remainder in whom 3 months after randomization the AHI remained $\geq 15$. The CSA-suppressed group experienced significantly better heart transplant–free survival than the untreated control group, whereas, in the CSA unsuppressed group, there was a nonsignificant trend for lower heart transplant–free survival (Figure 4). Because adherence to treatment was the same in the 2 groups, lack of efficacy likely accounted for the neutral effect of CPAP in this trial. Although the CANPAP study results do not support routine use of CPAP to treat CSA in HF patients, the post hoc analysis underscored the need for effective and prompt treatment of CSA if the hypothesis that suppression of CSA has cardiovascular benefit is to be tested in future trials.

A newer type of noninvasive positive airway pressure, adaptive servo ventilation (ASV), has been shown to immediately suppress CSA in HF patients, even in those whose CSA was found resistant to CPAP or to bilevel positive airway pressure. In 1 randomized trial, brain natriuretic peptide and nocturnal urinary metadrenaline concentrations were reduced by ASV, but there was no improvement in LVEF. In 2 other short-term randomized trials involving HF patients with either CSA, or with coexisting OSA and CSA, LVEF increased more in ASV than in CPAP-treated patients. Although these data suggest that ASV may be more effective in suppressing CSA than CPAP, it is premature to recommend ASV for CSA treatment in HF patients because its effects on cardiovascular morbidity and mortality have not been tested in large-scale, long-term randomized trials. Such trials need to be conducted to inform rational decisions as to whether ASV or other forms of positive airway should be administered with the goal of reducing cardiovascular mortality or morbidity. At present, the question as to whether OSA or CSA should be a specific target of therapy in chronic HF remains unanswered.

Arrhythmias
Several reports indicate that effective treatment of OSA can reduce the burden of brady- and tachyarrhythmias. In 1 observational study, there was reversal of sinus bradyarrhythmias and second-degree heart block. Another reported that abolition of OSA by tracheostomy reduced the frequency of tachyarrhythmias. The recurrence rate of AF 1 year after cardioversion was found to be significantly lower in patients with CPAP-treated OSA than in those with untreated OSA (42% versus 82%). In a small, 1-month randomized trial involving HF patients with OSA and frequent ventricular ectopy during sleep, Ryan et al found a significant reduction in the ectopic frequency in those treated with CPAP; these data therefore suggest a causal role for OSA as an initiator of ventricular arrhythmias.

An initial observation, from a randomized study, that atrial overdrive pacing caused a 50% reduction in both obstructive and central AHI in patients with bradyarrhythmias, was not confirmed by subsequent investigation. Consequently, neither CSA nor OSA constitutes an indication for this type of cardiac pacing.

Stroke
The effects of treating sleep apnea on short-term (1-month) clinical outcomes in patients with stroke have been assessed thus far in 3 randomized studies, of which only one performed by Ryan et al, which enrolled relatively young (60 years of age) patients with OSA undergoing inpatient rehabilitation within 1 month of their index event, found a substantial benefit with respect to overall stroke recovery, functional and motor outcomes, and severity of depression, but no improvement in cognitive performance. In comparison with the previous 2 studies performed on outpatients, the Ryan trial was conducted in an inpatient setting, where the ready availability of medical personnel to assist in the use of CPAP led to better compliance (>4 hours per night), and patients with CSA, in whom CPAP is less effective, were excluded. These protocol differences likely account for the superior outcomes documented.

In an observational study involving patients with ischemic cerebrovascular disease and OSA patients with an AHI $\geq 20$ treated with CPAP, but who could not tolerate it, had a greater hazard ratio for mortality during 5 years of follow-up than...
Heart Failure
Hypertension

Sympathetic
Excitation
Sleep Apnea

Figure 5. Working bidirectional model illustrating the potential for hypertension and heart failure to initiate or exacerbate sleep apnea, by stimulating the sympathetic nervous system and sympathetically mediate renin release to cause sodium and fluid retention, and the potential for sleep apnea to cause or worsen hypertension and heart failure by such sympathetic stimulation, and by causing repetitive increases in left ventricular wall tension during sleep.

those with an AHI <20 and those with an AHI ≥20 who tolerated CPAP (2.69 and 1.58, respectively). Although this study suggested that CPAP treatment for OSA could reduce the mortality rate in patients who have already experienced an ischemic cerebrovascular event, randomized trials are needed to verify this observation.

Prevention of Cardiovascular Diseases

Although there is evidence from observational and nonrandomized trial data suggesting that treatment of OSA has the potential to prevent fatal and nonfatal CVDs, there are no randomized trials that demonstrate primary or secondary prevention of CVDs by treating OSA or CSA either in symptomatic or asymptomatic patients. Thus, the role of treating sleep apnea to prevent CVDs remains unclear.

Conclusions

Data from epidemiological studies and randomized clinical trials strongly suggest that OSA is a common and treatable risk factor for development of hypertension, HF, arrhythmias, and stroke, especially in men. Mechanistic investigations stimulate us to propose now a model of bidirectional causality (Figure 5), in which, in susceptible individuals, hypertension and HF, by stimulating the sympathetic, renin-angiotensin-aldosterone systems to induce renal sodium retention, could initiate or exacerbate sleep apnea through nocturnal fluid shifts, and in which sleep apnea, by eliciting nocturnal and daytime sympathetic activation, could promote the development of hypertension, and when exacerbated by the adverse ventricular loading conditions of severe OSA, ventricular hypertrophy, dilatation, and failure.

Observational studies also report, first, an association between the presence of OSA and increased fatal and nonfatal cardiovascular event rates in a sleep clinic population and among patients with preexisting CAD, stroke, or HF, and, second, that among such patients, treatment of OSA by CPAP is associated with a trend toward fewer fatal and nonfatal cardiovascular events.

In HF patients, CSA also is associated with increased morbidity and mortality, but a randomized trial found that its treatment by CPAP did not reduce event rates or hospitalizations. However, in a subgroup of patients in whom CPAP suppressed CSA, morbidity and mortality were reduced in comparison with an untreated control group.

Despite our greater present understanding of the interrelationships between sleep apnea and CVD, several important questions regarding the clinical significance of these sleep-related breathing disorders for CVD remain unresolved: Does OSA cause CVD independently of coexisting cardiovascular risk factors? Does treating OSA reduce the risk of developing CVD? In patients with established CVD, does OSA worsen prognosis, and does its treatment improve cardiovascular outcomes including mortality? Finally, does alleviating CSA improve morbidity or mortality in patients with HF? The most important approach to answer one or more of these questions will be to conduct large-scale, long-term randomized trials to assess the effects of treating OSA and CSA on cardiovascular morbidity and mortality. Our specific concern is that a large number of asymptomatic individuals, identified as having OSA or CSA, may be offered treatment without a clear indication for therapy based on evidence from randomized trials of benefit. Several important clinical trials, involving sleep apnea patients without and with HF in whom cardiovascular morbidity and mortality are being assessed, are presently underway. Their results should inform guidelines committees seeking to determine evidence-based indications for treating sleep apnea with the objective of reducing cardiovascular morbidity and mortality.

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References


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Takatoshi Kasai, John S. Floras and T. Douglas Bradley

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