Special Review

Sleep Apnea and Heart Failure
Part I: Obstructive Sleep Apnea

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Heart failure (HF) affects 5 to 6 million North Americans and is increasing in prevalence.[1] Mortality remains high. In Ontario, for example, between 1994 and 1997, approximately 33% of patients diagnosed with HF on first admission to hospital died within 1 year.[2] Reductions in mortality demonstrated in randomized clinical trials of pharmacological agents, such as β-receptor blockers[3] and angiotensin-converting enzyme inhibitors,[4] have been slow to translate into substantial reductions in death and hospitalization rates in community-based HF populations. These figures have remained relatively constant between 1948 and 1997.[2,5–7] In more recent clinical trials, the addition of newer agents has had a marginal, neutral, or even adverse impact on the high residual mortality of optimally treated patients.[8,9] Accordingly, investigators such as Massie[10] have raised the concern that there may be limits to the benefits achievable through conventional pharmacological strategies. Resource-intensive interventions, such as left ventricular assist devices or heart transplantation, are available to only a small minority of patients. Therefore, there remains a need to develop novel, widely applicable, and cost-effective approaches to the therapy of HF.

An important limitation to the current guidelines for the evaluation and management of chronic HF is their focus on the patient as he/she presents while awake.[1] This approach presupposes that any mechanisms that might contribute to the pathophysiology or progression of HF are quiescent during sleep. Our objective in this review, therefore, is to highlight the pathophysiological and therapeutic implications of coexisting sleep apnea in patients with HF.

There are 2 major forms of sleep apnea: obstructive sleep apnea (OSA) and central sleep apnea (CSA). Because their pathophysiologies and clinical implications in the setting of HF are quite different, OSA and CSA will be dealt with separately in the 2 parts of this review. In Part I, we will provide a general overview of the effects of normal sleep on the cardiovascular system and then discuss the impact of OSA and its therapy on HF. In Part II, will focus on the pathophysiology and treatment of CSA.

Effects of Normal Sleep

For the most part, non-rapid eye movement (NREM) sleep, which constitutes approximately 85% of total sleep time, is a state of cardiovascular relaxation. Metabolic rate, sympathetic nervous system activity, heart rate, cardiac output, and systemic vascular resistance fall,[11,12] whereas vagal activity increases.[13] Intermittent surges in sympathetic discharge, heart rate, and blood pressure do occur in rapid eye movement (REM) sleep, but in general, REM comprises only 15% of total sleep time, and average blood pressure and heart rate remain below waking levels.[11] In general, however, patients with HF sleep fewer hours and suffer from interrupted sleep. More importantly, from the perspective of this review, at least 50% of patients with HF have OSA or CSA, both of which disrupt the normal relaxing effects of sleep on the cardiovascular system.[14,15]

The hemodynamic, autonomic, and chemical disturbances elicited by repetitive cycles of obstructive apnea during sleep have been characterized extensively in subjects with normal ventricular function.[16–18] However, it is only recently that their adverse implications in patients with HF have been appreciated.[19] Intermittent apnea-induced hypoxia, hypercapnia, surges in central sympathetic outflow and left ventricular afterload, daytime hypertension, and loss of vagal heart rate regulation are potent stimuli to myocyte necrosis and apoptosis, myocardial ischemia, arrhythmias, adverse cardiac remodeling, and accelerated disease progression in HF.[20,21] CSA shares many of these pathophysiological features of OSA[22–24] and has independent adverse effects on survival.[25,26] Therefore, the potential for OSA and CSA to accelerate the relentless progression of HF and the possible beneficial impact of their treatment on cardiovascular outcomes merit greater attention.

Sleep Apnea: Classification and Diagnosis

Obstructive apneas and hypopneas result from complete or partial collapse of a narrowed pharynx,[27] respectively, whereas central apneas and hypopneas arise from reductions in central respiratory drive[28] (Table 1). During obstructive apnea, the effort generated to produce airflow increases,

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TABLE 1. Definitions of Terms

Term	Definition
Apnea	Cessation of airflow for more than 10 seconds
Hypopnea	A reduction in but not complete cessation of airflow to less than 50% of normal, usually in association with a reduction in oxyhemoglobin saturation
Apnea-hypopnea index	The frequency of apneas and hypopneas per hour of sleep; a measure of the severity of sleep apnea
Obstructive sleep apnea and hypopnea	Apnea or hypopnea due to complete or partial collapse, respectively, of the pharynx during sleep
Central sleep apnea and hypopnea	Apnea or hypopnea due to complete or partial withdrawal of central respiratory drive, respectively, to the muscles of respiration during sleep
Oxygen desaturation	Reduction in oxyhemoglobin saturation, usually as a result of an apnea or hypopnea
Sleep apnea syndrome	At least 10 to 15 apneas and hypopneas per hour of sleep associated with symptoms of sleep apnea, including loud snoring, restless sleep, nocturnal dyspnea, headaches in the morning, and excessive daytime sleepiness
Polysomnography	Multichannel electrophysiological recording of electroencephalographic, electroculographic, electromyographic, electrocardiographic, and respiratory activity to detect disturbances of breathing during sleep
NREM sleep	Non-rapid eye movement, or quiet sleep
REM sleep	Rapid eye movement, or active sleep; associated with skeletal muscle atonia, rapid movements of the eyes, and dreaming
Arousal	Transient awakening from sleep lasting less than 10 seconds

causing the rib cage and abdomen to distort and move out of phase. In contrast, in central events respiratory movements are absent or attenuated, but in phase. The reported prevalence of OSA in otherwise healthy adults is approximately 4% in women and 9% in men. Of these, less than half report symptoms of a sleep apnea syndrome.[29] The prevalence of CSA in otherwise healthy adults has not been determined, but appears to be far less common than OSA.[29,30]

The diagnosis of sleep apnea is generally based on the demonstration of at least 10 to 15 apneas and hypopneas per hour of sleep (Table 1)[15,29] and when accompanied by 1 or more symptoms of snoring, restless sleep, morning headaches, and excessive daytime sleepiness, it constitutes a sleep apnea syndrome. Current standards for overnight polysomnography require the concurrent monitoring of sleep structure, cardiac rhythm, oxyhemoglobin saturation, and respiration, using noninvasive methods capable of discriminating between obstructive and central events, such as respiratory inductance plethysmography.[31]

Obstructive Sleep Apnea

Pathophysiology

Obstructive apneas are caused by collapse of the pharynx during sleep. In subjects with normal pharyngeal anatomy, the partial withdrawal of pharyngeal dilator muscle tone that accompanies the onset of sleep is insufficient to cause pharyngeal collapse. However, the pharynx of patients with OSA is anatomically narrowed and highly compliant. In this setting, the superimposition of the normal withdrawal of pharyngeal dilator muscle tone at sleep onset causes the pharynx to occlude, triggering apnea.[32] Obesity is the chief risk factor of OSA, partly because layering of fat adjacent to the pharynx narrows its lumen.[33] In addition to this mechanism, other factors may come in to play in HF. For example, periodic oscillations in ventilatory drive related to Cheyne-Stokes respiration may cause withdrawal of pharyngeal dilator muscle tone during the waning of ventilation, predisposing to upper airway narrowing or collapse.[34] In the recumbent position, fluid from the legs shifts to more central structures. If some of this fluid should accumulate in the upper airway, the pharynx could become narrowed and more susceptible to collapse.[35] However, there is as yet no direct evidence to support this possibility.

Mechanical and Hemodynamic Effects

Obstructive apneas during sleep elicit a series of mechanical, hemodynamic, chemical, neural, and inflammatory responses with adverse consequences for the cardiovascular system (Figure 1). Futile inspiratory efforts against the occluded pharynx cause abrupt reductions in intrathoracic pressure. These increase left ventricular transmural pressure (the difference between intra-cardiac pressure and intra-thoracic pressure) and hence afterload.[36] Venous return is also enhanced, resulting in right ventricular distension and a leftward shift of the interventricular septum. The latter impedes left ventricular filling.[37] Diminished left ventricular preload and augmented left ventricular afterload act in concert to reduce stroke volume.[17,38]

Neurohumoral Effects

Increased sympathetic nervous system activity, a cardinal feature of obstructive apnea, results from the interaction of several excitatory mechanisms normally dormant during sleep. During apnea, the reflex arising from pulmonary stretch receptors that suppresses central sympathetic discharge during normal breathing ceases, disinhibiting central sympathetic outflow. The ensuing hypoxia and hypercapnia further augment sympathetic activity by stimulating peripheral and central chemoreceptors.[39,40] The resulting vasoconstriction raises peripheral resistance, whereas increased cardiac sympathetic stimulation increases heart rate and reduces

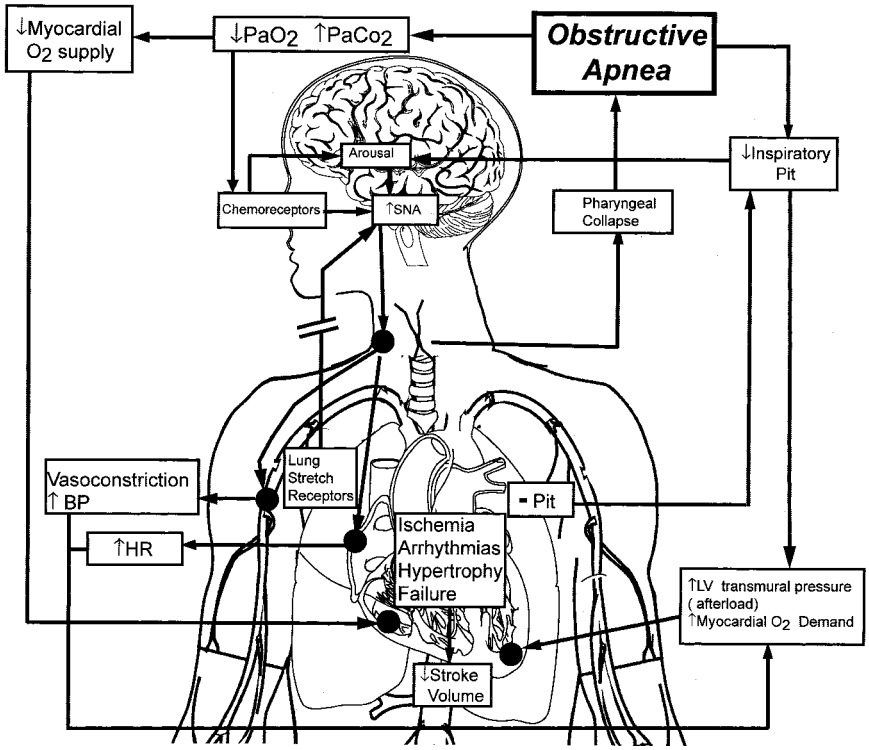

Figure 1. Pathophysiological effects of OSA on the cardiovascular system. Obstructive apneas increase left ventricular (LV) transmural pressure (ie, afterload) through the generation of negative intrathoracic pressure (Pit) and elevations in systemic blood pressure (BP) secondary to hypoxia, arousals from sleep, and increased sympathetic nervous system activity (SNA). Apnea also suppresses the sympathetic inhibitory effects of lung stretch receptors, further enhancing SNA. The combination of increased LV afterload and increased heart rate (HR) secondary to increased SNA increases myocardial O_2 demand in the face of a reduced myocardial O_2 supply. These conditions predispose a patient acutely to cardiac ischemia and arrhythmias, and chronically could contribute to LV hypertrophy and, ultimately, failure. The resultant fall in stroke volume will further augment SNA.

heart rate variability.[41] Although arousal from sleep at the termination of obstructive apnea facilitates the resumption airflow by stimulating pharyngeal dilator muscles,[37,42] the resulting excitatory input from cortical centers will cause a further burst of sympathetic outflow accompanied by a loss of vagal tone.[11,43] The immediate post-apneic period is therefore characterized by profound surges in blood pressure and heart rate. Sleep quickly resumes and with it, collapse of the pharynx. In severe OSA, these cycles of apnea and arousal can recur several hundred times each night, exposing the heart and circulation to high amplitude oscillations in central sympathetic nerve traffic, blood pressure, and heart rate.

The adverse effects of obstructive apnea on the cardiovascular system are not confined to sleep. Daytime sympathetic nervous activity and systemic blood pressure are increased in patients with OSA.[18,44] The mechanism for this is not certain, but intermittent apnea-related hypoxia may be playing a role, as hypoxia causes sympathetic activation and blood pressure elevations that persists after removal of the hypoxic stimulus.[45,46] There also appears to be a sustained reduction in vagal tone in patients with OSA, exemplified during wakefulness by a reduction in total heart rate variability and its vagally-mediated respiratory (high frequency) component.[41]

Inflammatory, Oxidative, and Vascular Endothelial Effects

There is increasing evidence that inflammatory mediators such as C-reactive protein, as well as oxidative stress play important roles in atherogenesis and arterial thrombus formation.[47] In a recent study, Shamsuzzaman et al[48] found that compared with control subjects matched for age, sex, and body mass index, patients with OSA had higher plasma C-reactive protein concentrations that were proportional to the frequency of apneas and hypopneas. Patients with OSA also demonstrate signs of increased oxidative stress, such as increased reactive oxygen species production in neutrophils[49] and monocytes.[50] In patients with OSA and coexisting coronary artery disease, increased oxidative stress is associated with elevated levels of the soluble circulating adhesion molecules intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin.[51] Increased expression of the adhesion molecules CD15 and CD11c in monocytes has also been reported in patients with OSA. Monocytes from OSA patients adhere more avidly to vascular endothelial cells in culture than those from control subjects.[52]

Intermittent apnea-related hypoxia and post-apneic reoxygenation probably contribute to generation of both reactive oxygen species and adhesion molecules. Conversely, treatment of OSA by continuous positive airway pressure (CPAP) lowers basal reactive oxygen species production by CD11+ monocytes, downregulates adhesion molecule expression (CD15 and CD11c on monocytes), and decreases leukocyte adherence to human endothelial cells in culture.[50] Activated leukocytes play an important role in the vascular endothelial inflammatory response to injury caused by hypoxia/reoxygenation that may alter endothelial reactivity and initiate atherogenic processes. However, as of yet there is no direct evidence that OSA causes atherosclerosis.

Patients with OSA have low plasma nitrite concentrations, suggesting reduced bioavailability of endothelially derived nitric oxide and altered endothelially mediated vasodilation.[52] Imadojemu et al[53] also found that reactive hyperemic blood flow and vascular conductance after forearm arterial occlusion were attenuated in patients with OSA compared with control subjects. After treatment of OSA by CPAP, reactive

TABLE 2. Independent Odds Ratios for Obstructive Sleep Apnea in Patients With Heart Failure

	Adjusted Odds Ratio (95% Confidence Interval)
Male	2.78 (1.47 to 5.24)
Body mass index, kg/m^2 (men only)*	1.68 (1.37 to 2.06)
Age, y (women only)*	1.11 (1.01 to 1.23)

Odds ratios are in comparison to patients without sleep-related breathing disorders.

*Odds ratios for these variables reflect the incremental increase in risk for a 5-unit increase.

Data are modified from Sin D, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med.* 1999;160:1101–1106.[13]

hyperemic blood flow and vascular conductance increased in association with a reduction in sympathetic nervous system activity. Another clinical manifestation of augmented sympathetic discharge and endothelial dysfunction in OSA is enhanced vascular responsiveness to neurogenic vasoconstrictor stimuli. For example, compared with control subjects, patients with OSA have an augmented pressor response to hypoxia.[54] Compromised endothelially mediated vasodilation in the setting of increased sympathetic vasoconstrictor discharge would predispose patients with OSA to the development of hypertension.[18,55,56]

Hypoxia has been shown to stimulate production of angiogenic substances like vascular endothelial growth factor (VEGF).[57] The plasma concentration of VEGF is increased in patients with OSA in proportion to the frequency of apneas and the degree of nocturnal hypoxia. In addition, VEGF concentrations fall in response to reversal of OSA by CPAP.[58,59] As of yet, however, there is no direct evidence of enhanced VEGF-induced angiogenesis in OSA. Nevertheless, variations in the VEGF response to nocturnal hypoxia may influence the cardiovascular system's response to tissue hypoxia.

Obstructive Sleep Apnea in Patients With Heart Failure

Epidemiology

In the Sleep Heart Health Study, comprising 6424 men and women, the presence of OSA (defined as an apnea-hypopnea index $\geq$11/h) conferred a 2.38 relative increase in the likelihood of having HF, independent of other known risk factors.[60] In the 2 largest case series of patients with HF undergoing polysomnography, OSA was detected in 37% of 450[14] and 11% of 81[15] subjects studied, with the prevalence of OSA greater in men (38%) than in women (31%).[14] Risk factors for OSA differ between men and women; the main risk factor in men is obesity, whereas in women it is older age (Table 2).

Clinical Features

The clinical features of OSA in HF are similar to those of OSA patients with normal left ventricular function. Patients are usually obese and have a history of loud habitual snoring. However, only a minority complain of excessive daytime sleepiness,[15] suggesting that many patients with HF have relatively asymptomatic OSA.

Implications for Progression of Heart Failure

The pathophysiologies of OSA and HF converge in 2 areas fundamental to progression of myocardial failure and premature mortality: the adverse impact of sympathetic nervous system activation and of vagal withdrawal on the cardiovascular system in general, and the detrimental effects of altered loading conditions and hypoxia on the failing ventricle in particular. In addition, the consequences of high sympathetic drive to the failing heart include myocyte necrosis and apoptosis, β-adrenoceptor downregulation and desensitization, arrhythmogenesis, and increased mortality rates.[20,21,61] Stimulation of renal sympathetic nerves promotes renin-angiotensin-aldosterone activation, as well as sodium and fluid retention.[21] Impaired baroreflex and tonic vagal heart rate control are additional markers of adverse outcome due in part to an increased risk of sudden death.[62] In contrast to HF patients without OSA, these disturbances of circulatory control are exacerbated during sleep, leading to increased myocardial oxygen demand in the setting of recurrent hypoxia, which can itself directly reduce myocardial contractility.[63] Consequently, these repetitive stresses place the patient with OSA and HF at greater risk of worsening ventricular dysfunction, arrhythmias, and, ultimately, reduced survival.

Systemic hypertension is the commonest risk factor for cardiac hypertrophy and failure in longitudinal studies.[64] Exposure of dogs to experimental OSA for several weeks leads to both nocturnal and daytime hypertension,[65] left ventricular hypertrophy, systolic dysfunction, and interstitial pulmonary edema.[37,66] A large prospective epidemiological study has also provided compelling evidence that OSA is a risk factor for the development of systemic hypertension, independent of other known risk factors.[44] Left ventricular hypertrophy is more closely linked to hypertension during sleep than during wakefulness.[67] Accordingly, the higher nocturnal blood pressure experienced in hypertensive patients with OSA than in those without may place them at greater risk for left ventricular hypertrophy.[68] Because output from the failing left ventricular is particularly sensitive to increases in afterload, the most direct mechanism by which OSA might compromise left ventricular systolic function is through its effect on blood pressure. When HF patients develop trains of obstructive apnea during sleep, blood pressure rises above, rather than descending below waking values.[69] Moreover, in a recent study, Sin et al[70] demonstrated that the presence of OSA in medically treated patients with HF was associated with elevated daytime blood pressure in proportion to the frequency of obstructive apneas and hypopneas. Mechanisms by which OSA could contribute to chronic hypertension in HF patients are similar to those described above for OSA patients with normal cardiac function.[18,45,55]

The repetitive generation of exaggerated negative intrathoracic pressure against the occluded pharynx is a cardiac load unique to OSA. Pressures as low as -65 mm Hg have been recorded during obstructive apneas in patients with HF.[71] When subjected to such abrupt increases in left ventricular afterload and myocardial oxygen demand, patients with HF

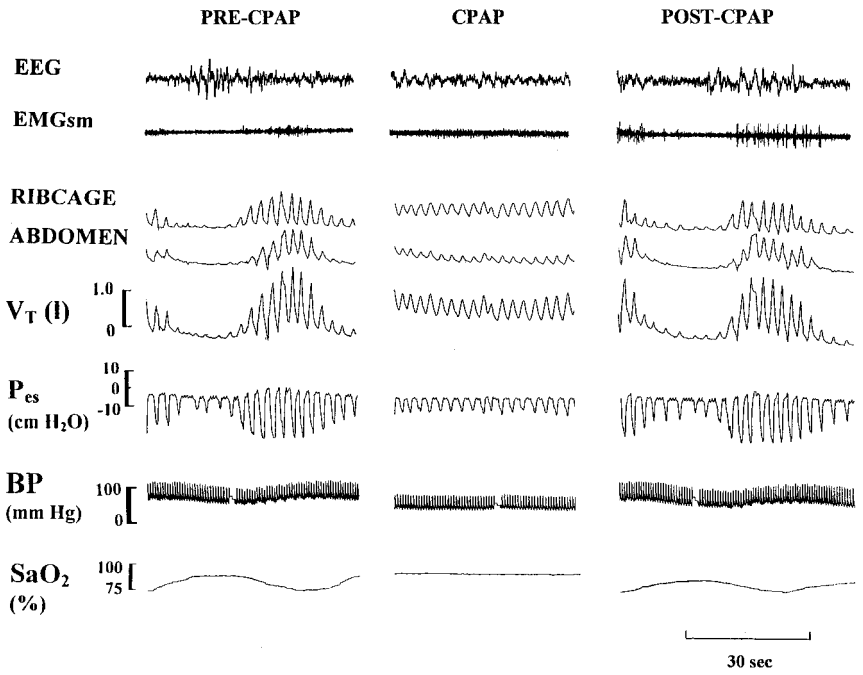

Figure 2. Effects of continuous positive airway pressure (CPAP) on obstructive sleep apnea (OSA) in a patient with heart failure. Abolition of obstructive apneas by CPAP prevents dips in oxygen saturation (SaO_2), dampens negative intrathoracic pressure (ie, esophageal pressure; P_{es}), swings and lowers blood pressure (BP). The combination of the latter two causes a marked reduction in left ventricular transmural pressure, an important determinant of afterload. EEG indicates electroencephalogram; EMGsm, submental electromyogram; and V_T, tidal volume. Reprinted with permission Tkacova R, Rankin F, Fitzgerald FS, et al. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. *Circulation*. 1998;98:2269–2275.[69]

experience more profound and prolonged reductions in stroke volume than control subjects with normal left ventricular function.[36] These obstructive events are replicated hundreds of times over the course of the night. If this scenario is considered comparable to the sequential administration of several hundred boluses of a potent pressor agent each day, the long-term implications of these repetitive increases in wall stress for the induction of genes involved in ventricular remodeling become obvious. Marked reductions in intrathoracic pressure generated during obstructive events could play a significant role in the development of myocyte slippage, contractile dysfunction, and adverse ventricular remodeling in such patients.[72] OSA also prevents the normal fall in heart rate that accompanies the onset of sleep.[69] When coupled with marked reflex increases in central sympathetic outflow, which are greater in HF than in individuals with normal left ventricular function,[73] these marked elevations in afterload and heart rate increase the metabolic demands of the myocardium in the face of reduced O_2 supply, cardiac output, and coronary perfusion, setting the stage for recurrent nocturnal ischemia and arrhythmias.[74] Conversely, abolition of OSA can reverse these pathophysiological processes and improve left ventricular structure and function.[69,71,75]

In addition to these adrenergic and mechanical actions, increased levels of inflammatory mediators, oxidative stress, and vascular endothelial dysfunction in OSA have the potential to accelerate atherogenesis.[47–50,55] Because ischemic heart disease is the commonest cause of HF in the industrialized world, OSA could potentiate myocardial dysfunction through these adverse influences on the coronary vasculature.

Treatment of Obstructive Sleep Apnea in Heart Failure

The full range of indications for and most effective means of treating OSA in patients with HF remain to be established. Nevertheless, as with patients with normal ventricular function, the most compelling indication for treatment of OSA would be a complaint of debilitating daytime sleepiness or related symptoms of sleep apnea. General therapeutic considerations for such patients include weight reduction, which may reduce the severity of OSA,[76] and abstinence from alcohol and sedatives, which predispose to pharyngeal collapse during sleep.[77]

Randomized trials in patients with OSA and excessive daytime sleepiness but with normal cardiac function have demonstrated that CPAP applied via a nasal mask alleviates OSA, improves sleep quality, reduces daytime sleepiness, augments neurocognitive function, and may lower nocturnal and daytime blood pressure.[78,79] On the other hand, a randomized trial of patients with relatively severe OSA (apnea-hypopnea index >30 per hour of sleep) but without a symptom of excessive daytime sleepiness demonstrated that although patients randomized to CPAP were compliant with it, they did not derive any symptomatic or neurocognitive benefit.[80] These findings support the use of CPAP for patients with symptomatic OSA, but do not support its use for those with asymptomatic OSA. In a non-randomized trial involving patients with nocturnal angina, elimination of OSA by CPAP reduced the frequency of ST-segment depression and angina during sleep.[81] Treatment of OSA by CPAP also reduces nocturnal and daytime sympathetic nervous system activity,[18,82] augments heart rate variability,[41] and may reduce oxidative stress, increase endothelially derived nitric oxide, and improve endothelially mediated vasodilatation.[49,52]

There is no evidence that pharmacological agents used to treat HF have any influence on the severity of OSA,[83] and thus far no randomized trials in HF have evaluated the impact of treating OSA on important clinical cardiovascular outcomes. However, acute abolition of OSA by CPAP in patients with HF prevents recurrent hypoxia, reduces nocturnal blood pressure and heart rate,[65] and increases arterial baroreflex sensitivity[84] (Figure 2). The first study to examine the effects

of treating OSA with CPAP on left ventricular function in patients with HF was uncontrolled. Eight patients with idiopathic dilated cardiomyopathy and coexisting OSA were studied. After 1 month of CPAP, mean left ventricular ejection fraction increased from 37% to 49% and dyspnea was reduced significantly.[71] These improvements reversed 1 week after withdrawal of CPAP. A randomized trial involving 24 patients with HF and OSA has been recently published.[75] The 12 patients randomized to CPAP used a mean pressure of 8.9 ± 0.7 cm H_2O for 6.2 ± 0.5 hours per night during the 1-month study. They experienced a significant reduction in daytime heart rate (from 68 ± 3 to 64 ± 3 bpm, $P=0.007$) and systolic blood pressure (from 126 ± 6 to 116 ± 5 mm Hg, $P=0.020$). Their mean left ventricular ejection fraction increased by 9% (from 25.0 ± 2.8 to 33.8 ± 2.4%, $P<0.001$). In contrast, those in the control group experienced no improvement in any of these variables.

In awake patients with HF, CPAP also increases heart rate variability and its vagal modulation.[85] In many respects, these effects of CPAP are analogous to the chronic effects of β-blockade in HF,[3] but they are achieved nonpharmacologically by reducing oxygen demand and increasing oxygen supply and by attenuating central sympathetic outflow. Although these short-term results are encouraging, there remains a need for randomized trials to determine whether the specific treatment of OSA in HF will improve long-term morbidity and mortality. However, such trials may be difficult to design and execute because of the inherent reluctance of many physicians to withhold CPAP, a standard therapy of OSA, from a control group for prolonged periods. This difficulty is compounded by the issue of whether a truly neutral placebo or "sham" CPAP can be administered to a control group over the course of a multi-year trial.[86] Nevertheless, as many patients with HF who have OSA do not have daytime sleepiness,[15,75] and because such patients do not derive symptomatic or neurocognitive improvement from CPAP therapy,[80] it may be feasible to carry out longer-term randomized clinical trials, as these patients lack the conventional clinical indications for treatment.[78]

Mandibular advancement devices have been shown in randomized trials to improve OSA and its symptoms, but they are generally not as effective as CPAP.[87,88] Surgical procedures designed to increase the caliber of the pharyngeal lumen, such as uvulopalatopharyngoplasty and laser assisted uvulopalatoplasty, are effective in less than 50% of patients and have not been subjected to randomized trials.[89] There have been no studies of the potential therapeutic effects of mandibular advancement devices or upper airway surgery on OSA in patients with HF. Until such studies are completed, these approaches cannot be recommended as therapy for OSA in this setting.

Conclusion

In a substantial proportion of patients with HF, OSA may play a role in the pathogenesis and progression of cardiac failure through mechanical, adrenergic, and vascular mechanisms. However, more research is required to determine basic mechanisms by which OSA exerts its adverse effects on the cardiovascular system. Such investigations could include studies of the effects of intermittent hypoxia on cardiovascular function at the cellular and molecular levels,and of genetic susceptibilities to adverse cardiovascular consequences of OSA and intermittent hypoxia. In addition, more clinical investigation, especially large scale randomized trials of various interventions for OSA in patients with HF, will be required to determine the effectiveness of these therapies on cardiovascular outcomes.

In the next issue of *Circulation*, we will address CSA, or Cheyne-Stokes respiration.[90] This breathing disorder has an inordinately high prevalence in patients with HF compared with the otherwise healthy population and appears to have adverse prognostic implications. In Part II, we will review the literature in this area and provide a broad perspective on the potential pathophysiological and clinical significance of coexisting CSA for patients with HF.

Acknowledgments

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