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Obstructive Sleep Apnea and Heart Failure: Pathophysiologic and Therapeutic Implications

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Heart failure (HF) is a common disorder afflicting approximately 4,000,000 Americans.[1] Although the prevalence of HF is growing as more patients survive myocardial infarction (MI) and ischemic heart disease, a great deal of progress has been made in the treatment of this disorder over the past 20 years. This progress is based on research that has defined various aspects of the pathophysiology of HF that are amenable to specific therapy. For example, treating hypertension with blood pressure (BP) lowering agents such as the angiotensin-converting enzyme (ACE) inhibitors and excess sympathetic nervous system activity with beta-adrenergic receptor blockers has lowered mortality rates in patients with HF.[2,3] One factor that may also play a role in the pathophysiology of HF – that is not ordinarily considered in its investigation and management – is obstructive sleep apnea (OSA). Since OSA is readily treatable, it is possible that its specific therapy in patients with HF could improve cardiovascular outcomes. Therefore, the focus of this issue of *Cardiology Rounds* is to review the pathophysiological and therapeutic implications of OSA for the failing heart.

Pathophysiology

OSA is a condition characterized by a recurrent collapse of the pharynx during sleep. Patients with OSA generally have an anatomically narrowed, highly compliant pharynx that becomes susceptible to collapse upon the normal withdrawal of pharyngeal dilator muscle tone at the onset of sleep.[4-6] Obesity is the most important risk factor for OSA because it is associated with the narrowing of the pharynx due to excessive fat deposition in the neck and lateral pharyngeal walls.[7] Other causes of pharyngeal narrowing include adenotonsillar hypertrophy (especially in children), micro- or retrognathia, and macroglossia that can be related to acromegaly or hypothyroidism.[8-10]

Normally, sleep is a time of cardiovascular relaxation due to reductions in metabolic rate and sympathetic nervous system activity (SNA) and increases in vagal parasympathetic outflow to the heart.[11-13] As a result, cardiac output, BP, and heart rate fall between wakefulness and non-rapid-eye movement (non-REM) sleep. However, OSA counteracts this state of cardiovascular quiescence through 3 key acute adverse effects on the cardiovascular system (Figure 1).

• First, during obstructive apneas, the patient makes ineffectual inspiratory efforts against the occluded upper airway. This generates exaggerated negative intrathoracic pressure that increases left ventricular (LV) afterload by increasing the difference between intra-LV and intrathoracic pressure (ie, LV transmural pressure). As a consequence, myocardial O_2 demand is increased. In addition, exaggerated negative intrathoracic pressure increases venous return to the right ventricle, while hypoxic pulmonary vasoconstriction increases pulmonary artery pressure and right ventricular afterload.[14,15] The resulting distension of the right ventricle causes a leftward shift of the interventricular septum that impedes LV diastolic filling.[16,17] As a result, stroke volume and cardiac output fall.[18] These adverse hemodynamic effects are more pronounced and longer lasting in patients with HF than in those with normal cardiac function.[19]

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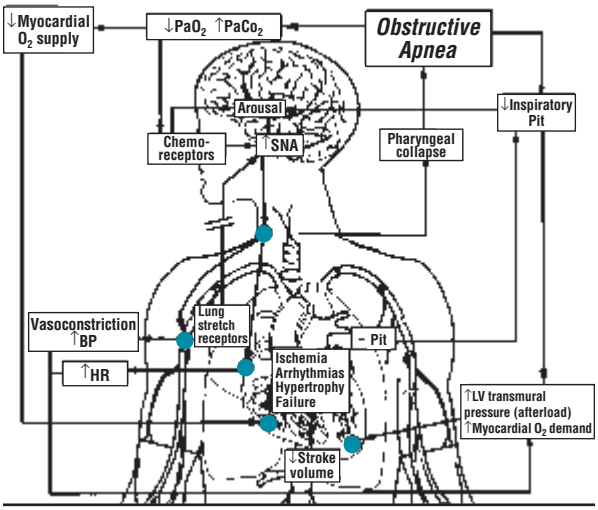
Figure 1: Pathophysiological effects of OSA on the cardiovascular system



Obstructive apneas increase left ventricular (LV) transmural pressure (ie, afterload) through the generation of negative intrathoracic pressure (Pit) and elevations in systemic 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) increases myocardial O_2 demand in the face of a reduced myocardial O_2 supply. These conditions predispose acutely to cardiac ischemia and arrhythmias, and chronically could contribute to LV hypertrophy and, ultimately, heart failure. The resultant fall in stroke volume will further augment SNA.

(Reproduced with permission from Bradley TD[16])
BP= blood pressure; HR = heart rate; LV = left ventricular; Pit = intrathoracic pressure.

• Second, simultaneous apnea-related hypoxia reduces O_2 delivery with the potential to provoke myocardial ischemia in susceptible individuals.[20] Hypoxia can also impair cardiac diastolic relaxation and contractility.[21]

• Third, the combination of inspiratory efforts, apnea-related hypoxia, and CO_2 retention triggers an arousal from sleep. These stimuli act synergistically to provoke sympathetic nervous system activity (SNA), that reaches a maximum just at the termination of apneas.[22,25]

Arousals also cause abrupt withdrawal of vagal outflow to the heart.[24] The net effect of these stimuli is repetitive surges in BP and heart rate that further increase LV afterload and myocardial O_2 demand.[23,24]

Over time, the cumulative effects of these acute, repetitive insults can have chronic adverse consequences for the cardiovascular system. Exposure of dogs to experimentally-induced OSA for several months causes nocturnal and daytime hypertension, LV hypertrophy, and dysfunction.[18] Rats exposed to intermittent hypoxia also develop hypertension that is prevented by sympathectomy.[26] These data indicate that hypertension associated with OSA is at least partially mediated by the sympathetic nervous system. Chronic exposure of the heart to excessive sympathetic stimulation can also lead to cardiac myocyte injury, necrosis, and fibrosis.[27] In patients with HF, elevated plasma norepinephrine levels are also associated with increased risk of death.[28] Thus, OSA may be a source of excess SNA in patients with HF. Taken together, these data indicate OSA may contribute to the development and progression of HF.

Epidemiology

OSA is common in the general population and has been reported to occur in 4% to 9% of adults between the ages of 30 and 60 years.[29] In large epidemiological studies, OSA is associated with an increased prevalence and incidence of hypertension;[30,31] and is the commonest risk factor for HF.[32] Therefore, it is not surprising that cross-sectional data from 6,500 subjects in the Sleep Heart Health Study demonstrated a significant increase in the odds ratio for HF associated with the presence of OSA that is independent of other known risk factors.[33] OSA is also common in the setting of HF where it has been reported to occur in 11% to 37% of patients, respectively, in the 2 largest studies.[34,35] OSA is more common in men than in women with HF. In men with HF, the main risk factor for OSA is obesity, whereas in women, it is age >60 years.[34] The reason for these gender-related differences in risk factors for OSA remains unclear. The presence of OSA in patients with HF is also associated with elevated BP that is proportional to the frequency of obstructive apneas and hypopneas.[36]

Clinical features

As in the otherwise healthy population, the usual presenting features of OSA in patients with HF are obesity and loud snoring, although obesity plays less of a role in women than in men.[34,35] Although HF patients with OSA may present with excessive daytime sleepiness, this complaint is surprisingly uncommon. For example, Epworth Sleepiness Scores are generally within normal limits.[37-39] This lack of sleepiness is striking, but the reason for it remains unclear. Nevertheless, this relative lack of hypersomnolence in HF patients with OSA makes it difficult to know when to perform a sleep study to establish a diagnosis. In general, among patients with HF, one should suspect OSA when there is a history of snoring, obesity, and BP that is difficult to control.[34-36]

Diagnosis

The diagnosis of OSA is best established by overnight polysomnography in a sleep laboratory and rests upon the demonstration of at least 10-15 apneas and hypopneas per hour of sleep.[34,35] When polysomnographically-confirmed OSA is accompanied by ≥1 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.[40]

Presently, the standard for diagnosis remains in-laboratory polysomnography, which is relatively expensive and may not be readily available. However, the development and validation of less expensive and more readily available techniques, such as ambulatory monitoring of oxyhemoglobin saturation, airflow, and chest wall motion may render widespread screening for sleep apnea feasible in the heart failure population.[33] Although a number of ambulatory devices are being developed for monitoring breathing during sleep, none of these devices has been validated for accuracy and reliability in detecting OSA in patients with HF. Therefore, until such techniques are validated, overnight polysomnography in a sleep laboratory remains the test of choice for diagnosing OSA in patients with HF.

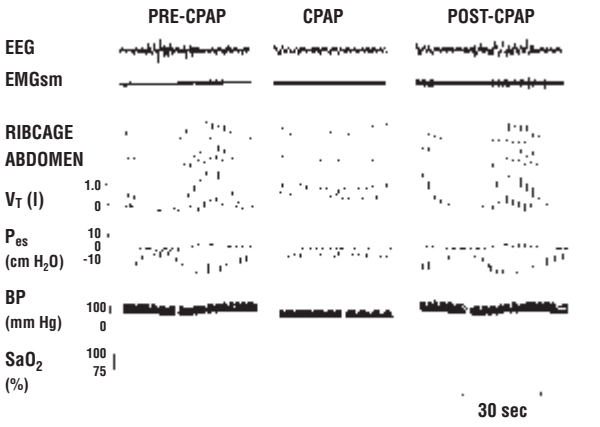
Treatment

The full range of indications for, and the most effective means of treating, OSA in patients with HF remain to be established. Nevertheless, in the absence of direct evidence from randomized trials in HF patients with OSA, treatment of OSA patients with HF should, in general, adhere to the principles of therapy established for treatment of OSA patients without HF. Accordingly, as in 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. In obese subjects, weight loss should be advised, as this has been shown to reduce the frequency of OSA and hypopneas.[41] One mechanism through which weight loss appears to work is by enlarging the pharyngeal lumen through regression of peripharyngeal fat.[42] Avoidance of alcohol and sedative medications should also be recommended since these agents can reduce the tone of the pharyngeal dilator muscles during sleep, rendering the upper airway more susceptible to collapse.[43]

In most patients with OSA, but with normal ventricular function, the treatment of choice is nasal continuous positive airway pressure (CPAP). 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 BP.[44-46] On the other hand, a randomized trial of patients with relatively severe OSA (apnea-hypopnea index >30 per hour of sleep), but without excessive daytime sleepiness, demonstrated that although patients randomized to CPAP were compliant with it, they did not derive any symptomatic or neurocognitive benefit.[47] These findings support the use of CPAP for patients with symptomatic OSA, but do not support its use for those with asymptomatic OSA.

Treatment of OSA by CPAP in patients with normal ventricular function also reduces nocturnal and daytime sympathetic nervous system activity,[23,48] augments heart rate variability,[49] and may reduce oxidative stress, increase endothelially derived nitric oxide, and improve endothelially

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; Pes) swings and lowers BP.

(Reproduced with permission from Tkacova R[25])
EEG = electroencephalogram; EMGsm = submental electromyogram; VT= tidal volume.

mediated vasodilatation.[50,51] Among patients with coronary artery disease and nocturnal angina, acute application of nocturnal CPAP sufficient to eliminate OSA, reduced the frequency of ST-segment depression and angina during sleep.[20] These findings suggest that alleviation of OSA (and its attendant hypoxia) and surges in BP cause reversal of cardiac ischemia.

There have been only a few trials testing the effects of CPAP in patients with HF and coexisting OSA. Acute application of CPAP to such patients abolishes OSA and intermittent hypoxia, and causes remarkable reductions in LV afterload through the combined effects of reducing BP and eliminating exaggerated negative intrathoracic pressure swings (Figure 2).[25] CPAP also causes acute increases in baroreflex sensitivity in such patients.[52] The effects of chronic application of CPAP to HF patients with OSA have been tested in only 3 studies.

- In the first study, OSA was treated by CPAP for 1 month in 8 patients with HF due to idiopathic dilated cardiomyopathy in a non-randomized, uncontrolled trial.[53] In association with the alleviation of OSA, left ventricular ejection fraction (LVEF) increased 12% from 37±4 to 49±5 ($P<0.001$), and cardiac functional status improved.
- In the second study, Kaneko et al studied the effects of CPAP in 24 HF patients with OSA in the setting of a randomized, controlled, clinical trial.[38] Subjects had to have an LVEF <45% while on optimal medical HF therapy and OSA with at least 20 apneas and hypopneas per hour of sleep. Subjects were randomized to a control group who continued to receive optimal medical therapy and a CPAP-treated group who, in addition to medical therapy, received nocturnal CPAP titrated to the optimum pressure. All subjects completed the trial. After 1 month, subjects in the control group did not experi-

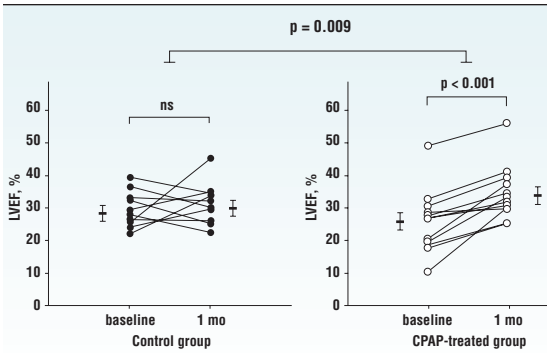
Table 1: Heart rate and blood pressure

	Control group			CPAP-treated group		
	Baseline	1 mo.	P-values	Baseline	1 mo.	P-values
Heart rate, bpm	67±4	67±4	ns	68±3	64±3	0.007*
Systolic BP, mm Hg	128±7	134±8	ns	126±6	116±5	0.020†
Diastolic BP, mm Hg	60±4	58±3	ns	62±4	59±2	ns

There were no significant differences in baseline values between the control and CPAP-treated groups. P-values refer to comparisons of within-group baseline to 1-month values.

* P=0.089 and † P=0.008 for between group comparisons. (Reproduced with permission from Kaneko Y[38])

Figure 3: Effects of nasal CPAP on LVEF in patients with heart failure and OSA



The control group experienced no significant change in LVEF from baseline to 1 month (from 28.5±1.8% to 30.0±2.1%). In contrast, LVEF increased by a mean of 8.8±1.6% in all 12 CPAP-treated subjects (from 25.0±2.8% to 33.8±2.4%, P<0.001).

(Reproduced with permission from Kaneko Y[38])

ence any improvements in OSA, BP, heart rate, or cardiac function. Subjects randomized to CPAP used it on average for 6.2 hours per night. In contrast to the control subjects, those randomized to CPAP experienced alleviation of OSA that was accompanied by significant reductions in daytime systolic BP (from 126±6 to 116±5 mm Hg, P = 0.02; Table 1) and heart rate (from 68±3 to 64±3 beats per minute, P=0.007), and a highly significant 9% increase in LVEF (from 25±3% to 34±2%, P<0.001; Figure 3). Since these improvements in cardiovascular function were observed during the daytime, several hours after CPAP had been removed, they indicated an important carry-over effect. The mechanism of this effect remains unclear, but it is very interesting that an intervention applied only at night can give rise to biological effects that are sustained into the daytime. Another interesting aspect to this study was that despite having moderately-severe OSA (approximately 45 apneas and hypopneas per hour of sleep), subjects had Epworth Sleepiness Scores within normal limits (mean score of 6.2 for all subjects), indicating that they did not suffer from hypersomnolence.[37] These findings, therefore, suggest that in the HF population, patients with OSA need not complain of excessive daytime sleepiness in order to benefit from CPAP therapy.

• In a third study, Mansfield et al also performed a randomized trial in 40 HF patients with OSA.[39] However, their entry criteria differed from those of Kaneko et al[38] in that neither HF. nor OSA, were as severe (LVEF had to be only < 55%, and the frequency of apneas and hypopneas had to be only > 5 per hour of sleep). The study period was also longer (3 months versus 1 month). Nevertheless, their findings confirmed those of Kaneko et al[38] that elimination of OSA by CPAP caused a significant 5% improvement in LVEF (from 38±3 to 43±0 percent, P<0.001). They also found that CPAP caused a reduction in overnight urinary norepinephrine levels, suggesting a reduction in sympathetic nervous system activity. However, there were no changes in daytime BP or heart rate. The lack of a fall in BP and the lesser degree of improvement in LVEF than in the study by Kaneko is likely related to less severe degrees of OSA and LV systolic dysfunction at baseline in the Mansfield study. Taken together, the findings of these 3 studies consistently demonstrate that alleviation of OSA by CPAP in HF patients can improve cardiovascular function over and above that due to optimal medical therapy.

Other therapies

There are other forms of therapy for OSA. Custom-made mandibular advancement devices can reduce the severity of OSA in patients with normal ventricular function. However, they are not as effective as CPAP in alleviating OSA and in improving symptoms.[54] Since these devices have not been tested in patients with HF, their use should probably be reserved for those who cannot tolerate CPAP. Generally, upper airway surgery, such as uvulopalatopharyngoplasty or laser-assisted uvulopalatopharyngoplasty, is not a very effective therapy for OSA in patients with normal ventricular function.[55] In addition, because it may require a general anaesthetic, it poses some risks in patients with impaired cardiac function. Therefore, it cannot be considered a safe and effective therapy for OSA in patients with HF. Tracheostomy has been used as an effective treatment for OSA because it completely bypasses the site of upper airway obstruction.[56] However, its efficacy has not been studied in HF patients with OSA. Tracheostomy also has significant side effects, such as recurrent bronchitis and skin breakdown around the stoma, and should, therefore, be reserved for those patients in whom CPAP is either ineffective or cannot be tolerated.

Conclusion

Obstructive sleep apnea is common in patients with HF, and produces many adverse hemodynamic and adrenergic effects that could contribute to the development or

progression of LV dysfunction and heart failure. Nevertheless, its potential impact in HF has received little attention in the cardiovascular literature. Clinical trials in which HF patients with OSA have been treated for 1 to 3 months have shown favorable effects on sympathetic nervous system activity, BP, LV systolic function, and functional class.[38,39,53] However, because these trials involved only small numbers of subjects and were relatively short in duration, long-term cardiovascular outcomes could not be assessed. Ideally, larger longer-term randomized trials should be performed to assess the effects of OSA therapy on cardiovascular outcomes in patients with HF. However, such trials may prove difficult to conduct because of the difficulty in leaving OSA untreated for prolonged periods in a control group. Nevertheless, the consistent results of trials of CPAP for OSA in patients with HF suggest that OSA should be considered a therapeutic target in patients with heart failure, particularly in those whose HF is relatively resistant to medical therapy. Therefore, more research should be undertaken to determine the role of OSA and its therapy in the pathogenesis and management of heart failure.

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Dr. Bradley has received peer-reviewed research funding from the Canadian Institutes of Health Research (CIHR) to conduct a randomized controlled trial of continuous positive airway pressure (CPAP) to treat heart failure. In partnership with the CIHR, 3 manufacturers of CPAP devices (Respironic, RedMed, and Tyco) have provided partial, arms-length funding flowing through the CIHR for this trial as well. These manufacturers played no role in the design of the trial and have no access to the data.