Cardiovascular effects of sleep-related breathing disorder

R Leung, JKW Chan, CKW Lai

Sleep-related breathing disorder is a prevalent medical condition that remains underdiagnosed in the community. This disorder has social, behavioural and neuropsychological impact, deleterious haemodynamic effects during sleep, and is associated with increased cardiovascular morbidity. This review aims to describe the current evidence for the association of sleep-related breathing disorder with hypertension, ischaemic heart disease, heart failure, and stroke, based on the knowledge of its haemodynamic effects during sleep.

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Introduction

Sleep-related breathing disorder (SBD) has emerged in the last 15 years as a rapidly expanding field in clinical medicine. It is characterised by habitual snoring, excessive daytime somnolence, and repetitive apnoea during sleep. The prevalence of SBD has been found to be high in western populations. A large epidemiological survey of a middle-aged working population aged 30 to 60 years in the USA showed that the prevalence of SBD, as defined solely by an apnoea-hypopnoea index (AHI) of ≥5 on overnight polysomnography, is 24% for males and 9% for females.[1] When the symptoms of sleep apnoea and the polysomnographic findings are considered together, 4% of men and 2% of women meet the diagnostic criteria for obstructive sleep apnoea (OSA). This is the most common form of SBD and results in sleep fragmentation and excessive daytime somnolence. In young adults in Hong Kong, the symptoms of sleep apnoea are common, with 10.0% reporting that performance ability is affected by severe daytime somnolence and 1.8% complaining of frequent choking attacks during sleep.[2] Two percent of those who underwent sleep monitoring at night had an AHI >5. The prevalence of SBD is even higher among elderly people, with up to 60% showing respiratory disturbances during sleep.[3]

Besides its social, behavioural and neuropsychological impact, there is mounting evidence to suggest that SBD is associated with increased cardiovascular morbidity and mortality.[4,5] The haemodynamic effects of SBD also impair cardiac function and complicate the natural course of congestive cardiac failure. In this review we will discuss the pathophysiological basis of the adverse cardiovascular effects of SBD, with particular emphasis on the current evidence for the importance of SBD in hypertension, ischaemic heart disease, heart failure, and stroke.

Haemodynamic changes during normal sleep

Sleep is characterised as a low metabolic state during which energy demand and sympathoneural activities are reduced. The low sympathoneural activities result in a lower heart rate, decreased total peripheral resistance, and hence decreased cardiac output. Blood pressure follows a circadian rhythm, falling at night and rising to its highest level in the morning. During sleep, blood pressure decreases by 15% during the transition from wakefulness to stage 4 sleep.[6] The reduction in cardiac output during sleep is also dependent on sleep stages; it falls with increasing sleeping time, reaching just 75% of the cardiac output in the awake state during the last rapid eye movement (REM) cycle of sleep.[7] The decrease in blood pressure and cardiac

Department of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
R Leung, MD, FRACP
JKW Chan, MB, BS, FRACP
CKW Lai, DM, FRCP

Correspondence to: Dr R Leung

output during sleep has also been described in hypertensive patients.[8] In REM sleep, there is often a return of sympathetic activity and an increase in respiratory drive.

Haemodynamic effects of sleep-related breathing disorder

Normal breathing has little effect on the cardiovascular circulation. However, during snoring and OSA, the change in intrathoracic pressure and resultant increased sympathoneural activities from hypoxaemia and frequent arousals may exert a wide array of physiological events which can have deleterious haemodynamic consequences (Fig 1).

Decreased intrathoracic pressure

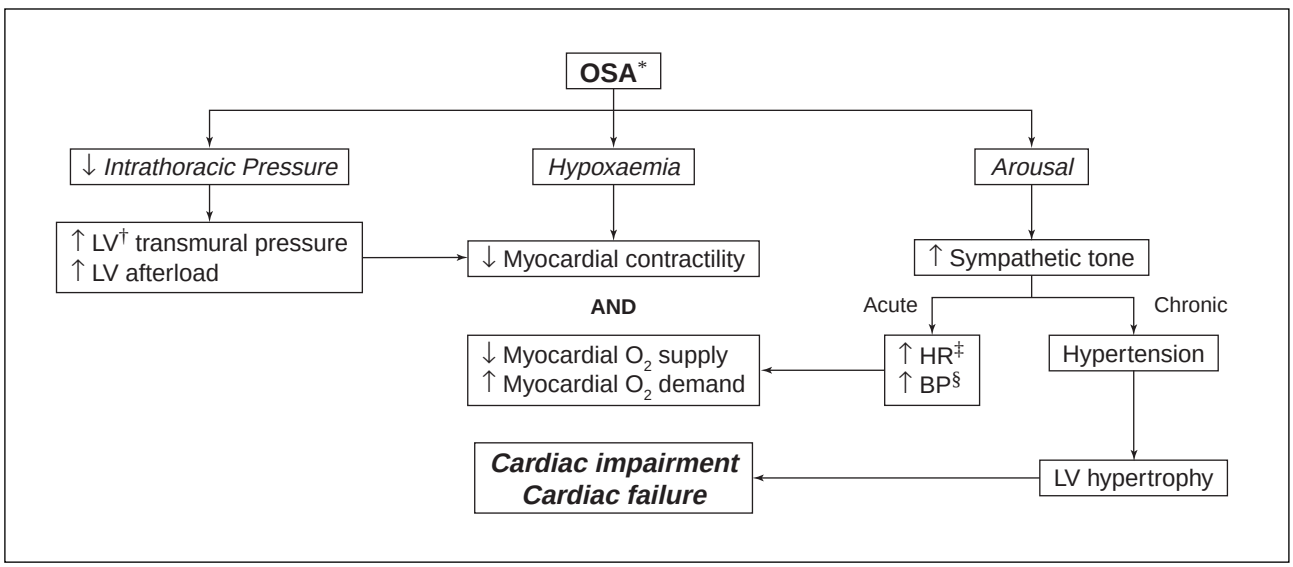
Intrathoracic pressure decreases markedly during the inspiration phase of obstructive breathing, reaching -50 to -80 cm H_2O. This negative intrathoracic pressure tends to encourage venous return and lead to increased right ventricular (RV) end-diastolic pressure, RV volume, and pulmonary arterial pressure. Because the ventricles share a common septal wall and are enclosed in the same pericardial sac, an increase in end-diastolic volume of one ventricle may cause impaired compliance in the other. On the left side of the heart, the reduction in intrathoracic pressure causes increased left ventricular (LV) transmural pressure during systole, which constitutes an increase in the afterload against which the LV needs to pump. In congestive heart failure, the repetitive increase in LV afterload during sleep may lead to further impairment of cardiac function resulting in decreased stroke volume and cardiac output.

Hypoxaemia

Arterial oxygen desaturation commonly occurs in SBD and central sleep apnoea (CSA). The primary response of the peripheral tissues to hypoxaemia is vasodilation but this is rapidly opposed by increased sympathetic activities leading to vasoconstriction and increased peripheral resistance, systemic and pulmonary arterial pressure, myocardial contractility, and cardiac output. The heart rate response to hypoxaemia is variable. The sympathetic activities are further increased by hypercapnia and acidosis, which often accompany hypoxaemia in OSA patients. In addition, both hypoxaemia and acidosis can directly impair myocardial contractility.[9] In patients with coronary heart disease, coexistent SBD and resultant hypoxaemia have been shown to precipitate acute ischaemic events.[10]

Arousals

In SBD, arousals usually occur at the end of the apnoeic cycles and are associated with increased electroencephalographic activities, and an abrupt increase in sympathetic activity, heart rate, and blood pressure.[11] In arousals occurring independent of SBD such as periodic leg movement disorders and in normal sleep, similar increases in sympathetic activities can sometimes be found.[10]



*OSA obstructive sleep apnoea
†LV left ventricular
‡HR heart rate
§BP blood pressure

Fig 1. Haemodynamic effects and consequences of obstructive sleep apnoea

Sleep-related breathing disorder and cardiovascular mortality

Three studies have shown an increased mortality rate in patients with OSA.[4,5,12] In a non-randomised retrospective study, He et al[12] followed 385 patients with OSA over an 8-year period, 246 of whom received no specific treatment, while the others received continuous positive airway pressure (CPAP), tracheostomy, or uvulopalatopharyngoplasty. An important finding of the study was that the mortality rate, irrespective of the cause of death, was significantly higher in patients with an apnoea index (AI) >20 than in those with an AI <20 (cumulative survival, 0.63 and 0.96; P<0.05). An 8-year cumulative mortality of 37% was found for patients with an AI >20, compared with 4% for those with an AI <20. There were six deaths in the treated group but all six received uvulopalatopharyngoplasty and none of the patients treated with CPAP or tracheostomy died. Nearly 50% of the patients, however, were lost to follow-up, making it difficult to draw conclusions from the study results.

In the Stanford Sleep Disorders Clinic Study,[4] 198 OSA patients (190 men, mean age 52 years, mean body mass index [BMI] 31 kg/m^2) were followed for 5 years. Seventy-one patients had tracheostomy, while the rest were treated conservatively and were recommended to lose weight. Fifty-six percent of the subjects had cardiovascular disease at study entry and the frequency distributions of hypertension, ischaemic heart disease and cerebrovascular disease at entry were similar between the two groups. By the end of the 5-year follow-up, a total of 14 deaths—all in the conservative treatment group—had been recorded. Eight of the 14 deaths were deemed cardiovascular in nature. The age-adjusted cardiovascular mortality was 5.9/100 patients per 5 years for the conservative treatment group, but was 0/100 for the tracheostomy group. At 11-year follow-up, the difference in cardiovascular mortality remained significantly higher in the conservative treatment group.

A similar study in New York[5] involved 190 OSA patients (178 men, mean age 50 years, mean BMI 34 kg/m^2), 48 of whom received tracheostomy while the rest were treated conservatively and instructed to lose weight. A smaller group consisting of 43 patients was followed up for 10 years. There were no significant differences in the overall survival rates between the two groups at 5 years and 10 years. However, 12 of 22 deaths in the conservative group were cardiovascular deaths compared with two of six deaths in the tracheostomy group, with an odds ratio of 2.0 (95% confidence interval=0.2-20.0), indicating a trend towards protection from cardiovascular mortality with active treatment of OSA.

The above studies were prospective investigations performed on retrospectively selected cohorts. All three studies showed consistent trends which suggests that SBD is a significant risk factor for cardiovascular mortality in middle-aged adults.

Sleep-related breathing disorder and systemic hypertension

An association between SBD and systemic hypertension has been suggested by earlier epidemiological studies,[13,14] although there were doubts regarding causality. In studying 7511 Finnish subjects aged 40 to 69 years using a written questionnaire, Koskenvuo et al[13] found that hypertension was reported by 22% of habitual snorers in men and 35% in women. After adjusting for age and BMI, the risk ratios for hypertension in habitual snorers remained significant at 1.5 for men and 2.8 for women.

Gislason[14] studied a random sample of 4064 middle-aged men in Sweden and found that 15.5% of subjects habitually snored and 21.5% of habitual snorers reported hypertension. It was assumed that habitual snoring was a marker for OSA. In the 40 to 49 years age group, the prevalence of hypertension increased from 6.5% in non-snorers to 10.5% in habitual snorers. For the population as a whole, the prevalence of hypertension depended on age and BMI, but not self-reported snoring, suggesting an association of hypertension with age and weight, but not sleep apnoea.

In an early study, Hoffstein[15] analysed data from 372 snorers and showed that diastolic blood pressure does not directly correlate with snoring, but may influence blood pressure via its association with obesity, OSA, and nocturnal hypoxaemia. Looking from a different angle, a French study did not find any difference in sleep architecture and the prevalence of sleep apnoea between 21 hypertensive subjects and 29 normal controls.[16] In another negative study, Raucher et al[17] found no significant difference in blood pressure and the prevalence of hypertension between habitual snorers and subjects with OSA. The BMI was the only predictive factor of hypertension in both groups, suggesting that the high prevalence of hypertension in male snorers was more directly associated with obesity than with OSA. Similarly, Millman et al[18] found a high prevalence of hypertension (45%) in 206 patients with

OSA. Only age and BMI, however, were predictors of hypertension in this population.

Inconsistencies from these early studies have arisen from the failure to allow for common confounders for both SBD and hypertension, namely age, obesity, BMI, smoking, the lack of prospective data, and the use of questionnaires to assess snoring, as a surrogate measure of SBD without objective assessments of sleep parameters. In fact, snoring alone in the absence of sleep apnoea was later found not be associated with hypertension[19,20] and the apparent association between snoring and hypertension could be confounded by age, obesity and alcohol consumption.[21] The relevance of habitual snoring for the prevalence of hypertension differs in various age groups and seems to be more important in the 40 to 50 years age group. The underlying problems associated with snoring may lead to the development of other risk factors for hypertension, such as increased weight due to daytime sleepiness, which may exacerbate the hypertension.

A recent population study by Hla et al[22] helped to clarify the SBD-hypertension relationship. After adjusting for age, sex, and BMI, they found a dose-response relationship between the severity of OSA, as measured by AHI, and the risk of hypertension. Subjects with an AHI >5 had twice the risk of developing hypertension, while the risk increased to five-fold if the AHI was >25. More importantly, the increase in blood pressure was also observed when the subject was awake, which is consistent with previous findings of heightened sympathetic activities in awake patients with OSA.[23]

In another group of epidemiological studies, the prevalence of SBD, mainly OSA, in hypertensive patients was investigated and frequencies as high as 30% to 50% were reported.[24-26] These prevalence rates were significantly higher than in controls who were matched according to age, weight, and sex, but as the hypertensive subjects were derived from tertiary referral centers in these studies, an element of referral bias could have contributed to the high prevalence. It is important to note that many hypertensive patients with polysomnographic evidence of OSA did not complain of any sleep-related symptoms, suggesting that OSA could be a silent risk factor for essential hypertension.[25,26]

The proposed mechanisms for systemic hypertension in SBD relate to the augmented sympathetic activities caused by hypoxaemia, hypercapnia, acidosis, and frequent arousals. The hypertension and increased sympathetic activities in SBD, as reflected by elevations in urine and plasma catecholamines,[27,28] are evident also during awake hours.[28,29] Sympathetic activities, as measured by urinary and plasma catecholamines, have been shown to diminish after tracheostomy[29] and nasal CPAP.[28] The efficient treatment of OSA may thus be one of the methods by which blood pressure can be lowered. If OSA contributes to the pathogenesis of hypertension, treatment of OSA should lead to an improvement in blood pressure control. The results were not conclusive, however, despite a few small studies which have demonstrated a reduction in blood pressure with treatment of OSA in hypertensive patients. In early studies of OSA patients receiving tracheostomy, blood pressure was found to return to normal both during sleep and awake hours.[30,31] Wilcox et al[32] treated 10 hypertensive and four normotensive patients with nasal CPAP for 4 weeks and measured 24-hour ambulatory blood pressure. Ten of 14 patients tolerated CPAP, and all showed significant reductions in both systolic and diastolic blood pressure on 24-hour monitoring. On the other hand, Rauscher et al[33] looked at 60 patients with OSA and hypertension who were assigned to treatment with either nasal CPAP or weight loss alone for 512 days. They found that weight loss rather than the elimination of OSA by CPAP contributed to the reduction in blood pressure on follow-up. The study was not randomised, however, since the control group consisted of patients who had initially refused CPAP treatment.

It should be noted that around half of the patients with sleep apnoea are normotensive and more than half of the patients with hypertension do not have sleep apnoea. Thus, although sleep apnoea may be a contributor to hypertension, the cause is clearly multifactorial. A controlled, blinded, crossover trial on the treatment of OSA with either CPAP or tracheostomy in hypertensive patients is indicated to definitely resolve this question. Available evidence suggests that the association between SBD and hypertension appears to be due to similar risk factors for both conditions. It is important to have a higher index of suspicion for SBD in patients with hypertension, although routine sleep study is not indicated in patients without other features to suggest SBD.

Sleep-related breathing disorder and pulmonary hypertension

Sleep-related breathing disorder is associated with cyclical elevation of pulmonary artery pressure during sleep, due to the increased sympathetic tone caused by hypoxaemia and increased right ventricular volume from increased venous output. This is possibly a re-

sult of the exaggerated negative intrathoracic pressure during obstructive breathing. However, chronic pulmonary hypertension and cor pulmonale have been shown to only affect 12% to 20% of SBD patients.[34] In the same study, those who developed right heart failure had more pronounced hypoxaemia and hypercapnia than SBD patients without evidence of cor pulmonale. The group with cor pulmonale also had evidence of chronic airflow obstruction which suggested that the development of right heart failure in patients with OSA was not due to nocturnal hypoxaemia alone. It appeared that daytime hypercapnic respiratory failure was also required, such that the pulmonary vasculature was exposed to sustained gas exchange derangements. This gave rise to the notion of an 'overlap syndrome' of OSA and chronic obstructive pulmonary disease, the combination of which is thought to be synergistic in giving rise to chronic pulmonary hypertension and cor pulmonale.[35]

Studies have shown that abolition of OSA by tracheostomy or nasal CPAP can reverse daytime respiratory failure in patients with combined OSA and chronic obstructive pulmonary disease,[36,37] indicating that although the development of respiratory failure and cor pulmonale in patients with OSA is multifactorial, reversal of OSA alone is sufficient in most cases to abolish right heart failure. The reason for this is unclear, but the relief of upper airway obstruction may potentially reduce the load on the respiratory system and reset the chemoreceptors, thereby improving the ventilatory drive. This is supported by an increased chemosensitivity to daytime $PaCO_2$ after treatment with nocturnal CPAP.[38] In contrast, other studies on the effects of long-term CPAP treatment of SBD on pulmonary hypertension have found no significant decrease in pulmonary pressure after therapy.[39]

Sleep-related breathing disorder and ischaemic heart disease

Ischaemic heart disease is the most common cause of mortality in many countries and the underlying pathology is usually atherosclerosis of coronary arteries resulting in imbalance between myocardial oxygen supply and demand. Acute ischaemic events may be precipitated by coronary vasospasm, rupture of atheromatous plaque, and increased platelet adhesiveness. Studies have shown that mortality[40] and myocardial infarction[41] occur more commonly in the morning than at other times of the day, suggesting that sleep-related events may be important. Indeed, in an analysis of 460 consecutive cases of sudden death in men aged 35 to 76 years, habitual snorers died more often while sleeping and were four times more likely to die of a cardiovascular cause between 4 a.m. and 8 a.m., compared with non-snorers.[42]

In SBD, the large swings in blood pressure, heart rate and increased myocardial contractility from heightened sympathetic tone may lead to increased oxygen demand.[43] Hypoxaemia may further limit coronary blood flow by causing coronary vasospasm. Increased platelet aggregability has been associated with high plasma catecholamines in the morning after awakening.[44] During obstructive breathing, marked distortion of the thoracic cavity containing the heart can occur and coronary vessels may be distorted within each apnoeic cycle, thereby increasing arterial wall stress and the risk of rupturing atheromatous plaques. Nocturnal ischaemic events can also lead to arousals in the absence of respiratory events, which can disrupt sleep architecture and cause daytime symptoms.

Over the past 10 years, a number of epidemiological studies have linked ischaemic heart disease with underlying SBD. Koskenvuo et al[13] found that men with habitual snoring were twice as likely to report a history of angina pectoris after adjusting for age, BMI and hypertension. The determination of the presence or absence of snoring in that study, however, was through a self-administered questionnaire, rather than by direct documentation of snoring. In addition, it was impossible to separate snorers with and without sleep apnoea, because polysomnography was performed in only a small minority of the subjects. Thus it is uncertain whether the association of snoring and ischaemic heart disease was related to snoring per se or to the presence of a subgroup of snorers who suffer from sleep apnoea. Similar relationships could not be found in snoring women.

In a case-control study, Hung et al[45] evaluated 101 male myocardial infarct (MI) survivors and 50 controls with no evidence of ischaemic heart disease and a negative exercise stress test. Sleep-related breathing disorder was more common in MI survivors (mean AI=6.9) compared with controls (mean AI=1.4). After taking BMI, hypertension and smoking into account, subjects with an AI >5.3 were found to have a risk of MI of 23.3 times that of subjects with an AI <2. Unfortunately, the authors did not report the time at which MI occurred in their study group. Another study of similar design comparing 100 MI survivors with 50 normal controls found an odds ratio of 2.35 for MI in every-night snorers compared with non-snorers after adjusting for smoking, hypertension, diabetes mellitus, and alcohol consumption.[42] A recent prospective study

evaluated 142 male subjects with ischaemic heart disease who were randomly selected from the coronary angiography list in a teaching hospital, and found that 37% had an AHI >10 compared with 20% in 50 age-matched controls.[43] Another prospective study compared tracheostomy and conservative treatment in patients with OSA, and found that 15 new cardiovascular accidents developed in the conservative group over 7 years compared with two events in the tracheostomy group.[44] The odds ratio of new cardiovascular problems was 2.3 after adjusting for age, BMI, and AI at study entry, suggesting a significant reduction in cardiovascular morbidity by effective treatment of OSA.

Although SBD and ischaemic heart disease often coexist, it is uncommon to see ischaemic changes in an electrocardiogram (ECG) during sleep studies. However, in a study of 10 patients with advanced ischaemic heart disease and nocturnal angina, Franklin et al[10] found SBD in nine subjects and ischaemic changes from the ECGs of four patients who were awakened by nocturnal angina at the time of the sleep study. Eighty percent of the ischaemic episodes were preceded by apnoea. More importantly, when these patients were treated with nasal CPAP, as the mean AHI reduced from 40/hour to 11/hour, the nocturnal chest pain disappeared in all but one patient; those who became pain-free at night also noticed improvement of heart failure symptoms from New York Heart Association (NYHA) class III to class II, immediately after CPAP was started.

Sleep-related breathing disorder and heart failure

Congestive heart failure (CHF) is a common medical condition which has become an increasingly frequent reason for hospital admissions in the last 2 decades. Data from the Framingham study showed that hypertension, ischaemic heart disease, LV hypertrophy, and diabetes mellitus were important risk factors for CHF.[45] More importantly, despite improved treatment and prevention of relevant risk factors, CHF remains a highly lethal disease with no significant change in survival between 1948 and 1988, and the 5 years mortality remains >50%.[46] Sleep-related breathing disorder shares a number of common risk factors with CHF and, in fact, SBD and heart failure often coexist; the prevalence of SBD in patients with heart failure is as high as 45% according to recent studies.[47-50] Three quarters of documented cases of SBD associated with heart failure have features of CSA with Cheyne-Stokes respiration (CSA-CSR), while OSA occurs less frequently (Table). In patients with CHF due predominantly to systolic dysfunction, LV ejection fraction is an independent risk factor of SBD.[50] Up to one third of CHF patients have predominantly diastolic dysfunction with normal systolic function. We have investigated a group of 20 patients with isolated diastolic failure based on characteristic echocardiographic features and found SBD in 50% of subjects; 35% had OSA; and 15% had predominantly CSA-CSR.[51] The commonly encountered symptoms of CHF such as tiredness, malaise, and dyspnoea may be related to the associated SBD.

From the aforementioned haemodynamic effects during obstructed breathing, namely increased sympathetic drive, increased LV afterload, and alteration in myocardial oxygen demand/supply ratio, it is conceivable that untreated OSA could worsen LV function and precipitate heart failure. In patients with normal daytime cardiac function, nocturnal pulmonary oedema has been ascribed to underlying OSA. On the other hand, treatment of OSA with nasal CPAP has resulted in improvement in LV function in patients with coexistent CHF,[52] as well as those without CHF.[53] In an open study of eight men with dilated cardiomyopathy taking stable medication, Malone et al[54] found OSA in all patients and treated them with nasal CPAP for 4 weeks. At the end of the treatment period, the

Table. Prevalence of sleep-related breathing disorder in heart failure

Authors (ref no.)	No. of subjects	Investigations	SBD*	CSA†	OSA‡
Cripps et al,[51] 1992	34	SaO_2§	59	38	21
Lofaso et al,[52] 1994	20	PSG‖	45	40	5
Blackshear et al,[53] 1995	100	SAO_2	43	27	16
Javaheri et al,[54] 1995	42	PSG	45	32	13
Mean			**46**	**33**	**13**

*SBD sleep-related breathing disorder
†CSA central sleep apnoea
‡OSA obstructive sleep apnoea
§SAO_2 arterial oxygen percent saturation
‖PSG polysomnography

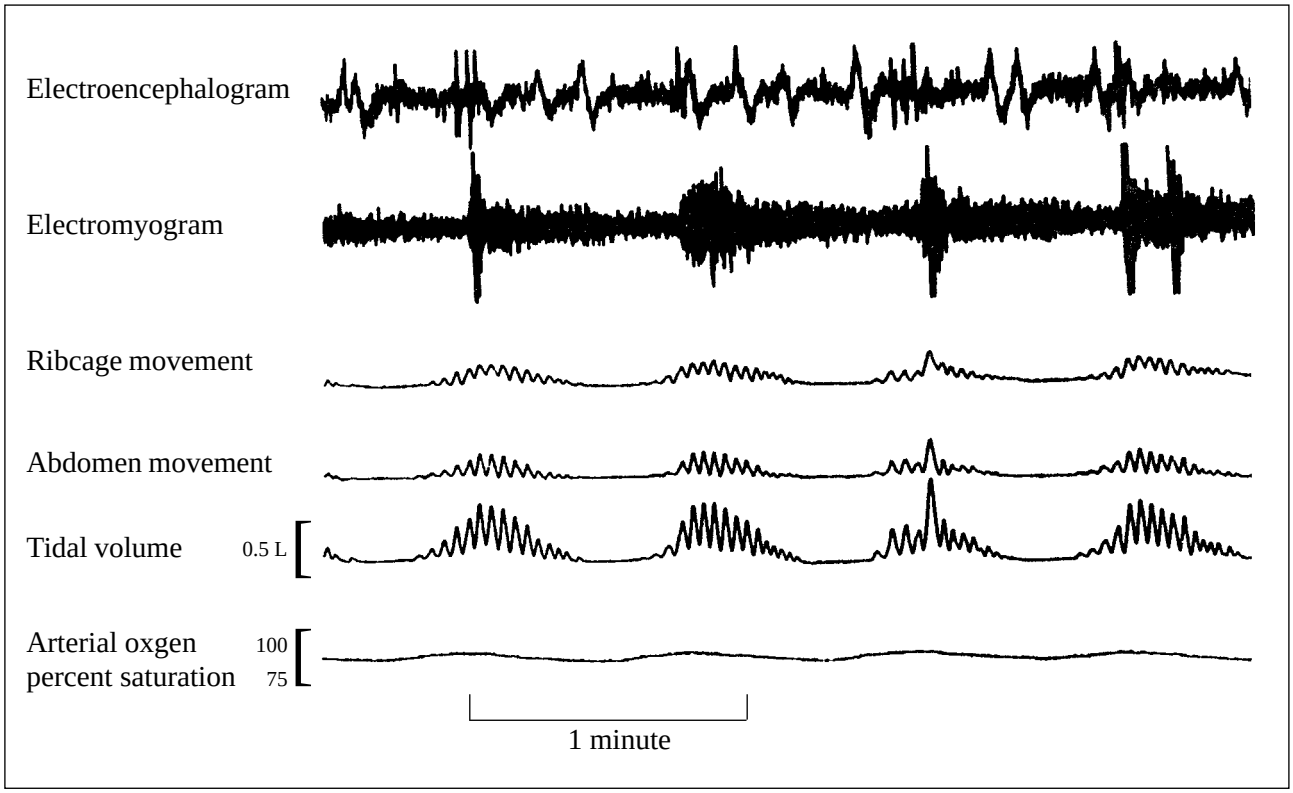


Fig 2. Polysomnographic features of Cheyne-Stokes respiration

mean AHI decreased from 54.1/hour to 1.0/hour, and LV ejection fraction increased from 37% to 49%. When CPAP was withdrawn for 1 week in a subgroup of subjects who demonstrated initial improvement, there was a significant reduction in LV function to pretreatment level. When OSA patients unselected for CHF were treated with long-term CPAP over 1 year, an improvement in the LV ejection fraction from 59% to 63% has been demonstrated.[53] Taken together, these studies show that untreated OSA may lead to or aggravate LV dysfunction and that the treatment of SBD can improve ventricular function in selected patients.

CSA-CSR, on the other hand, is more of a result of CHF rather than a cause. It has a characteristic polysomnographic feature with a waxing and waning pattern of tidal volumes and is more marked in sleep stages 1 and 2 as shown in Figure 2. As with OSA, CSA-CSR is associated with sleep fragmentation, hypox-aemia, frequent arousals, and a resultant increase in sympathoadrenal activities. Naughton et al[28] showed that both overnight urinary and daytime plasma nora-drenaline levels were high in CSA-CSR and correlated with the severity of oxygen desaturation and frequency of arousals during sleep. Indeed, CSA-CSR may coexist with OSA and be precipitated by upper airway occlusion. The mechanisms for CSA-CSR in CHF are not entirely clear. In CHF, the circulation time between lung and chemoreceptors in the carotid bodies are prolonged, which may lead to instability of ventilation with a tendency to hyperventilate.[54] The resultant reduction in $PaCO_2$ would in turn lead to apnoea and hypercapnia, completing the cycle of CSR. Other investigators have found that an exaggerated ventilatory response in patients with CSA-CSR results in low $PaCO_2$ while awake.[55] The overactive ventilatory response may be exacerbated further by the stimulation of juxtacapillary receptors in the lung parenchyma during hypoxaemia and pulmonary oedema.

In a recent prospective study of 16 males with severe (NYHA class III and IV) but stable CHF, the presence of CSR significantly increased mortality.[56] Nine of the 16 patients studied had evidence of CSR and seven did not; both groups were matched for age, weight, and cardiac and lung function. At the end of the 4-year follow-up, there were five cardiac deaths and two heart transplants in the CSR group compared with one non-cardiac death in the non-CSR group. The mortality correlated with the presence of CSR, AHI, and arousal index, suggesting that CSR may accelerate the deterioration of cardiac function. Increased plasma noradrenaline has previously been shown to be an important predictor of poor prognosis in CHF.[57] Chronic CPAP therapy over 1 month has been shown to attenuate sympathoadrenal activities and increase plasma noradenaline levels in CHF-CSR patients,[32] indicating a possible benefit on CHF mortality from

CPAP. Other studies, however, have failed to confirm any improvement in cardiac function and have found that many patients were unable to tolerate nasal CPAP.[58,59]

If CHF-CSR were caused predominantly by an overactive ventilatory response to chemical stimuli, then supplemental inhalation of O_2 or CO_2 may theoretically dampen this ventilatory response and attenuate CSR. Studies to date have shown a reduction in AHI and improvement in sleep architecture in the short term, but the effects of inhalation of O_2 and CO_2 on cardiac function and their long-term safety are unknown.[60,61] In contrast, CPAP therapy may improve cardiac function by several mechanisms. It reduces the negative intrathoracic pressure swings during inspiration thereby decreasing LV transmural pressure and LV afterload, and by eliminating SBD, CPAP normalises sympathetic tone and prevents the deleterious effects on myocardial function caused by hypoxaemia. A number of early short-term studies (1 night to 2 weeks) failed to demonstrate any benefits of CPAP in CSA-CSR. Naughton et al[62] studied the effects of chronic CPAP therapy over 3 months in patients with CSA-CSR in a randomised, controlled trial. Twelve patients were given CPAP in addition to conventional medical therapy including angiotensin converting enzyme inhibitors, and the pressure was titrated slowly over 2 days to 4 weeks to the highest tolerable pressure of 7.5 to 12.5 cm H_2O. Compared with the control group who received medical treatment only, the CPAP-treated group showed significant improvements in sleep parameters, cardiac symptoms and LV ejection fraction, together with a reduction in hospital stay. Long-term CPAP may therefore improve ventricular function in selected patients with SBD. However, until definitive studies in this field are completed, the long-term efficacy of nasal CPAP treatment on cardiac function in patients without SBD needs to be evaluated on an individual basis.

Sleep-related breathing disorder and cerebrovascular disease

The incidence of non-haemorrhagic cerebrovascular events peaks during sleep[63,64] and bears close resemblance to the relationship of AMI with sleep. In a case-control study, Palomaki et al[65] found that 70 of 167 (42%) of men with stroke had the disease onset during sleep or immediately upon waking. Those with early morning strokes were more likely to be habitual snorers (68%) than patients who developed stroke at other times of the day (41.2%). The risk of stroke increased by three-fold in habitual snorers compared with non-snorers, and was independent of age, hypertension, BMI, alcohol consumption, and diabetes mellitus. In another case-control study, the same group of investigators found an increased risk of stroke of 10.3 times for habitual snorers and 2.8 times for frequent snorers, compared with non-snorers.[66] However, these studies used snoring as surrogate marker for SBD, and at present there is no prospective evidence to suggest a direct association between SBD and stroke.

Several mechanisms have been proposed to explain the association between SBD and stroke. Hypertension is a common risk factor for both conditions and the severe bradycardia and tachycardia accompanying recurrent apnoeas may compromise cardiac output and reduce cerebral perfusion. Some SBD patients remain hypotensive throughout all stages of sleep and are thought to have defective sympathetic vasomotor response to hypoxaemia resulting in a predominantly vasodilatory response causing profound hypotension and cerebral ischaemia.[67] The intracranial pressure may increase up to eight times the normal value during obstructed breathing in OSA patients; this can theoretically affect cerebral blood flow. It has been speculated that the repetitive vibration from snoring during sleep may cause injury to vessel walls of the carotid arteries and the ascending aorta, thus promoting plaque rupture and dislodgment of wall thrombi to form emboli.

Conclusion

Sleep-related breathing disorder is a common medical condition which has apparent associations with various cardiovascular diseases such as hypertension, ischaemic heart disease, CHF, and stroke, although direct evidence of cause and effect is lacking at present. The adverse pathophysiological consequences of SBD have been extensively studied, but the long-term sequelae on cardiovascular morbidity and mortality have not been well established. Furthermore, the severity of SBD that is associated with excess cardiovascular mortality which warrants treatment is unclear. This would require long-term prospective controlled studies in matched groups of treated and untreated patients with SBD. Currently, such studies are not feasible due to ethical reasons, as the available effective treatments for SBD cannot be withheld for prolonged periods of time. Medical practitioners should nevertheless maintain a heightened index of suspicion of SBD in patients with cardiovascular disease.

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