Cardiovascular and cerebrovascular diseases are the most common diseases in industrialized societies. The main objectives of this article were to summarize the physiological effects of sleep apnea on the circulatory system and to review how treatment of this condition influences cardiovascular disease.

Acute sleep apnea has a number of hemodynamic consequences, such as pulmonary and systemic hypertension, increased ventricular afterload and reduced cardiac output, all of which result from sympathetic stimulation, arousal, alterations in intrathoracic pressure, hypoxia and hypercapnia.

When chronic, sleep apnea-hypopnea syndrome is associated with systemic hypertension, ischemic heart disease, congestive heart failure, and Cheyne-Stokes respiration in patients with congestive heart failure. Nocturnal treatment with continuous positive airway pressure decreases both the number of central apneic episodes and blood pressure in patients with sleep apnea-hypopnea syndrome and arterial hypertension.

Key words: Sleep apnea. Cardiovascular disease. Treatment with continuous positive airway pressure.

**INTRODUCTION**

Cardiovascular and cerebrovascular disease are the most common ailments of industrialized societies, and great efforts have been made to reduce their associated morbidity and mortality. Epidemiological studies have shown that a relationship exists between non-treated sleep apnea and the appearance of cardiovascular and cerebrovascular complications, quality of life, traffic accidents and increased mortality.

The study of sleep apnea-hypopnea syndrome (SAHS)—a phenomenon that usually occurs at night but which has consequences during the day—has led to some of the most important advances in our understanding of chronobiology and its medical ramifications. The main aim of the present work is to review the physiological consequences of SAHS with respect to the circulatory system, and to discuss the effects of the treatment of this problem on cardiovascular disease (Figure 1).

**Acute Effects of Sleep-Associated Respiratory Disorders on the Cardiovascular System**

In normal subjects, blood pressure falls by some 15% during sleep, the largest reductions occurring during the third and fourth phases. The heart rate is...
similarly reduced, as is the activity of the autonomic nervous system and vascular resistance. This leads to a state of “hemodynamic repose,” which is characterized by a reduction in cardiac output. The simultaneous reduction in the influence of the sympathetic nervous system along with centrally-induced respiratory hypoventilation may be associated with the activity of brain stem connections of sympathetic neurons involved in respiratory and cardiovascular control. During rapid eye movement (REM) sleep, however, the activity of the autonomic nervous system, blood pressure and the heart rate, all increase to levels similar to those seen when subjects are awake. A dissociation between respiratory and vascular control therefore occurs during REM sleep.

Unlike the normal physiological effects of sleep on the cardiovascular system, apnea triggers a number of hemodynamic effects including high systemic and pulmonary blood pressure, an increase in the ventricular afterload, and a reduction in cardiac output—all of which are a result of sympathetic stimulation, arousals, changes in intrathoracic pressure, hypoxia, and hypercapnia.6

**Neurohormonal Response**

Episodes of apnea cause an increase in the activity of the sympathetic nervous system, vasoconstriction, and high systemic blood pressure. Different types of heart rhythm impairments are commonly seen; supraventricular arrhythmias are the result of changes in sympathetic tone, whereas ventricular arrhythmias are thought to be related to hypoxia.

**Arousal**

Arousal is a defense mechanism that activates the muscles that dilate the upper airway, thus preventing suffocation. The degree to which this mechanism contributes to the increase in sympathetic activity is unknown. Periodic respiration without arousals in humans can induce transitory changes in the heart rate and blood pressure. The same is seen in a canine model when apneas with or without arousals are induced.7

**Effect of Intrathoracic Pressure**

The increase in positive intrathoracic pressure during apnea increases the transmural pressure of the left ventricle, and therefore the ventricular afterload. The venous return to the right ventricle is also increased, leading to distension and the deviation of the interventricular septum. This, in turn, may hinder the filling of the left ventricle. There is evidence to suggest that high negative intrathoracic pressure can impair the relaxation of the left ventricle, which would also hinder its filling. The overall result of these phenomena (which is proportional to the negative intrathoracic pressure present) is a reduction in the beat volume and the cardiac output.
As a result of all these changes and of the increased concentration of catecholamines and other circulating hormones (atrial natriuretic peptide, renin-angiotensin-aldosterone etc), systemic blood pressure during sleep increases.6,7

Hypoxia
A reduction in the partial pressure of oxygen in the arteries under normal conditions is mainly detected by the carotid bodies. This leads to vasoconstriction of the vascular bed and an increase in the secretion of catecholamines. Pulmonary vasoconstriction occurs as a response to alveolar hypoxia, and in patients with SAHS, recurrent episodes of hypoxia during sleep lead to repeated increases in pulmonary arterial blood pressure. However, few such patients develop pulmonary hypertension; this is usually seen in those who suffer chronic alveolar hypoventilation and hypercapnia.7

Cardiovascular Disease and Sleep Apnea-Hypopnea Syndrome

High Blood Pressure
It is well established that, after a number of years, high blood pressure (HBP) leads to cardiovascular disease. The same may be true of SAHS. Only in 10% of patients with HBP is the underlying cause detected. However, in this context, SAHS acquires particular interest since it is a treatable cause of HBP. The relationship between SAHS and HBP has been reported in the literature since the beginning of the 1980s. It is thought that 40%-60% of patients with SAHS also have HBP, and that approximately one third of those with HBP have SAHS. However, the relationship between these 2 problems has been widely questioned since the patients that suffer them share certain characteristics that might act as confounding factors (sex, age, an association with obesity, the consumption of alcohol and tobacco, etc).8,9

Patients with SAHS experience cyclical increases in blood pressure related to the obstructive respiratory events that occur during the night. This involves the action of central and peripheral chemoreceptors, baroreceptors, pulmonary afferent nerves, hypoxia, and hypercapnia, increases in negative intrathoracic pressure, and arousals. The result is a series of autonomic, hemodynamic, and humoral changes that give rise to a pressor effect when the apnea episode ends. However, there is debate over whether such transitory changes in blood pressure during the night could lead to sustained HBP during the day. During sleep, intermittent hypoxia in rats and the interminent occlusion of the upper airway in dogs has been shown to provoke sustained high blood pressure when these animals are awake and breathing normally. Further, in rats, the removal of the carotid chemoreceptors prevents the development of HBP. These experiments would appear to show that hypoxia-hypercapnia and changes in pleural pressure are major pathophysiological factors involved in the increase in sympathetic vasoconstrictor tone and the appearance of daytime HBP.6

In recent years, considerable effort has gone into demonstrating the link between SAHS and HBP. In the 2 largest studies involving the general population,10-12 the subjects were divided into subgroups depending upon the number of apnea-hypopnea events (apnea-hypopnea index; AHI) suffered per hour. HBP was defined as >140/90 mm Hg when receiving anti-hypertension treatment. The Wisconsin study10 was a cross-sectional study that lasted for 4 years for 709 patients, and up to 8 years for a subgroup of 184 patients. The Sleep Heart Health Study11,12 was a cross-sectional study involving 6841 patients. Table10-12 shows the prevalence of HBP and the odds ratio (OR) for the association between SAHS and HBP in the different subgroups after adjustment for sex, age, body mass index, neck and waist circumference, and the use of alcohol and tobacco. The authors of both studies conclude that, independent of confounding factors, a relationship does exist between SAHS and HBP, and that this follows a dose-dependent pattern with respect to SAHS severity. This causal relationship was confirmed by the Wisconsin study10 in the subgroup that was monitored for 8 years. Other authors have reported similar results, and even suggest that this relationship is stronger in young people of normal weight.13

Compared to a placebo, treatment with continuous positive airway positive (CPAP) is reported to significantly reduce blood pressure in patients with confirmed hypertension,14,15 and that this beneficial effect is greater in patients with more severe SAHS and those who take anti-hypertension medication, independent of baseline blood pressure. It would therefore seem clear that SAHS is an independent risk factor for HBP during the day; this condition therefore has important public health implications.

Ischemic Heart Disease
Both cross-sectional and case-control studies have shown that sleep-associated respiratory problems are common in patients with coronary heart disease in its different manifestations, both in men and women.16 More than 30% of patients with ischemic heart disease suffer associated SAHS. Schaller et al17 reported a high prevalence of SAHS in patients with angiographically-confirmed heart disease, and concluded that moderate...
SAHS (AHI>20) is an independent risk factor for myocardial infarction (AMI) (OR=2.0; 95% confidence interval [CI], 1.0-3.8).

In the Sleep Heart Health Study,12 an observational, multicenter, epidemiological study involving 6424 patients aged over 40 years, polysomnograph results were used to assess the relationship between sleep-associated respiratory problems and cardiovascular disease. A relationship was found between the former and coronary events (OR=1.27; 95% CI, 0.99-1.62), although more modest than between SAHS and heart failure or cerebrovascular accidents.12

It has also been reported that patients with coronary heart disease and SAHS experience myocardial ischemia during episodes of apnea, mainly during REM sleep. Depressions of the ST segment are common in patients with severe SAHS and in those with a history of nocturnal angina.17

When patients with SAHS suffer an AMI, there is a tendency for this to occur between 12:00 pm and 06:00 am, i.e., during the night. In contrast, in patients without SAHS, the risk of sudden death of cardiac cause is greater between 06:00 am and 12:00 am.18

In patients with ischemic heart disease, the presence of sleep-associated respiratory problems tends to be an indicator of poor prognosis.19 No controlled studies on the effectiveness of CPAP treatment in this type of patient have been performed, but this treatment has been reported capable of significantly reducing the number of nocturnal ischemic events and of preventing the depression of the ST segment.20

### Congestive Heart Failure

Epidemiological studies have shown a relationship to exist between SAHS and heart failure. The results of the Sleep Heart Health Study11 show apnea with an AHI>11 to be associated with an OR for heart failure of 2.38, independent of other risk factors.

In two studies involving patients with heart failure due to systolic dysfunction,11,22 11% of 81 patients and 37% of 450 patients respectively suffered obstructive apnea. In another study involving patients with heart failure due to diastolic dysfunction23 (the result of reduced distensibility of the left ventricle), 55% had an AHI of >10.

Heart failure could also lead to obstructive sleep apnea, either through the capacity of periodic respiration to induce the collapse of the upper airway, or through the retention of liquid and its accumulation in the soft tissues of the neck and pharynx.23 The negative influence of apnea on heart function appears to be more intense in patients with a background of structural disease, in whom the effect on the afterload is more serious.

In the one study that has investigated the effect of the treatment of SAHS on systolic function, and which involved eight patients with dilated cardiomyopathy of unknown origin, Malone et al24 showed that treatment with CPAP for one month improved their left ventricular ejection fraction (LVEF) by between 37% and 49%.

### Cheyne-Stokes Respiration and Congestive Heart Failure

Cheyne-Stokes respiration with central sleep apnea is a form of periodic respiration common in patients with chronic heart failure (30%-40% of such patients).21,22 There is growing evidence that this combination is a sign of disease progression and poor prognosis. Cheyne-Stokes respiration appears to be the result of an instability in the central control of breathing. Naughton et al25 propose that, in patients with chronic heart failure and Cheyne-Stokes respiration, central apnea is provoked by a reduction in pCO2 below the apneic threshold caused by hyperventilation. During apnea or hypopnea, the pCO2 gradually increases, resulting in periodic respiration and hyperventilation until the pCO2 once again falls below the apneic threshold. Hyperventilation may be the result of the stimulation of pulmonary vagal irritant receptors by pulmonary congestion (Figure 2). There may also be a pathophysiological component in...
SAHS derived from reduction in oxygen levels, arousals, sympathetic activation and an increased heart rate and blood pressure. In patients with chronic heart failure and hypocapnia, Javaheri et al.21 found a high prevalence of central apneas and a greater number of ventilatory excursions than in normocapnic patients; this was clinically related to a greater number of sudden deaths.26-28

Several forms of continuous positive pressure, including CPAP and bilevel pressure, have been found to reduce the frequency of central events in patients with chronic heart failure, although the mechanism involved has not been fully elucidated. The use of CPAP for short periods in stable chronic heart failure reduces the left ventricular afterload, increases the cardiac output, and reduces the activity of the autonomic nervous system. Its use over a period of 1-3 months can relieve periodic respiration, increase the LVEF and inspiratory muscular strength, and reduce mitral regurgitation and atrial natriuretic peptide levels.29-31

In a randomized, controlled study involving 66 patients with chronic heart failure (29 with Cheyne-Stokes respiration and 37 without this problem), Sinn et al.32 reported that, after a 5 year follow-up period, those who completed their initial treatment with CPAP showed a significantly lower combined mortality/heart transplant rate.

Currently, the Canadian Continuous Positive Airway Pressure Trial for Congestive Heart Failure is trying to determine whether CPAP helps resolve SAHS.33 Results obtained by this group, led by Douglas Bradley,34 have recently been published. Two-hundred and fifty-eight patients with chronic heart failure, an LVEF of 24.5±7, and a central apnea-hypopnea index of 40±16 events per hour, were randomized to receive either CPAP (n=128) or conventional treatment (n=130). Follow-up was for 2 years. The members of the CPAP group experienced a greater reduction in the number of apneas and hypopneas suffered, in their noradrenaline concentration, and a greater increase in their mean nocturnal oxygen saturation. The ejection fraction and the 6-minute walk test performance were also improved. No significant differences were seen between the number of hospitalizations, quality of life, the concentration of atrial natriuretic peptide, or in percentage survival. In their conclusions the authors mention that no data are available that suggest the use of CPAP can increase the survival of patients with central sleep apnea and heart failure.

The Insuficiencia Respiratoria y Trastornos del Sueño de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR)35 group performed the first placebo-controlled study to analyze the effects of CPAP on the ejection fraction of patients with stable congestive heart disease receiving optimum treatment, and with systolic dysfunction (ejection fraction ≤40%) and sleep apnea (either central or obstructive). In their population of 72 patients the percentage with Cheyne-Stokes respiration was close to 19%, a figure far from the 40% suggested by American epidemiological data. Among those randomized to the treatment group, the SF-36 questionnaire revealed improvements in the...
LVEF and quality of life. The only beneficial cardiovascular effects were seen in patients with an LVEF of ≥30%. Further research is required to determine whether treatment with CPAP leads to greater survival in patients still showing a degree of myocardial contractile reserve.

CONCLUSIONS

The observational and epidemiological studies performed to date show there is an association between sleep apnea and cardiovascular disease. Much research effort is now being directed into establishing causality. Given that the majority of patients with SAHS are asymptomatic, it is important to determine whether early diagnosis and treatment might modify the course of cardiovascular disease and have a positive impact on survival. To advance our knowledge of the impact of sleep-associated respiratory problems, animal models are required that will allow their pathophysiological mechanisms to be explored. In addition, close collaboration between epidemiologists and specialists in respiratory medicine and cardiovascular disease will be necessary.

REFERENCES


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