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REVIEW

Sleep Apnea Syndrome: More Than Benign Snoring Implications for the Cardiovascular System

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KEY WORDS: *sleep apnea; snoring; cardiovascular disease; hypertension; arrhythmias; Cheynes-Stokes respiration*

List of Abbreviations
ADMA = asymmetric dimethylarginine
AHI = apnea-hypopnea index
ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CAD = coronary artery disease
CHF = congestive heart failure
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
CRP = C-reactive protein
CRT = resynchronization therapy
CSA = central sleep apnea
CVD = cardiovascular disease
ICAM = intercellular adhesion molecule
IL = interleukin
NO = nitric oxide
OSA= obstructive sleep apnea
PFO = patent foramen ovale
REM = rapid eye movement
SAHS = sleep apnea-hypopnea syndrome
TNF = tumor necrosis factor
VCAM = vascular cell adhesion molecule
VEGF = vascular endothelial growth factor

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ABSTRACT

Sleep disordered breathing is a rather common problem in the general population. Apnea during sleep can be divided into three types: central, obstructive and mixed. In central apneas there is lack of both airflow and respiratory efforts. It is recognized by its waxing-waning pattern of respiration called Cheyne-Stokes respiration. Central sleep apnea is most commonly seen in patients with heart failure and its prevalence among this group of patients is estimated to be as high as 30-40%. Obstructive sleep apnea occurs approximately in 5-15% of the general population. It usually affects middle-aged men with an increased body-mass index and a large neck circumference. It is characterized by repetitive complete or partial obstruction of the upper airway during sleep, which is followed by increasing and ineffective respiratory efforts.

Sleep fragmentation in patients with sleep apnea-hypopnea syndrome results in sleepiness, fatigue, morning headaches and depression. This daytime presentation together with loud snoring, choking and pauses of respiration during sleep should make primary care physicians suspicious of sleep disordered breathing. The best method used for the diagnosis of sleep apnea syndrome is overnight polysomnography. The pathophysiologic mechanisms, which take place in sleep apnea, include sympathetic activation, hypercoagulability, inflammation and production of pro-inflammatory cytokines, endothelial dysfunction, oxidative stress and metabolic dysfunction. All these mechanisms are associated with the development and progression of cardiovascular disease. There is a strong linkage between sleep apnea and hypertension, systolic and diastolic dysfunction of the left ventricle, congestive heart failure, coronary artery disease, cardiac arrhythmias, stroke and pulmonary disease.

Given the increased morbidity and mortality of patients with sleep apnea, an effective treatment must be started as soon as possible after the diagnosis is made. Currently, nasal continuous positive airway pressure constitutes first line therapy. This therapy improves both quality of sleep and cardiovascular and general outcomes.

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INTRODUCTION

Apnea in adults is defined as the cessation of airflow (>90% reduction in tidal volume) for ≥10 s. Hypopnea is characterized by a decrease but not complete cessation of airflow by 30-50% of normal (reduction in tidal volume of 50-90%) usually in association with a reduction in oxyhemoglobin saturation by at least 3% - 4%. These breathing disorders are commonly encountered during sleep and have been strongly associated with the pathogenesis and progression of cardiovascular disease (CVD).[1]

The American Academy of Sleep Medicine formulated the definition for Sleep Apnea Hypopnea Syndrome (SAHS), also referred as Sleep-Disordered Breathing Disorders, which is limited during sleep and is characterized by the following diagnostic criteria: either excessive daytime sleepiness not explained by other factors or a variety of symptoms, such as choking, gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration, accompanied by overnight polysomnography demonstrating ≥5 obstructive breathing events per hour during sleep.[2] Sleep apnea can be divided into 3 types: central, obstructive and mixed. Central sleep apnea (CSA) is defined as a situation in which there is absence of both respiratory efforts and airflow. Obstructive sleep apnea (OSA), on the other hand, is a condition described as repetitive complete or partial obstruction of the upper airway during sleep, characterized by increasing and ineffective respiratory efforts. Finally, mixed sleep apnea is the combination of the previous two disorders.

EPIDEMIOLOGY

Charles Dickens -the novelist- was the first to describe a sufferer from OSA named Joe, in his novel "The Posthumous Papers of the Pickwick Club", published in 1836. Joe was an obese boy, who snored loudly and was excessively sleepy. Broadbent in 1877 was the first physician who described the clinical features of OSA.[3] The first international symposium of hypersomnia with periodic breathing was organized in Italy in 1972 from Lugarasi and Sadoul. Guilleminault et al[4] reported the occurrence of this syndrome in nonobese patients and children; the term 'Pickwickian syndrome' (extreme obesity and excessive sleepiness) is outdated and has been supplanted by 'obesity-hypoventilation syndrome' which is characterized by chronic hypoventilation and hypercapnia during wakefulness.[5]

The prevalence of OSA varies in adults from 1% to 5% in men and 1.2% to 2.5% in women between the ages of 30 and 60 years. Young et al[6] estimated that among middle-aged adults, 93% of women and 82% of men with OSA have been underdiagnosed. Sleep apnea is more frequent among older people and its effects can be more severe than in younger people because there is a physiological decline in sleep quality with age. Its prevalence in the elderly (age >65 years) has been reported to be as high as 62%.[7] The variability in the incidence of OSA is due to differences in the population studied in various trials regarding age, body mass index and genetic factors, as well as differences in monitoring sleep and the criteria used to define an apneic or hypopneic event.[8] Parish et al[9] estimate that the occurrence of OSA ranges from 5% to 15% in the general population while women after menopause develop OSA at a rate similar to men.[10] During the last few decades pediatric OSA has been recognized as a cause of significant morbidity among children and its prevalence diagnosed by varying criteria ranges widely from 0.1 to 13%, although most studies report a figure between 1 and 4%.[11] Central sleep apnea is less common than OSA in the general population as it concerns <10% of the patients with sleep disordered breathing reported at most sleep laboratories.[12] Obstructive sleep apnea correlates with obesity and CVD, especially hypertension, while CSA is frequent in patients with heart failure.

The severity of SAHS is determined by the apnea-hypopnea index (AHI), which is the number of apneic and hypopneic events per hour of sleep. Using the AHI we can divide sleep apnea syndrome into 3 levels of severity: mild (AHI = 5-14 events per hour), moderate (AHI = 15-29 events per hour) and severe (AHI ≥30 events per hour). An AHI <5 is considered normal and patients with very severe OSA may have an AHI exceeding 100. Most of the studies have shown that ≈1 in 5 adults has at least mild OSA and 1 in 15 has moderate or severe OSA. It is estimated that >85% of patients with clinically significant and treatable OSA have never been diagnosed and referral populations of OSA patients represent only the 'tip of the iceberg' of OSA prevalence.[1] The "Wisconsin Sleep Cohort study" reported that SAHS is associated with lower general health status before and after adjustment for age, sex, body mass index, smoking status, alcohol usage or history of cardiovascular conditions.[13] Four major studies of OSA showed that the prevalence of severe OSA is 7% to 14% in men and 2% to 7% in women, while the prevalence of mild OSA is 17% to 26% in men and 9% to 28% in women.[14]

PATHOPHYSIOLOGY OF SLEEP DISORDERED BREATHING

Obstructive sleep apnea is characterized by periodic collapse of the upper airway during sleep leading to obstruction. The site of upper airway obstruction lies in the pharynx, velopharynx, oropharynx and hypopharynx. The pharyngeal luminal area depends on two opposite forces: the intrapharyngeal negative suction pressure and the dilating forces of the pharyngeal muscles. The pharyngeal muscles are activated by the central nervous system in order to maintain the pharyngeal patency in healthy awake individuals. The activation is

normally reduced during sleep. The reduced neural activation, combined with anatomical abnormalities of the pharynx, for example excess posterior pharyngeal tissue, an enlarged tongue or a low-hanging palate, leads to repetitive hypopneic or apneic episodes during sleep in patients with OSA. Pharyngeal muscle activation is also impaired by alcohol, sleep deprivation, anesthesia and sedative hypnotics. Another mechanism of OSA is nasal obstruction frequently observed in allergic rhinitis, hypertrophic tonsils and bony structural defects.

The total occlusion or the narrowing of the upper airway reduces ventilation and gas exchange in the alveolar membrane of the lung tissue, resulting in hypoxia and hypercapnia. As the oxygen saturation decreases and the levels of $PaCO_2$ increase, chemoreceptors in the carotids, the aorta and the brain stem are activated. Respiratory effort increases in response to these stimuli and provokes repeated arousals during the night, fragmenting sleep. The arousal from sleep leads to a surge of the dilator muscles of the pharynx and resolves the obstruction. Hypoxia and hypercapnia are the major stimuli for sympathetic hyperactivity and the cyclical changes in vagal tone. The imbalance of the autonomous nervous system during sleep is the key mechanism for the association of sleep apnea with CVD. The sympathetic surge occurring at the end of the apneic event leads to vasoconstriction and increases of peripheral vascular resistance in the systemic and pulmonary circulation. Moreover, there is an increase in circulating catecholamines and sympathetic activity during the day in patients with OSA compared with healthy controls.[15,16]

Central sleep apnea and Cheyne-Stokes respiration, a disorder most commonly seen in patients with heart failure, can be defined as a form of periodic breathing in which apneas and hypopneas alternate with ventilatory periods having a waxing and waning pattern of tidal volume. Cheyne-Stokes respiration generally occurs in patients with congestive heart failure (CHF) because of hyperventilation and increased carbon dioxide chemosensitivity. The key mechanism is fluctuation of $PaCO_2$ below and above the apneic threshold.[17] Patients with congestive heart failure and CSA have lower $PaCO_2$ both during wakefulness and sleep, than those without CSA. In a study by Sin et al,[18] the major risk factor for CSA was hypocapnia during wakefulness ($PaCO_2$ <38 mmHg; odds ratio 4.33). Other risk factors for CSA were male gender (odds ratio 3.5), atrial fibrillation (odds ratio 4.13) and age >60 years (odds ratio 2.37).

In patients with CHF, left ventricular filling pressure is increased. Pulmonary congestion provokes hyperventilation through stimulation of pulmonary vagal irritant receptors. This phenomenon results in hypocapnia. When $PaCO_2$ falls below the apnea threshold an episode of central apnea is triggered. During apnea, hypoxemia and hypercapnia occur, initiating breathing and sometimes leading to arousal. Hyperventilation following arousals leads to a decrease in $PaCO_2$, thus a new episode of apnea is triggered (Fig. 1). This cycle is repeated through the night.

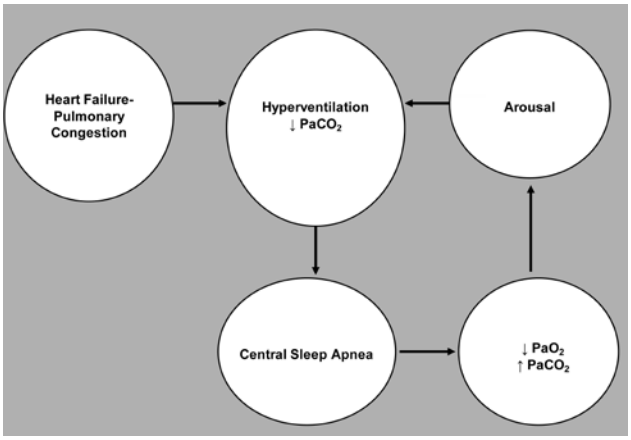

FIGURE 1. Sleep fragmentation due to central sleep apnea in patients with heart failure.

Unlike OSA, arousals in CSA occur after the onset of ventilation. An arousal in OSA represents a defense mechanism that relieves obstruction and terminates apnea. On the contrary, the resumption of airflow in CSA is not always dependent on arousal. Arousals actually trigger and propagate central apneas as mentioned already. Cheyne-Stokes respiration-CSA appears predominantly during non-rapid eye movement (nREM) sleep, while OSA is more common during rapid eye movement (REM) sleep. During REM phase arousability to respiratory stimuli, ventilatory surge and hypocapnia are reduced compared with the lighter stages of nREM sleep.

Another mechanism for hypocapnia resulting in CSA in heart failure is increased carbon dioxide chemoreceptor responsiveness. Increases in sensitivity of chemoreceptors increase the tendency to hyperventilate and reset the prevailing $PaCO_2$ closer to the sleeping apneic threshold. Under this condition, even a modest increase in ventilation can drive $PaCO_2$ below the apneic threshold and trigger a central apnea. Lorenzi et al[19] studied the effect of inhaled CO_2 on CSA, in patients with heart failure and came to the conclusion that a rise of $PaCO_2$ by just 1-3 mmHg was enough to eliminate central apneas and hypopneas. CO_2 inhalation has the same impact on idiopathic CSA. Prolonged circulation time due to diminished cardiac output in heart failure causes a delay in transmitting changes in arterial blood gas within the lung tissue to peripheral chemoreceptors. This could destabilize the respiratory control system by means of influencing periodic breathing cycle length.

Cheyne-Stokes respiration provokes rises in heart rate and blood pressure similar to OSA, and the responsible mechanism is again an increase in sympathetic nervous activity. Severe CSA is associated with impaired cardiac autonomic control and increased cardiac arrhythmias. Central sleep apnea is also highly prevalent in patients without overt heart failure

but with asymptomatic left ventricular dysfunction. Fifty-five per cent of 47 patients with left ventricular ejection fraction ≤40% studied by Lanfranchi and colleagues[20] had CSA with an AHI ≥15 and the severity of CSA was not related to the severity of hemodynamic impairment measured by exercise tolerance and echocardiographic indices. In the same study the prevalence and severity of CSA were higher in patients with ischemic cardiomyopathy than in patients with nonischemic cardiomyopathy ($P < 0.05$).

Continuous positive airway pressure (CPAP) treatment of both obstructive and central apneas in patients with heart failure improves ejection fraction, functional class and transplant-free survival. Treatment with CPAP in OSA resolves obstruction and decreases mean intrathoracic pressure. In addition, it eliminates post-apneic surges of sympathetic activation and rises of blood pressure, resulting in a reduction of cardiac afterload. Through these mechanisms CPAP treatment improves cardiac function. Treatment of OSA with CPAP reduces atrial natriuretic peptide (ANP), while levels of brain natriuretic peptide (BNP) are not associated with OSA in patients with or without coexisting heart failure.[21] Supplemental O_2 reduces the severity of CSA by suppressing respiratory drive and raising $PaCO_2$ above the apnea threshold.

CLINICAL PRESENTATION AND DIAGNOSIS OF SLEEP DISORDERED BREATHING

The clinical features that should make primary care physicians suspicious of SAHS are daytime sleepiness, morning headaches, choking, loud snoring and pauses of inspiration reported by sleep partners. Other common symptoms are personality changes, depression, irritability, aggressiveness, decreased libido, sexual dysfunction and even impotence.[22] These symptoms are attributed to fragmentation of sleep and frequent arousals and correlate with the severity of OSA. Nocturnal symptoms are more specific than daytime symptoms. Seventy five percent of patients experience apneic episodes terminated by gasps, choking sounds, snorts, vocalizations and brief arousals. Loud snoring followed by periods of silence is a usual symptom. About 50% of patients have diaphoresis and restlessness. Other nocturnal symptoms include dryness of mouth in 74% of patients, nocturia in 28%, esophageal reflux, drooling in 36% and dyspnea.

In OSA patients, physical examination usually reveals anatomic obstruction of the upper airway due to septal deviation, adenotonsillar hypertrophy, retrognathia, dental malocclusion, narrow maxillas and mandible. Obesity and body mass index >30 kg/m^2, neck circumference >40 cm, male gender or postmenopausal status in women and positive family history of OSA make the diagnosis of sleep apnea more probable.[23] Other risk factors for OSA are race, age >40, alcohol ingestion before bedtime, underlying hypertension, metabolic syndrome, Down syndrome and Marfan disease (Table 1).

In order to appropriately evaluate a patient with suspected SAHS, a detailed history and physical examination is needed. However, the predictive value of clinical features in diagnosing OSA had a sensitivity of 60% and a specificity of 63% in a report by Hoffstein and Szali.[24] Various scales have been used to evaluate daytime sleepiness. Among them, the "Stanford Sleepiness Scale" and the "Epworth Sleepiness Scale" are most commonly used to measure the severity of the condition.[25,26] The major challenge for the clinician is the differential diagnosis between benign snoring and snoring related to apnea. The gold standard for the diagnosis is overnight *polysomnography*. This includes electroencephalographic, electrooculographic, electromyographic, oxygen saturation, oral and nasal airflow, respiratory effort, electrocardiographic and leg movement recordings. Although home studies have been used, equipped with portable devices, in order to measure oxygen saturation, heart rate, respiratory effort and airflow, they have had a lower efficacy for the diagnosis compared with full night polysomnography. Overnight oximetry alone measures only nocturnal desaturation and does not provide information about sleep architecture. Split night-full night polysomnography may be considered as an option for the diagnosis. In this case the first half of the night is spent in diagnostic recording and the other half is used to titrate CPAP, the most popular therapy currently used for OSA. This method allows a quicker diagnosis at reduced expense in some cases.

Considering the expense required for the diagnosis, one could wonder why it is so important to distinguish patients with sleep disordered breathing. The answer to this question arises from a large number of population studies connecting sleep disordered breathing with CVD and higher mortality. He et al[27] reported that about 40% of patients with severe OSA died during a follow- up period of 8 years. Partinen et al[28] observed

TABLE 1. Risk Factors for Obstructive Sleep Apnea (OSA)

Body mass index (BMI) >30 kg/m^2
Neck circumference >40 cm
Male gender or postmenopausal status in women
Positive family history of OSA
Race
Age >40 years
Alcohol ingestion before bedtime
Underlying hypertension
Metabolic syndrome
Down syndrome
Marfan disease

a higher risk of death due to vascular disease in patients with untreated OSA. Sleep disordered breathing has been shown to be associated with increased risk for stroke, coronary artery disease and heart failure. In a large trial by Partinen and Guilleminault,[29] OSA patients were twice as likely to have hypertension, three times as likely to have ischemic heart disease and had four times as much cerebrovascular disease compared with the general population. The increased risk of CVD is not the only reason for increased mortality and morbidity of the syndrome. Automobile crashes and work-related accidents are other possible causes of enhanced mortality in patients with OSA. Masa et al[30] reported that habitually sleepy drivers, with disturbances in sleep architecture caused by respiratory disorders, have a higher incidence of crashes and the incidence depends on the AHI. Findley et al[31] found that the accident rate in OSA patients decreased after treatment with CPAP.

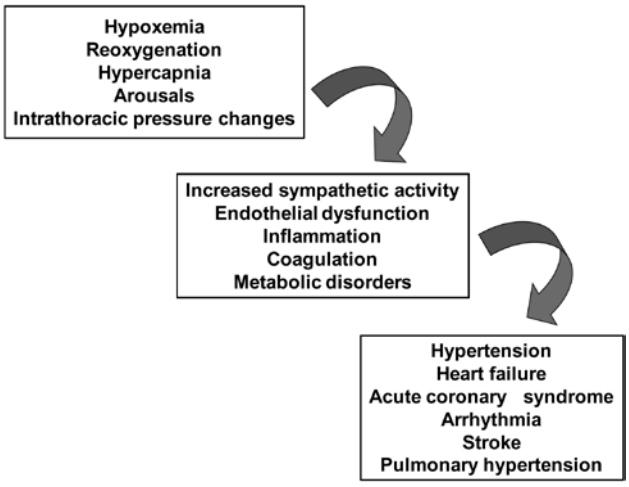

FIGURE 2. Association of obstructive sleep apnea with cardiovascular disorders and possible mechanisms leading to atherosclerosis and progression of cardiac and vascular pathology.

MECHANISMS LINKING SLEEP APNEA TO CHRONIC CARDIOVASCULAR DISEASE

Several mechanisms have been implicated in the association of sleep apnea with chronic cardiovascular disease (CVD), such as sympathetic activation, thrombophilia, a pro-inflammatory response, endothelial dysfunction, and propensity to metabolic disorders (Fig. 2).

SYMPATHETIC ACTIVITY

The activity of the sympathetic nervous system is abnormal in patients with sleep apnea.[32] During hypoxemia and apnea the sympathetic nervous activity is increased and reaches its peak at apnea termination and arousal from sleep, with blood pressure reaching levels as high as 240/130 mmHg toward the end of apneic episodes. Patients with sleep apnea have higher levels of sympathetic nervous system activity and of circulating catecholamines even when awake and normoxic. Because of chronic sympatho-excitation, untreated patients with sleep apnea syndrome have increased resting heart rates, decreased heart rate variability and increased blood pressure variability. In patients with CVD reduced heart rate variability is associated with poorer outcomes although acute or chronic treatment with CPAP at night reverses both the sympathoexcitation[33] and the hypertension[34] associated with OSA. In addition to catecholamines, levels of other circulating hormones have been found to be higher in patients with OSA. These are renin, aldosterone and vasopressin which play an important role in the regulation of blood pressure and the effective blood volume.

COAGULATION

There is strong evidence that sleep disordered breathing results in a hypercoagulable state.[35] Patients with OSA have increased levels of total serum fibrinogen.[36,37] Fibrinogen enhances thrombosis and atherosclerosis by affecting platelet aggregation and blood viscosity. Platelet aggregability is proportional to the levels of circulating catecholamines. Shortly after arousal there is a surge in plasma catecholamines and a simultaneous increase in platelet activation which can explain the peak occurrence of stroke and acute cardiovascular events early in the morning. Hui et al[38] confirmed increased platelet activation in 42 patients with OSA (AHI >10) compared to a non-OSA, age- and body mass index- matched control group. They also concluded that CPAP therapy reduced platelet activation at one night and at three months of follow-up. More studies are needed to confirm that treatment of OSA may be cardioprotective. In addition to these abnormalities, fibrinolytic activity is reduced and plasminogen activator inhibitor is elevated in OSA patients.

In a trial by Winnicki et al[39] the effects of severe repetitive hypoxemia on serum erythropoietin were studied. Untreated patients with severe OSA had a higher level of serum erythropoietin which decreased after CPAP treatment. Increased levels of erythropoietin and concomitant increases in hematocrit and blood viscosity may be another possible explanation for hypercoagulability in OSA patients.

INFLAMMATION

Inflammation is an important component in the pathogenesis of atherosclerosis and the progression of CVD. Repeated hypoxia, which is the major pathophysiological event in sleep apnea, provokes the production of inflammatory cytokines, such as tumor necrosis factor–a (TNFa), interleukin (IL)-6 and an increase in adhesion molecules, serum amyloid A- and C-reactive protein levels (CRP).[40] Both CRP and IL-6 are

considered to be important risk factors for atherosclerosis and coronary artery disease. Plasma levels of these substances increase in OSA and decrease with CPAP therapy.[41] Levels of circulating intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 which are also markers of inflammation, have been found increased in OSA patients,[42] while Zhang et al[43] have observed decreased levels of the anti-inflammatory adipokine and adiponectin in OSA.

Homocysteine and cysteine which are regarded as cardiovascular risk factors are also evaluated in different studies. Plasma levels of homocysteine are elevated in OSA patients regardless of the presence of cardiac dysfunction,[44] while cysteine levels were found increased in patients with OSA and decreased significantly after 6 months of effective CPAP therapy.[45] Kokturk et al[46] have shown that OSA patients with and without CVD have significantly higher levels of homocysteine when compared with patients with CVD without OSA, and serum homocysteine levels were independently associated with the severity of OSA.

The sleep apnea syndrome is characterized by repeated nocturnal episodes of apnea and hypoxemia, which are followed by arousals and reoxygenation. This circle leads to production of highly reactive free oxygen radicals from the polymorphonuclear neutrophils. Exposure of the vascular wall to ischemia-reoxygenation injury and free oxygen radicals may induce oxidative stress to the endothelium resulting in increased risk for atherosclerosis. Patients with OSA have been found to have markedly enhanced neutrophil superoxide generation that decreases with CPAP therapy.[9]

ENDOTHELIAL DYSFUNCTION

Hypoxia and hypercapnia possibly stimulate the release of vasoactive substances that cause damage to the vascular endothelium in patients with sleep apnea. Endothelin-1 for example is a vasoconstricting substance synthesized in the endothelium which increases in OSA patients and decreases with CPAP therapy. In addition to this finding, patients with OSA have impairment of the endothelial function, even in the absence of any overt cardiovascular disease. Endothelial dysfunction can be expressed by reduced vasodilating response to acetylcholine and isoproterenol.[47] Zhang et al[48] demonstrated the effect of CPAP therapy on endothelial dysfunction in patients with OSA and coronary artery disease, by means of measuring morning plasma nitric oxide, endothelin levels, and total ischemic burden of the myocardium. Their conclusion was that CPAP treatment plays an important role in the improvement and protection of endothelial function and myocardial ischemia.

Different metabolic and molecular mechanisms are implicated in the pathogenesis of endothelial dysfunction as a consequence of hypoxia in patients with OSA. For example, reduced levels of circulating nitric oxide (NO) in OSA patients are probably related to depressed nocturnal synthesis of NO due to reduced oxygen supply, suppressed transcription of the endothelial NO synthase gene and elevated NO synthase inhibitors.[49] Vascular endothelial dysfunction in OSA, before and after treatment with CPAP, was assessed in 10 male patients aged 36-69 years old by measuring flow mediated vasodilation of the brachial artery and plasma concentration of asymmetric dimethylarginine (ADMA).[50] ADMA is an endogenous inhibitor of endothelial NO synthase and its levels are elevated in patients with cardiovascular risk factors including hyperlipidemia, hypertension, diabetes and hyperhomocysteinemia. The conclusion of this study was that CPAP therapy improves endothelial function by decreasing ADMA concentration and thereby augmenting NO production. However, several studies on the endothelial responses to endogenous vasodilators, such as NO, have led to conflicting results.

Levels of vascular endothelial growth factor (VEGF), a glucoprotein that induces the proliferation of endothelial cells, increases vascular permeability and enhances production of NO and prostacyclin have been estimated in OSA patients with mixed results. Some but not all investigators have found higher levels of VEGF in subjects with OSA and regarded hypoxia and oxygen desaturation as the stimuli for this elevation.[51-53] Elevated levels of serum VEGF in OSA patients are not associated with the severity of the disease but with patient's age[54] and decrease with CPAP therapy.[55]

Intercellular adhesion molecule (ICAM) 1, VCAM 1, E-selectin and matrix metalloproteinase-9, substances involved in the development of atherosclerosis, are elevated in OSA patients and decrease after CPAP treatment.[56] Abnormal leukocyte aggregation to the endothelium, increased expression of CD15 and CD11c monocytes and increased adhesion of monocytes in patients with OSA, are other possible mechanisms for atherogenesis.[9] Endothelial dysfunction is often related to hypertension, hyperlipidemia, diabetes and smoking. Sleep apnea may be an independent risk factor for the development of endothelial dysfunction, despite its link to the above mentioned comorbidities.

METABOLIC DISORDERS

A large number of studies suggest an independent and causal relationship between OSA and metabolic syndrome, which further increase cardiovascular risk since the metabolic syndrome is recognized as a risk factor for cardiovascular morbidity and mortality. Patients with OSA usually have obesity with central adiposity, glucose intolerance, dyslipidemia, and hypertension. Since these abnormalities are the major characteristics of the metabolic syndrome, it has been suggested that its definition - also known as syndrome X - should include OSA (syndrome Z)[57] as an additional vascular risk factor.

The prevalence of metabolic syndrome is higher in patients with OSA than in the general population (15-20% for Europeans) or in obese subjects without OSA; the studies published todate estimate that the risk of metabolic syndrome in OSA

patients is at least 5-fold compared with controls.[58] Coughlin and colleagues[59] suggested that the prevalence of metabolic syndrome defined by the National Cholesterol Education Program (NCEP) is about 40% greater in patients with OSA, while Papanas et al[60] have shown that among men with metabolic syndrome, who are free from comorbidities and report symptoms suggestive of sleep-disordered breathing, high serum glucose is associated with a significant increase in the frequency of OSA, even after adjustment for body mass index.

The metabolism is affected by OSA indirectly because the amount and/or quality of sleep are decreased resulting in increased evening cortisol, sympathetic activation and insulin resistance.[58] Obesity affects 60 to 90% of OSA patients and weight loss ranging from 9 to 18% of body weight was associated with reduction in the AHI by 30 to 75%.[61] In the general population snoring was shown to be a risk factor for the development of diabetes over 10 years independently of confounding factors.[62] The Sleep Heart Health Study, performed in 2656 individuals showed that sleep-related hypoxemia is associated with glucose intolerance independently of age, sex, body mass index and waist circumference[63] and OSA severity was associated with the degree of insulin resistance after adjustment for obesity. The Wisconsin Sleep Study[13] demonstrated a significant cross-sectional association between OSA and type 2 diabetes for all degrees of OSA, which persisted for moderate to severe OSA after adjustment for obesity. Sleep restriction was also shown to be associated with reduced leptin (a hormone that suppresses appetite), increased appetite and resistance to the metabolic effects of leptin.[64] In animal studies it has been demonstrated that leptin could prevent respiratory depression in obesity, suggesting that a deficiency in leptin levels or activity may induce hypoventilation in obese subjects.

Alterations in glucose metabolism are also encountered in OSA patients without diabetes; patients with OSA have hyperinsulinemia, fasting hyperglycemia and higher levels of glycosylated hemoglobin. Obstructive sleep apnea is regarded a highly prevalent comorbidity of type 2 diabetes and it has been proved that increasing severity of OSA is associated with poorer glucose control, independently of adiposity or other confounders.[65] The treatment of choice for OSA, CPAP, both ameliorates breathing disturbances and improves several markers of glucose metabolism and insulin resistance, such as glycated hemoglobin, fasting glucose / insulin, and insulin resistance.[66] In type 2 diabetic patients with OSA observational studies using continuous glucose monitoring techniques have reported positive effects of CPAP on glycemic control, already present during the first night of treatment, as variability of glycemic values decreased compared with baseline conditions. Although the effects of CPAP treatment on the metabolic syndrome are controversial, it was recently suggested that treatment indications of CPAP should be reevaluated; for OSA patients who meet the criteria of metabolic syndrome initiating CPAP treatment at lower AHI levels may contribute to the prevention of CVD development.[67]

Other markers of glucose metabolism have been assessed in OSA patients, such as insulin growth factor (IGF)-1 and adiponectin. A high IGF-1 concentration is predictive of decreased risk of type 2 diabetes and impaired glucose tolerance, whereas low IGF-1 concentrations were found to be associated with increased risk of CVD.[68] The complex interactions between IGF-1, its binding proteins and insulin sensitivity promote IGF-1 as an important regulator of glucose homeostasis. While fasting insulin and blood glucose are subject to short-term changes, IGF-1 is a more stable variable subject to long-term regulation. Adiponectin is known to counteract the effects of insulin resistance, and the effects of OSA treatment on adiponectin have been assessed with controversial results. Some studies found increased adiponectin after 1 night or 2 weeks of CPAP treatment, while other studies found no change in adiponectin levels after OSA treatment for 1 night or 1–3 months.[58] Research should elucidate the interactions between metabolic syndrome and OSA and define their implications.

TREATMENT

Given the increased morbidity and mortality among patients with SAHS,[69] an effective treatment must be started as soon as the diagnosis is made. The goal of therapy[70] is to restore sleep architecture and thus improve daytime functioning. Effective treatment results in a decrease in AHI and an increase in oxyhemoglobin saturation. The first therapeutic approach to a patient with a mild degree of sleep apnea includes weight loss, avoidance of the supine posture during sleep-positional therapy, abstinence from alcohol, tobacco and sedatives and avoidance of sleep deprivation. Treatment of comorbid conditions, such as hypothyroidism, should also be considered.

Various drugs have been investigated for the management of OSA with no success. Acetazolamide, theophylline, nicotine, opium antagonists and medroxyprogesterone have been used to increase respiratory drive. Clonidine has been used in order to reduce REM sleep as well as various antidepressants. The aim of pharmacotherapy is among others to activate the upper airway dilator muscles. Most of the drugs have been found to be scarcely effective and those with good results in some patients, i.e. acetazolamide and protriptyline, have been associated with intolerable side effects. The use of stimulants, however, such as modafinil may be considered as an adjunctive therapy for daytime sleepiness.[71] Given the fact that various inflammatory mediators are involved in the pathogenesis and progression of CVD in OSA patients, drugs like aspirin and statins, which lower these measures of inflammation, can be used with anticipated benefit.

First-line therapy for moderate to severe sleep apnea syndrome is positive airway pressure therapy, which is associated with 64% reduction of cardiovascular risk and cardiovascular

outcomes independently from age and preexisting comorbidities.[72] Therapy with CPAP (Fig. 3) can be applied in three forms with continuous, bilevel and autotitrating function. Nasal CPAP functions as a pneumatic stent that prevents the collapse of the pharynx due to negative inspiratory pressure. In this manner the upper airway remains open during inspiration and nocturnal oxygenation, sleep architecture and daytime functioning are improved. In order to increase tolerance of positive airway pressure treatment in patients with OSA, bilevel assisted ventilation and autotitrating positive airway pressure have been used as alternatives, with similar improvement in daytime sleepiness in most studies. Autotitrating positive airway pressure continuously adjusts pressure to patient's needs, thus the overall mean airway pressure can be reduced.[73] Bilevel assisted ventilation allows independent adjustment of inspiratory and expiratory pressures and is indicated for patients who experience discomfort exhaling against positive pressure with CPAP, or have restrictive thoracic disorders, chronic obstructive pulmonary disease or central sleep apneas.

Compliance to CPAP therapy ranges from 50% to 100%.[74] Reasons for no adherence are noise from the device, bed partner intolerance, mask discomfort, skin abrasions, conjunctivitis, mask rubbing, nasal congestion, rhinorrhea, sneezing, epistaxis, nasal dryness, sinus discomfort, chest discomfort, aerophagia, claustrophobia and difficulty exhaling. Finally, pneumothorax and pneumocephaly are rare side-effects. Compared with other therapeutic approaches, nasal CPAP is a cost effective treatment of choice for sleep apnea syndrome. Effective CPAP treatment lowers apnea-hypopnea index as shown in many clinical trials. In a study designed by Clark et al there was a 60% decrease in the AHI in OSA patients treated with nasal CPAP.[75] D'Ambrosio et al[76] studied the impact of nasal CPAP therapy on quality of life in OSA patients. After 8 weeks of treatment with CPAP there was a significant improvement in all aspects of life quality, such as vitality (75%), social functioning (95%) and mental health (96%).

FIGURE 3. An example of a mask providing continuous positive airway pressure (CPAP), which is the first line therapy for the sleep apnea-hypopnea syndromes (SAHS).

Oral devices are considered a treatment option for snoring, but they should not be recommended in CSA and patients with severe OSA. These devices displace the tongue and jaw forward in order to augment the posterior pharyngeal area. Compared to CPAP, oral devices have poorer results even in mild to moderate OSA. Surgical approaches are recommended for patients with discrete craniofacial abnormalities rather than simply obese patients. In selected patients, and in hands of experienced medical staff, the success rate can be as high as 90%. Complications include bleeding, infections, upper airway obstructions caused by surgical edema, hematomas and facial anesthesia. An effective alternative to therapy in morbidly obese patients is tracheotomy. Although it is easy to perform, hygiene issues and inconvenience do not allow its widespread use.

COMORBID CONDITIONS ASSOCIATED WITH SLEEP APNEA

The pathophysiological phenomena that take place in sleep apnea lead to increased sympathetic activation, increased oxidative stress, inflammation, vascular endothelial dysfunction, increased platelet aggregability and metabolic dysrhythmia. These mechanisms may be implicated in the pathogenesis and promotion of CVD, such as hypertension, coronary artery disease, congestive heart failure, systolic and diastolic dysfunction of the left ventricle, cardiac arrhythmias, stroke, pulmonary hypertension and all-cause mortality.[77]

HEART FAILURE

Sleep-related breathing disorders are common in heart failure. Sleep apnea in patients with CHF can be obstructive (due to upper airway collapse), central (characterized by Cheyne-Stokes respirations) or a combination of both. In the Sleep Heart Health Study, OSA was found to be an independent risk factor for CHF.[63] In this study patients with AHI >11 were found to have a 2.38 relative risk for CHF, which was higher for OSA than all other cardiovascular diseases. It has been noted that at least 45% of patients with systolic heart failure have an AHI ≥10 and at least 40% have an AHI ≥15.[78] In two large studies of patients with CHF, the prevalence of OSA was 11% among 81 patients and 32% among 450 patients.[79,80] Among patients with heart failure the prevalence of OSA was greater in men (38% versus 31%; P <0.005) and risk factors for OSA were also different between men and women; among men only body mass index and among women only age were significantly associated with OSA. Chan et al[81] estimated that approximately 50% of patients with isolated diastolic heart failure have an AHI of at least 10 per hour.

Cheyne-Stokes breathing and CSA are also common

among patients with CHF with a prevalence estimated to be as high as 30% - 40%. Moreover, they are highly prevalent in patients with left ventricular dysfunction even without overt heart failure and is a common disorder in men, but a rare one in women with CHF. It has been reported by Tkacova et al[82] that some patients with CHF present with shifts from OSA to CSA, which have been attributed to overnight episodes of a reduction in PCO_2, episodes of an increase in circulatory delay and deterioration in cardiac function; this finding implies that abolition of OSA would improve nocturnal hemodynamic function in patients with CHF.

Sleep disordered breathing predisposes to progression of heart failure, through activation of adrenergic and inflammatory mechanisms that worsen prognosis. Central sleep apnea is associated with a poorer outcome, increased arrhythmic risk, cardiac transplantation and death, while OSA is associated with both systolic and diastolic dysfunction of the left ventricle. Yet to be established is whether OSA can cause heart failure or increase mortality in heart failure patients. A recent study suggested that the presence of untreated OSA (AHI >15) in patients with heart failure is associated with increased risk of death compared with patients with an AHI <15 independently of other confounding factors[83].

Obstructive sleep apnea potentially contributes to progression of heart failure through different mechanisms,[78,84] the most common been hypertension. Hypoxemia, catecholamine surge, nocturnal rise of blood pressure and daytime hypertension predispose to hypertensive heart failure. Multiple mechanisms contribute to systolic dysfunction. Inflammatory cytokines affect directly myocardial contractility. Peripheral vasoconstriction due to sympathetic surges results in an increase of afterload. The increase in negative intrathoracic pressure, which is caused by repeated respiratory efforts against the occluded upper airway, leads to abrupt changes in cardiac transmural pressure and concomitant increase in wall stress. It also increases venous return to the right ventricle. A leftward shift of interventricular septum affects diastolic filling of the left ventricle. The combination of increased afterload and reduced preload leads to a reduction in stroke volume. Regarding diastolic dysfunction, hypertension and effects of endothelin and catecholamines on cardiac structure play the most important role. In several case reports, patients with OSA appear to have acute nocturnal pulmonary edema with normal left ventricular systolic function. These cases suggest that OSA and its adverse effects can cause acute left ventricular failure in susceptible individuals. After induction of recurrent obstructive apneas to anesthetized dogs, Fletcher and colleagues[85] demonstrated the development of interstitial pulmonary edema.

Congestive heart failure itself can contribute to the development of OSA. Patients with heart failure are exposed to periodic breathing. During periodic breathing, respiratory drive declines and as a result of this, pharyngeal dilator muscles drive declines as well, leading to collapse of the upper airway. The critical pressure, below which collapse occurs, is the pressure of the diaphragm. Another possible mechanism predisposing patients with CHF to OSA is edema. Edema may involve the neck and the soft tissues of pharynx and can lead to further narrowing of the airway, particularly in the supine position.

Recent observational data suggest a trend to a lower mortality rate in heart failure patients with CPAP-treated OSA compared with untreated OSA, although randomized clinical trials are needed to test the hypothesis whether CPAP treatment of patients with OSA and heart failure leads to mortality benefit. Patients with left ventricular systolic dysfunction and OSA who were treated with cardiac resynchronization therapy (CRT) showed reduction of AHI and CRT-mediated reduction of mitral regurgitation[86] while lack of AHI reduction after months of CRT was regarded as an independent risk factor of death and major cardiac events during follow-up[87]; yet further studies are needed to further elucidate this issue.

HYPERTENSION

Hypertension is highly prevalent in individuals with OSA with estimates ranging from 50% to 90%,[88] whereas 30% and more of middle-aged men with hypertension also have OSA which is underdiagnosed. Most of the literature agrees that OSA is strongly associated with hypertension and that there is a causal relationship between them, independent of possible confounding variables such as obesity, male gender, age, coexisting CVD, tobacco and alcohol use. The relationship between OSA and systemic hypertension[89] can be explained by acute and chronic increases in sympathetic nerve activity as a response to hypoxia. Patients suffering from respiratory disturbances during sleep have been found to have higher levels of sympathetic activity and circulating catecholamines not only during the apneic episodes but also while awake. Increased sympathetic activity results in a concomitant increase in heart rate, cardiac output, peripheral vascular resistance and tubular sodium reabsorption in the kidney, mechanisms which may contribute to elevated blood pressure. Moller et al[90] performed 24-hour blood pressure monitoring and measured plasma levels of vasoactive hormones such as renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin and endothelin-1 in 24 OSA patients and 18 matched controls. Patients with OSA were found to have higher blood pressure and heart rate, while there was no sleep-related blood pressure drop, and higher levels of angiotensin II and aldosterone. After 14 months of CPAP therapy there was reduction in blood pressure and plasma renin and angiotensin II concentrations. Tsioufis et al[91] evaluated aortic stiffness of newly diagnosed hypertensive patients with or without OSA by means of carotid-femoral pulse wave velocity measurements and concluded that OSA has an incremental effect on aortic stiffening, as it accelerates vascular damage and increases cardiovascular risk.

In a healthy individual blood pressure drops during the

night about 15% below daytime levels. This pattern is similar to hypertensive patients named as "dippers". In contrast, OSA patients are "non dippers". Portallupi and associates[92] described the presence of unsuspected OSA in 10 of 11 patients with a "nondipping" pattern of nocturnal blood pressure and daytime hypertension, but in none of 10 "dipping" hypertensive patients. This study implies that many hypertensive patients, who do not demonstrate a fall in nocturnal blood pressure have undiagnosed OSA. "Nondipping" is a condition associated with a higher risk of cardiovascular complications, even in the absence of daytime hypertension, therefore the debate about whether OSA leads to daytime hypertension may not be of importance.

Nieto et al[93] proposed vascular dysfunction as a possible mechanism for the correlation between OSA, hypertension and CVD. In the "Wisconsin Sleep Cohort Study", a large population study with 893 subjects, patients with an AHI >15, had an odds ratio of 4.5 for developing hypertension, compared with those without sleep apnea.[94] When adjusted for confounding variables, the relative risk was 2.9 indicating that OSA is an independent risk factor for hypertension. In another study of 1741 patients, OSA was found to be independently associated with elevated blood pressure in both men and women, after adjustment for possible co-variables such as age, body mass index, gender, menopause, hormone replacement therapy, alcohol use, smoking and race.[95] The 'Sleep Heart Health Study' concluded that mean systolic and diastolic blood pressure increased significantly with SAHS, mainly for patients with a baseline AHI > 30, although some of this association was explained by body mass index.[96,97]

Treatment with CPAP reduces nocturnal blood pressure in OSA patients[98] but its effect on daytime hypertension remains controversial. Four major recent studies describe the effects of CPAP treatment on blood pressure.[99] In those studies, only severe OSA was associated with substantial reduction in blood pressure after CPAP therapy, while patients with minimal symptoms and few apneic events did not benefit from treatment. Faccenda et al[100] studied 68 patients with OSA and hypertension and demonstrated a 1.5 mmHg fall in diastolic blood pressure after initiation of nasal CPAP therapy. Dimsdale and coworkers[101] demonstrated a fall in daytime blood pressure and a smaller effect on nocturnal blood pressure in 39 patients treated with CPAP. They also found a reduction in daytime plasma norepinephrine concentrations and nocturnal urinary norepinephrine levels. A fall in daytime blood pressure was also found in the placebo group using nasal CPAP. In a study at the Oxford Centre for Respiratory Medicine by Pepperell et al[102] therapeutic nasal CPAP reduced mean arterial pressure by 2.5 mmHg whereas subtherapeutic nasal CPAP increased blood pressure by 0.8 mmHg. Such a benefit was seen in both systolic and diastolic blood pressure, during sleep and wake and was larger in patients with more severe OSA.

According to Barbe et al,[103] patients having CPAP treatment for more than 5.6 hours/night during one year demonstrate a small but rather beneficial reduction in blood pressure (systolic blood pressure by 1.89 and diastolic blood pressure by 2.19). Finally, Becker et al[104] showed a substantial decrease in daytime and nocturnal hypertension in patients with severe OSA (mean AHI 64) receiving full treatment with CPAP. Although the initiation of partially therapeutic nasal CPAP led to a reduction in AHI of 50%, no blood pressure reduction was seen in the partially treated group. This study emphasizes the importance of complete resolution of OSA and suggests that there are moderate and variable effects of CPAP on blood pressure in patients with OSA; patients with more severe OSA, difficult to control hypertension and better CPAP compliance, have more substantial blood pressure reduction with CPAP. Three meta-analyses have been published recently regarding the effect of treating OSA with CPAP on blood pressure. Overall a modest but significant net reduction in blood pressure was found (≈2 mmHg) and CPAP was found to reduce systolic blood pressure by ≈3 mmHg (P = 0.10) and diastolic pressure by 2 mmHg (P = 0.05) in patients with more severe OSA (AHI >30).[105-107]

The Joint National Committee (JNC VI) in 1997 suggested that OSA should be excluded as a possible contributory factor to resistant hypertension when obesity coexisted. Nevertheless, the most recent set of guidelines (JNC VII) included OSA as first in the list of causes of hypertension.[108] Among antihypertensive agents including atenolol, amlodipine, enalapril, hydrochlorothiazide and losartan, β-blockers were found to be most effective in lowering daytime blood pressure in hypertensive OSA patients, but they were found to have little effect on nocturnal blood pressure. This finding is compatible with the hypothesis that sympathetic overactivity is the key mechanism in the development of hypertension in OSA patients. There is no current evidence that any specific antihypertensive drug attenuates sleep apnea severity although a recent report suggests that cough and rhinopharyngeal inflammation induced by angiotensin-converting enzyme inhibitors may worsen the AHI which decreases when the drug is discontinued.[109] Resolution of OSA with tracheostomy was associated with a reduction in nocturnal blood pressure. The data from studies of OSA imply that many cases of idiopathic hypertension and hypertension resistant to therapy may actually be secondary to undiagnosed and untreated sleep apnea syndrome. When left untreated, OSA leads to structural changes in the vasculature to the point that they become irreversible. This is why treatment of OSA is ineffective in lowering blood pressure in some cases.

STROKE

The reported prevalence of sleep apnea after stroke varies between 50% and 70%. There is convincing evidence that sleep apnea is associated with the occurrence of stroke but further studies are needed in order to confirm a causative relationship independent of other factors. In the Sleep Heart Health Study

there was a small but significant increase in the prevalence of stroke among OSA patients[110] and in a cross-sectional study of Japanese men, brain magnetic resonance imaging revealed silent brain infarction in 25% of patients with moderate to severe OSA.[111] Patients with stroke have a higher incidence of OSA as shown in various studies[112,113] and post-stroke AHI is high for patients maintained in the recumbent position (especially within the 24 hours of stroke). Yet a recent study from Sweden noted that among 132 patients who were admitted for in-hospital rehabilitation and underwent overnight cardiorespiratory sleep monitoring, only 23 patients had OSA – 28 patients had CSA and 2 patients had mixed apnea.[114]

Many patients who suffered a stroke have coexisting sleep apnea which can affect potential recovery.[115] A study by Parra et al[116] focused on the impact of sleep disordered breathing on two-year survival of patients with a first ischemic attack. The investigators concluded that sleep disordered breathing is an independent risk factor for increased mortality after a first stroke. For each additional unit of AHI there is a 5% increase in mortality risk, suggesting an association between mortality rate and severity of sleep apnea.

Obstructive sleep apnea could predispose to stroke through blood pressure swings, reduction in cerebral blood flow, impaired endothelial function, prothrombotic/ proinflammatory states, hypercoagulability and impaired cerebral hemodynamics.[117] Patients with OSA have an abnormal cerebral autoregulation of blood flow and a diminished vasodilator response to hypercapnia. During apneas, hypoxia and hypercapnia lead to a reduction of cerebral blood flow. Vasoconstriction, due to diminished response of cerebral vessels to hypercapnia, results in a significant rise in intracranial pressure. These phenomena cause a further decrease in cerebral perfusion in areas of the brain with already borderline or poor circulation while blunted cerebral blood flow in patients with OSA has been reported to normalize after 4-6 weeks of CPAP therapy.[118]

It remains unclear whether sleep apnea following a stroke is a consequence of the stroke rather than a preexisting condition. When sleep apnea is present after a stroke, it can further affect daytime functioning and rehabilitation of the patient. Apnea-related hypoxia can lead to the production of γ–aminobutyric acid, a neuroinhibitory peptide which can further compromise cognition.[119] In older studies it has been suggested that central apneas are associated with bilateral hemispheric and brain stem infarction. More recent trials suggest that the occurrence of OSA may precede the occurrence of stroke; researchers have found that stroke severity does not predict the presence of severity of OSA and, when present, it is a sign of underlying cardiac dysfunction.[120] Stroke may promote central apneas only in the immediate post-stroke period, when brain inflammation and edema are present. As these resolve, so do central apneas.

Recent 10-year follow-up data from patients with stroke, showed an increased risk of death in patients with OSA (adjusted hazard ratio 1.76; $P = 0.03$) independently of age, sex, body mass index, smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination Score and Barthel Index of Activities of Daily Living. Post-stroke mortality was not also increased for CSA patients.[121] Obstructive sleep apnea in the post-stroke patients reduces motivation, decreases cognitive capacity and may increase the risk of recurrent stroke and death. The application of CPAP offers to patients with OSA the opportunity to increase the rehabilitation potential after stroke but Bassetti et al[122] found that only 15% of patients with sleep apnea and acute ischemic stroke continued CPAP chronically.

CORONARY ARTERY DISEASE

Obstructive sleep apnea is a common condition among patients with coronary artery disease (CAD); its prevalence has been shown to be up to 2-fold greater than in non-CAD subjects. In a study of >200 consecutive patients without a history of CAD who underwent electron-beam computed tomography within 3 years of polysomnography, the median coronary artery calcification score (Agaston units) was 9 in OSA and 0 in non-OSA patients ($P < 0.001$),[123] confirming an independent association between subclinical CAD and OSA.

The presence of OSA is associated with nocturnal angina, nocturnal ST-segment depression and adverse outcomes in these patients. Hung and his associates[124] described OSA as a strong risk factor for myocardial infarction, such as obesity, smoking and hypertension. In the Sleep Heart Health Study OSA was found to be an independent risk factor for CAD. However, the study showed only a modest increase in the odds ratio of CAD in patients with severe OSA compared with controls. Patients with OSA have ST-segment changes indicative of ischemia during sleep that is proportional to oxyhemoglobin desaturation and severity of OSA. Various studies have reported a prevalence of ST-segment depression ranging from 20% to 100%.[125-127]

The mechanism of provoked ischemia in OSA is related to increases in myocardial oxygen demand during the post-apneic surge in blood pressure and heart rate, at a time when oxygen saturation reaches its nadir. The risk of myocardial infarction is greater at this time. Usually the patient rises from sleep with complaints of angina. The acute changes that provoke ischemia in OSA are hypoxemia, hypercapnia, sympathetic activation, surges in blood pressure and post-apneic tachycardia. Chronic mechanisms involve daytime hypertension, production of vasoactive and trophic substances such as endothelin, activation of inflammatory processes and hypercoagulable state. Reduced capacity for fibrinolysis increases the risk of occlusion. All these mechanisms contribute to the development and progression of CAD. It is not yet known whether OSA causes nocturnal ischemia in the absence of CVD. On the other hand, changes of cardiac function after a myocardial infarction provoke the development of OSA or affect its severity.

Obstructive sleep apnea is a predictor of poor outcome in patients with CAD. In a study of 62 patients with known CAD, those having OSA had a significantly higher mortality (38%), compared to those without OSA (9%), during a five-year follow up after adjusting for other confounding variables.[128] Pecker et al[129] showed that 37% of patients with OSA initially suffered from CVD compared with only 7% in patients who received proper treatment. A recent study of >500 subjects reported that people with OSA are more likely than those without OSA to have a family history of premature death from CAD independently of gender, body mass index and personal history of CAD[130]. It seems that OSA affects the timing of sudden cardiac death (more than half of sudden cardiac deaths in OSA patients occur during the sleeping hours 10_{PM} and 6_{AM} while non-OSA patients experience cardiac death between 6 and 11_{AM}) although it is not known whether OSA increases the risk of sudden cardiac death.[131]

A long-term prospective study evaluated the benefits of OSA treatment on the rate of CAD. Investigators concluded that treatment of patients is associated with a decrease in the occurrence of new cardiac events and an increase in time to such events,[132] while older studies have shown that treatment with CPAP reduces the total duration of ST-segment depression in subjects with sleep apnea.[133]

CARDIAC ARRHYTHMIAS

The repetitive oscillations between sympathetic and parasympathetic predominance in OSA during sleep, depending on the ventilatory phase of the apneic episode and the phase of sleep, provide the perfect milieu for the development of cardiac arrhythmias. When parasympathetic tone predominates, bradyarrhythmias may occur; when sympathetic tone predominates, both atrial and ventricular tachyarrhythmias may occur.[134] Arrhythmias in OSA patients result from the dysfunction of the autonomic nervous system on the heart and are usually not related to primary lesions of the sinus node, atrioventricular node or His–Purkinje system. The most commonly seen arrhythmia in OSA patients is the periodic variability of the cardiac rhythm which is characterized by bradycardia at the beginning of apnea followed by tachycardia at the end of the apneic event. The severity of bradycardia depends on the degree of hypoxemia. The basic mechanism implicated in this type of arrhythmia is hypoxia, leading to changes in the autonomic balance. Convincing evidence for this is the abolition of the arrhythmia with atropine and after tracheotomy. Moreover, the periodic variability of the cardiac rhythm is absent in patients with autonomic neuropathy, Shy-Drager syndrome or patients with OSA that have undergone heart transplantation.

The prevalence of bradyarrhythmias in patients with OSA ranges from 7 to 50% depending on the severity of OSA (number of apneic episodes, severity of associated hypoxemias) and the duration of cardiac monitoring. In a study of 400 patients with OSA sinus bradycardia, sinus pause >2.5 s and second-degree atrioventricular conduction block were found in 7%, 11% and 8% respectively.[135] Prolonged sinus arrest up to 13 s and Mobitz II conduction disturbances have also been observed. Severe bradyarrhythmias have been associated with a very low oxygen saturation (<72%). Koehler et al[136] concluded that approximately 90% of bradycardic episodes occur during REM sleep and during apneic episodes that lead to a 4% decrease in oxygen saturation. Becker et al[137] reported that 7.5% of patients with OSA had significant bradyarrhythmias (2^{nd} and 3^{rd} degree atrioventricular block, sinus pauses >2 s) which were strongly correlated with OSA severity and the degree of nocturnal desaturation (AHI >60). By contrast, studies by Flemons et al[138] and the more recently Sleep Heart Health Study[139] showed no increased prevalence rates of bradyarrhythmias in OSA patients. In a report by Simantirakis et al[140] 23 patients with moderate to severe OSA had an insertable loop recorder implanted and two 24-hour Holter recordings during a period of 16 months; the loop recorder revealed severe cardiac rhythm disturbances (cardiac pauses >3 s and bradycardic episodes <40 bpm) in 47% while the Holter monitoring noted arrhythmias in only 13% of the patients, suggesting that the observed rate of bradyarrhythmias in OSA patients is strongly related to the extent of cardiac monitoring. This study also observed that arrhythmic episodes tended to decrease 8 weeks after the initiation of CPAP and no episodes were recorded during the last 6 months of follow-up.

Supraventricular tachyarrhythmias have also been associated with OSA. Correlation of atrial fibrillation and OSA is ascribed to various mechanisms; hypoxia and hypercapnia have a direct negative effect on electrical stability of the heart. Moreover, they activate chemoreceptors which in turn stimulate sympathetic nervous activity leading to vasoconstriction and increased blood pressure. Afterload increases due to peripheral vasoconstriction, while hyperventilation against the occluded airway leads to an increase of venous blood return and of intrathoracic pressure. These mechanisms result in an increase of the dimensions of the atria. Obstructive sleep apnea is also associated with vasoconstriction in the pulmonary vasculature and pulmonary hypertension. All these hemodynamic, neurohormonal and metabolic changes, combined with increased circulating catecholamines, augment the risk for occurrence of atrial fibrillation in patients with sleep apnea. The increasing number of clinical reports associating sleep apnea and atrial fibrillation led Ghias et al[141] to an experimental model according to which dogs were anesthetized and ventilated by positive pressure respirator inducing controlled periods of apnea. During apnea, atrial and pulmonary vein programmed pacing was performed and neural activity was monitored from the ganglionated plexi adjacent to the right pulmonary veins. Recorded ganglionated plexi neural activity progressively increased by pacing before the onset of atrial fibrillation showing reproducible occurrence of atrial fibrilla-

tion. When radiofrequency ablation of the ganglionated plexi of the right pulmonary artery or autonomic blockade occurred, atrial fibrillation inducibility was significantly inhibited.

A study by Porthan et al[142] assessed the prevalence of sleep apnea syndrome in subjects with "lone" atrial fibrillation. Although the prevalence of sleep apnea was high in the atrial fibrillation group (32%), it did not differ from the control subjects. However, in another study by Gami et al[143] the prevalence of sleep apnea in patients with atrial fibrillation (n=151) was significantly higher (48%) compared with patients (n=312) without the arrhythmia (32%) (p=0.0004, odds ratio 2.19). In a study of 400 adults with moderate to severe OSA, nocturnal episodes of atrial fibrillation were observed in 3% of patients and all patients who received definite treatment of OSA had complete resolution of atrial fibrillation up to 6 months later.[135] It is estimated that ≈50% of patients presenting for cardioversion of atrial fibrillation have OSA compared to 30% likelihood of OSA in the general cardiology clinic population. Atrial fibrillation is frequently seen in patients with sleep disordered breathing and coexisting heart failure or coronary bypass graft surgery. The syndrome is related to a higher risk of recurrence of atrial fibrillation after successful cardioversion.[144] Patients who are treated successfully with pulmonary vein isolation have a 48% prevalence of OSA while patients with therapy-resistant symptomatic paroxysmal atrial fibrillation (defined as arrhythmia recurring after ≥ 2 isolation procedures) have higher prevalence of OSA (87%),[145] a finding which further underlines the possibility of a causal relationship between the two diseases.

Up to 66% of patients with sleep apnea have ventricular ectopy.[146] The prevalence of ventricular ectopy in OSA patients is higher compared to matched controls (0%-12%). Oxygen desaturation plays an important role for this phenomenon but the exact underlying mechanism is not yet fully elucidated. Shepard et al[147] related the higher incidence of premature ventricular beats in sleep apnea patients to oxyhemoglobin saturation < 60%. Nevertheless, the incidence of non-sustained ventricular tachycardia is equal among patients with sleep apnea and non-apneic controls. Although sleep apnea, obstructive or central, in patients with heart failure is associated with worsening of the ejection fraction and high incidence of ventricular arrhythmias, the number of shocks among patients with sleep apnea and an implantable cardioverter defibrillator, and those having a defibrillator but no breathing disorders, was the same in a recent trial.[148]

Treatment with CPAP improves or even abolishes most of the arrhythmias. Harbinson et al[149] studied 45 patients with OSA and AHI > 50. Disturbances of the cardiac rhythm were observed in 35 patients, 8 of whom had serious ones. Seven out of eight did not demonstrate arrhythmias after using the mask. Patients with significant bradycardia due to sleep apnea treated with CPAP have an excellent prognosis relating to the risk of death from syncope. Untreated OSA patients who experience successful cardioversion for atrial fibrillation have an 82% risk for recurrence of atrial fibrillation within 1 year, which is double the risk seen in effectively treated OSA patients.

The relationship between sleep apnea and cardiac pacing constitutes a significant area of research. Currently cardiac pacing is not indicated, even in cases of severe bradycardia during the apneic episodes. According to the European Multi-Center Polysomnographic Study, patients with pacemakers have a remarkably high prevalence of SAHS[150] raising the question of whether primary treatment of sleep apnea would have changed the need for pacing in some patients and suggested that paced patients should be evaluated for OSA because of its detrimental cardiovascular effects. Treating apnea with CPAP or with tracheotomy generally reduces the number of bradyarrhythmias. Moreover the results of several trials suggest that atrial overdrive pacing reduces the number of apneic events through the night.[151] Garrigue et al[152] studied the results of overdrive pacing in a small number of patients with central or obstructive apnea (50% reduction in obstructive apneas) and concluded that cardiac pacing reduces AHI in both types of apnea. The mechanism of action of atrial pacing in central apnea relies on two phenomena, counteraction of parasympathetic activity and improvement of cardiac failure. The increase in heart rate improves cardiac output, which in turn mitigates pulmonary subedema. In this way, gas exchange within the lungs is improved, hyperventilation is diminished and the number of central apneic events is reduced. In obstructive apnea, excess vagal tone causes muscular relaxation in the area of pharynx and obstruction. Pacing in this case counteracts vagal activity and increases the sympathetic tone. However, the effect of pacing in sleep apnea has not been confirmed by other more recent studies involving different populations[153,154] and its role in the treatment of this syndrome needs to be further studied, especially for those patients who do not meet the common indications for implantation of a permanent pacemaker.

Likewise, there are no data supporting the use of implantable defibrillators or antiarrhythmic drugs for patients with ventricular arrhythmias and sleep apnea syndrome. The prevalence of ventricular tachycardia in OSA patients is not higher than non OSA subjects, whereas all reports of ventricular tachycardia in this population refer to non-sustained ventricular tachycardia. On the other hand, patients with SAHS and a low ejection fraction have ventricular arrhythmias more often than patients with heart failure of the same degree but no respiratory disturbances. Finally, the indication for an electrophysiology study should rely only on the presence of daytime symptoms.

PULMONARY HYPERTENSION

Hypoxemia causes constriction of the pulmonary vasculature, and through this mechanism, raises the pulmonary vascular resistance and the pulmonary artery pressure. However, OSA does not lead to overt pulmonary hypertension and right

heart failure in the absence of daytime hypoxia and coexistent pulmonary disease. In several studies, the prevalence of daytime pulmonary hypertension in patients with sleep disordered breathing ranges from 20% to 41% without underlying lung disease.[155,156] The degree of pulmonary hypertension in these studies depends on body mass index and low daytime PO_2, rather than severity of OSA. Therapy with CPAP improves pulmonary hypertension and decreases pulmonary vascular resistance as well as pulmonary artery acute responses to hypoxemia. The greatest benefit of treatment with CPAP has been observed in patients with baseline pulmonary hypertension. In a recent randomized crossover study of 12 weeks of effective versus sub-therapeutic CPAP in 23 patients with OSA, effective CPAP was associated with decreases in echocardiographic measurements of pulmonary artery systolic pressure.[157]

PATENT FORAMEN OVALE

Patent foramen ovale (PFO) a common condition found in 25% of the adult population, constitutes a risk factor for cryptogenic stroke and a potential contributor to hypoxemia in patients. In patients with OSA the prevalence of PFO is estimated to be about 69% when assessed by means of contrast transesophageal echocardiography[158] and could be further increased if contrast transcranial Doppler has been used in routine. Both OSA and PFO are usually undiagnosed in primary care practice, yet cardiologists and pulmonologists should get familiar with their association; although OSA patients have comparable baseline O_2 saturations regardless of the presence of a PFO, when the Valsalva maneuver is performed a significantly greater fall in O_2 saturation is observed in patients with PFO. In a group of 209 subjects diagnosed with OSA, the hypothesis that oxygen desaturation index / apnea-hypopnea index ratio (ODI/AHI) could be a clinically useful screening tool in detecting OSA patients with a high likelihood of a PFO was tested and it was found that prevalence of PFO was 60% for ODI/AHI $\geq$0.06 and 13% for ODI/AHI $\leq$0.33.[159] Percutaneous occlusion with device implantation in PFO patients probably improves sleep apnea symptoms[160,161] but further studies should be performed in order to prove such a statement.

ASTHMA

Asthmatic patients with coexisting OSA and snoring experience frequent nocturnal exacerbations of their disease. Effective treatment of sleep apnea improves symptoms of asthma. Various mechanisms have been proposed for the interaction between OSA and asthma. It has been hypothesized that inflammatory mediators, secreted as a response to hypoxemia, cause bronchoconstriction. Nasal inflammation leads to increased levels of NO, IL-6 and 8-isoprostane, while systemic inflammation is associated with higher levels of reactive oxygen radicals, ICAM–1, monocyte chemo-attractant protein 1 and IL-8.[162]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Patients with COPD may also have OSA. Approximately 10% of patients with OSA have a coexisting pulmonary disease.[163] A recent population study found that symptoms related to obstructive sleep apnea are common in subjects with asthma, bronchitis and rhinitis.[164] Sanders et al[165] concluded that, although OSA and COPD are not clearly correlated, the degree of nocturnal hypoxia is greater in patients with both diseases. Weitzenblum[166] supports the idea that the prevalence of OSA syndrome is not greater in COPD patients than in the general population, but this association is not rare since they are both frequent diseases. The mechanism of oxygen desaturation is different among OSA and COPD patients. While apnea is the most typical cause of oxygen desaturation in OSA patients, REM sleep-associated hypoventilation is the main reason for hypoxemia in COPD.

CONCLUSION

The sleep apnea-hypopnea syndrome (SAHS) is a rather common problem in the general population. It implicates different pathophysiological mechanisms, such as increased sympathetic activation, increased oxidative stress, inflammation, vascular endothelial dysfunction, increased platelet aggregability, and metabolic disorders, all leading to enhanced risk for CVD and lower general health status. Not only cardiologists and pulmonologists but also physicians in the primary care practice should get familiar with the diagnosis and treatment of SAHS taking into account the fact that treatment with CPAP is associated with improvement of various clinical disorders, such as heart failure, hypertension, stroke, coronary artery disease and arrhythmias, and leads to a better clinical outcome.

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