

Obstructive Sleep Apnea Syndrome and Cardiovascular Diseases

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a chronic disease characterized by recurrent episodes of partial or complete upper airway collapse and obstruction during sleep, associated with intermittent oxygen desaturation, sleep fragmentation, and symptoms of disruptive snoring and daytime sleepiness. Increasing focus is being placed on the relationship between OSAS and all-cause and cardiovascular disease-related mortality, but it still largely unclear whether this association is causative or simply speculative and epidemiological. Basically, reliable clinical evidence supports the hypothesis that OSAS might be associated with essential and resistant hypertension, as well as with an incremental risk of developing stroke, cardiac rhythm perturbations (e.g., atrial fibrillation, bradyarrhythmias, supraventricular and ventricular arrhythmias), coronary artery disease, acute myocardial infarction, and heart failure. Although it is still unclear whether OSAS might represent an independent risk factor for several acute or chronic conditions, or rather might trigger cardiovascular disease in the presence of traditional cardiovascular risk factors (e.g., obesity, diabetes, and dyslipidemia), there is a plausible biological background underlying this association, in that most of the mechanisms implicated in the pathogenesis of OSAS (i.e., hypoxia, hypercapnia, negative intrathoracic pressure, micro-arousal, sympathetic hyperactivity, metabolic and hormonal changes, oxidative stress, phlogosis, endothelial dysfunction, hypercoagulability, and genetic predisposition) might also be involved in the pathogenesis of cardiovascular disorders. In this article we discuss the different aspects of the relationship between OSAS and pathogenically different conditions such as systemic hypertension, coronary artery disease, stroke, metabolic abnormalities, arrhythmias, and heart failure, and we also discuss the kaleidoscope of phenomena implicated in the pathogenesis of this challenging disease.

KEYWORDS: Sleep apnea, cardiovascular disease, hypertension, stroke, acute myocardial infarction

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Obstructive sleep apnea syndrome (OSAS) is a chronic disease characterized by recurrent episodes of partial or complete upper airway collapse and obstruction during sleep, associated with intermittent oxygen desaturation, sleep fragmentation, and symptoms of disruptive snoring and daytime sleepiness. It occurs in patients of all ages, from the premature infant to the elderly, with a prevalence related to age and sex. In the general population of adult men and women, the prevalence is ~3 to 7% and 2 to 5%, respectively,^{1,2} increasing significantly in the elderly from 5% to 9%.³ The prevalence of OSAS in children is between 1% and 3%,⁴ although some studies have also reported higher values (e.g., from 5 to 6%).⁵

OSAS is a complex, multifactorial disorder. The most significant risk factor seems to be upper body obesity⁶ estimated with body mass index (BMI) and neck circumference, followed by male gender,⁷ age between 40 and 65 years, cigarette smoking,⁷ use of alcohol,⁸ and physical inactivity.⁹ Others less relevant risk factors include hypothyroidism,¹⁰ acromegaly,¹¹ use of benzodiazepines,¹² upper airway structural abnormalities, and use of exogenous testosterone.¹³ A genetic predisposition, independent from familial obesity, has also been reported in several studies on first-degree relatives and siblings.^{14–18} In particular, it has been observed that a person with one first-degree relative with OSAS has a 40 to 60% higher risk of developing the disease as compared with an individual with no familial predisposition.¹⁶ After accounting for socioeconomic status, age, and geographic region, Friberg et al reported that boys with at least one sibling with OSAS had an increased risk of having the disease. The standardized incidence ratio, defined as the ratio of observed to expected cases, was 33.2 in boys and 40.5 in girls, respectively.¹⁸ Regardless of the etiological factors implicated in the pathogenesis, OSAS is associated with all-cause and cardiovascular disease-related mortality,^{19,20} with a reported hazard risk between 1.97¹⁹ and 6.24,²⁰ which seems to depend on demographic differences in the populations investigated.

It is unclear, however, whether this condition is an independent risk factor for cardiovascular disease,²¹ thus representing a trigger for several acute or chronic cardiovascular conditions such as hypertension, heart failure, arrhythmias, renal disease, stroke, myocardial infarction, sudden death,²² or whether it determines cardiovascular disease (CVD) only in association with other traditional cardiovascular risk factors, such as obesity, diabetes, and dyslipidemia and thereby is without a cause-and-effect relationship.^{6,23} In this review we discuss the different aspects of the relationship between OSAS and pathogenically different conditions such as systemic hypertension, coronary artery disease, stroke, metabolic abnormalities, arrhythmias, and heart failure. We also discuss the kaleidoscope of phenomena

implicated in the pathogenesis of this challenging disease, including perturbations of the autonomic nervous system,²⁴ hypoxemia-reoxygenation cycles leading to endothelial dysfunction,²⁵ systemic inflammation,²⁶ metabolic-endocrine deregulation,²⁷ and coagulation-fibrinolysis imbalance.^{28,29}

PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA SYNDROME

How sleep-disordered breathing (SDB) might contribute to the elevation of blood pressure (BP) and increased cardiovascular risk has been the subject of several studies, both in the human and the animal model. In healthy individuals, cardiac vagal tone increases with respect to wakefulness and consequently metabolic rate, whereas sympathetic nervous activity, BP, and heart rate all decrease during sleep (in particular, non-REM sleep).³⁰ This normal behavior is disrupted in people suffering from SDB, where repeated episodes of intermittent hypoxia and hypercapnia occur during respiratory efforts to overcome the pharyngeal obstacle. Moreover, these episodes are characterized by continuous changes in pulmonary volume, intrathoracic pressure, and micro-arousals.³¹ After these events, OSAS patients show permanent oscillations in their hemodynamic parameters during the night. The heart rate, BP, and cardiac output vary incessantly due to the repetition of respiratory events and the rapid changes in alertness (micro-arousals) caused by the ventilatory anomalies. In fact, intermittent increases in heart rate and arterial pressure occur in association with decreases in left ventricular stroke volume immediately following apnea termination.³²

The major contributors to acute hemodynamic modifications occurring in OSAS patients are hypoxemia, hypercapnia, changes in pulmonary volume/intrathoracic pressure, and micro-arousals. Their causative role has been investigated both in OSAS patients and in healthy subjects, and it was concluded that all these factors contribute in the long term to increased autonomic nervous system (ANS) drive, generation of reactive oxygen species (ROS), impaired endothelial function, and metabolic abnormalities, which in turn stably increase both the BP and the cardiovascular risk (Fig. 1).

Short-Term Modifiers of Hemodynamic Parameters: Hypoxia, Hypercapnia, Negative Intrathoracic Pressure, and Micro-Arousal

Hypoxemia plays probably the leading role in the pathophysiology of OSAS.³³ Hypoxia is per se a stimulus able to heighten BP and blunt vascular responsiveness both in OSAS patients and healthy subjects. Patients suffering from OSAS show greater increases in heart rate and mean arterial pressure than control subjects and a

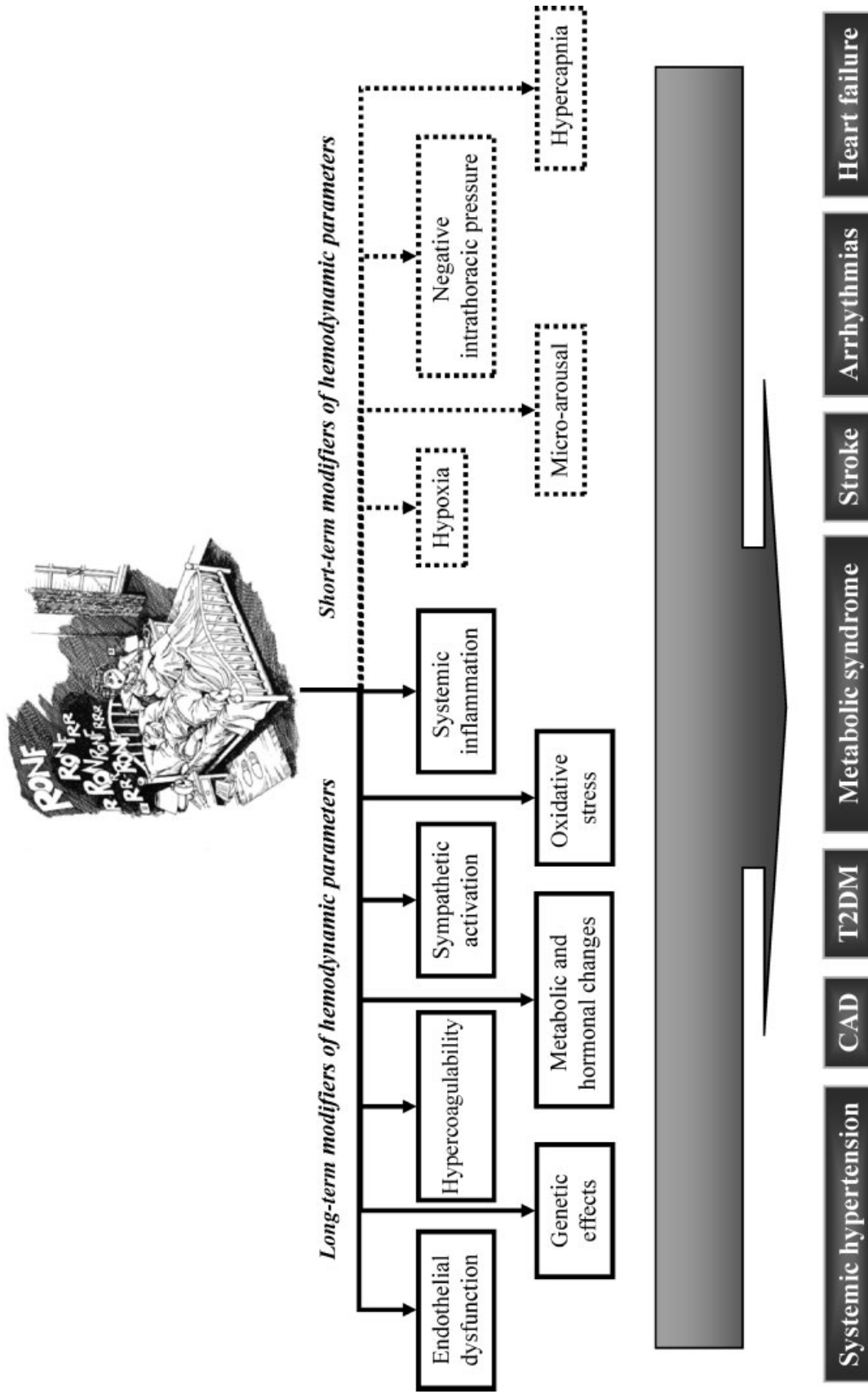


Figure 1 The major contributors to acute hemodynamic modifications occurring in patients with obstructive sleep apnea syndrome. CAD = coronary artery disease; T2DM = type 2 diabetes mellitus.

relative increase in muscle sympathetic nerve activity (MSNA), despite higher ventilation and BP.³⁴ Similarly, after 14 nights of nocturnal sustained hypoxia, healthy volunteers showed a significant increase in mean arterial pressure, MSNA, forearm vascular resistance, and forearm blood flow, a response partially corrected by vascular infusion of the α -blocker phentolamine.³⁵

Although it is a sympathetic stimulation factor, hypercapnia plays a secondary role in the pathophysiology of OSAS, at least in humans. In contrast to rats exposed to intermittent hypoxia where the sympathetic response increases due to both hypercapnia and hypoxia,³⁶ some studies in humans demonstrated that the sympathetic response to hypercapnia is not increased in apneic patients as compared with control subjects,³⁴ although others authors consider its role still plausible.³⁷

By measuring esophageal pressure during apneic episodes, it has been demonstrated that very negative intrathoracic pressures could alter the mechanical properties of the left ventricle (LV). The existence of a sudden restoration of the LV function during normalization of esophageal pressure could lead to the post-apnea hypertensive peak.³³

Micro-arousal is a common pattern in OSAS^{38,39} and is thought to cause periodic fluctuation in BP. Micro-arousal (even as a nonrespiratory event) can also trigger a hypertensive peak during the change to the subject's state of alertness.³² The BP peak obtained in normal subjects is proportional to the intensity of the nonrespiratory micro-arousal produced.⁴⁰

Long-Term Modifiers of Hemodynamic Parameters: Sympathetic Activity, Metabolic and Hormonal Changes, Oxidative Stress, Phlogosis, Endothelial Dysfunction, Hypercoagulability, and Genetic Effects

The ANS plays an essential role in the genesis of the organism's acute and chronic responses to OSAS, and it at least partly explains the physiopathological mechanisms behind the chronic cardiovascular consequences linked to OSAS, particularly hypertension.³³ In dogs, as well as in rats, repetitive episodic hypoxia mimicking OSAS leads to sustained increase in BP, whereas sleep fragmentation produced only acute but not chronic changes in BP.⁴¹⁻⁴³

Since the early 1980s, a predominant role of ANS in the pathophysiology of OSAS has been delineated also in humans: Vagus nerve stimulation explains the initial bradycardia during the apneic phases,⁴⁴⁻⁴⁶ whereas in the long term, adaptation to hypoxia and hemodynamic changes occurring at repetitive apneas determines a constantly increase sympathetic activity, which occurs not only during sleep but also while awake,^{47,48} with an effect independent from obesity.^{49,50} The urinary and

plasma levels of catecholamines are also increased in these patients.⁵¹⁻⁵⁴

As already described, hypoxia is probably the major trigger of ANS stimulation, although repeated arousals and abnormal respiratory efforts might also play a role.⁵² In a series of experiments aimed to elucidate the role of chemoreceptors and baroreceptors in this setting, Narkiewicz and colleagues found that OSAS is associated with a selective amplificatory effect of autonomic, hemodynamic, and ventilatory responses to peripheral tonic chemoreceptor activation by hypoxia.^{34,55} Moreover, normotensive patients with OSAS have a blunted increase in MSNA for the same difference in mean arterial pressure in response to baroreceptor deactivation (obtained by nitroprusside infusion) but not to baroreceptor activation (tested by phenylephrine infusion). Interestingly, this response is not accompanied by any impairment of baroreflex control of heart rate.⁵⁶ Other groups confirmed the impairment of chemoreceptors and baroreceptors in these patients.⁵⁷⁻⁵⁹ Several studies have found that continuous positive airway pressure (CPAP) reduces the hyperactivation of the adrenergic system by ameliorating the oxygenation in OSAS patients.^{48,60-62}

Besides the altered secretion of catecholamines, the renin-angiotensin system and other vasoactive hormones have also been measured in OSAS, obtaining controversial results. Independent research groups found higher plasma level of endothelin-1 but not angiotensin II, renin, and aldosterone in patients with OSAS,^{63,64} whereas Møller and colleagues observed increased plasma angiotensin II and aldosterone but not endothelin-1. In the latter study, long-term CPAP reduced BP, and this decrease was correlated with the reductions in plasma renin and angiotensin II levels.⁶⁵ Others studies showed that aldosterone can sustain a resistant form of hypertension in OSAS, independently from renin stimulation.^{66,67} Increased levels of serum angiotensin II and vascular endothelial growth factor and vascular endothelial growth factor mRNA expression were also found in leukocytes of patients with OSAS,⁶⁸ but recent studies suggest caution in interpreting these findings.⁶⁹

Both insulin resistance and the metabolic syndrome amplify the effects of OSAS on sympathetic-adrenergic stimulation.⁷⁰ There are also some reports that OSAS might be associated with markers of insulin resistance⁷¹⁻⁷⁴ and could itself trigger type 2 diabetes mellitus (T2DM).^{75,76} Moreover, CPAP may ameliorate some of the metabolic disturbance linked to insulin resistance in OSAS.^{71,73,76-78} To support this association, it was shown that hypoxia also alters glucose metabolism in healthy volunteers.⁷⁹

It has been observed that OSAS patients have a very high prevalence of metabolic syndrome, as defined in the National Cholesterol Education Program Adult Treatment panel III.⁸⁰

Several studies have evaluated the association of leptin, a hormone derived by adipocyte, and OSAS. Leptin is almost invariably associated with OSAS, but controversies exist about the independency of this association from body fat as well as on the effect of CPAP on its plasma level. As such, a leading role of leptin in the pathogenesis of OSAS remains unproved as yet.⁸¹⁻⁹³

ROS, elicited by chronic intermittent hypoxia, trigger oxidative damages in rats' brain and provoke hypersomnolence and cognitive impairment that closely resembles that of OSAS patients.⁹⁴⁻⁹⁸ In humans, despite some controversies,⁹⁹ intermittent hypoxia has been associated with an increase in oxidative stress in OSAS patients, as differently measured in biological samples and in leucocytes cultures,¹⁰⁰⁻¹⁰⁶ an effect that could be at least partially reversed by CPAP therapy.^{100-102,104,106,107}

Inflammatory mediators are increased in OSAS patients, who are characterized by elevated levels of C-reactive protein (CRP),¹⁰⁸⁻¹¹⁰ adhesions molecules,¹¹¹ inflammatory^{106,108-110,112-118} but also anti-inflammatory cytokines,¹¹⁹ matrix metalloproteinase-9,¹²⁰ and vascular endothelial growth factor,¹²¹⁻¹²⁶ independently from obesity.¹⁰⁸⁻¹¹⁰ The beneficial effect of CPAP therapy has been documented in most studies.^{106,112-114,118,127,128} Interestingly, the administration of etanercept, a medication that neutralizes tumor necrosis factor (TNF)- α , was associated with a significant reduction of objective sleepiness in obese patients with OSAS, and its effect was approximately threefold higher than that of CPAP.¹²⁹

Endothelial dysfunction is an additional hallmark of OSAS patients,^{117,130-132} as demonstrated by altered flow-mediated dilatation¹³³⁻¹³⁸ and forearm blood flow after acetylcholine or bradykinin infusion, independent from hypertension.^{135,136,139-141} Treatment aimed at improving the oxygenation such as CPAP,¹⁴¹⁻¹⁴⁴ modified Herbst mandibular advancement splint,¹⁴⁵ tonsillectomy in children,¹³⁷ as well as antihypertensive drugs,^{142,146} antioxidants,¹⁴⁷ and allopurinol,¹⁴⁸ were proven to ameliorate the endothelial function. This latter finding further underlines the significant contribution of oxidative stress in this setting.¹⁴⁸

The altered endothelial function is paralleled by an increase in arterial stiffness,^{136,149-152} an effect improved by the use of antihypertensive drugs¹⁴⁹ and by the presence of subclinical and overt carotid atherosclerosis.^{136,150,153-156} Homocysteine levels are also increased in patients with OSAS, but the pathogenetic role of this sulfur-containing amino acid remains uncertain.^{157,158}

A few studies in OSAS patients have documented platelet hyperactivation^{131,132} and some (but not all) have also noted the presence of a hypercoagulable state¹⁵⁹⁻¹⁶³ with increased levels of plasminogen activator inhibitor-1^{161,164,165} that can be lowered by CPAP.¹⁶¹

Regarding potential genetic factors contributing to OSAS, there is no convincing evidence to date that variants in putative genes might be associated with the disease. But most of the completed genetic studies were quite small for sample size, and no genomewide association study has been performed for this pathology.¹⁶⁶ Nevertheless, interesting data are emerging from a mouse model of impaired circadian rhythm. Mice knockouts for genes implicated in circadian rhythm maintenance (i.e., cryptochrome-1 and cryptochrome-2) express an increased amount of the 3β -hydroxyl-steroid-dehydrogenase in the adrenal zona glomerulosa, with enhanced production of aldosterone and a tendency to develop salt-sensitive hypertension.¹⁶⁷ These data are in agreement with the possible primary role of an independent aldosterone secretion in OSAS patients with resistant hypertension,^{66,67} so their role in patients with OSAS or other forms of sleep disturbance deserves further scrutiny.

OBSTRUCTIVE SLEEP APNEA SYNDROME AND HYPERTENSION

Epidemiological and Experimental Evidence of Obstructive Sleep Apnea Syndrome Causing Hypertension

Regardless of the definition used for sleep disorders or OSAS, these pathologies have been increasingly and strikingly associated with essential¹⁶⁸⁻¹⁷⁰ and resistant hypertension for > 20 years so far.^{171,172}

Both the European and American clinical practice guidelines recognize OSAS as a secondary form of hypertension.^{26,173} However, because the effects of OSAS are closely related to those of obesity, the independent association of breathing disorders with hypertension are sometimes confounded by the high prevalence of obesity in OSAS patients, especially at younger ages.^{174,175}

A review of epidemiological and experimental data is helpful to unravel this issue. Participants in the Sleep Heart Health Study, a community-based study involving 6132 subjects recruited from ongoing population-based studies (age > 40 years) were investigated for SDB. After adjusting for anthropometric variables (including BMI, neck circumference, and waist-to-hip ratio), the odds ratio (OR) for hypertension, comparing the highest category of apnea hypopnea index (AHI) (≥ 30 per hour) with the lowest category (< 1.5 per hour), was 1.37.¹⁷⁶

In the same cohort followed prospectively, the ORs for incident hypertension increased with increasing baseline AHI. This relationship was attenuated, however, and nonstatistically significant after adjustment for baseline BMI.¹⁷⁷ Conversely, in 709 participants of the Wisconsin Sleep Cohort Study, SDB at baseline was associated with the presence of

hypertension independently of known confounding factors including obesity measures.¹⁷⁸ In another prospective two-step study involving >16,000 people in the first phase and >1700 in the second, SDB was independently associated with hypertension. The strength of the association was proportional to the severity of the disorders. The ORs increased from 1.6 for simple snoring to 6.8 for moderate or severe SDB (obstructive apnea/hypopnea index ≥ 15.0).¹⁷⁹ The relation between SDB and hypertension seems to have a specific association pattern with age because it is attenuated in subjects >60 years.^{179,180} The lack of significant association between OSAS and hypertension in the elderly may be due to the fact that OSAS significantly affects survival rate or that, alternatively, significant CVD has already occurred by that age, so the contribution of OSAS on disease progression seems less important. SDB has instead adverse consequences from childhood. In a population of children 5 to 12 years of age, systolic BP was elevated in association with the AHI, reaching a mean of 12.9 mm Hg for AHI ≥ 5 after adjusting for BMI, waist circumference, and other confounding factors.¹⁸¹ In total, these studies underline that although obesity is a common finding in people with SDB, OSAS is independently associated with both the incidence and prevalence of hypertension.

Characteristics of Hypertension in Patients with Sleep-Disordered Breathing

Interesting clues come from ambulatory BP monitoring in patients with OSAS. These patients do not show the usual fall in BP (~10 to 20%, the so called physiological dipping) that occurs during the night in normal subjects. As such, BP dipping is often insufficient or lacking in these patients.¹⁸²⁻¹⁸⁶ In the clinical setting, a documented nondipper profile on the 24-hour ambulatory BP monitoring should thereby suggest the possibility of OSAS.^{168,172,187} Masked hypertension is another common finding, occurring in 30% of these patients.¹⁸⁷ Moreover, in comparison with people without OSAS, these subjects have an increased in BP variability,¹⁸⁸ which can increase the overall cardiovascular risk.

The increase in peripheral arterial resistance, due to constantly elevated sympathetic activity, explains the predominantly diastolic nature of the hypertension found in OSAS. Therefore, isolated diastolic hypertension and sometimes systolic/diastolic hypertension are profiles more likely related to OSAS as compared with isolated systolic hypertension.^{180,189}

Therapeutic Trials

Several trials have tested nasal CPAP or bilevel positive airway pressure (BPAP) for their effects on BP. Most of these trials have a limited sample size and other

important limitations, including the lack of a control group, no randomization of therapy, brief duration, and office measurement of BP.¹⁹⁰⁻²⁰⁷ Data are additionally confounded by different inclusion criteria, with different important covariates such as obesity that may play a primary role. Taken into account all these limitations, three meta-analyses have tried to pull together these data and to provide a definitive answer on this issue.²⁰⁸⁻²¹⁰ It seems hence plausible that CPAP or BPAP has a small but significant effect especially on diastolic BP (1 to 2 mm Hg), with a possible positive effect on BP profile during the night.^{193,211,212} Patient characteristics that predict a better BP response include adherence to therapy, severity of OSAS, and uncontrolled or untreated hypertension.³³

Other procedures aimed at increasing oxygenation such as a facial mask were adopted and compared in OSAS patients for assessing the BP response, but the outcome was controversial.^{202,213} Also, there are no convincing data concerning conventional antihypertensive treatment to suggest a particular agent or class of agents in these patients. Due to the ANS hyperstimulation at which both OSAS and obesity concur in at least half of these patients, it seems that β -blockers could be preferable as also suggested by a comparative study. Unfortunately, well-powered randomized trials are completely lacking, so that definitive conclusions cannot be drawn.²¹⁴ Chronic baroreceptor stimulation has been recently proposed for refractory or resistant hypertension. It might be of interest to investigate the effect of this procedure on BP in patients with SDB because ANS stimulation and baroreceptor impairment are strongly implicated in the pathophysiology of OSAS.²¹⁵

OBSTRUCTIVE SLEEP APNEA SYNDROME AND STROKE

Several prospective studies have reported that OSAS is associated with an incremental risk of developing stroke^{19,216,217} and that 70 to 95% of patients with acute stroke or transient ischemic attack manifest OSAS.^{218,219} Artz et al reported an OR for stroke of 4.33 (95% confidence interval [CI], 1.32 to 14.24; $p=0.02$) in patients affected by SDB.²¹⁶ Accordingly, the cross-sectional data from the Sleep Heart Health Study demonstrated greater odds for stroke in the highest AHI quartile than in the lowest quartile (1.58; 95% CI, 1.02 to 2.46).²²⁰ Moreover, OSAS represents a poor prognostic marker; patients affected by this condition show a higher mortality, neurological deterioration, and lower functional abilities after stroke.^{19,221,222}

Overall, it seems more plausible that OSAS precedes and represents an independent risk factor for cerebrovascular events^{19,223,224} rather than a consequence.^{225,226} Several mechanisms have been implicated to explain the association between cerebrovascular

disorders and OSAS. Relevant differences in cerebral blood flow and intracranial pressure have been observed between OSAS patients and healthy subjects^{227,228} other than an impaired cerebral autoregulation.²²⁹ Dikmenoglu et al observed that plasma viscosity is high both in the morning and in the evening in severe OSAS patients, probably related to low nocturnal mean oxygen saturation, thus predisposing these patients to stroke.²³⁰ Moreover, loss of cerebrovascular reactivity and increase of arterial stiffness have been demonstrated, especially during consecutive respiratory events periods.²³¹ The patients with severe OSAS have a mean intima-media thickness of the carotid arteries, a marker associated with a high risk of stroke, which was also proven to be significantly higher than those of patients with mild OSAS and control subjects.²³² Finally, the prevalence of patent foramen ovale, an interatrial communication that can potentially give rise to ischemic stroke by means of paradoxical embolization, is significantly higher in subjects with OSAS than in normal controls.²³³

Coagulation disorders have been described in OSAS patients, including a high morning plasma fibrinogen level,²³⁴ platelet hyperaggregability,^{235,236} and decreased fibrinolysis,²³⁷ all of which may play an important role in the pathogenesis of stroke.

Some randomized controlled trials have investigated the effect of CPAP on stroke patients affected by OSAS,^{238,239} but results are not encouraging, probably due to the poor patient compliance or the small size of the study populations.

OBSTRUCTIVE SLEEP APNEA SYNDROME AND ENDOCRINE-METABOLIC DISORDERS

Growing evidence suggests that OSAS may be causally related to various metabolic abnormalities, including insulin resistance, glucose intolerance, T2DM, and the metabolic syndrome,^{75,240,241} independently of adiposity.^{240,242,243} The increasing severity of OSAS in patients with T2DM is associated with a higher degree of insulin resistance and poorer glucose control, independent of adiposity and other confounders.²⁴⁴ Although a trend toward a higher prevalence of abnormal glucose metabolism has been observed in patients affected by OSAS as compared with control subjects, the real prevalence varies widely among the different populations. In an Asian population, Otake et al found that >25% of OSAS patients were diagnosed as having T2DM.²⁴⁵ In Hispanic and African Americans, the prevalence of T2DM was 30% in the group with OSAS as compared with 19% in those without.²⁴⁶ In European populations, Meslier et al reported that the frequencies of T2DM and impaired glucose tolerance in the OSAS patients were 30% and 20%, respectively,²⁴⁷ whereas they were shown to be 11% and 30% in the study of Levinson et al.²⁴⁸ In a Swedish study, the

prevalence of T2DM in OSAS patients was 18.9% in men and 14.8% in women,²⁴⁹ similar to the Wisconsin Sleep Cohort (14.7%).²⁵⁰ In the study of Coughlin et al, the subjects with OSAS had a high incidence of metabolic syndrome (87%) as compared with controls (35%).⁸⁰ These discrepancies in prevalence have been explained by significant differences in age, sex, ethnicity, hypertension, or obesity grade of the study population. In a longitudinal study, Botros et al demonstrated an increased risk of diabetes among patients with sleep apnea (hazard ratio per quartile of OSAS severity: 1.43; CI, 1.10 to 1.86; $p=0.008$), independently of other risk factors including age, race, sex, baseline fasting glucose, BMI, and changes in BMI.⁷⁵

Several factors implicated in the pathogenesis of OSA (e.g., intermittent hypoxia with generation of ROS, elevated sympathetic nervous activity with stimulation of the renin-angiotensin-aldosterone system, sleep fragmentation, and low quantities of slow-wave sleep and cumulative sleep loss,^{48,251-253} seem to have adverse effects on glucose tolerance. In particular, it has been demonstrated that repeated episodes of hypoxia followed by reoxygenation (a hallmark of OSAS) produce increased levels of proinflammatory cytokines and mediators (i.e., interleukin [IL]-6, CRP, leptin, TNF- α , IL-1 β), induce intercellular adhesion molecule-1, vascular cell adhesion molecule-1, other than the production endothelin-1 following the oxidative stress.²⁵⁴ Moreover, it is plausible that the increase in insulin resistance observed in OSAS patients may depend on the impaired regulation of leptin.²⁵¹

West and colleagues failed to observe any improvement of glycemic control or insulin resistance in T2DM patients treated with CPAP.²⁵⁵ In contrast, the study performed by Dawson et al⁷⁸ suggests that sleeping glucose levels decrease and are more stable when patients with T2DM and OSAS are treated with CPAP. Analogously, Babu et al²⁵⁶ reported a reduction in hemoglobin A1c level that was significantly correlated with days of CPAP use. CPAP therapy also determines a significant reduction of nocturnal glucose variability and improves overnight glucose control.²⁵⁷

Several hormonal axes are impaired in OSAS.²⁵⁸ The imbalance of the pituitary-gonadal axis²⁵⁹ determines variable degrees of hypogonadism in men, independently of increasing age or obesity,²⁶⁰ and lower serum estradiol and progesterone²⁶¹ in women, suggesting that OSAS may also be associated with impaired ovarian function. No dysfunction of the hypothalamic-pituitary-thyroid axis has been reported, whereas the involvement of the hypothalamic-pituitary-adrenal axis has been shown by an exaggerated response of adrenocorticotrophic hormone to corticotropin-releasing hormone,²⁶² leading to altered cortisol levels, decreased pancreatic β -cell activity, elevated growth hormone

levels, and alterations in neuroendocrine control of appetite.^{48,263}

OBSTRUCTIVE SLEEP APNEA SYNDROME AND MYOCARDIAL ISCHEMIA

Several investigations have demonstrated an increased risk of developing coronary artery disease (CAD) in patients with OSAS,^{264–269} suggesting an independent association even after the adjustment for traditional confounders between these two diseases in both middle-aged men and women.^{266,268,270} In the study of Schäfer et al,²⁶⁷ 30.5% of angiographically proven CAD patients were found to have OSAS, whereas OSAS was only present in 19.7% of control subjects. Lee et al recently observed a high prevalence of previously undiagnosed OSAS in patients admitted with acute myocardial infarction (AMI).²⁷¹

Patients affected by OSAS are also characterized by worse outcomes of CAD,^{272,273} and they have a higher degree of late lumen loss, which is a marker of restenosis and vessel remodeling after elective percutaneous intervention.²⁷⁴ The OSAS may inhibit the recovery of LV function in patients with AMI.²⁷⁵ The coronary atherosclerotic plaque volume shows a correlation with the frequency of obstructive sleep apnea/hypopnea episodes and sleep fragmentation.²⁷⁶

The severity of OSAS seems to be independently associated with the presence and extent of subclinical coronary disease assessed by coronary artery calcification, also in patients without clinical coronary disease.²⁷⁰ Moreover, OSAS is associated with a family history of premature mortality from ischemic heart disease.²⁷⁷

The previously described long-term modifiers of hemodynamic parameters, such as the increase of sympathetic activity, the promotion of oxidative stress with following endothelial dysfunction, systemic inflammation, and the hypercoagulability state (all these conditions are involved in the pathogenesis of OSAS) lead to a high-risk proatherogenic state that predisposes to acute ischemic events. It has been proposed recently that activation of the endothelin system, mediated by hypoxia inducible factor-1 activity, might be responsible for the enhanced susceptibility to chronic intermittent hypoxia leading to myocardial ischemia.²⁷⁸ These hemodynamic and neurohormonal abnormalities appear more frequently during the night, which might explain the larger incidence of cardiac events in this period.²⁷⁹

The treatment of OSAS with CPAP in patients affected by coronary disease leads to a significantly decreased risk for the composite end point of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization, mainly by reducing sympathetic nerve activity.^{280–282} The same treatment in patients with nocturnal angina

leads to reduced frequency of ST-segment depression and relief of nocturnal angina.^{265,283}

OBSTRUCTIVE SLEEP APNEA SYNDROME AND ARRHYTHMIAS

Several forms of cardiac rhythm perturbations have been documented in patients with OSAS, including both supraventricular and ventricular arrhythmias,²⁸⁴ which have also been associated with the onset of sudden death.²⁸⁵ OSAS is indeed associated with electrocardiogram modifications^{286–292} that can predict future cardiovascular events¹⁸⁸ and predispose to arrhythmia.^{286,288–292} The most common forms of arrhythmias observed in OSAS are nonsustained ventricular tachycardia, sinus arrhythmia (also termed *cyclic variation of heart rate*) characterized by bradycardia during the apneic phase with subsequent tachycardia on resumption of respiration, second-degree atrioventricular conduction block, and premature ventricular contractions.^{293,294}

Several studies have focused on the risk of atrial fibrillation (AF) in OSAS patients. In the Sleep Heart Health Study,²⁹⁵ individuals with severe sleep apnea had four times the odds of having AF (OR: 4.02; 95% CI, 1.03 to 15.74) and three times the odds of having nonsustained ventricular tachycardia (OR: 3.40; 95% CI, 1.03 to 11.20) as compared with individuals without OSAS, even after adjusting for possible confounding factors.

The leading mechanisms implicated in the development of AF in OSAS patients include (1) an atrial chamber enlargement due to impairment of intrathoracic pressure, (2) tissue stretch and remodeling at the site where the nidus is localized and from which electrical discharges propagate in AF,²⁹⁶ (3) the repetitive oxy-hemoglobin desaturation and the reoxygenation that may activate atrial catecholamine-sensitive ion channels thereby resulting in focal discharges that initiate AF,²⁹⁷ and (4) an instability in autonomic tone.²⁹⁸

It has been demonstrated that improving the nocturnal oxygenation can restore these abnormalities.^{289–291} Moreover, Kanagala and colleagues observed that AF recurred 1 year after electrical cardioversion in only 42% of OSAS patients treated with CPAP, compared with 82% of untreated OSAS patients.²⁹⁹ A recently published study performed in a large population of Japanese OSAS patients demonstrated the efficacy of CPAP in preventing OSAS-associated arrhythmias.³⁰⁰

These studies have reported an increased association between OSAS and bradyarrhythmias^{301,302} due mainly to parasympathetic hyperactivity that occurs during the apneic phase. In contrast, the Sleep Heart Health Study failed to demonstrate a significant association between bradycardia and OSAS.²⁹⁵ Despite these contradictory results, CPAP therapy has been shown to abolish most bradyarrhythmias in OSAS patients.³⁰³

OBSTRUCTIVE SLEEP APNEA SYNDROME AND HEART FAILURE

Heart failure (HF) is frequently observed in OSAS patients, with a prevalence between 11% and 37%.^{304,305} The prevalence is higher in men than in women.³⁰⁵ Data obtained in the Sleep Heart Health Study from 6424 men and women have shown a 2.38 times increased likelihood of having HF in association with OSAS, independent of other risk factors.²²⁰ The presence of OSAS 21 days after an AMI is also associated with impaired recovery of left ventricular systolic function.²⁷⁵ Untreated OSAS is also associated with an increased risk of death in patients with HF.³⁰⁶

OSAS is not only a consequence of HF but indeed represents a risk factor for this condition,²²⁰ independent of hypertension.³⁰⁷ A causative relationship between OSAS and LV remodeling has been demonstrated, most likely attributable to oxidative stress following hypoxemia.³⁰⁸ Other mechanical factors such as the increased cardiac muscle work index due to the increased negative intrathoracic pressure during obstructed breaths³⁰⁹ and the changes in venous return due to the negative intrathoracic pressure generated from the inspiratory effort might lead to LV remodeling.³¹⁰ This clinical picture is further worsened by the onset of arrhythmias.

Several grades of cardiac alterations have been reported in OSAS patients, from silent or subclinical echocardiographic left ventricular abnormalities to symptomatic systolic dysfunction. Treatment of OSAS with CPAP seems to improve LV ejection fraction in patients with congestive HF. An Australian study has shown an improvement in LV ejection fraction from 38% to 43%,²⁰⁶ and the study of Kaneko et al has shown improvements in LV ejection fraction from 25% to 34% following treatment with CPAP for 1 month.²⁰⁵

CONCLUSIONS

Taken together, reliable clinical evidences support the hypothesis that OSAS might be associated with essential and resistant hypertension, as well as with an incremental risk of developing stroke, cardiac rhythm perturbations (e.g., AF, bradyarrhythmias, supraventricular and ventricular arrhythmias), CAD, AMI, and HF. There is a strong biological background underlying these associations, in that most of the mechanisms implicated in the pathogenesis of OSAS (i.e., hypoxia, hypercapnia, negative intrathoracic pressure, micro-arousal, sympathetic hyperactivity, metabolic and hormonal changes, oxidative stress, phlogosis, endothelial dysfunction, hypercoagulability, and genetic predisposition) might also be involved in the pathogenesis of these cardiovascular diseases.

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