Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a prevalent condition in the general population. It is associated with increased cardiovascular risk and often goes unrecognized. Its diagnosis requires a high degree of clinical suspicion, particularly on the part of cardiologists, and it may be confirmed by polysomnography. Continuous positive airway pressure (CPAP) therapy is highly effective, since it improves sleep breathing pattern, promotes restful sleep and thus enhances the quality of life of these patients, in addition to attenuating or reversing many cardiovascular complications related to OSAHS.

Chart 1 shows some important definitions for interpreting and diagnosing this condition.

**PATHOPHYSIOLOGY**

Increased upper airway collapse during sleep is associated with increased respiratory effort and change in nasal and oral airflow, which may trigger hypoxemia and hypercapnia. This process results in arousal with resumption of breathing. Abnormal respiratory events and arousals may alternate many times during the night.

During each episode of obstructive apnea/hypopnea, the inspiratory effort against an occluded airway is accompanied by negative pressure in the pleural space. As apnea persists, hypoxemia and hypercapnia become more marked, leading to pulmonary vasoconstriction and the development of transient pulmonary hypertension. There is however, a stimulation of the sympathetic nervous system, causing systemic vasoconstriction and arterial hypertension; in some cases, systolic blood pressure may reach significantly high nocturnal levels, even in subjects with normal daytime blood pressure.

Additionally, the hypoxia and subsequent reoxygenation phenomenon, repeated many times during the night, causes changes in reperfusion, with free radical production, and oxidative stress is now considered a major contributor to the cardiovascular consequences observed in this group of patients. Association of OSAHS with obesity, predominance in male and postmenopausal women, as well as the systemic effects triggered with its onset, strongly suggest that OSAHS is a systemic disease, rather than a local abnormality. Other important evidence favoring the systemic disease.
hypothesis for OSAHS is its correlation with higher inflammatory cytokine levels and insulin resistance. Inflammatory cytokines, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and interleukin-6 (IL-6) are involved in the physiological regulation of sleep\(^{28}\) and are abnormally elevated in apneic patients, when compared to normal and obese subjects\(^{29,30}\). However, the correlation between OSAHS and insulin resistance seems to be independent of obesity\(^{31}\).

**CARDIOVASCULAR CONSEQUENCES**

The main cardiovascular consequences are changes in autonomic nervous system activity, arterial hypertension, cardiac arrhythmias, coronary artery disease, stroke, and congestive heart failure.

**Changes in autonomic nervous system activity**

Heart rate and blood pressure changes observed in obstructive sleep apnea are likely to be secondary to autonomic nervous system activation during every apneic event\(^{32}\). This was demonstrated even in patients with mild OSAHS\(^{33,34}\). During these events, a progressive increase in sympathetic activity occurs, reaching its peak at apnea termination, followed by a marked decrease during recovery\(^{35,36}\).

However, the mechanisms by which OSAHS causes persistent sympathetic activation, that is, even during wakefulness, are not entirely clear. Some evidence emphasizes the role of hypoxia in this phenomenon:
urinary norepinephrine concentrations are inversely proportional to nadir nocturnal oxyhemoglobin saturation. Furthermore, the ventilatory changes that determine hypoxia and hypercapnia cause an increase in muscle sympathetic nerve activity, which may persist for up to twenty minutes following stimulus withdrawal\textsuperscript{18}. The carotid sinus seems to play a role in the process between exposure to intermittent nocturnal hypoxia and development of sustained elevation in autonomic activation levels, because baroreflex regulation and sensitivity are reduced in patients with OSAHS, compared to controls\textsuperscript{18}.

Current evidence suggests that the intermittent nocturnal hypoxic stimulus of peripheral chemoreceptors increases the sympathetic tone in these patients even during wakefulness and optimal oxygen supply\textsuperscript{19,40}. Moreover, autonomic nervous system studies employing heart rate variability demonstrate that the high-frequency component (parasympathetic tone) of heart rate variability of OSAHS patients declines and the low-frequency component (sympathetic tone) increases. This abnormal pattern seems to reflect sympathetic predominance in the autonomic modulation of OSAHS\textsuperscript{41}.

**Chart 1 – Term Definition**\textsuperscript{17-19}

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnography</td>
<td>Polygraphic sleep recording, including electroencephalogram (EEG), electroocculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), and respiratory parameters.</td>
</tr>
<tr>
<td>NREM sleep</td>
<td>Characterized by electroencephalographic slow waves associated with specific graphic elements.</td>
</tr>
<tr>
<td>REM sleep</td>
<td>Characterized by EEG desynchronization, rapid eye movements, muscle atonia, and dreams.</td>
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<tr>
<td>Arousals</td>
<td>Transient awakening lasting more than three seconds.</td>
</tr>
<tr>
<td>Apnea</td>
<td>Reduction of &gt; 80% in oronasal airflow during more than ten seconds.</td>
</tr>
<tr>
<td>Hypopnea</td>
<td>Reduction of &gt; 20% in oronasal airflow during more than ten seconds, usually accompanied by either a decrease in oxyhemoglobin saturation or an arousal</td>
</tr>
<tr>
<td>Apnea-hypopnea index (AHI)</td>
<td>Frequency of apneic or hypopneic episodes per hour of sleep; it is a measure of sleep apnea severity.</td>
</tr>
<tr>
<td>Oxygen desaturation</td>
<td>Decrease of &gt; 3% in oxyhemoglobin saturation, often caused by apnea or hypopnea.</td>
</tr>
<tr>
<td>Obstructive sleep apnea-hypopnea syndrome</td>
<td>AHI &gt; five per hour of sleep accompanied by symptoms such as snoring, restless sleep, nocturnal dyspnea, morning headaches, excessive daytime sleepiness, and arterial hypertension.</td>
</tr>
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</table>
Hypertension

OSAHS is an independent risk factor for systemic arterial hypertension (SAH)\(^{52-47}\). SAH prevalence in OSAHS patients ranges from 40% to 90%, and the opposite, OSAHS prevalence in SAH patients, ranges from 22% to 62%\(^{44}\). Recent studies corroborate this high prevalence between both conditions\(^{45}\) and show that, in four years, subjects with apnea/hypopnea index (AHI) greater than fifteen per hour of sleep have a five-fold risk (45% likelihood) of developing SAH\(^{53}\). A study with 44 patients with drug-resistant hypertension showed that 83% had OSAHS\(^{45}\). OSAHS patients show great blood pressure (BP) variability during the night, and they may not experience the nocturnal dip observed in normal patients, resulting in higher mean night-time BP values, even when daytime BP is normal. This BP behavior may be due to negative intrathoracic pressure with reduced cardiac output and differential activation of baroreceptors, hypoxia, hypercapnia, breathing-related arousal and increased sympathetic activity\(^{50}\).

Continuous positive airway pressure (CPAP) has proved to be effective in the treatment of patients with OSAHS and SAH\(^{51,52}\). In a series of eleven patients with refractory SAH, CPAP reduced nocturnal blood pressure\(^{53}\). Furthermore, in twelve patients with severe OSAHS, the use of CPAP decreased plasma norepinephrine and urinary catecholamine metabolites\(^{54}\).

Thus far, therefore, OSAHS should be considered in the differential diagnosis of refractory systemic arterial hypertension, and the use of CPAP may help in reducing both daytime and night-time blood pressure\(^{55,56}\).

Cardiac arrhythmias

Some authors have already studied the relationship between OSAHS and cardiac arrhythmias\(^{57,58}\); however, there is no consensus in the medical literature concerning results\(^{57,58}\) and prevalence of tachyarrhythmia and bradyarrhythmia. This may be partly explained by the unknown incidence of OSAHS in the general healthy population and by the high incidence of hypertension and cardiovascular diseases in OSAHS patients. However, it is known that the use of CPAP in OSAHS patients may reduce cardiac arrhythmias, just as artificial cardiac stimulation may attenuate breathing disorders\(^{59,60}\). Figure 3 shows an example of sinus pause associated with apneic event in an OSAHS patient.

Atrial fibrillation (AF) deserves underscoring, because it has been studied in the largest number of clinical trials related to sleep-disordered breathing\(^{61-66}\). Its prevalence seems to increase in patients with OSAHS and congestive heart failure (CHF) or recent myocardial revascularization\(^{61,62}\). As already stated, OSAHS causes intermittent hypoxemia, sympathetic activation, and abrupt changes in blood pressure, which may be related to the development and recurrence of AF. In a prospective study\(^{62}\) of patients referred for electrical cardioversion of atrial fibrillation/atrial flutter, 82% of the untreated or inadequately treated OSAHS patients experienced recurrent AF, compared to 42% of the treated patients. Moreover, in the untreated group, recurrence was even higher among those who showed greater drop in oxygen saturation during the apneic event. These data suggest that appropriate treatment with CPAP may reduce AF recurrence in OSAHS patients.

Ventricular ectopies were reported in up to 66% of OSAHS patients. However, in a prospective study of 147 patients who underwent simultaneous polysomnography and Holter monitoring, no increase in ventricular arrhythmias was found\(^{67}\). In view of discrepant reports in the medical literature, it is difficult to establish a direct relationship between the syndrome and ventricular arrhythmias. Yet, analyzing the relationship between ventricular ectopies and oxyhemoglobin desaturation in patients with OSAHS\(^{45}\), a marked increase is found in ventricular ectopy frequency when oxygen saturation drops below 60%, and the relationship between apneic events and ventricular arrhythmias seems to exist solely in patients with important desaturation during the night.

Patients with this syndrome experience ventricular arrhythmias mainly during sleep, unlike patients with normal sleep\(^{68}\), and ventricular tachycardia is more common in OSAHS patients (0-15%) than in the general population (0-4%)\(^{69}\). Bradyarrhythmias are strongly associated with OSAHS. Guilleminault et al.\(^{70}\) have found sinus pause (> 2.5 seconds), second-degree atrioventricular block, and sinus bradycardia in 11%, 8%, and 7% of the patients, respectively. Koehler et al.\(^{71}\) analyzed factors involved in heart blocks in patients with OSAHS and concluded that most cases occur during REM sleep and periods with oxygen desaturation of at least 4%.

Despite conflicting reports in the literature, oxygen saturation drop during apneic episodes seems to be an important factor triggering cardiac arrhythmias in patients with sleep apnea-hypopnea syndrome, and its frequency is associated with hypoxia severity.

Coronary artery disease

Despite the growing incidence of OSAHS and the concomitant increase in cardiovascular mortality\(^9\), most studies face important limitations, because many risk factors, such as obesity, masculine gender and age, among others, are the same as those for hypertension and coronary artery disease (CAD). Therefore, it seems difficult to pinpoint the risk for CAD attributed to OSAHS; however, convergent observations suggest that OSAHS is an important factor associated with CAD.

In OSAHS, the increase in peripheral sympathetic nerve activity during sleep to twice the normal values persists during wakefulness\(^{72}\) and may contribute to acute coronary events in the early morning hours. In
addition to autonomic nervous system involvement, both the inflammation and endothelial injury observed in OSAHS are likely to participate in the mechanisms involved in CAD73.

In a well-conducted study evaluating the impact of OSAHS therapy on long-term cardiovascular outcomes (86.5 ± 39 months) in CAD patients, those appropriately treated experienced a significant reduction in cardiovascular event risk, defined as cardiovascular death, acute coronary syndrome, admission for heart failure, or need of myocardial revascularization74.

Nocturnal ST-segment changes consistent with myocardial ischemia are common in patients with OSAHS and CAD. Mooe et al75 evaluated the occurrence of nocturnal myocardial ischemia and its relationship to sleep-related breathing disorders. ST-segment depressions occurred in 31% of the patients studied. Temporal association between electrocardiographic findings and apneic events was found in 19% of the cases, more frequently in men (p < 0.01) and in more severely disordered breathing.

### Stroke

Among stroke patients, sleep-disordered breathing incidence, the obstructive form predominantly, may exceed 50%76. It remains quite unclear, however, whether these events detected after stroke are a consequence of the cerebrovascular event or a preexistent condition. As with coronary artery disease, OSAHS and stroke also share many risk factors, and it is equally difficult to prove a cause-effect relationship.

Dziewas et al77 analyzed the frequency of sleep-disordered breathing in groups of patients with first and recurrent ischemic stroke. Patients with recurrent stroke showed higher mean apnea-hypopnea index (AHI) when compared to patients with first-ever stroke (26.6/h vs. 15.1/h, p < 0.05) and most commonly had OSAHS. In the multivariate analysis adjusted for clinical variables and risk factors, sleep apnea was considered an independent risk factor for stroke recurrence, and the authors advocate the use of polysomnography in this group of patients for risk stratification.

OSAHS most probably contributes to recurrent stroke through several mechanisms, such as systemic arterial hypertension, increased platelet aggregation, blood hypercoagulability, and endothelial dysfunction, among others. Moreover, blood flow to the brain declines during apnea, due to reduction in cardiac output, which may predispose risk subjects to stroke, such as those with atheromatous lesions in carotid and vertebral circulations. This may be significantly more important during REM sleep, when brain oxygen demand is higher.

In addition, apnea may impair cognitive function in patients with previous history of stroke, since it causes excessive daytime sleepiness and poor concentration.
Inflammatory, endothelial, and thrombotic changes in OSAHS

Decline or absence of physiological mechanisms involved in vascular relaxation was demonstrated in response to endothelium-dependent substances (increased vasoconstrictor, endothelin, and reduced nitric acid and prostacyclin availability)²⁴,⁸⁵. Another evidence of endothelial damage was documented by enhanced expression of adhesion molecules, leading to increased adherence of monocytes to endothelial cells⁶⁸. OSAHS may also trigger recurrent oxidative stress⁸⁷, probably owing to greater production of oxygen-reactive species by monocytes and granulocytes. These findings reinforce previous results regarding increased production of superoxide radicals from polymorphonuclear neutrophils in patients with OSAHS⁶⁸ and low levels of nitric oxide⁶⁹. Plasma homocysteine levels were also reported to be elevated in this syndrome⁹⁰, as a result of endothelial dysfunction combined with excessive production of free radicals. Serum haptoglobin and amyloid A protein were also reported to be higher⁹¹,⁹².

The relationship between inflammatory process and cardiovascular diseases has been repeatedly postulated⁹³. OSAHS patients are chronically exposed to recurrent hypoxia and sleep fragmentation, showing increased C-reactive protein and interleukin-6 levels, when compared to controls⁹⁴. It is also likely that C-reactive protein levels in these patients are higher because of associated obesity⁹⁵. All these endothelial, blood clotting, and inflammatory changes may contribute somewhat to higher cardiovascular risk and atherogenesis in OSAHS patients. Finally, CPAP therapy may improve these changes; however, discontinuation of therapy leads to the reappearance of abnormalities⁹⁶-¹⁰³.

REFERENCES


