Physiopathology of obstructive sleep apnea-hypopnea syndrome*

Andrea Barral Martins¹, Sérgio Tufik², Sonia Maria Guimaraes Pereira Togeiro Moura³

Abstract
The physiopathology of obstructive sleep apnea-hypopnea syndrome is multifactorial. Gender and obesity status, as well as genetic, anatomic, and hormonal factors, together with respiratory drive, interact in a diverse manner in the physiopathology and clinical expression of the disease. Obesity is the main risk factor, since increases in body mass index, visceral fat, and neck circumference are strong predictors of the disease. Progesterone increases the activity of the upper airway dilator muscles and therefore plays a protective role in premenopausal women. This explains the fact that the prevalence of the disease is higher in postmenopausal patients with polycystic ovary syndrome, as well as in males. Evidence supports the fact that, as individuals grow older, there is a decrease in muscle tonus, with a consequent reduction in the dimensions of the upper airway lumen. Craniofacial anomalies, such as in retrognathia or micrognathia, are accompanied by posterior positioning of the tongue and can result in narrowing of the upper airway lumen. Finally, decreased respiratory drive has been detected in patients with obstructive sleep apnea-hypopnea syndrome and hypercapnia.

Keywords: Sleep apnea obstructive/physiopathology; Body mass index; Obesity.

* Study carried out at the Universidade Federal de São Paulo (UNIFESP, Federal University of São Paulo) – São Paulo, Brazil.
1. Postgraduate student in Sleep Medicine at the Universidade Federal de São Paulo (UNIFESP, Federal University of São Paulo) – São Paulo (SP) Brazil.
2. Full Professor of Biology and Sleep Medicine at the Universidade Federal de São Paulo (UNIFESP, Federal University of São Paulo) – São Paulo (SP) Brazil.
3. Professor responsible for the specialization course in Sleep Medicine, Department of Biology and Sleep Medicine Universidade Federal de São Paulo (UNIFESP, Federal University of São Paulo) – São Paulo (SP) Brazil.
Correspondence to: Sônia Maria G. P. Togeiro. Rua Napoleão de Barros, 1.113, Vila Clementino, CEP 04024-000, São Paulo, SP, Brasil.
Phone 55 11 5083-7664. E-mail: sonia@psicobio.epm.br
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Introduction

This review aims to analyze the principal articles in the literature regarding the pathophysiology of obstructive sleep apnea-hypopnea syndrome (OSAHS). We address the concept of the disease and the influence of sleep on respiration, as well as the interaction of anatomical, functional, genetic and neural factors in its genesis (Chart 1).

Concept

Individuals with OSAHS present recurrent episodes of partial or complete upper airway obstruction during sleep. Despite inspiratory effort, airflow is decreased (hypopnea) or completely interrupted (apnea). The lack of adequate alveolar ventilation generally results in oxyhemoglobin desaturation and, in cases of prolonged events, in a progressive increase of arterial carbon dioxide tension (PaCO$_2$). These respiratory events are normally interrupted by micro-arousals. According to the American Academy of Sleep Medicine criteria, OSAHS should be suspected in patients presenting excessive daytime sleepiness unattributable to other factors, as well as in those presenting at least two of the following symptoms, likewise unexplained by other factors: choking during sleep, recurrent arousals, nonrestorative sleep, daytime fatigue/difficulty in concentration and five or more obstructive respiratory events per hour of sleep, as determined through all-night polysomnography. These events can be, variously, episodes of apnea, hypopnea or respiratory effort related to awakening.

Anatomy

The upper airways are divided into four anatomical subsegments: the nasopharynx, located between the nostrils and hard palate; the retropalatal pharynx,
located between the hard palate and soft palate; the oropharynx, which extends from the soft palate to the epiglottis; and the hypopharynx, which extends from the base of the tongue to the larynx.

The last three subsegments compose the collapsible portion of the pharynx. The absence of bone and cartilage in these segments enables their lumen to remain permeable due to the action of muscles, which actively constrain and dilate the lumen of the upper airways. Soft tissue structures, including the tonsils, soft palate, uvula, tongue and lateral wall of the pharynx, form the walls of the upper airways. The principal craniofacial bone structures that determine the dimensions of the upper airways are the mandible and hyoid bone. It is believed that the muscles and soft tissues are supported by these structures.

Measurements of the tranverse area of the various upper airway segments can be taken in different ways: acoustic reflection; conventional or high resolution tomography; or magnetic resonance imaging. Studies using these various techniques have obtained a great diversity of values. That simple difference in the findings might be justified by individual variability, but also by the different locales of measurement. There is a consensus that the smallest upper airway diameter during wakefulness is found in the retropalatal oropharynx, which makes this point a potential locale for its collapse during sleep. However, it is known that obstruction can occur, either simultaneously or sequentially, in any of the four subsegments.

**Respiration and Sleep**

Pulmonary ventilation is controlled by two systems: an automatic one located in the brainstem; and a voluntary one in the cerebral cortex. The central chemoreceptors are sensitive to variations in pH; the increase of carbonic gas reduces pH, thereby stimulating those receptors. The peripheral chemoreceptors are sensitive to a decrease in arterial oxygen tension and in pH. Those chemoreceptors stimulate the respiratory centers located in the brainstem and control ventilation in an automatic or metabolic manner. Voluntary control is capable of dominating the function of the brainstem, within certain limits. For example, we can reduce PaCO₂ through voluntary hyperventilation. However, hypoventilation is more difficult, since the interruption of ventilation is limited by metabolic factors.

The increase in PaCO₂ stimulates the respiratory center and increases ventilation. Active hypercapnia activates the upper airway dilator muscles and decreases their collapsibility by increasing the tension of the upper airway walls.

During sleep, the only respiratory control system that is active is the automatic one. Therefore, respiration during sleep depends on metabolic factors as well as on the activation of central and peripheral chemoreceptors. Sleep reduces the sensitivity of the chemoreceptors, de-activates bulbar neurons and decreases overall motor activity, i.e. there is relaxation of the muscles, including those of the upper airways. Those phenomena are well tolerated by normal people, although they can lead to respiratory disorders in some individuals.

Some OSAHS patients present chronic hypoxemia, which can affect the synthesis and activity of various neurotransmitters, thereby altering the function of central and peripheral chemoreceptors responsible for ventilatory control. It is believed that the alterations resulting from sleep disorders perpetuate themselves during wakefulness. Patients with OSAHS and hypercapnia present a lower ventilatory response to hypercapnia, even during wakefulness. However, when treated with nasal continuous positive airway pressure, such patients present an increase in the diurnal ventilatory response to hypercapnia and to hypoxemia, which improves diurnal gas exchange. However, respiratory drive is within normal parameters in patients with OSAHS and normocapnia.

The alterations that occur in ventilation during sleep depend on the phases of sleep. In stages 3 and 4, ventilation is extremely regular with no alteration of the flow volume and respiratory frequency. In a normal individual, there are no apnea episodes in slow-wave sleep. In rapid eye movement (REM) sleep, ventilation becomes irregular with variable flow volume and respiratory frequency, there is a loss of upper airway muscle tonus in relation to non-REM (NREM) sleep and, at certain moments, the arousal threshold can be high. Therefore, REM sleep is the moment of greatest risk for patients presenting severe, prolonged episodes of sleep apnea. Episodes of apnea and hypopnea occur at maximum frequency during REM sleep, stage 1 NREM sleep and stage 2 NREM sleep. Occasionally,
Apnea is more frequent in NREM sleep than in REM sleep. However, even in such patients, those events that occur in REM sleep are more severe and are longer in duration.\(^2\)

In calm respiration, the lungs are actively inflated through the contraction of the diaphragm, the external intercostal muscles and the accessory muscles involved in inspiration. In that process, other muscles play a small role. Such muscles include the muscles of the nasal alae, which promote the opening of the nostrils, and the small muscles of the neck and head, i.e. the upper airway muscles (larynx and pharynx).\(^{2,7}\) The coordinated activation of those muscles maintains the permeability of the segments of the airways that are prone to occlusion. A wave of activation begins at the muscles of the nasal alae and moves caudally, preceding inspiration. If the activity of the upper airway muscles are uncoordinated or reduced, the negative pressure generated by the contraction of the diaphragm can exceed the support pressure of the pharyngeal abductor muscles and cause occlusion or subocclusion of the pharynx.\(^7\)

In variable extrathoracic obstruction of the upper airways, there is a tendency toward collapse during inspiration, whereas they remain open during expiration.\(^6\)

Therefore, considering the upper airway architecture as an extrathoracic structure, the most critical moment of the respiratory cycle for collapse would be inspiration. However, among OSAHS patients, there is an accentuated reduction in upper airway diameter at the end of expiration, so that period should also be considered critical.\(^9\)

Negative intrathoracic pressure is transmitted to the upper airways during inspiration, thereby promoting a reduction in the transverse area of the pharynx.\(^2\) The permeability of the upper airways is maintained through the balance between intrathoracic pressure and the abduction force of the pharyngeal muscles.\(^2\) During wakefulness in normal individuals, the dimensions of the upper airways remain practically constant throughout inspiration, being smallest at the end of expiration. Inspiration is the period of ventilation in which the pharyngeal dilator muscles are most active to maintain pharyngeal permeability. It is believed that the upper airways are more compliant and collapse more easily in OSAHS patients, which is why the dilator muscles are more active during wakefulness and why there is a decrease in activity during sleep.\(^9\)

In normal individuals, high negative intrathoracic pressure is necessary for the upper airways to collapse, whereas, in OSAHS patients, such collapse occurs at slightly negative pressures or even positive pressures.\(^{2,9}\)

**Pathophysiology**

**Age**

The effect of age on OSAHS prevalence in the general population merits greater clarification. Studies involving men and women between 20 and 100 years of age have been carried out in order to identify age-specific prevalences. Among women, those over 65 years presented the highest prevalence of OSAHS, whereas the highest prevalence in men was seen among those in the 45 to 64 age bracket.\(^{10,11}\) When the sample was stratified by decade of age, was assessed by classifying the sample by decade, a peak in the prevalence was observed in women from 60 to 69 years of age and in men from 50 and 59 years of age.\(^{10,11}\) With respect to severity, one study shows that OSAHS is less severe in the elderly than in the young, which suggests that the diagnostic criteria should be adjusted for age.\(^{11}\)

It is known that aging correlates positively with obesity and neck circumference, i.e., body weight and neck circumference increase with age; it is also known that obesity and increased neck circumference are risk factors for sleep apnea.\(^{12}\) The data regarding age-related changes in the activity of the pharyngeal dilator muscles are controversial. Some studies show similarities between the young and elderly during sleep and wakefulness, whereas more recent studies have demonstrated decreased activity of these muscles in the elderly.\(^2\) Some authors showed that upper airway diameter decreases with aging both in men and women.\(^{12}\)

In women, aging also leads to another very important risk factor, menopause.\(^{10}\)

**Gender**

The prevalence of sleep apnea is greater in men than in women. Using clinical criteria and polysomnography, the prevalence was found to be 1.2% in women and 3.9% in men.\(^{10}\) Estimates show that the male/female ratio varies from 2:1 to 4:1.\(^{10}\)
The prevalence of sleep apnea is higher in menopausal women than in premenopausal women. However, the prevalence is still significantly lower in menopausal women than in men when adjusted for age and body mass index (BMI). Hormone replacement therapy for postmenopausal women seems to be associated with a lower prevalence of sleep apnea and makes the prevalence of sleep apnea in postmenopausal women equal to that seen in premenopausal women. Some authors showed that, among women presenting OSAHS, 100% of premenopausal women were obese (BMI > 32.3 kg/m²), as were 100% of postmenopausal women undergoing hormone replacement therapy. However, the prevalence of obesity in postmenopausal women not undergoing hormone replacement therapy is similar to that observed in men of the same age (49.4% vs. 42.1%). This confirms, once again, that age, obesity and menopause are risk factors for sleep apnea.

Another difference between the genders is related to genioglossus muscle tone, which is believed to be greater in women, suggesting a defense mechanism for the maintenance of upper airway permeability. Therefore, in the dorsal decubitus position, men present a greater reduction in the dimensions of the upper airway lumen than do women. Another situation corroborating this hypothesis is that, when there is an increase in neck circumference due to fat accumulation, the transverse diameter of the upper airways remains greater in women than in men, suggesting once again that women present a better defense mechanism.

**Anatomical factors**

Alterations in the external anatomy of the head and neck can be risk factors for developing OSAHS, irrespective of obesity. Craniofacial anamolies can involve a delay in the development of the mandible, which produces mandibular retroposition. This micrognathia or mandibular hypoplasia is associated with the posterior positioning of the base of the tongue, which narrows the upper airways. The presence of an ogival palate in individuals with OSAHS is also common because the posterior position of the tongue can force the lateral palate processes to expand over the tongue, wrongly positioned, before the fusion of the middle line. In the Kushida morphometric model, in addition to the height of the palate, the 'overjet' (the horizontal anteroposterior distance from the upper incisors to the lower incisors) is taken into consideration, as is the distance between the second maxillary and mandibular molars (in millimeters). Those measurements can indicate a small oral cavity, which can result in narrowing of the upper airway and predispose the individual to OSAHS. These alterations occur independently of patient weight, which explains the presence of OSAHS in slim individuals.

In normal individuals, the upper airways present a lateral diameter larger than the anteroposterior diameter. In OSAHS patients, the inverse occurs: the lateral diameter becomes smaller than the anteroposterior diameter, which corresponds to a narrowing at a critical point, i.e., the retropalatal airway. The structures that can cause that effect are the lateral pharyngeal walls and the lateral pharyngeal fat pad. The lateral pharyngeal walls are thicker in OSAHS patients. This finding led some authors to conclude that the thickening of the lateral pharyngeal walls rather than the size of the tongue, tonsils or soft palate is the principal causative anatomical factor of upper airway narrowing in OSAHS patients. However, the explanation for the narrowing of the lateral walls is unknown. There is speculation that the muscle mass of the lateral walls...
increases due to the weight gain or ‘respiratory exercise’ that occurs in sleep apnea, or even due to a fold in the pharyngeal wall (which can be reversed by using continuous positive airway pressure).

**Body fat**

Obesity is an important pathogenic factor in sleep apnea. Approximately 70% of OSAHS patients are obese, and obesity is the only significant risk factor that is reversible. Obesity is evaluated by measuring BMI and classifying individuals based on the degree of obesity, beginning with type 1 obesity (BMI > 25 kg/m²). Some authors have stated that a BMI of > 30 kg/m² is a risk factor for obstructive sleep apnea.

Other studies have shown that central obesity, reflected by the waist/hip ratio, is a similar or even better predictor for sleep apnea than is BMI, and that the correlation between abdominal and neck circumference is a very significant factor, which lends credence to the idea that apnea is directly related to central obesity. The body circumference indices identify individuals presenting central obesity patterns that increase the risk of having problems related to obesity, regardless of BMI. Central or visceral obesity has been more frequently associated with apnea than have other forms of obesity. Some authors analyzed the distribution of body fat using magnetic resonance imaging of the neck and abdomen in patients under clinical suspicion of having sleep apnea. The results showed a significant correlation between sleep apnea and the quantity of intra-abdominal fat, as well as a borderline correlation between sleep apnea and subcutaneous abdominal fat and no correlation between sleep apnea and parapharyngeal or subcutaneous fat in the neck region.

Abdominal circumference is measured at the height of the umbilicus, while standing, at the end of expiration. Abdominal obesity, a risk marker, is defined as an abdominal circumference > 94 cm in men or > 80 cm in women. An abdominal circumference > 102 cm in men or > 88 cm in women indicates a high risk of arterial hypertension, dyslipidemia, diabetes mellitus and cardiovascular disease.

Neck circumference is a predisposing factor for OSAHS. In one study, the cut-off point was estimated at 40 cm, and other authors later identified the ideal locale of measurement as being the cricothyroid membrane. It is assumed that the increased deposition of fat or soft tissue in the region of the neck or adjacent to the upper airways is responsible for sleep apnea in obese individuals. A large neck circumference probably reflects greater deposition of fat and soft tissue, which is more significantly associated with sleep apnea. Among other conditions, acromegaly, Down’s syndrome, hypothyroidism, genetic syndromes and deposition diseases (such as mucopolysaccharidoses and amyloidosis) can promote upper airway narrowing, which is a predisposing factor for sleep apnea.

Leptin is an antioesity hormone that is predominantly produced by the white fatty tissue. High leptin levels are correlated with adiposity indices, including BMI and percentage of body fat. Leptin bonds with specific receptors in the hypothalamus and changes the expression of neuropeptides that regulate neuroendocrine functions such as caloric intake and energy expenditure. A large percentage of obese people have high levels of circulatory leptin, which indicates that obesity is a state of resistance to leptin in many situations. It is possible that defects in receptors and nonreceptors are responsible for leptin resistance in the obese. Studies suggest that obesity and obstructive apnea are both related to the aforementioned resistance.

**Female and male hormones**

There is some evidence that hormonal status might influence the dilatory activity of upper airway muscles. In premenopausal women, the musculature of the genioglossum is highly active in comparison to that seen in postmenopausal women and in men of the same age. It is therefore believed that, prior to menopause, progesterone might be protective against sleep apnea. The highest progesterone levels are seen in the luteal phase of the menstrual cycle. In that period, women experience an increase in respiratory drive, which shows one of the functions of that hormone. Exogenous progesterone has been associated with a slight but definitive improvement in ventilation during sleep in men and women with sleep apnea. Another important hormone is estrogen, and its administration is associated with a decrease in plasma levels of interleukin 6, which are higher in patients with sleep apnea. Therefore,
the prevalence of OSAHS is lower in postmenopausal women undergoing hormone replacement therapy (receiving progesterone and estrogen), since they have two protective mechanisms.

In contrast, the exogenous administration of testosterone in women and healthy men has been associated with greater upper airway collapsibility, thereby inducing sleep apnea without causing weight gain.\(^{10,21,22}\) It is believed that high levels of androgens might alter the composition of body fat and lead to a greater deposit of soft tissue in the pharynx, which can also result in relaxation of the pharyngeal dilator muscles.\(^{21}\) Apnea is resolved after the exogenous withdrawal of the hormone or, in cases of tumors that produce testosterone, after tumor resection.\(^{10}\)

Testosterone plays another important role at the central level, in the central chemoreceptors that control ventilation.\(^{22}\) When an individual hyperventilates voluntarily or is in a high altitude situation (attempting to capture more oxygen in rarefied air), the level of \(\text{PaCO}_2\) lowers, and the central chemoreceptors understand that ventilation is no longer necessary, resulting in central apnea. The lowest level of \(\text{PaCO}_2\) capable of causing central apnea varies individually. However, we know that the threshold for hypocapnic apnea is lower in women than in men, i.e. women tolerate a much lower \(\text{PaCO}_2\) level than do men. Although the exact role testosterone plays in the central chemoreceptors is unknown, one hypothesis is that it increases the sensitivity of the chemoreceptors to minimal variations in \(\text{PaCO}_2\).\(^{22}\)

Some authors conducted a study involving eight premenopausal women receiving testosterone. They showed an increase in the hypocapnic threshold and a facilitation of the development of central apnea when ventilatory alterations were caused during NREM sleep. The mechanism of action of testosterone was related to the increase in sensitivity of the central chemoreceptors, since there was insufficient time for the development of anatomical alterations in the upper airways.\(^{22}\)

Polycystic ovary syndrome (POS) is an endocrine disorder that is more common in premenopausal women. Some authors compared eighteen young obese POS patients with eighteen healthy young women, paired by weight and age, and concluded that those in the first group had a significantly higher chance of developing sleep apnea than did those in the control group.\(^{21}\)

Another study, involving 53 women with POS and a control group, showed a much higher prevalence of sleep apnea in the group of POS patients, at a ratio of 30:1. The authors of that study also concluded that even nonobese premenopausal women with POS presented a higher prevalence of sleep apnea.\(^{23}\) The use of oral contraceptives seems to protect women with POS from developing OSAHS.\(^{23}\) There are studies showing that women with OSAHS have a higher level of circulating androgen hormones than do normal women paired by age and weight.\(^{21}\)

Therefore, women diagnosed with POS should be carefully investigated for signs and symptoms related to sleep-disordered breathing. We can conclude that, in relation to sleep apnea, female hormones are protective and male hormones are harmful.

**Genetic factors**

Familial aggregation for OSAHS has been shown in studies involving families with various affected members. Genetic factors related to craniofacial structure, distribution of body fat, neural control of the upper airways and the central respiratory drive interact to produce the phenotype of the syndrome.\(^{24}\) Therefore, members of the same family that share those genetic characteristics might present OSAHS. The prevalence of OSAHS in first-degree relatives of OSAHS probands varies from 22 to 84% in the various studies. Therefore, the importance of investigating family history in the evaluation of patients is quite evident.\(^{25}\)

The literature suggests that ethnic factors must be considered in the investigation of individuals with OSAHS, since there are cephalometric differences that can influence the pathogenesis of the disease. One recent study suggests that the anthropometric measurement of the head is an important criterion for evaluating the susceptibility to OSAHS.\(^{26}\) Specific genes responsible for the development of OSAHS have yet to be identified.

**Conclusion**

The prevalence of OSAHS is high, and the clinical expression of the disease is variable. Anatomical, functional, neural and genetic factors interact in its genesis (Chart 1).
References