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OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR DISEASES

APNEIA OBSTRUTIVA DO SONO E DOENÇA CARDIOVASCULAR

Luciano Ferreira Drager[1,2]
Dalva Poyares[3]

1. Department of Internal Medicine, School of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.
2. Hypertension Unit, Instituto do Coração (InCor), São Paulo, SP, Brazil.
3. Department of Psychobiology, Universidade Federal do Estado de São Paulo, São Paulo, SP, Brazil.

Correspondência:
Luciano Ferreira Drager, Instituto do Coração, Hypertension Unit. Av. Dr. Enéas de Carvalho Aguiar, 44, 2º andar, Bloco II. CEP: 05403-900.
luciano.drager@incor.usp.br

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ABSTRACT

Obstructive sleep apnea (OSA) is a prevalent condition that has been associated with several cardiovascular sequelae, among which hypertension is the best documented condition. However, coronary artery disease, cardiac arrhythmias, stroke and increased risk for cardiovascular mortality have been described in the literature in both the general population and in clinical settings, with different levels of evidence. We also emphasize the higher prevalence of OSA in patients with established cardiovascular disease, possibly due to the coexistence of common risk factors such as age, male sex and overweight/obesity. In this article we will briefly discuss the association of OSA and each of these clinical conditions, as well as the current evidence for the effect of OSA treatment with continuous positive airway pressure (CPAP) on the prevention of cardiovascular outcomes and mortality.

Keywords: Sleep Apnea; Obstructive; Hypertension; Cardiovascular Diseases; Disease Prevention.

RESUMO

A apneia obstrutiva do sono (AOS) é uma condição prevalente, que tem sido associada com diversas consequências cardiovasculares, sendo a hipertensão arterial a mais bem descrita. Entretanto, doença arterial coronariana, arritmias cardíacas, acidente vascular cerebral e risco aumentado de mortalidade cardiovascular têm sido descritos na literatura em populações clínicas e na população geral, com diferentes níveis de evidência. Ressaltamos também a maior prevalência de AOS em pacientes com doenças cardiovasculares estabelecidas, possivelmente explicada pela coexistência de fatores de risco comuns tais como a idade, o sexo masculino e o sobrepeso/obesidade. Neste artigo discutiremos brevemente a associação de AOS e cada uma dessas condições clínicas, bem como o que há de evidência até o momento para o efeito do tratamento da AOS com a pressão positiva contínua de vias aéreas (CPAP) na prevenção dos desfechos cardiovasculares e mortalidade.

Descritores: *Apneia Obstrutiva do Sono; Hipertensão; Doenças Cardiovasculares; Prevenção de Doenças*

INTRODUCTION

Obstructive sleep apnea (OSA) is one of the most common sleep disorders. It is characterized by intermittent collapse of the upper airways during sleep, causing total obstruction (apnea) and partial obstruction (hypopnea).[1] Breathing pauses lead to increased respiratory effort and generate reduced intrathoracic pressure that increases the transmural pressure of the left ventricle, cyclic drops in oxygen saturation (known as intermittent hypoxia), hypercapnia (usually mild), and sleep fragmentation.[2] Among these characteristics, intermittent hypoxia is considered one of the main factors leading to adverse cardiovascular repercussions during sleep.[2] The mechanisms involved include activation of the sympathetic nervous system, systemic inflammation, increased production of reactive oxygen species, endothelial dysfunction, and insulin resistance, among others.[2]

The prevalence of OSA in the general population is high and depends on the diagnostic criteria. In adults, it affects about 9.6% of women and 24.8% of men.[3] In patients with systemic arterial hypertension (SAH), it is estimated to affect around 56%.[4] In resistant hypertensive patients, OSA is the most commonly associated condition, with a prevalence of 64%.[5] OSA is probably the most common cause of secondary SAH.[5] This higher prevalence of OSA in patients with cardiovascular disease is partially explained by the coexistence of common risk factors, such as age, male sex, and overweightness/obesity.

The gold standard treatment for moderate to severe OSA is the use of a device to provide continuous positive airway pressure (CPAP). Positive pressure ensures the maintenance of upper airway patency during sleep, leading to an increase in nocturnal oxyhemoglobin saturation and decrease in arousals

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related to respiratory events.[1] Given that it promotes a significant reduction in respiratory events in OSA, CPAP has been the most studied treatment when evaluating the cardiovascular consequences of this sleep disorder in non-randomized and randomized studies. Thus, this article aims to describe the cardiovascular consequences of OSA, focusing on the treatment of this sleep disorder and the potential preventive effect of this treatment on cardiovascular diseases.

OSA AND SYSTEMIC ARTERIAL HYPERTENSION (SAH)

Episodes of apnea and hypopnea are associated with cyclic increases in blood pressure (BP). Another OSA-associated pattern is the "non-dipper" pattern, characterized by a reduction or absence of the nocturnal decrease in BP associated with OSA.[6] This BP pattern is considered a risk factor for the onset of cardiovascular disease. Recent data suggest that changes in the pattern of nocturnal fall in BP, especially in the riser BP patternw (mean BP higher while asleep than while awake), increases the chance for the presence of OSA by approximately three to four times.[6] Moreover, OSA is associated with target organ damage, which is usually attributed to SAH.[7] The Wisconsin cohort showed an independent association between the presence of OSA in the initial assessment and onset of SAH in the follow-up, with a dose-response relationship between OSA severity and risk of onset of SAH.[8] Consistent with this, a Spanish cohort study with a mean follow-up of 12.2 years also showed an independent association between the most severe forms of OSA and the incidence of SAH.[9] Interestingly, a subgroup of patients treated with CPAP showed a protective effect against the onset of SAH (Figure 1).

Regarding the effect of OSA treatment on BP, the results are generally modest, which is partially explained by the inclusion of both normotensive and hypertensive patients and that adherence to the use of CPAP was not always adequate.[10] In a meta-analysis (1166 participants), it was found that treatment of OSA with CPAP led to a reduction in systolic blood pressure of 3.20 mmHg (95% CI: -4.67 to -1.72) and a reduction in diastolic blood pressure of 2.87 mmHg (95% CI: -5.18 to -0.55).[11] Randomized studies have shown that the impact of OSA treatment on blood pressure is greater in patients with resistant hypertension (around 5 mmHg on average), but in general it does not lead to pressure control in these patients.[12,13] When only randomized studies (n = 309) were considered, a reduction of 3.9 mmHg in mean 24-hour systolic blood pressure with CPAP versus drug therapy (95% CI: -7.1 to -0.8, p = 0.014) and a reduction of 3.5 mmHg in the mean 24-hour diastolic blood pressure versus drug therapy (95% CI: -5.3 to -1.6) were observed.[14] Interestingly, a study showed that the presence of changes in the nocturnal fall in BP was a predictor of better CPAP response regarding the reduction of BP in patients with OSA.[15]

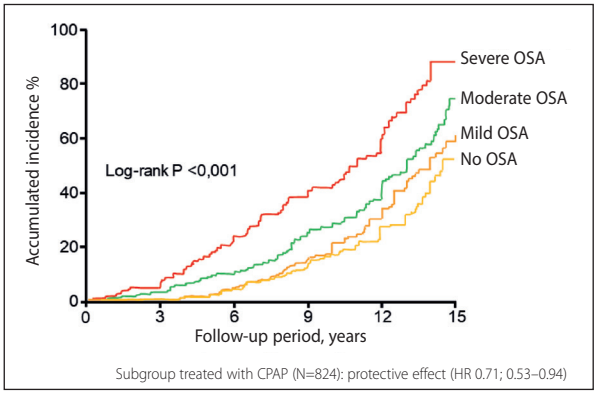

Figure 1. Presence of OSA and incidence of SAH. Modified from Marin et al. JAMA 2012.[9]

ARRHYTHMIAS

Growing evidence correlates the presence of OSA with various types of arrhythmias.[16] For example, the occurrence of bradycardia associated with apneic and hypopneic events leads to parasympathetic hyperactivation to reduce oxygen consumption by the cardiac muscle in the context of hypoxemia. When hypoxemia occurs in the absence of ventilation, stimulation of the carotid chemoreceptors has a vagotonic effect causing bradycardia. When ventilation is restarted, even in the presence of hypoxemia, stretching of the lung receptors inhibits vagal pacing, which results in tachycardia mediated by non-antagonized cardiac sympathetic discharge.[16] Furthermore, apnea simulates the "diving reflex," which is associated with bradycardia resulting from parasympathetic hyperactivation.[16]

The prevalence of bradyarrhythmias in patients with OSA depends on the severity of OSA and predisposing factors.[17] Koehler et al. observed second- or third-degree atrioventricular block and/or sinus arrest greater than two seconds in 7% of patients with OSA, and the occurrence of bradyarrhythmias was associated with the degree of obesity and severity of OSA.[18] Roche et al. reported that nocturnal paroxysmal asystole were significantly more prevalent in patients with OSA than those without OSA (10.6% vs. 1.2%, respectively; p<0.02) and that it was positively associated with the severity of the disease.[19]

Treatment with CPAP in patients with OSA may bring benefits in reducing bradyarrhythmias, in some cases, avoiding the unnecessary implantation of pacemakers. In a study involving patients with OSA and nocturnal bradycardia (including episodes of pauses longer than two seconds and second- or third-degree atrioventricular block), there was a significant reduction in the number of episodes after treatment with CPAP, avoiding pacemaker implantation.[20] In patients with OSA continuously monitored using an implantable loop recorder, a reduction in the number of bradyarrhythmias was observed in the first eight weeks of CPAP therapy, and there was a progressive benefit in the following six months.[21] These data reinforce the importance of screening for OSA in patients with nocturnal bradyarrhythmias to prevent the performance of unnecessary procedures.

Atrial fibrillation (AF) and OSA: AF is the most frequent cardiac arrhythmia and is associated with significant morbidity and mortality. Due to its importance, an increasing number of investigations in recent years have associated AF with OSA, including paroxysmal AF and its chronic and persistent forms.[22,23] A meta-analysis including six studies (~4,000 patients) showed that patients with OSA diagnosed using polysomnography had about 40% higher risk of AF recurrence after catheter ablation than those without OSA.[24] Regarding the effect of OSA treatment on AF recurrence, two meta-analyses evaluated the overall effect of OSA treatment

with CPAP, finding a 40% reduction in the risk of recurrence.[25,26] Figure 2 shows the data from one of these studies. In this study, consecutive patients with acute AF who arrived at the emergency room and were successfully reverted underwent sleep evaluation to examine whether they had OSA.[27] At the end of one year, the researchers observed that patients with untreated OSA had a higher recurrence of AF when compared to the control group (without OSA). Interestingly, AF recurrence was significantly reduced in patients with OSA who underwent treatment with CPAP. (Figure 2)

Ventricular arrhythmias are more prevalent in individuals with OSA than in individuals without OSA. The apnea and hypopnea index and degree of nocturnal desaturation seem to be associated with the density of arrhythmias. Mehra et al. reported an increased prevalence of non-sustained ventricular tachycardia (5.3 versus 1.2%) and complex ventricular extrasystole (25 versus 14.5%) in individuals with OSA when compared to individuals without OSA, respectively. Moreover, individuals with OSA are three times more susceptible to unsustainable ventricular tachycardia and almost two times more susceptible to complex ventricular extrasystole.[28] At least two studies evaluating patients with OSA, heart failure, and ventricular arrhythmia showed that the treatment of OSA with CPAP can reduce the density of ventricular arrhythmias.[29,30]

OSA AND SUDDEN CARDIAC DEATH

The clinical significance of cardiac arrhythmias in OSA is also related to the possibility of more severe complications, including sudden cardiac death. OSA patients had an increased risk (2.6×) of sudden cardiac death during the night, which was a markedly different pattern from that of the general population without OSA, with a higher rate of fatal events during the day.[31] It is possible to speculate that the increased likelihood of non-fatal nocturnal myocardial infarction may be accompanied by increased risk of fatal myocardial infarction and sudden death. In more than 10,000 individuals, the presence of OSA and significant oxygen desaturation were associated with an almost doubled increase in the risk of sudden death, regardless of known risk factors.[32]

OSA AND STROKE

Stroke is the second leading cause of death worldwide. Most strokes (approximately 85%) are ischemic and result from a transient or permanent reduction in brain blood flow in a specific area of the brain. Subsequent brain injury with disruption of the blood-brain barrier initiates a cascade of inflammation, oxidative stress, excitotoxicity, and apoptosis. Several of these mechanisms have been described in OSA, which provides biological plausibility to infer that OSA contributes to the occurrence of stroke.[33] In fact, the association between OSA and stroke was confirmed in a meta-analysis including 12 prospective studies with 25,760 individuals in total reporting a 2.15 times higher risk (95% CI: 1.42–3.24) of stroke in individuals with marked OSA.[34]

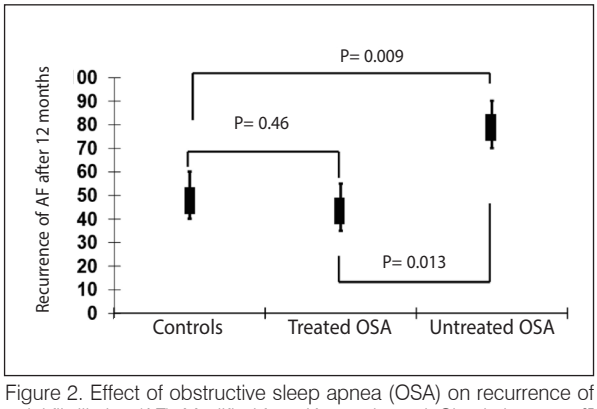

Figure 2. Effect of obstructive sleep apnea (OSA) on recurrence of atrial fibrillation (AF). Modified from Kanagala et al. Circulation 2003.[27]

Despite the small number of studies investigating the effects of CPAP in patients with OSA and stroke, it is still unclear whether the treatment of OSA with CPAP can reduce the risk of stroke in patients without previous cerebrovascular events.[35]

The results in patients who had previous coronary events or stroke are also conflicting. The multicenter SAVE Study addressed this issue including 2,717 patients aged between 45 and 75 years with a previous history of coronary disease or stroke and OSA. Patients were selected for treatment with CPAP or usual care for an average of 3.7 years. In this study, the use of CPAP did not prevent a new recurrence of stroke in the studied population compared to the group that received routine treatment. However, in a sub-analysis, a lower risk of a compound outcome was found for brain events in the group of patients who used CPAP for at least 4 hours/day (risk ratio: 0.52; 95% CI: 0.30–0.90; p=0.02).[36] A meta-analysis including the SAVE study and other smaller studies suggests that the treatment of OSA with CPAP may improve post-stroke neurofunctional parameters and potentially reduce the recurrence of stroke.[37]

OSA, CORONARY HEART DISEASE, AND CARDIOVASCULAR MORTALITY

Several observational studies have demonstrated that OSA is independently associated with an increased risk of myocardial infarction and cardiovascular mortality.[38-40] A recent meta-analysis of these studies found a hazard ratio of 2.21 for cardiovascular mortality (95% CI: 1.61 to 3.04; P= 0.000). However, an increase in cardiovascular mortality was not found in patients with moderate OSA (hazard ratio 1.40; 95% CI, 0.77 - 2.53) but only for severe OSA (hazard ratio 2.65; 95% CI, 1.82 - 3.85).[41]

It is important to highlight here the distinct pattern of the potential effect of CPAP treatment on cardiovascular morbidity and mortality. In patients without previous cardiovascular events, treatment with CPAP led to a reduction in the risk of fatal and non-fatal cardiovascular events in men (Figure 3)[38], the elderly[39], and women[40] with OSA.

However, in the secondary prevention setting, these data were not consistent. In the SAVE study,[36] a reduction in cardiovascular mortality was not observed in the treatment of OSA with CPAP. However, CPAP was used for about 3.3 hours per night. Although the effect on the main outcome (mortality) was neutral, the study revealed several important findings.[36] Although the patients included in the study were not highly symptomatic, there was improvement in the degree of sleepiness and symptoms of anxiety and depression in the group randomized to CPAP treatment. As already mentioned, in the subgroup of patients who

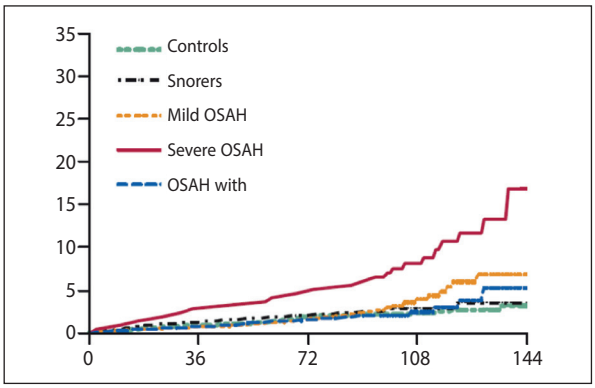

Figure 3. Impact of obstructive sleep apnea (OSA) treatment on primary prevention of fatal cardiovascular events in men. Modified from Marin et al. Lancet 2005.[38]

used CPAP for at least four hours per night, there was a decrease in the number of episodes of stroke.[36] This study shows the complexity of OSA and reinforces the need for good adherence to treatment to definitively understand the real impact of OSA treatment using CPAP on cardiovascular outcomes.[41]

CONCLUSIONS

The current literature suggests that OSA may predispose cardiovascular disease in the primary prevention setting, but the evidence is based on observational studies. In the secondary prevention setting, treatment of OSA can prevent recurrence of AF. However, in patients with previous cardiovascular disease, the increased risk attributed to OSA in observational studies was not confirmed by recent randomized trials. Thus, although OSA may not be an additional risk factor for cardiovascular diseases, the neutral effects of CPAP can be partially explained by the exclusion of severe hypoxemic patients and the low adherence to CPAP observed in these studies.[42] Therefore, additional efforts to improve the use of CPAP or the development of new treatments may help to understand the extent of the effect of OSA in cardiovascular disease and to promote the adoption of preventive measures in this regard.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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