Recent Advances of the Impact of Obstructive Sleep Apnea on Systemic Hypertension

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Abstract

Obstructive sleep apnea (OSA) is a common clinical condition in the general population, especially among patients with cardiovascular diseases. More than just a local phenomenon of upper respiratory tract obstruction, OSA leads to systemic consequences that may include intermittent hypoxia, sudden reduction of the intrathoracic pressure, and the occurrence of micro-awakenings with sleep fragmentation. In the past decades, innumerous evidences have consistently pointed to OSA as an important factor related to the presence of cardiovascular diseases. In particular, the relationship between OSA and systemic hypertension (SH) is the one supported by the largest body of evidence. Currently, there are data suggesting that OSA is an important secondary cause of SH. More importantly, OSA is independently associated with poorer blood pressure control, changes in sleep dip, and presence of target-organ damage such as left ventricular hypertrophy and microalbuminuria. Randomized studies suggest that the management of OSA, especially with continuous positive airway pressure (CPAP) - which is considered the standard treatment for OSA - promotes a significant 24-hour blood pressure reduction, and this effect is more significant in the subgroup of patients with uncontrolled SH and drug-resistant SH. Despite all those evidences, OSA has still been underdiagnosed. The objective of this review is to discuss the recent advances in the pathophysiological mechanisms, clinical presentation, and treatment of OSA, as well as the benefits this treatment can bring on blood pressure.

Introduction

Obstructive sleep apnea (OSA) is an important sleep-related breathing disorder characterized by recurrent obstruction of the upper airway leading to repeated breathing pauses either complete (known as apnea) or partial (known as hypopnea). The breathing pauses are associated with intermittent hypoxia, reduced intrathoracic pressure during breathing effort and frequent awakenings with subsequent sleep fragmentation[1]. The interest on this clinical condition has considerably increased in the past three decades, not only because of the obesity epidemics observed in different populations (which, concurrently, leads to an increased incidence of OSA), but also because of the consistent evidence that OSA is closely related to the occurrence of innumerous cardiovascular diseases. Among them, the relationship between OSA and systemic hypertension (SH) is the one more strongly supported by the literature. In 2002, we published the first review on OSA and SH in *Arquivos Brasileiros de Cardiologia*[2]. As from that first review, a large set of evidence stressed the importance of OSA in the pathophysiology, clinical presentation and outcome of the hypertensive patient. As a consequence, one year after that first review, the VII Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[3] included OSA as a new cause of secondary SH. The same procedure was adopted by the V Brazilian Guideline on Hypertension, published more recently[4]. In the present review, we will discuss the recent advances on epidemiological evidence, the pathophysiological mechanisms, clinical presentation (which includes the characteristics that help suspect OSA in hypertensive patients) and the management of OSA focused on the benefits regarding blood pressure. Also, we will outline some future perspectives of investigation that may contribute to increase our understanding of the impact of OSA on SH.

Keywords

Sleep apnea, obstructive/therapy; hypertension; cardiovascular diseases.

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Manuscript received May 05, 2010; revised manuscript received May 07, 2010; accepted September 20, 2010.

Epidemiology

Epidemiologic studies conducted in the United States have shown that OSA affects one in every four men and one in every ten women in the general population[5]. A study recently published in Brazil evaluated the prevalence of OSA in a sample of 1,042 individuals, representative of the population of São Paulo. The authors found alarming results: the diagnosis of 32.8% of the participants was consistent with OSA, thus suggesting that this disorder is much more common than estimated[6]. More than being a common clinical condition, OSA may have a serious impact on the quality of life of the patients, due to the possibility of causing excessive daytime sleepiness, impaired performance of daily activities,

irritability, mood lability, and others[7]. More recently, OSA has also been independently implicated in the increase in overall and cardiovascular mortalities[8-11].

Particularly in patients with SH, the prevalence of OSA is even higher than in the general population. In hypertensive individuals, the prevalence ranges from 38% to 56%[12,13] and may reach 82% in individuals with drug-resistant SH[14]. In one of these studies, Gonçalves et al[15] found a prevalence of OSA of 71% versus 38% in individuals with and without drug-resistant SH, respectively. Their article does not state that OSA necessarily leads to significant SH, but rather that the presence of OSA is common among hypertensive individuals. As will be further discussed in this article, in addition to being a common disorder, OSA actively participates in the modulation of blood pressure and in the outcome of hypertensive patients.

The epidemiologic study on the relationship between OSA and SH that has been the most frequently cited in the literature is the Wisconsin cohort, which assessed 709 normotensive individuals by polysomnography[16]. After a four-year follow-up, there was an increase in the incidence of SH in individuals with OSA. Also, the authors found a dose-response relationship between severity of OSA (as measured by the apnea-hypopnea index - AHI, see ahead) and the risk of development of SH. Patients with moderate and severe OSA (AHI ≥ 15 episodes per hour of sleep on polysomnography) showed an approximately three-fold increase in the risk of development of SH during the four-year follow-up in comparison to individuals not presenting any event during sleep. Other cohorts that followed showed results similar to those already described[17,18].

In the overall population, the risk factors for OSA include age between 40 and 70 years, male gender, obesity, presence of excessive sleepiness, snoring, structural abnormalities of the upper airways, alcohol abuse, and family history of OSA[19]. However, these risk factors may not be valid for specific populations such as those with cardiovascular diseases. In fact, recent evidences suggest that the male gender, excessive daytime sleepiness and snoring seem not to be good predictors of the presence of OSA in the population of hypertensive patients[13,20]. On the other hand, the presence of metabolic syndrome proved to be an excellent predictor of OSA in patients with hypertension[13].

Pathophysiology

Although the mechanisms through which OSA promotes increased blood pressure are not fully understood, several studies point to the possible involvement of factors such as neurohormonal activation, changes in the chemoreflex, decreased baroreceptor sensitivity, endothelial dysfunction, disorders of water and salt metabolism, and others[21] (Figure 1).

Neurohormonal activation in OSA includes increased sympathetic activity during sleep and wakefulness, as well as increased angiotensin II and aldosterone levels. This is probably the main mechanism involved in the genesis of SH in patients with OSA. Management of OSA based on the use of continuous positive airway pressure (CPAP) masks during the night results in a significant reduction of the sympathetic activity, as verified by determination of plasma and urine levels of norepinephrine, as well as by the fibular nerve activity[22], which permits the confirmation of the importance of this pathophysiological mechanism. Likewise, some studies have suggested that the treatment of OSA also contributes to a reduction of renin and angiotensin II levels[23].

The mechanisms involved in the increased sympathetic activity in OSA are apparently linked to the chemoreflex activation, which is the predominating mechanism in the regulation of the ventilatory and circulatory response to changes in arterial oxygen (O_2) and carbon dioxide contents (CO_2)[24]. The chemoreflex activation leads to an increase in sympathetic activity, heart rate, blood pressure and minute-volume[25]. The carotid body, which is the first chemoreceptor to detect changes in partial arterial O_2 pressure, mediates the reflex increase in sympathetic activity and blood pressure during chronic intermittent hypoxia. There is evidence showing that chronic intermittent hypoxia exerts two effects on the carotid body[26]: 1) augmentation of the hypoxic sensory response (by means of reactive-oxygen species generation), and 2) induction of the so-called long-term facilitation, which is the mechanism that sustains the sympathetic hyperactivation after long periods following the end of hypoxia, and which can contribute to explain blood pressure elevation during the day.

Arterial baroreceptors are sensory nervous terminations sensitive to stretching and are located in strategic regions such as the carotid sinus and aortic arch[27]. The arterial baroreflex is the primary mechanism of compensatory response to acute changes and continuous blood pressure fluctuations that occur in different situations. A decreased baroreflex control of the heart rate is described in OSA[28]. However, it is not clear whether the decreased baroreflex control in OSA represents a neural adaptation or whether it is secondary to the decreased compliance of the carotid artery and aorta[29] which, as we know, promotes the adaptation of the arterial baroreceptors in hypertension[30,31]. This baroreflex dysfunction seems to be responsible for the loss of blood pressure control during apneas, whereas the chemoreflex dysfunction would be responsible for the 24-hour blood pressure variations[26].

Endothelial dysfunction has been consistently reported in patients with OSA; however, this relationship does not depend on other confounders such as obesity[32-34]. Just like it has been suggested in the genesis of essential hypertension, endothelial dysfunction is also believed to participate in the genesis of OSA-induced SH. Reduced nitric oxide availability, increased endothelial apoptosis, and decreased hypoxia-induced cell repair capacity characterized by a decreased production of endothelial progenitor cells are some of the mechanisms proposed[35]. Even with the support of a causality relationship, several studies have demonstrated that the treatment with CPAP reduces endothelial dysfunction in parallel with an increased endothelial repair capacity[34,35].

Another factor related to endothelial dysfunction and increased vasomotricity in OSA is increased endothelin concentration. Endothelin levels are increased in OSA[36] and positively correlate with the severity of OSA[37]; its concentration decreases with treatment of this condition[38]. Despite these evidences, the relative role of endothelin in the genesis of OSA-induced SH is not yet defined, since there is no consensus in the literature[39].

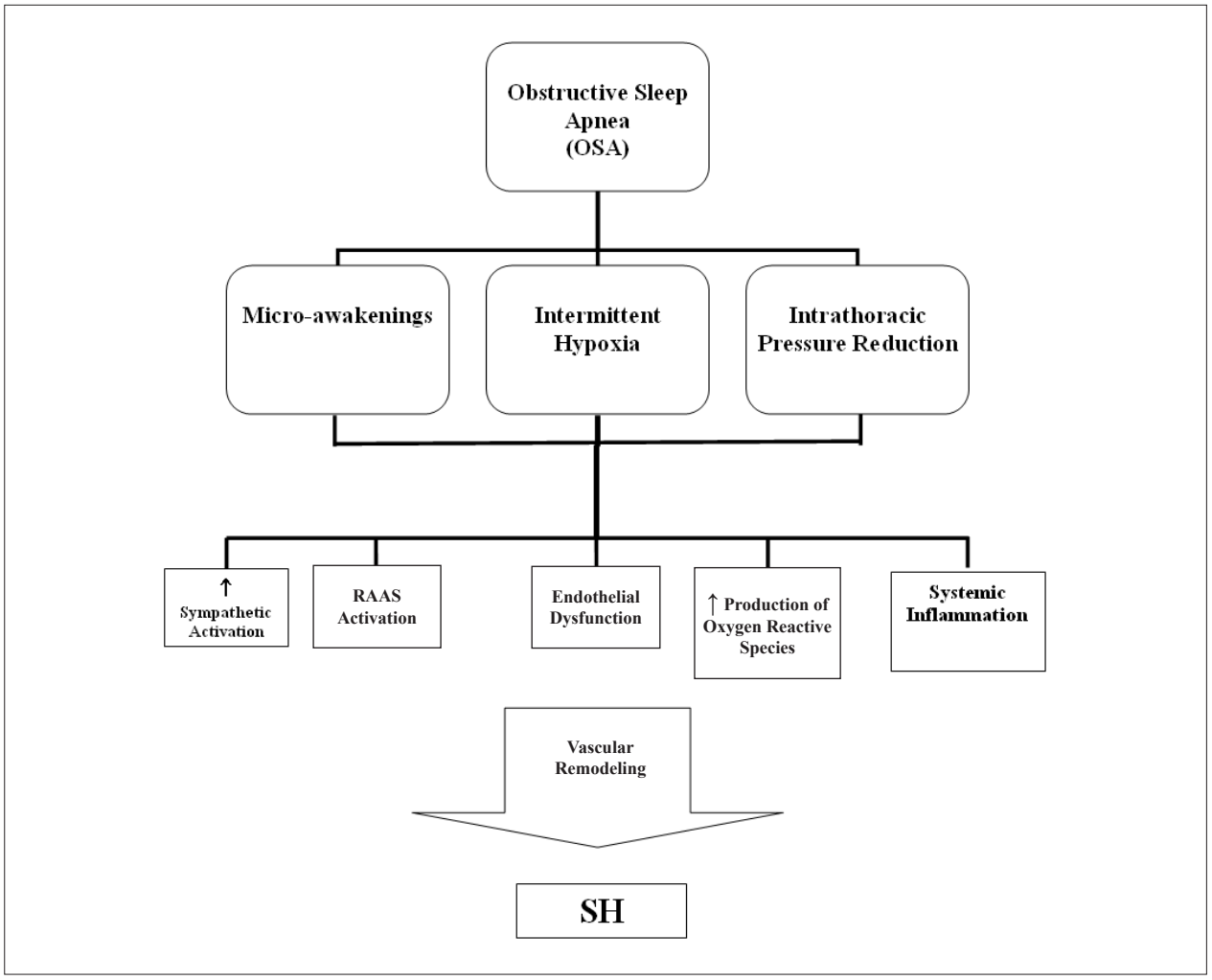

Figure 1 - Schematic figure summarizing the main mechanisms involved in the genesis of systemic hypertension (SH) and obstructive sleep apnea (OSA). In the upper part of the figure, the three main components of OSA are shown. Hypercapnia is present in OSA; however, it was not included due to the lack of evidence on its relative role in the genesis of SH. On the other hand, although intermittent hypoxia is the main factor related to vascular damage, the other factors mentioned may also contribute to the development of SH.

Activation of the renin-angiotensin-aldosterone system by independent pathways of renin production is seen in OSA, and demonstrated by means of increased angiotensin II and aldosterone levels in comparison to individuals with similar body mass index[23]. These patients can show low plasma rennin activity and a high aldosterone/renin ratio, and this can lead to a wrong diagnosis of primary hyperaldosteronism[40]. The finding of elevated aldosterone levels is important in the treatment, because it suggests an additional effect of aldosterone inhibitors in blood pressure control of these patients, when associated with the treatment of OSA[41]. On the other hand, individuals with OSA and increased aldosterone levels may present with more fluid retention. This retention may contribute to more tissue edema in the airways and the generation of more obstructive apneas[42], which may lead to a cycle that perpetuates SH. However, the role of the renin-angiotensin-aldosterone system in OSA is also not fully understood, since there is still no consensus in the literature as regards the participation of this axis in the genesis of OSA-related hypertension[43].

Clinical presentation

Despite scientific evidences, OSA is still underdiagnosed in the overall population, and this is also true for hypertensive patients. There are multiple causes for this problem: lack of knowledge on the part of the hypertensive patient's physician; difficulty of access to the diagnosis and treatment of OSA; and absence of symptoms such as daytime sleepiness in a significant percentage of hypertensive patients (see epidemiological aspects)[13].

In order to suspect OSA in hypertensive patients, the physician should actively look for signs and symptoms and not just wait for the patient to address the issue, because patients frequently do not complain about their quality of sleep to the general practitioner/cardiologist. As previously described, the presence of metabolic syndrome is an important marker of OSA among patients with hypertension[13]. Other predictors are age between 40 and 70 years and a high risk for OSA as assessed by the Berlin questionnaire[13,44].

The best test for the diagnosis of OSA is nocturnal polysomnography, whose sensitivity and specificity are close to 95%[1]. It consists of the simultaneous monitoring of electroencephalography; electrooculography; electromyography, oxygen saturation; air flow; thoracic and abdominal movements; and heart rate. Thus, nocturnal polysomnography permits not only the assessment of the architecture and efficiency of sleep, but also the diagnosis and differentiation of sleep disorders. In OSA, we observe that during breathing events there is active thoracic and abdominal movement translated into useless attempts to open the obstructed airway. The breathing events are followed by oxygen desaturation, and frequently end with micro-awakenings, moments at which the airway is cleared. OSA is classified as mild, moderate and severe according to the number of respiratory events (apneas and hypopneas) per hour of sleep. A normal value is considered when the number of events is lower than 5 per hour of sleep. Mild, moderate and severe OSA are defined as an apnea-hypopnea index between 5 and 14.9; 15 and 29.9 and ≥ 30 events per hour of sleep, respectively.

Pattern of blood pressure behavior

Typically, patients with OSA may present with diastolic hypertension alone as the first manifestation of SH[45,46]. The causes for this phenomenon are not yet fully understood; however, it has been hypothesized that it could be partly explained by an increased peripheral vascular resistance due to sympathetic hyperactivity commonly seen in these patients. One study showed a significant association between OSA and the occurrence of combined systolic and diastolic hypertension only in patients < 60 years old, but no association was observed between isolated systolic hypertension and OSA in any age range[47].

One of the remarkable characteristics of OSA is the occurrence of changes in sleep dip observed on ambulatory blood pressure monitoring (ABPM). In fact, changes in nocturnal dip are one of the findings that most frequently lead general practitioners and cardiologists to consider the diagnosis of OSA, although this finding is not pathognomonic of OSA. The change in blood pressure is attributed to the sympathetic activation by breathing events and frequent awakenings that occur during sleep in these patients. This change seems to be more common in black patients and those with SH[48]. However, abnormal nocturnal dipping is also frequent in normotensive patients with OSA, which suggests a possible contribution of this factor to in explaining the increased cardiovascular risk in OSA, even in the absence of other associated conditions[49].

Another finding that seems to be common in patients with OSA and may also contribute to an increased cardiovascular risk is the occurrence of masked SH[50]. Recent evidence suggests that individuals with OSA and masked SH present with more significant arterial stiffness than individuals with isolated OSA and controls[50]. However, arterial stiffness in patients with OSA without masked SH was also more significant in the control group; therefore, this may suggest that the vascular damage promoted by OSA is not mediated only by variations in and sustained increase of blood pressure[50].

OSA and target-organ damage

Recent evidences suggest that the presence of OSA is associated with a higher frequency of target-organ damage regardless of other confounding factors such as SH and obesity[51,52]. However, the presence of OSA and SH in the same individual seems to have an additive effect on the occurrence of vascular damage and cardiac remodeling when compared to each factor individually[52,53] (Figure 2). Although the mechanisms of cardiac remodeling in OSA are not fully understood, increased arterial stiffness of the great arteries is believed to contribute to increase the left ventricular afterload[52]. Also, negative intrathoracic pressure during apneas may contribute to increase the left ventricular transmural pressure. Other findings directly related to vascular remodeling and increased left ventricular afterload are the increase in the left atrium[54] and ascending aorta[55]. These data suggest that OSA may worsen the outcome of hypertensive patients and predispose to the occurrence of complications such as heart failure. However, further evidence is necessary to draw definitive conclusions on this issue.

Treatment

To date, approximately 30 non-controlled studies and 22 controlled studies have demonstrated a mean reduction in blood pressure by approximately 2.5 mmHg with the use of CPAP treatment. However, few randomized clinical trials have studied populations with predominance of uncontrolled hypertensive patients. One of these studies involved the treatment with CPAP or sham CPAP (that is, CPAP with very low pressures and no therapeutic effect) for two months in patients with daytime sleepiness and OSA. The authors found a reduction by 10 mmHg in 24-hour systolic and diastolic blood pressure in the CPAP group[56]. In another study with a shorter follow-up and smaller number of participants, in which the patients without daytime sleepiness made a crossover for the use of CPAP, there was no reduction of blood pressure with the use of CPAP[57]. Thus, the presence of daytime sleepiness seems to be predictive of blood pressure response to CPAP treatment, although the mechanisms are unknown. To date, the largest study to evaluate the impact of CPAP on the reduction in blood pressure included 359 hypertensive patients without daytime sleepiness. Patients were randomized to CPAP or conservative treatment[58]. This study found a small reduction only in diastolic pressure (2.2 mmHg) by the end of a 12-month follow-up in the group treated with CPAP. This beneficial effect was found mainly in patients who used CPAP for more than 5.6 hours per night. We should point out that only half of the participants used antihypertensive drugs and that blood pressure assessment was made on an outpatient basis, without the use of ABPM[58]. Table 1 shows the main randomized studies in which at least 50% of the participants were hypertensive[56-60].

Summarizing these findings, a systematic review[61] and four meta-analyses[62-65] assessing the impact of CPAP on blood pressure have been published in the past few years. All point to a blood pressure reduction with the use of CPAP. Only one of them[62] did not show a beneficial effect of CPAP treatment on blood pressure control. However, when analyzed in only

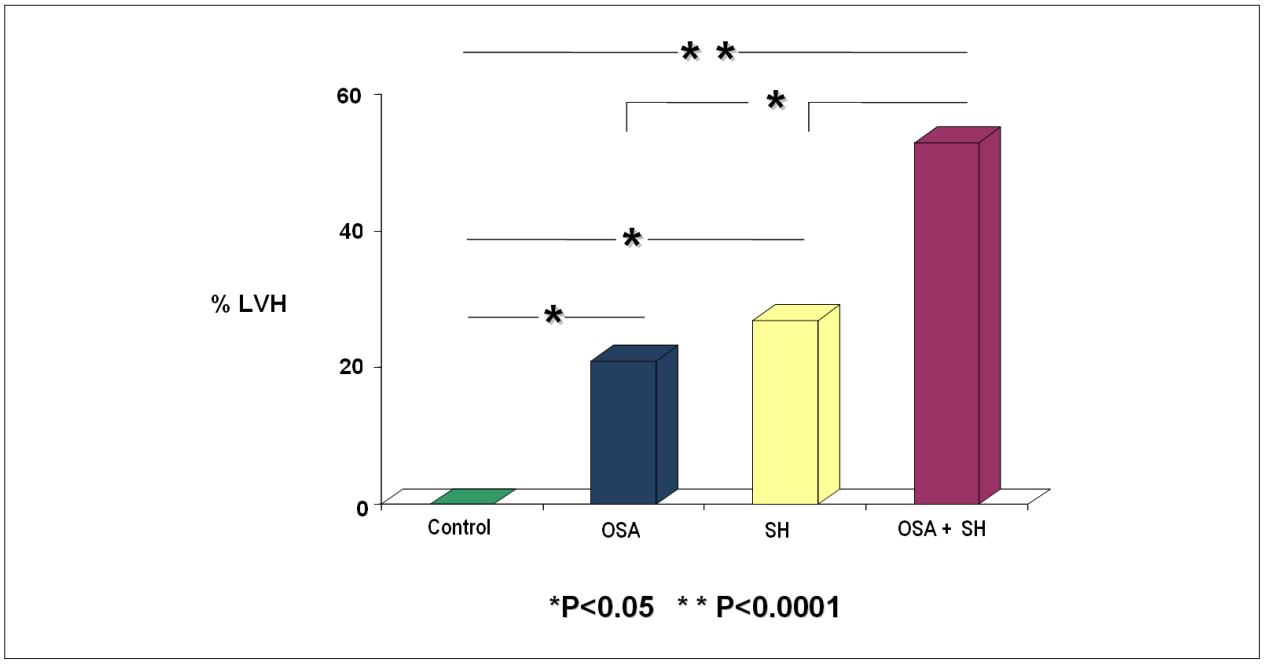

Figure 2 - Percentage of left ventricular hypertrophy (LVH) in healthy individuals (controls), normotensive patients with obstructive sleep apnea (OSA), patients with systemic hypertension without OSA (SH) and patients with both clinical conditions (OSA + SH). Participants matched for age, gender and body mass index. Modified from Drager LF et al, CHEST 2007[52].

Table 1 - Randomized interventional studies with CPAP in non-resistant hypertensive patients

Study	N° of patients	SH (%)	Initial SBP (mmHg)	Initial DBP (mmHg)	Length of time of CPAP use	SBP reduction (mmHg)	Comments
Barbé et al[58]	359	100	141.0 (15.0)	85.0 (11.0)	1 year	-1.9 (-3.9; 0.1)	Open, usual, manual
Becker et al[56]	32	66	136.1 (15.3)	82.3 (14.1)	9 weeks	-10.9 (-19.8; -2.0)	Double blind, sham, ABPM
Kaneko et al[59]	24	50	127.0 (22.6)	61.0 (13.9)	4 weeks	-18.0 (-36.5; 0.5)	Open, usual, manual
Mills et al[60]	17	52	152.2 (20.7)	83.4 (12.1)	2 weeks	-1.8 (-16.2; 12.6)	Single blind, sham, manual
Robinson et al[57]	32	100	143.0 (17.3)	86.7 (11.1)	4 weeks	-2.3 (-10.6; 6.0)	Double blind, sham, ABPM

Values expressed as mean (SD), percentage or confidence interval. SH - systemic hypertension; SBP - systolic blood pressure; DBP - diastolic blood pressure. Double blind, single blind or open corresponds to the study design. Sham and usual correspond to the type of control: sham CPAP or usual treatment, respectively. ABPM or manual correspond to the method used for blood pressure measurement: ambulatory blood pressure monitoring or manual measurement, respectively.

six studies with more severely ill patients (AHI > 30 events/hour), the result showed reduction in systolic blood pressure by 3.3 mmHg and in diastolic blood pressure by 2.03 mmHg. In Haentjens et al's study[63], which analyzed 12 placebo-controlled trials using ABPM for the assessment of blood pressure, there was a reduction by 1.77 and 1.79 mmHg in the mean 24-hour systolic and diastolic blood pressures, respectively. The most recent meta-analysis evaluated 818 patients and showed a reduction by 2.46 mmHg in systolic blood pressure and by 1.83 in diastolic blood pressure after the use of CPAP[65]. We should point out that these levels of blood pressure reduction can account for a long-term reduction of cardiovascular events. However, the studies chosen for inclusion in these meta-analyses are subject to criticism; they included normotensive patients, and this may have contributed to the small blood pressure reduction[66]. On the other hand, an important finding of one of the meta-analyses was that the magnitude of blood pressure reduction was directly associated with the number of hours of CPAP use during sleep[65]. Current evidences of the beneficial effects of the treatment of OSA in patients with refractory SH[67-69] are even weaker, although recent studies point to a greater blood pressure reduction (Table 2).

As regards alternative treatments of OSA, the use of mandibular advancement devices, which pull the mandible forward and, consequently, the base of the tongue, has proved efficient in reducing blood pressure and should be considered an alternative treatment for patients not complying with CPAP or those with mild/moderate OSA[70,71].

There is no definitive study on the use of specific antihypertensive medications for hypertensive patients with OSA. Clonidine may decrease REM sleep and then reduce the episodes of apnea during this sleep phase and improve nocturnal hypoxemia[72]. A comparison between five classes of drugs commonly used (atenolol, amlodipine, enalapril,

Table 2 - Interventional studies with CPAP in resistant hypertensive patients

Study	Design	Nº of patients	Initial SBP (mmHg)	InitialSBP (mmHg)	Length of time of CPAP use	SBP reduction (mmHg)	Comments
Dernaika et al67	Observational	98	146.0 (8.4)	84.8 (7.2)	1 year	-5.6 (-2.0; -8.7)	Control group - non-refractory SH
Logan et al68	Interventional, open	11	147.2 (3.3)	88.3 (2.2)	8 weeks	-12.3 (-16.1; -8.52)	No control group
Martinez-Garcia et al69	Interventional, open	33	155.1 (15.4)	90.5 (9.8)	8 weeks	-7.3 (-13.1. -3.1)	Control group - patients intolerant of CPAP

Values expressed as mean (SD), percentage or confidence interval.

losartan and hydrochlorotiazide) did not show any significant influence on the severity of OSA. All drugs showed similar effects on daytime blood pressure, but atenolol reduced nighttime blood pressure more effectively in comparison to the other drugs[73]. Finally, as previously mentioned in the present study, the antagonism of the renin-angiotensin-aldosterone system by means of spironolactone may be beneficial to the treatment of blood pressure in patients with OSA and resistant SH[41]. This beneficial effect may be mediated by edema reduction in the upper airways, because recent evidences suggest that, during the night, there is increased venous return from the legs and consequent fluid accumulation in the airway tissues, which could be one of the factors responsible for the increased collapsibility of the airways, especially in men[74,75].

Future perspectives

The body of evidence points to OSA as an important secondary cause of SH. Even in individuals already with SH, the presence of OSA may contribute to worsen blood pressure control and increase the occurrence of target-organ damage. Despite the small mean blood pressure reduction achieved with the treatment deemed standard for OSA (considering all studies including individuals with controlled blood pressure and normotensive individuals), the benefit of CPAP in terms of blood pressure reduction seems to be greater for the cases of resistant SH. Although evidences from an observational study show a possible reduction in the occurrence of fatal and non-fatal cardiovascular events with OSA treatment[8], to date no randomized study has proven this effect. Also, it remains to be demonstrated whether blood pressure reduction is involved in decreased OSA-mediated cardiovascular risk. Further studies are required to define efficient options to treat OSA and, at the same time, reduce the cardiovascular risk. Another area of growing interest is the analysis of the impact of antihypertensive drugs already available and new generations of drugs on the treatment of SH in individuals with OSA. Despite some promises of mutual benefit in the treatment of SH and OSA[41], further studies are necessary.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by FAPESP.

Study Association

This study is not associated with any post-graduation program.

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