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A Critical Review on Management of Hypertension in Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) is an underdiagnosed condition associated with essential hypertension (HTN), resistant HTN (r-HTN), and cardiovascular disease (CVD). The purpose of this review is to provide an update on HTN and its association with OSA. As obesity increases in the 21st century, OSA and HTN are common sleep disorders. OSA has been linked to cardiovascular morbidity and mortality in numerous studies. It is well established that OSA and HTN are associated. Various factors contribute to HTN in OSA, such as sympathetic tone, renin-angiotensin-aldosterone system dysfunction, endothelial dysfunction, and altered baroreceptor reflexes. A multifactorial approach to treating OSA involves Continuous positive airway pressure (CPAP), oral appliances, lifestyle modification, and antihypertensive medications. Both OSA and HTN must be diagnosed and treated promptly in order to help address the growing burden of cardiovascular morbidity and mortality caused by these two conditions.

Keywords: Obstructive sleep apnea, Hypertension, Cardiovascular disease

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Introduction

Approximately 15 to 24% of adults suffer from OSA. In this condition, the upper respiratory airways collapse recurrently during sleep, resulting in breathing reduction (hypopnea) or cessation (apnea) that causes transient hypoxemia and hypercapnia. By briefly hyperventilating after awakening from sleep, most apneic episodes are averted [1]. In addition to daytime somnolence, fatigue, headaches, and decreased concentration, this perpetual sleep fragmentation also contributes to excessive daytime sleepiness (EDS). Depending on the number of apneic and hypopneic episodes per hour, OSA syndrome (OSAS) is categorized into mild, moderate, and severe forms [2, 3].

Obesity, male sex, and aging are major risk factors for OSA. It can be challenging to determine the independent effects of OSA on HTN since these conditions are often associated with and predispose to HTN [4-6]. There is increasing evidence that OSAS independently contributes to considerable cardiovascular morbidity and mortality, such as heart failure, arrhythmia, and large vessel disease. Nighttime catecholamine surges may also precipitate arrhythmias that lead to angina, myocardial infarctions, and sudden cardiac deaths. Regardless of other known risk factors for HTN, repetitive nocturnal apneic episodes can result in acute autonomic and cardiopulmonary disturbances [7, 8].

High blood pressure has been linked to increased cardiovascular morbidity and mortality in numerous studies. Due to elevated nocturnal readings and nondipping blood pressure patterns, recent studies have implicated a stronger correlation between elevated ambulatory blood pressure monitor (ABPM) readings and cardiovascular events [3, 9-12]. In patients with OSAS, nocturnal catecholamine surges, as well as elevated nocturnal blood pressure, contribute to poor outcomes. Based on the findings of the MAPEC study, bedtime chronotherapy combined with a standard HTN medication to target sleep blood pressure significantly reduces the risk of CVD [13-18]. OSAS is characterized by intermittent hypoxia, changes in intrapleural pressure, and sleep fragmentation, which trigger endothelial dysfunction, sympathetic activation, and renin-angiotensin-aldosterone system activation as well as increased oxidative stress. There is an increase in CVD morbidity and mortality as a result of all of these factors [14].

Prevalence of OSA and HTN

Developing countries continue to experience an increase in OSA prevalence accompanied by an increase in obesity. OSA is estimated to affect 24% to 26% of men between 30 and 70 years of age and 17% to 28% of women between 30 and 70 years of age, though its prevalence may vary across different populations and age groups [15]. In addition to HTN, 26.4% of adults suffer from the disease. An overwhelming amount of epidemiological evidence supports the causal, bidirectional relationship between OSA and chronic HTN. The prevalence of OSA is higher in hypertensive patients, not only because it predisposes patients to HTN. It is estimated that between 30 and 70% of OSA patients have HTN [16-18]. There was a higher prevalence of HTN among patients with severe OSA (53%) than among those with moderate OSA (46%). OSAS is markedly underdiagnosed in hypertensive patients, and the prevalence of OSA in them is estimated at 30 - 50% [19]. In the subset of patients with r-HTN, the prevalence increases substantially to 83%. r-HTN was most closely associated with OSA (64%), even more so than

primary hyperaldosteronism (5.6%). r-HTN patients have a 2.5-fold higher risk of OSA than other hypertensives [3, 20-24].

There have been numerous cross-sectional studies that have demonstrated an association between OSA and HTN independent of age, weight, and other confounding factors. Consequently, OSA was listed in the JNC VII guidelines as the most common cause of secondary HTN. Both the Wisconsin sleep cohort study (WSCS) and the sleep heart health study (SHHS) indicate a causal relationship between the two. After accounting for the effect of BMI, the SHHS results that followed 2470 patients for 5 years did not show a statistically significant association with HTN, whereas the WSCS showed a statistically significant association with HTN with increasing severity of OSA [25-27]. Due to the SHHS cohort's older average age (60 vs 47), some of this discrepancy can be explained. Another study found a dwindling correlation between OSAS severity and incident HTN with age, which is confirmed by another study with a cutoff age of 60. According to the WSCS, OSAS severity and HTN incidence increased with increasing age, sex, BMI, and initial blood pressure, regardless of confounding risk factors such as age, sex, and BMI [28]. The odds of incident HTN and nondipping nocturnal blood pressure were higher among subjects with AHI > 15 than those with AHI 5. OSAS may be associated with depression and stroke in further prospective analyses of the WSCS data. After an 18-year mortality follow-up on the WSCS sample, those with severe sleep disordered breathing (SDB), with AHI > 30, had a 3 times higher all-cause mortality and 5.2 times higher cardiovascular mortality rate than those without SDB. After excluding those who received CPAP, the hazard ratio for all-cause mortality increased from 3.0 to 3.8 [29-32]. Furthermore, the Vitoria sleep cohort (VSC), which monitored 1180 subjects from 30 to 70 years old for 7.5 years, demonstrated a positive correlation between incident HTN and increasing SDB, but when age was controlled for, this association became attenuated and no longer statistically significant [3]. The association between OSAS severity and HTN was further diminished when sex, BMI, neck circumference, fitness level, alcohol, tobacco, and coffee consumption were adjusted for. A difference in the population sample and methods might explain the disparity observed between the WSCS, the SHHS, and the VSC [33]. In comparison with WSCS and VSC, the SHHS sample was older, but more obese (BMI = 28 versus 26 kg/m^2); more hypertensive (51% versus 28% in WSCS and 24% in VSC); and more racially diverse [34]. As well as being more obese (BMI = 29), the WSCS cohort had a higher male preponderance (56% versus 48% in the VSC) and originated from a working population as opposed to a general population [35]. SDB was diagnosed with unattended at-home polysomnography in the VSC and SHHS, while it was diagnosed with in-lab polysomnography in the WSCS. WSCS used a reference point of 0 while SHHS used a range of 0 - 4.9. Because very few patients have an AHI of 0, VSC used 0 - 2.9 as their reference range for respiratory disturbance index (RDI) [36]. Additionally, a cross-sectional study in Canada showed that an increase in the AHI by one event/h increased the risk of HTN by 1%. Participants who did not receive CPAP therapy, compared with those who did, had higher rates of HTN, according to data from a prospective study in Spain [37-41].

According to population-based studies using 24 h ABPM, participants who have a dip in blood pressure during the night (nondippers) and those who increase their blood pressure at night (risers) exhibit higher rates of end organ damage, stroke, heart failure, and renal disease progression than hypertensives with preserved dipping, i.e., a nocturnal decrease of > 10% in blood pressure [42]. In OSA patients with ABPM, nocturnal BP dipping is less frequent than in those without. Untreated patients with mild to severe OSA showed an 84% prevalence of nondipping. According to a subset of the WSCS cohort, nondipping was positively correlated with OSA severity at baseline. Also, nocturnal CPAP use among nondippers lowers blood pressure more effectively than antihypertensive drugs, suggesting OSA is to blame [43]. A clinical study found that men are more likely to develop OSAS than women by 8 - 10 times and epidemiological studies found that the prevalence is approximately 2 - 3 times higher for men. Despite the lack of a clear explanation, factors such as fat distribution, upper airway anatomy, craniofacial configuration, and hormonal variations across genders may be responsible for the increased male predominance [44-49]. There is less common evidence of atypical symptoms for females with OSA, including snoring, apnea, and EDS, as well as a lower AHI, typically specific to REM sleep [50]. Thus, OSA may be grossly underdiagnosed in women owing to an altered presentation. Despite the high prevalence of OSAS observed in males, the effect of sex on incident HTN in OSA has been relatively inconsistent [3, 51-53].

Pathophysiology of HTN in OSA

Various factors contribute to the pathophysiology of HTN in OSA, including sympathetic tone, peripheral vasoconstriction, increased renin-angiotensin-aldosterone activity, and altered baroreceptor reflexes [54]. Hypoxemia caused by intermittent apneic episodes stimulates the carotid body chemoreceptors, stimulating the medullary cardiorespiratory centers [55]. During post apneic hyperventilation, the nocturnal catecholamine surges result in a nocturnal increase in heart rate and blood pressure that can reach 240/130 mm Hg. In some cases, nocturnal BP surges lead to failure of the usual "dipping" phenomenon, whereas in others, they can precipitate cardiovascular events such as coronary spasm, angina, and arrhythmias [56].

After a single night of exposure to intermittent hypoxia (3 mm for mean diastolic), Tamisier et al. [56] found that ambulatory blood pressure increased significantly during the day (3 mm for mean diastolic). After 2 weeks of exposure, daytime pressures increased by 8 mm Hg systolic and 5 mm Hg diastolic without apparent changes in vascular reactivity or systemic inflammation. In addition, the study assessed muscle sympathetic nerve activity (MSNA) and found that MSNA increased as exposure progressed, while baroreflex control of sympathetic outflow declined [57-61]. Accordingly, sympathoactivation induced by intermittent hypoxia may contribute to elevated blood pressure by reducing baroreflex inhibition, thus contributing to elevated blood pressure.

Simultaneous reflex stimulation of the respiratory centers occurs as a result of hypoxia, in addition to the increased sympathetic response [62]. As a result of lung inflation, vagal stretch receptors are stimulated reflexively, which lessens sympathetic activity and maintains autonomic homeostasis. An exaggerated sympathetic response to hypoxemia occurs when there is inadequate lung inflation during apneic episodes [63]. Despite the absence of hypoxia, OSA patients have an elevated sympathetic tone as a result of this amplified chemoreflex sensitivity. Aside from impaired pulmonary stretch receptors and baroreceptors, OSAS exhibits blunted heart rate variability and increased blood pressure variability, a sign that the autonomic system is dysfunctioning and is a potential predictor of HTN and CVD. In patients with preexisting CVD, it is also associated with an increased risk of end organ damage [64-66]. When OSAS causes intermittent negative intrathoracic pressure coupled with transient nocturnal catecholamine surges, it exerts profound mechanical stress on the heart, gradually resulting in left ventricular hypertrophy and atrial remodeling. Even in the absence of sustained diurnal HTN, 24 h ABPM evaluates the risk of heart failure and arrhythmias such as atrial fibrillation [67]. During NREM sleep, which comprises the majority of sleep time, sympathetic activity declines and parasympathetic activity increases, contributing to a slight dipping of both systolic and diastolic blood pressure at night by about 10 - 15%.

A nocturnal surge in blood pressure and predominant sympathetic activity defines REM sleep, which is punctuated intermittently by NREM sleep. In OSAS patients, generalized skeletal muscle atonia during REM sleep makes the airway more susceptible to collapse, enhancing apneic episodes and intensifying nocturnal sympathetic hyperactivity [3, 68].

As with ischemia reperfusion injury, recurrent nocturnal hypoxemia with subsequent reoxygenation induces oxidative stress in the body, releasing reactive oxygen species, inflammatory cytokines, and vasoactive substances, thereby causing endothelial damage [69]. In some studies, OSAS patients showed reduced response to vasodilators such as acetylcholine. Forearm blood pressure flow after acetylcholine was reduced in OSA patients compared with controls in Carlson et al.'s study, but not in hypertensive or normotensive subjects. The findings of this study did not appear to be consistent with those of other studies [70]. Nitrogen monoxide levels were also found to be reduced in OSAS patients, and the degree of reduction was consistent with the severity of OSAS. In vitro studies have shown that endothelin levels increase in hypoxia [71]. It was found that OSAS patients had higher nocturnal levels of endothelin-1 than controls, with the magnitude corresponding to elevated blood pressure and increasing AHI. Furthermore, elevated endothelin levels declined after 4 h of CPAP treatment, suggesting that endothelin plays a role in the pathogenesis of OSA-related HTN. OSAS patients also have elevated levels of C-reactive protein [72]. CRP levels were reported to be higher among those with impaired nocturnal BP dipping compared to those with relatively preserved dipping. Additionally, sleep deprivation can cause inflammation in the body on its own. Sleep deprivation and recurrent hypoxemia may cause OSAS patients to produce more inflammatory mediators, upregulate leukocyte adhesion molecules, increase serum amyloid A, CRP, and circulating angiogenic inhibitors, resulting in increased production of inflammatory mediators, endothelial damage, and vasoconstriction, leading to vascular complications (Table 1).

Table 1: Analysis on association of OSA with the risk of HTN [73].

Year	Number of studies	Total sample size	OSA (OR (95% CI)) for HTN
2016	6	20,367	1.41 (1.29 - 1.89)
2018	26	51,623	1.80 (1.54 - 2.06)
2020	10	13,274	1.80 (1.36 - 2.38)
2021	8	3484	6.44 (5.38 - 7.71)

OSAS patients are prone to obesity and obesity is widely known as a risk factor for glucose intolerance. Enhanced resting sympathetic tone can also result in reduced adiponectin levels, as can recurrent hypoxemia and sleep debt. In trials showing mild reversal of glucose intolerance with CPAP use in OSA patients, several studies report an association between OSA and insulin resistance independent of obesity. OSA patients with obesity have increased arterial stiffness, which may influence cardiovascular risk independently of metabolic changes. Mean arterial blood pressure ($p = 0.003$) and OSA severity (AHI; $p = 0.001$) were correlated with arterial stiffness. Another mechanism that may contribute to HTN in OSAS is increased renin-angiotensin-aldosterone activity. The carotid body has been shown to produce more angiotensin I in response to periodic hypoxia and to stimulate angiotensin II receptors, as well as to produce more renin and aldosterone following periodic hypoxia. As a result of a meta-analysis of 13 studies, it was found that OSAS patients with HTN had higher levels of Ang II compared to controls, and OSAS patients with normotensive OSAS had higher levels of aldosterone compared to the normotensive OSAS patients. CPAP therapy and subsequent BP reduction resulted in a decline in these elevated markers, indicating that the RAAS plays a causal role in OSA mediated HTN. After adjusting for confounding risk factors, hyperaldosteronism patients were 1.8 times more likely to have OSA than those without (18% vs 8.8%). In conjunction with rostral fluid displacement during sleep, excess aldosterone causes fluid retention, resulting in increased obstruction of the upper airways. In patients with r-HTN, spironolactone decreased OSAS severity by 50%, further supporting the hypothesis that aldosterone may contribute to OSAS development or exacerbation [73-75].

Epidemiological studies suggest that OSA and HTN are bidirectional. Experimental data in animals has shown that acute fluctuations in blood pressure increase upper airway obstruction, supporting the idea of reciprocal causality. As a result, phenylephrine-mediated increases in blood pressure in humans were associated with lower daytime genioglossus electromyographic activity. Upper airway collapsibility can be caused by either an inhibitory effect of baroreceptor activation on upper airway dilating muscle or an increase in mean arterial pressure that increases brain perfusion [76] (Figure 1).

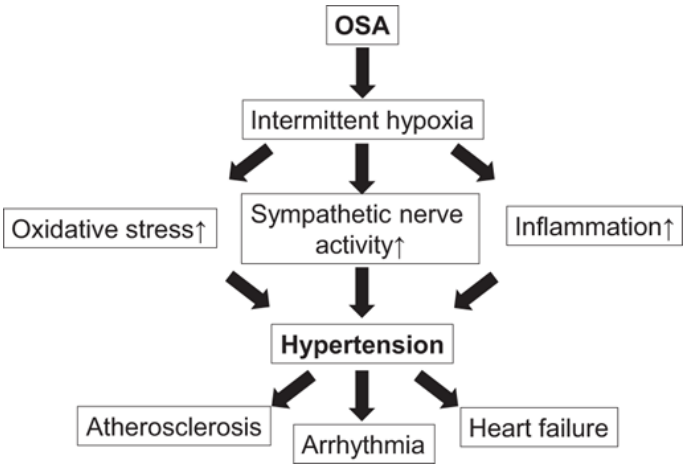

Figure 1: OSA and HT [77].

Efficacy of treatment

Oral appliances

In patients with mild to moderate OSA, oral appliances are recommended as an alternative to CPAP. This intervention has only been studied in a few clinical trials, most of which were observational with small sample sizes. Among 399 OSAS patients who participated in a meta-analysis of seven studies, oral appliances were found to have a similar effect on blood pressure to CPAP. Due to the observational nature of most studies in this meta-analysis, it is difficult to determine that oral appliances actually reduce blood pressure in patients with OSA [77]. It was found that oral appliances therapy reduced blood pressure in patients with OSA and HTN. Excluding patients with normal baseline ambulatory blood pressure increased the trend towards treatment effect. It was found that no matter how effective oral appliances are in patients with mild to severe OSA levels, they are not effective in all cases. There is a wide range in the degree of bias in studies and in the definitions of what constitutes success in treatment. CPAP therapy is intolerant of OSA patients who prefer alternate therapy, according to recent data. Oral appliances have better compliance and are noninferior to CPAP in terms of blood pressure. Furthermore, CPAP and oral appliances both lower morning blood pressure [78-80].

CPAP therapy

Due to the multifactorial nature of HTN, CPAP remains the mainstay therapy for OSAS, but its impact on blood pressure reduction has been variable. Patients with OSAS have been observed to benefit

from CPAP therapy by attenuating their nocturnal sympathetic surge and reducing their nocturnal blood pressure. There has been little to no evidence that long-term CPAP therapy can reduce daytime blood pressure in OSAS patients and the results of several trials evaluating this have been disappointing. There is only a mild decrease in blood pressure of about 1.3 to 3 mm Hg with CPAP, according to a number of meta-analyses. CPAP's modest BP lowering effects, although not comparable to antihypertensive drugs, are nevertheless significant because they decrease stroke and ischemic heart disease mortality by 6 - 8% and 4 - 5%, respectively [81-83].

Nevertheless, the generalizability of these studies is limited by variables affecting both the population of the study (such as age, sex, BMI, baseline severity of both HTN and OSA, and concomitant antihypertensive drug use) as well as the methodology (such as sample size, method of BP evaluation, e.g., office BP versus ABPM, use of a placebo as a control group, compliance with CPAP, duration of CPAP, and overall length of treatment and follow-up). In patients with baseline AHI > 30 and a high BMI, the magnitude of the drop in BP differs according to several factors, including CPAP compliance, duration of CPAP therapy and its use during REM sleep, presence of EDS, baseline BP, and severity of OSAS [84]. The most benefit from CPAP therapy was observed in patients with high baseline blood pressure, untreated HTN, nocturnal HTN, and nondipper pattern. Based on a meta-analysis. CPAP has been shown to improve cardiovascular morbidity and mortality in nondippers by recovering their nocturnal dipping pattern since those with nocturnal rising BP patterns are at the greatest risk. The HIPARCO randomized clinical trial in Spain corroborated these findings, finding that patients who received CPAP therapy tended to dip more than those who did not (35.9% dipping in CPAP group versus 21.6% in control; adjusted OR = 2.4; p = 0.02). With CPAP therapy used for at least four hours per night, blood pressure drops by 1.3 mm Hg per hour, with a drop of 1.3 mm Hg in BP detected per hour [85].

In patients with moderate to severe OSA, therapeutic and subtherapeutic CPAP were compared in a randomized controlled trial. The therapeutic CPAP group was treated with increasing pressure until all sleep stages were avoided during which the patient lied supine, with no apneas, hypopneas, or snoring [86]. There was a pressure difference between 6 and 12 cm H_2O in the most effective case of treatment. Subtherapeutic treatment involved maintaining the pressure at the lowest level possible (3 or 4 cm H_2O for the CPAP device). After an average treatment of 9 weeks, far substantial reductions in mean BP (9.9 ± 11.4 mm Hg) and both nocturnal and daytime systolic and diastolic BP (10 mm Hg approximately) were noted in the therapeutic CPAP group, most likely owing to the length of the trial and treatment pressure used (compared to 1.3 - 3 mm Hg in most trials lasting for about 4 - 6 weeks) [87]. Even though subtherapeutic CPAP reduced AHI by 50%, it did not result in any meaningful change in blood pressure (p = 0.01). It is possible that short-term controlled studies may not completely reveal the actual consequences of scrupulous long-term CPAP therapy on HTN and its cardiovascular sequelae due to OSA-mediated HTN chronic etiology involving endothelial dysfunction and cardiovascular remodeling [88].

Although CPAP therapy has been shown to reduce AHI by more than 50% following CPAP therapy, this effect appears independent of normalization of oxygen saturation alone. A study comparing CPAP with oxygen therapy in OSAS patients showed BP reductions with CPAP but not oxygen, which corrected nocturnal hypoxia but did not lower BP [89]. Patients without EDS are likely to have lesser efficacy with CPAP-mediated BP reduction, despite having severe OSA with an AHI > 30/h and not reporting daytime somnolence. In addition to improved subjective somnolence, some patients also reported improved blood pressure with CPAP treatment. The likelihood of adherence to CPAP treatment is also less for those with few daytime symptoms.

Lifestyle modifications

Considering obesity is the single biggest risk factor for OSA, even modest weight reductions can lessen OSA-induced HTN and OSA-induced sleep apnea. According to a study of participants from the WSCS, an increase of 10% in weight was associated with an increase of 32% in AHI and a 6-fold increase in moderate to severe SDB odds. An AHI decrease of 26% was predicted by a 10% weight loss, as opposed to a 10% weight gain [90].

In OSA patients receiving treatment with CPAP and antihypertensives, a lifestyle modification approach, including weight loss, should be recommended as part of an integrated approach that includes both lifestyle modifications and antihypertensives [91]. CPAP alone, a weight-loss intervention, or a combined CPAP and weight-loss intervention was assessed in a 24 week randomized controlled trial. We observed a greater reduction in blood pressure in the combined-intervention group (14.1 mm Hg) than in either of the weight-loss or CPAP groups (6.8 mm Hg). A significant drop in mean arterial pressure was also associated with combination therapy. According to these findings, lifestyle modifications and weight loss may have a synergistic effect on HTN management in OSA patients.

Antihypertensive drugs

As with patients with severe OSA who are not compliant with CPAP or do not tolerate CPAP, hypertensive patients with mild to moderate OSA are ideal candidates for hypertensive therapy. Antihypertensive medications should not be prescribed to OSA patients based on lack of adequate evidence. Nevertheless, owing to the pathophysiological mechanisms that cause and maintain HTN in OSA, such as the overactivity of the sympathetic and RAAS systems, it may be more effective to treat HTN in OSA patients with antihypertensive drugs that modulate their activity, such as B-blockers and aldosterone antagonists [3, 92]. The level of aldosterone in OSA patients is generally normal, except for those with severe OSA or HTN that is resistant to treatment. OSA can be significantly reduced with spironolactone, an aldosterone antagonist. Aldosterone antagonists, ACE inhibitors, and angiotensin receptor blockers (ARBs) have moderate antihypertensive effects in moderate OSA patients. A powerful aldosterone antagonist may even be more effective in severe OSA. Three hundred and fifteen patients received nebivolol (n = 16) or valsartan (n = 15) for six weeks to compare B-blockers with calcium channel blockers. In spite of both drugs effectively lowering systolic and diastolic blood pressure, nebivolol had a significantly greater effect on heart rate reduction than valsartan (p = 0.001), which may help patients with nocturnal tachycardia. It showed that in comparison to ACE inhibitors, calcium channel blockers, and ARBs, B-blockers (atenolol) significantly reduced nocturnal diastolic and systolic blood pressure better. Across the different antihypertensive classes, there was no difference in daytime BP or OSA severity (Table 2).

Several studies have found that antihypertensive drug-mediated nocturnal blood pressure reduction does not significantly reduce SDB severity measured by AHI, suggesting that nocturnal high blood pressure contributes only minimally to OSA severity and apneic events [93]. B-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, ARBs, hydrochlorothiazide, methyldopa, and clonidine are all commonly used antihypertensive drugs that produced the results. Although there was no change in AHI during NREM sleep or for overall sleep duration in hypertensive OSA patients, a recent study revealed a weak correlation between drug therapy and reduced nocturnal BP and apneic episodes during REM sleep [94, 95]. Further sup-

Table 2: Classification of antihypertensive drugs.

Class of drugs	Drugs	Frequency	Percentage	Total
ACE inhibitor	Captopril	5	0.77	-
	Lisinopril	90	13.8	15.34
	Ramipril	5	0.77	-
ARBs	Candesartan	32	4.91	-
	Irbesartan	16	2.45	8.44
	Losartan	3	0.46	-
	Telmisartan	4	0.61	-
Alpha blocker	Tamsulosin	34	5.21	5.21
Beta blocker	Propanolol	6	0.92	12.88
	Bisoprolol	78	11.96	-
Calcium channel blocker	Amlodipine	217	33.28	34.20
	Diltiazem	6	0.92	-
Diuretic	Furosemide	79	12.12	23.93
	Spironolactone	77	11.81	-
Total	-	652	100	100

porting the hypothesis that elevated blood pressure may influence upper airway collapse based on sleep stage. Antihypertensive drug therapy has also been shown to resolve some apnea/hypopnea symptoms. There was a statistically significant reduction in both nocturnal blood pressure and arterial heart rate when both metoprolol and cilazapril were administered to hypertensive OSA patients. In a study, cilazapril was observed to have an effect in all sleep phases, therefore making it more favorable for the sleep disturbances associated with OSA than metoprolol, which did not cause any changes during REM sleep. Both OSA severity and HTN are improved by diuretics, especially spironolactone, which relieves pharyngeal edema and secondary upper airway destabilization [3, 96].

The majority of these studies, however, relied on noninvasive methods to measure blood pressure and used very small samples (12 - 24 patients), a variable population, short duration of treatment and follow-ups, and lacked placebo effects. In patients with SDB, invasive BP measurements are the most accurate method for assessing mean nocturnal blood pressure as it varies greatly during apneic cycles (between 150 and 300 mm Hg). As a result, antihypertensive agents are not definitively recommended for the treatment of OSA. A few incriminating studies have advised against treating hypertensive OSA with ACE inhibitors. The discontinuing enalapril resulted in an increase in exhaled nitric oxide, a marker for airway inflammation, as well as an exacerbation of OSA. Weight gain caused by B-blockers can aggravate OSA [97]. Furthermore, this study reported significant sleep impairment in 186 OSA patients with HTN with an 8% decrease in sleep efficiency ($p = 0.004$) as well as a 41 min reduction in total sleep time ($p = 0.005$). The duration of sleep was not affected by any other antihypertensive drugs, including diuretics and beta-blockers. The majority of these adverse effects require a long time before they can be detectable, regardless of these results. Hence, these limited studies cannot provide an adequate assessment of these medications' impact on OSA severity due to their short duration. In an analysis of HeartBEAT data (Heart biomarker evaluation in apnea treatment), it is found that severe untreated OSA and resistant elevated blood pressure were strongly associated with high cardiovascular risk or established CVD in patients at high cardiovascular risk or with established CVD. Therefore, CPAP should be used in conjunction with antihypertensive medications in these patients [98, 99].

Upper airway surgery

Patients with OSAS have also been studied for the impact of surgery such as tonsillectomy and uvulopalatopharyngoplasty (UPPP). The SKUP3 randomized controlled trial improved sleepiness, nocturnal respiration, and quality of life in a selected group of patients with moderate to severe OSA as well as significantly lowering blood pressure. Children who suffer from OSA can undergo tonsillectomy and adenoidectomy surgeries [100, 101]. Among children receiving tonsillectomy and adenoidectomy for OSA treatment, Gaddam et al. [74] measured the nocturnal DBP index of nonobese children versus obese children with tonsillectomy and adenoidectomy.

Conclusion

HTN in OSA can be exacerbated by a number of mechanisms, and individual susceptibilities vary greatly. Sympathetic tone, inflammation, endothelial dysfunction, peripheral vasoconstriction, elevated RAAS, heightened chemoreflex, and blunted baroreflex sensitivity are some of these effects. A rise in blood pressure, however, may inhibit the muscles of the upper airway. In hypertensive patients, pharyngeal edema and subsequent airway obstruction can be caused by increased RAAS activity and rostral fluid displacement during sleep. Children with OSA may undergo tonsillectomyes and adenoidectomyes, while adults may undergo modified UPPP, as well as noninvasive treatments such as CPAP therapy, oral appliances, and lifestyle modifications. Finally, antihypertensive drugs have been studied as a treatment option. As a result of these measures, patients with OSAS are able to address the issues of r-HTN, which is associated with CVD morbidity and mortality. Thus, both OSA and HTN require prompt diagnosis and treatment in order to address the growing cardiovascular morbidity and mortality associated with them. In the future, medical advancements may lead to new treatment modalities.

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Conflict of Interest

None.

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