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REVIEW

Hypertension and obstructive sleep apnea

Anping Cai[1], Ling Wang[1] and Yingling Zhou

Obstructive sleep apnea (OSA) is a major modifiable risk factor of hypertension and hypertensive patients with OSA are at increased risk for cardiovascular diseases. A substantial number of studies have revealed that OSA and hypertension have synergistic effects on the cardiovascular system and, therefore, it is clinically important and relevant to increase our understanding of the pathophysiological interactions between OSA and hypertension. In our present review, after briefly reviewing the characteristics and pathophysiological effects of OSA, we focus on the current understanding of OSA-associated hypertension, the potential approaches for treatment of OSA and the effect of OSA treatment on hypertension management. We hope our present review will shed light for future studies that investigate effective therapeutic strategies to simultaneously improve the management of OSA and hypertension.
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INTRODUCTION

It is now well known that obstructive sleep apnea (OSA) is one of the common secondary causes of blood pressure (BP) elevation.[1] Moreover, hypertensive patients with OSA are at increased risk of developing resistant hypertension[2] and experiencing cardiovascular alterations and events[3–5] compared with their hypertensive counterparts without OSA. Importantly, it has been reported that ~50% of OSA patients have hypertension[6] and that ~30% of hypertensive patients are suffering from OSA.[7] Therefore, it is essential to identify, diagnose and treat OSA, to effectively improve the control of hypertension and to reduce the incidence and prevalence of hypertension-associated cardiovascular events. In recent decades, population-based studies have demonstrated that OSA and hypertension impose great economic and health burdens on individual patients and society as a whole. Furthermore, there is accumulating evidence regarding the synergistic effects that OSA and hypertension exert on the cardiovascular system, owing to the large number of clinical and experimental studies. Therefore, we believe that it is clinically important to review the pathophysiological interactions between OSA and hypertension, to help us understand and manage these diseases effectively and efficiently.

In our present review, we focus on the following aspects. We first review the characteristics of OSA, then the general pathophysiological effects OSA has on cardiovascular systems and then illustrate the underlying mechanisms by which OSA contributes to the pathogenesis of arterial hypertension and other categories of OSA-associated hypertension. Finally, we present the potential approaches in managing OSA and the effects of OSA improvement in BP reduction.

DEFINITION, DIAGNOSIS AND RISK FACTORS OF OSA

OSA occurs during nocturnal sleep and the diagnosis of OSA requires polysomnography to assess key variables such as arterial oxygen saturation, chest and abdomen respiratory movement, electroencephalogram findings and quantified air flow; all of these indices are subsequently used to determine the apnea–hypopnea index.[8] In brief, the apnea–hypopnea index is the total number of episodes of apnea (complete blockade of airflow for >10 s) and hypopnea ($>50\%$ reduction in respiratory airflow accompanied by $>3\%$ reduction in arterial oxygen saturation for >10 s) per sleep hour; patients with OSA are classified into mild (5–15), moderate (15–30) and severe (>30) categories.[8] In addition to the apnea–hypopnea index, typical clinical symptoms of OSA including daytime sleepiness and fatigue, frequent awakening during sleep, snoring, nocturia, reduced concentration and impaired memory are also important clues for clinical diagnosis.[8] In recent decades, a substantial number of studies have identified multiple sensitive predictors that are useful to identify high-risk population. For example, patients with any anatomical abnormality of the upper airway (such as pharyngeal collapse due to macroglossia and adenotonsillar hypertrophy,[9] or tongue displacement and pharynx narrowing due to retrognathia),[10] which Asian and non-obese populations are predisposed to, can develop OSA. Second, epidemiological studies have shown that males are predisposed to OSA,[11] and that the odds of developing OSA gradually increases with age and

Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
Correspondence: Professor Y Zhou, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan Road 2, Guangzhou 510080, China.
E-mail: drcacocolacai@gmail.com
[1]These authors are the co-first authors.
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weight gain.[12] Third, hereditary factors may also have a role in OSA development, as reported by Buxbaum *et al.*[13] Last but not least, smoking, alcohol abuse, hormone depletion in postmenopausal women and nasal congestion due to allergic rhinitis are also considered to be significant risk factors for OSA.[11] Owing to the high prevalence of OSA in the general population, it is crucial to prevent OSA development. We believe that designing a model to assess the risk of OSA in each individual would be helpful and future, large prospective studies are warranted to define the model's variables and cutoff values. Thus, taking into account the common risk factors and the typical clinical manifestations of OSA (Figure 1) is important for the timely identification of the unrecognized OSA population and the proper use of polysomnography is helpful to accurately diagnose and evaluate the severity of OSA.

PATHOPHYSIOLOGICAL EFFECTS OF OSA ON THE CARDIOVASCULAR SYSTEM

OSA confers pathophysiological effects on the cardiovascular system through a variety of mechanisms (Figure 2). Fundamentally, periodic hypercapnia and hypoxemia due to apnea–hypopnea episodes causes sympathetic nerve activation and serum catecholamine elevation,[14,15] both of which subsequently increase heart rate and BP. In addition, the frequent arousals and sleep deprivation due to periodic asphyxia also result in sympathetic nerve activation[16] and contribute to tachycardia and hypertension. Over time, these hemodynamic changes ultimately lead to left ventricular hypertrophy and heart failure.[17] Second, it has been reported that hypoxemia promotes oxidative stress, systemic inflammation and endothelium dysfunction,[18,19] all of which can contribute to the development of atherosclerotic cardiovascular diseases. Third, to counteract the narrowing pharynx, negative intra-thoracic pressure is generated and it increases the mechanical stress on the ventricles and atria.[20] Over time, cardiac remodeling, including left ventricle hypertrophy and left atrial enlargement, occurs and these maladaptive changes can manifest ultimately as overt cardiovascular diseases such as diastolic heart failure and atrial fibrillation.[20,21] Last but not least, other pathophysiological effects including impaired baroreflex sensitivity and the continuous activation of the renin–angiotensin–aldosterone axis also contribute to OSA-associated cardiovascular disorders.[16] Collectively, the accumulated clinical data strongly support the notion that OSA has a central role in the pathogenesis of cardiovascular disease; it is clinically important to effectively control OSA, to reduce the adverse effects OSA imparts on the cardiovascular system.

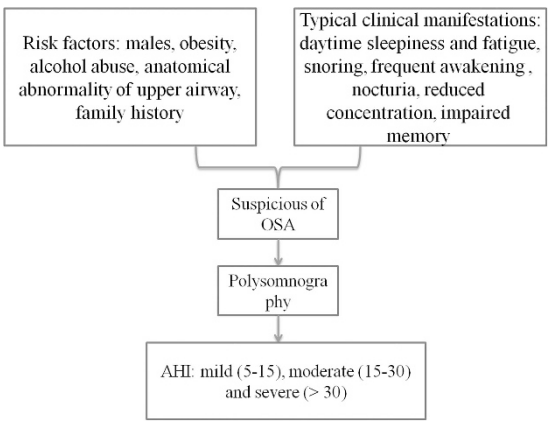

Figure 1 Screening and diagnostic algorithm for OSA.

PATHOPHYSIOLOGICAL MECHANISMS OF OSA ON HYPERTENSION

The relationship between OSA and hypertension has been extensively investigated[2,22–24] and there is compelling evidence to indicate that there is a dose–effect relationship[25–27] between the severity of in the OSA and degree of the BP elevation. The pathophysiological mechanisms by which OSA contributes to BP elevation are multi-factorial. On the one hand, hypoxemia induced by OSA causes systemic inflammation and oxidative stress, which result in increased endothelin-1 generation and decreased nitric oxide production in endothelial cells, increased arterial peripheral resistance and BP elevation.[28,29] On the other hand, the periodic hypoxemia, frequent arousals and sleep deprivation all cause sympathetic nerve activation that leads to increased cardiac output and peripheral vessel constriction, and thereby promotes BP elevation.[30] It has been reported that patients with OSA have a higher prevalence of isolated diastolic hypertension[31] and the underlying mechanism might be due to the tachycardia and shortening of cardiac diastole. Third, it has been reported that in comparison with subjects without OSA, subjects with OSA have significantly increased renin generation induced by efferent renal sympathetic nerve activation and this effect leads to elevations in plasma angiotensin-II and aldosterone. Together, these effects cause BP elevation by means of vasoconstriction and sodium–water retention, respectively. Furthermore, it has been reported that primary hyperaldosteronism is highly prevalent in subjects with OSA; therefore, it is important to screen for primary hyperaldosteronism in patients with OSA. Research has demonstrated that patients with both OSA and primary hyperaldosteronism are more likely to develop drug-resistant hypertension. Last but not least, it has been demonstrated that the sleep deprivation from OSA is associated with endothelial dysfunction and arterial stiffness,[32] both of which initiate and accelerate the development of hypertension. The proposed mechanisms by which OSA causes hypertension are listed in Figure 3. Collectively, the pathophysiological effects of OSA on hypertension are multi-factorial and they are due to the high prevalence of OSA in hypertensive subjects. We believe that improving OSA should result in profound benefits in hypertension management.

DIFFERENT CATEGORIES OF HYPERTENSION RELATED TO OSA

A substantial number of epidemiological studies have revealed that there are special categories of hypertension related to OSA; the most common and clinically relevant categories are resistant hypertension, nocturnal hypertension and masked hypertension.[33,34]

OSA and resistant hypertension

Resistant hypertension, which is defined as BP that remains higher than 140/90 mm Hg despite treatment with three different classes of anti-hypertensive medicines (including diuretics) at their optimal doses, is a common secondary effect of OSA.[35,36] For example, Calhoun *et al.*[37] observed that 90% of male patients and 77% of female patients with resistant hypertension had OSA. In another clinical study conducted by Ruttanaumpawan *et al.*,[38] they reported that OSA was associated with an increased risk of resistant hypertension, with an adjusted odds ratio of 1.025 (95% confidence interval of 1.002–1.049). Furthermore, two cross-sectional studies revealed that there was dose–effect relationship between the severity of OSA and the magnitude of BP increase, as well as the number of anti-hypertensive medicines used to manage hypertension.[39,40] In recent times, a clinical study revealed that clinically significant OSA was independently associated with concentric hypertrophy in patients with resistant

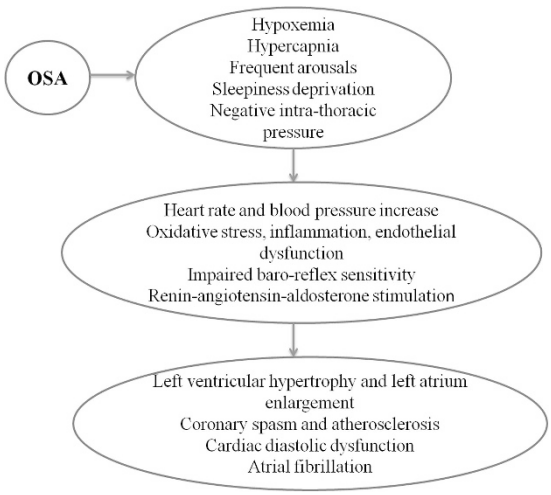

Figure 2 Pathophysiological effects of OSA on the cardiovascular system.

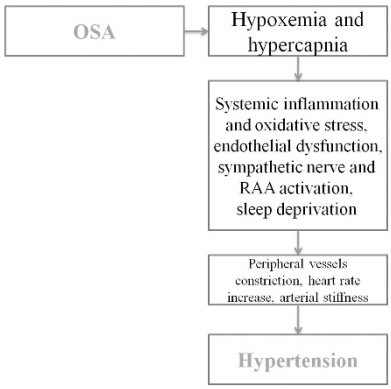

Figure 3 Pathophysiological mechanisms of OSA-associated hypertension.

hypertension,[41] which suggests that OSA might accelerate the adverse cardiovascular remodeling in subjects with resistant hypertension.

A substantial number of mechanisms contribute to OSA-related resistant hypertension. In addition to the aforementioned pathophysiological effects of OSA that can lead to BP elevation, primary hyperaldosteronism is also believed to be responsible for these phenomena.[33] It has been reported that primary hyperaldosteronism is highly prevalent in patients with concomitant OSA and resistant hypertension, as evidenced by the finding that both the urine and plasma levels of aldosterone were significantly higher in this population.[42,43] On the one hand, sodium and water retention caused by hyperaldosteronism can lead to volume overload and BP elevation.[43] On the other hand, parapharyngeal edema induced by fluid retention could exacerbate OSA and thereby promote further BP elevation.[44,45] Previous studies have suggested that this vicious cycle can be interrupted by treatment with aldosterone antagonists and continuous positive airway pressure (CPAP) therapy.[46,47] Nonetheless, randomized controlled clinical trials are still needed to provide solid evidence that these therapeutic modalities help improve BP control in subjects with resistant hypertension. Furthermore, it is also clinically important to examine the cardiovascular benefits of these therapies.

OSA and nocturnal hypertension

According to the circadian patterns of BP, high BP could be broadly classified into two categories: dipping and non-dipping. Briefly, a dipping pattern is when there is more than a 10% decrease in nighttime BP compared with daytime BP. By contrast, nocturnal hypertension is present when there is less than a 10% of reduction (non-dipping) in BP at night or when the nighttime BP is higher (riser) than during the day. A number of previous studies have revealed that nocturnal hypertension imposed greater adverse effects on the cardiovascular system than daytime hypertension.[48,49] It has been reported that the prevalence of nocturnal hypertension is substantially higher in subjects with OSA. For example, Loredo *et al.*[50] reported that ~84% of patients with OSA in their study experienced nocturnal hypertension. Data from the Wisconsin Sleep Cohort Study indicated that there was a dose–effect relationship between the severity of OSA and the risk of nighttime BP elevation.[51] The main mechanism contributing to nighttime BP elevation is the sympathetic overactivation caused by hypoxemia, frequent arousals and sleep deprivation. Treatment of OSA with CPAP therapy reversed the nighttime BP elevation.[46] It is clinically important to screening for OSA in patients with non-dipping or difficult-to-treat hypertension.

OSA and masked hypertension

Masked hypertension is the term used to describe the condition when the BP measured in the office is within the target range but the BP assessed at home or by 24-h ambulatory BP monitoring is above the normal range. An epidemiological study conducted by Baguet *et al.*[52] revealed that the incidence of masked hypertension in subjects with newly diagnosed OSA was nearly 30%. Another study revealed that among 61 male participants who were identified as normotensive by a clinic BP evaluation, one-third had masked hypertension and the patients with OSA had a higher incidence of masked hypertension than those without OSA.[53] These data suggest a potential association between OSA and masked hypertension; however, large, prospective studies are needed to corroborate these findings and to help physician identify those patients who are at increased risk of incident masked hypertension. Moreover, experimental and clinical studies are needed to elucidate the mechanisms.

APPROACHES FOR MANAGING OSA-ASSOCIATED HYPERTENSION

In addition to anti-hypertensive drugs, there are some other highly effective non-pharmacologic modalities for treating OSA-associated hypertension. For example, effective control of the co-morbidities that contribute to OSA and hypertension, such as obesity, smoking and alcohol abuse, is considered to be the most cost-effective strategy.[54,55] Surgical correction of the anatomical abnormalities of the upper airway is also a highly effective and efficient method. In addition, the use of oral appliances and CPAP therapy can also decrease BP in hypertensive patients with OSA. Clinical studies have revealed that oral appliance therapy was not only beneficial for OSA improvement but also for BP reduction.[56,57] In a recent randomized trial, Andrén *et al.*[58] evaluated 72 patients with OSA and hypertension, who were randomized to receive either 3 months of wearing an oral appliance with mandibular advancement or control treatment. The efficacy of the oral appliance treatment was ascribed to the improvement in hypoxemia and its associated adverse effects, and these benefits have also been confirmed in clinical studies of CPAP treatment on OSA and OSA-associated hypertension. For example, in a randomized controlled trial, CPAP treatment significantly reduced systolic BP (SBP) in subjects with OSA. Drager *et al.*[59] revealed that in pre-hypertensive or hypertensive patients with OSA, CPAP treatment substantially reduced the daytime systolic blood and the nighttime SBP and diastolic BP, when compared with the control group. In a recent published meta-analysis,[60] CPAP therapy was significantly associated with 24-h

ambulatory SBP and diastolic BP (DBP) reduction. Moreover, CPAP seemed more beneficial for decreasing nocturnal SBP than for diurnal SBP, and patients with resistant hypertension seemed to benefit most from CPAP therapy. In brief, the benefits derived from CPAP treatment may be associated with amelioration of hypoxemia and decreased nocturnal sympathetic nervous activation, and the resulting improvements in arterial oxygen saturation could mitigate the systemic inflammation and oxidative stress. Moreover, reduced negative intra-thoracic pressure caused by the positive pressure ventilation could also result in beneficial hemodynamic changes. All of these favorable effects of CPAP treatment simultaneously improve hypertension control. However, adherence is the most critical pre-requisite to obtain the benefits of CPAP treatment. A recent clinical study revealed that a singular pre-CPAP treatment cluster of three plasma microRNAs predicted the BP response to CPAP treatment in patients with resistant hypertension and OSA;[61] in the future, precision medicine using microRNA measurement could help target CPAP therapy in hypertensive subjects with OSA. For physicians considering which anti-hypertensive drugs to prescribe, there is no solid evidence to support the use of one specific drug class over another. There is no solid evidence of apnea–hypopnea index improvement with the commonly used anti-hypertensive medicines, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, calcium channel blocker, diuretic, β-blocker and α-receptor antagonist. Nonetheless, in patients with hyperaldosteronism, aldosterone antagonists should be the first choice agents. Moreover, diuretics may have a greater role in BP control by improving parapharyngeal edema. Overall, it is recommended that physicians treat patients with OSA-associated hypertension with a combination of various therapeutic modalities.

CONCLUSION

It is clinically important to screen for OSA in hypertensive patients, especially those patients who exhibit predominant diastolic BP elevation, difficult to control BP and nocturnal BP elevation. Increasing our understanding of the interplay of the mechanisms of OSA and hypertension is critical for the effective management of OSA-associated hypertension. More studies, especially in precision medicine, are warranted to investigate effective therapeutic strategies to improve the management of OSA and hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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