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Review
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Obstructive sleep apnea syndrome (OSAS) related hypertension: A review of pathophysiology and potential therapeutic approaches

Obstrüktif uyku apne sendromu (OUAS)'na bağlı hipertansiyon: Patofizyolojisi ve tedavi yaklaşımlarına dair bir derleme

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder related with cardiovascular diseases, including hypertension. There are lots of evidence supporting the relationship between OSAS and hypertension, modulated by multiple factors, but the exact mechanisms underlying this complex cause and effect relationship remain unclear. The alternating pattern of OSAS-related hypertension is closely related with target organ damage, especially in the heart and brain. In this review, the etiological factors, clinical types, probable pathophysiologic mechanisms, diagnostic methods, and current therapeutic approaches to OSAS-related hypertension is discussed in the light of current literature.

Keywords: Obstructive sleep apnea syndrome, Hypertension, CPAP, Upper airway surgery

Öz

Obstruktif uyku apne sendromu (OUAS), hipertansiyon da dahil olmak üzere kardiyovasküler hastalıklarla ilişkisi olan yaygın bir uyku bozukluğudur. OUAS ve hipertansiyon arasındaki ilişkiyi destekleyen birçok kanıt mevcuttur; ancak bu kompleks sebep-sonuç etkileşiminin altında yatan kesin mekanizma halen net değildir. OUAS ile alakalı hipertansiyonun değişken yapısı, kalp ve beyinin de dahil olduğu hedef organ hasarı ile yakından ilişkilidir. Bu derlemede, OUAS ile ilişkili hipertansiyonun etyolojik faktörleri, klinik tipleri, olası patofizyolojik mekanizmaları, tanı yöntemleri ve güncel tedavi yaklaşımları güncel literatür ışığında tartışılmıştır.

Anahtar kelimeler: Obstruktif uyku apne sendromu, Hipertansiyon, CPAP, Üst havayolu cerrahisi

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent disease characterized by total (apnea) or partial (hypopnea) intermittent upper airway obstruction for at least 10 seconds during sleep. During the apnea/hypopnea period, blood oxygen saturation decreases, and attacks are terminated by a hypoxia-induced sudden deep breath and awakening. This condition causes poor night-time sleep quality which is related with daytime sleepiness [1]. The American Academy of Sleep Medicine Task Force defines OSAS with an apnea-hypopnea index (AHI) >5, accompanied by excessive daytime sleepiness. The apnea-hypopnea index (AHI) is the average number of apneas and hypopneas per hour of sleep and is a parameter to indicate the severity of OSAS (AHI = 5–15 is mild, AHI = 16–30 is moderate, an AHI >30 is severe OSAS) [1,2].

Obstruction arises due to various anatomical problems in the upper airways, such as hypertrophy of palatine tonsils and adenoids (the most common cause in children), decreased tonus of the neck muscles, maxillary and mandibular retroposition, retrognathia and nasal obstruction caused by allergic rhinitis (AR) [2]. Authors also report other risk factors for OSAS, including premature birth, parental smoking for children/smoking for adults, alcohol abuse, low socioeconomic status, obesity, ageing and male gender [3,4,5]. Epidemiological studies reveal OSAS prevalence to be 3-7% and 2-5% among adult males and females worldwide, respectively [4]. Considering the substantial risk of morbidity and mortality, these rates are remarkable for health care providers. Late or undiagnosed OSAS and neglected treatment may cause significant complications, such as cognitive dysfunction, decreased work performance, and neurological, metabolic, and cardiovascular diseases [2,4,5]. Owing to its high prevalence and serious complications, OSAS is acknowledged as a public health problem.

How to diagnose OSAS?

Early diagnosis of OSAS is important to prevent serious complications. The first step of diagnosis in patients with suspected OSAS is to obtain a detailed history and conduct either the ‘Epworth Sleepiness Scale’ or ‘Berlin Questionnaire’, both of which are self-administrated. The former measures the patient's level of daytime sleepiness [6] and the latter determines the risk factors for sleep apnea [7].

The common diagnostic test for OSAS is overnight polysomnogram. It records multiple signals, including heart rate, breathing rate, electroencephalogram (EEG), electromyogram (EMG), oronasal airflow and oxygen saturation to diagnose sleep disorders in a sleep laboratory [4,8]. Because most of the patients are unaware of their pathological situation-especially patients that live/sleep alone, 70-80 % of OSAS cases remain undiagnosed [9].

OSAS and cardiovascular diseases

Polysomnographic follow-up studies indicate that hypoxia induced apnea-hypopnea periods during night sleep result in short-term changes in cardiovascular parameters, such as heart rate (HR) and blood pressure (BP) [8]. One of the most common complications of long-term untreated OSAS are cardiovascular problems, including nocturnal or persistent systemic hypertension, cardiac ischemia, pulmonary hypertension, congestive heart failure, stroke, and arrhythmia [5,10]. Vascular damage, such as increased carotid wall thickness and decreased arterial elasticity are also serious complications of OSAS related with high morbidity and mortality [11].

The mechanism underlying the relationship between OSAS and cardiovascular diseases is multifactorial. Because of many confounders such as age, obesity and smoking which take part in etiologies of both OSAS and cardiovascular diseases, it is difficult to differentiate the cause-effect relationship between the two diseases. However, there is increasing evidence that the comorbidity of OSAS and cardiovascular diseases arise independently from the confounders [5,12].

Is OSAS an independent cause of hypertension?

OSAS is known as the most common cause of secondary hypertension and remittent hypertension-related organ damage [13]. Rates of hypertension among OSAS patients range from 35% to 80%, depending on severity and duration of untreated OSAS [8]. On the other hand, 40% of hypertensive patients are also suffering from OSAS [14].

How can OSAS trigger the increase in BP? The first theory of this complex mechanism is the dysregulation of cardiovascular autonomic innervation due to sympathetic surge [8]. Apnea/hypopnea periods decrease blood oxygen levels, and hypoxia stimulates the medullary cardiorespiratory centers via chemoreceptors on the carotid body. Catecholamine surges during sleep effect autonomic cardiac modulation and cause a transient increase in heart rate and BP [15]. The indicator of severity of hypertension is considered as the hypoxia level attributed to apnea duration. Longer apnea durations cause deeper hypoxia and stronger sympathetic activation, and consequently, higher BP [13]. Also, a decrease in the sensitivity of baroreceptors and pulmonary receptors that affect cardiovascular reflexes was reported, probably due to activation of chemoreceptor reflexes [16]. Another mechanism which probably affects the sympathetic system is negative intrathoracic pressure, which occurs due to breathing against upper airway obstruction. This generates mechanical stress on the heart and large arteries by increasing left ventricular transmural pressure [1].

The second theory is oxidative stress, which increases during periodic nocturnal hypoxemia, and is thought to induce inflammatory reactions and endothelial damage. Previous studies provided lots of evidence that inflammatory process caused by OSAS takes part in the pathogenesis of hypertension. Troncoso Brindeiro et al. [17] inspected the results of sleep apnea models in rats, which were exposed to eucapnic intermittent hypoxia during sleep, and observed the secretion of excessive vascular reactive oxygen species, increased plasma endothelin-1 levels and elevated arterial BP. All were normalized after reducing oxidative stress by administration of superoxide dismutase mimetics. Endothelin-1 causes hypertension by altering endothelial function and reducing elasticity of the arterial wall. Higher levels of TNF-α (a cell-signal protein that takes part in systemic inflammation), neuropeptide-Y (a neurotransmitter in the central nervous system and a co-transmitter of noradrenaline, which increases BP) [18] and increased platelet/lymphocyte ratio

(a new biomarker for systemic inflammation) accompanying increased platelet distribution width (PDW) [19] were found in patients with OSAS-induced hypertension compared to controls and those with hypertension without OSAS.

Renin-angiotensin-aldosterone system (RAAS) activation is one of the theoretical mechanisms underlying hypertension with OSAS. There are limited data on this mechanism, but most of them point to the accuracy of this theory. A novel study [20] demonstrated that renal RAAS activity, which was measured by the level of reno-vasoconstriction, due to the effect of angiotensin II, and urine analytes associated with the RAAS signaling pathway were increased in patients with OSAS-related hypertension. In a similar study [21], alterations in effective renal plasma flow (ERPF) because of angiotensin II effect- another indicator of RAAS activity, was found to increase significantly in OSAS-related hypertension, but not in OSAS patients. OSAS can be related with several types of hypertension, which are explained below:

1. Nocturnal hypertension (NH): NH is an abnormal circadian rhythm-related BP which increases during night sleep. In normotensive subjects, nighttime BP is 10-20 % lower than daytime BP, due to the circadian rhythm of neurohumoral mechanisms. However, obstructive sleep apnea episodes trigger unusual night-time BP surges [22]. A night-time BP >110/65 is diagnosed as NH, according to the new 2017ACC/AHA guidelines [23]. Several studies indicate that remittent hypertension, especially elevations in nighttime BP levels and night-day ratio has the highest risk for end-organ damage and mortality caused by cardiovascular diseases [12,22,24].

2. Persistent hypertension (PsH): This type of hypertension is defined as high arterial BP levels (generally both systolic and diastolic) despite medical therapy with 3 antihypertensive drug combinations, including one diuretic, with all drugs at optimal doses. One third of hypertensive patients meet these criteria and OSAS is common in PsH patients. PsH is positively correlated with the severity of OSAS [1,25]. In several studies, treatment of OSAS was shown to decrease BP levels in PsH patients [25,26].

3. Masked hypertension (MH): MH is a type of hypertension with normal office BP measurements, but high ambulatory BP that can only be evaluated by ambulatory BP monitoring (ABPM). MH is often overlooked in OSAS patients, but it should be investigated in all patients with BP levels of 125/83 and above. In a current study, 30% of patients newly diagnosed with OSAS without previously known cardiovascular disease were shown to have MH by measuring 24h-ambulatory BP. This was almost equal to the rates of continuous hypertension (35.4%) [27].

4. Pulmonary hypertension (PH): OSAS-induced PH is not as common as systemic hypertension, but its prognosis is worse when untreated. Hypoxia-induced pulmonary BP elevation is thought to stem from hypoxic pulmonary vasoconstriction [28]. Pulmonary hypertension causes right ventricular distension, which affects left ventricular filling and stroke volume. Between 17-42% of OSAS patients suffer from daytime PH, and it was proven that complication rates of PH accompanying OSAS are high, including increase in right cardiac afterload, cardiac arrhythmia, or ischemic heart disease [29].

Therapeutic approach to OSAS-related hypertension

Lifestyle changes

The first and the most crucial step for attenuating severity of both OSAS and OSAS-related hypertension is weight loss. Obesity is a common risk factor for both OSAS and hypertension [1]. More than 60% of OSAS patients are overweight [30]. Follow-up studies demonstrate that weight loss increases the effectiveness of therapeutic techniques of OSAS treatment, particularly in patients with a body-mass index of (BMI) >25 [31]. The other beneficial modifications are giving up smoking, alcohol, and bedtime sedative-tranquilizers. Tobacco smoking is found to be related with sleep-disorders including snoring and OSAS, probably due to inflammation and increased reactivity of the upper airway, and it has a synergistic effect with OSAS on causing cardiovascular disease [32]. Many studies agree that alcohol and sedative-tranquilizer drug administration before bedtime decreases oropharyngeal muscle tone and disrupts nocturnal respiration by causing apnea-hypopnea periods [33,34].

CPAP (Continuous Positive Air Pressure) therapy

CPAP therapy is administered with a mask connected to a flow generator to keep airways open with the help of positive pressure. This is the most appropriate procedure for patients with moderate (AHI>20) and severe (AHI>30) OSAS, and obese patients with nocturnal hypertension. Although CPAP therapy intolerance is not rare, it is still the gold standard treatment for elective cases [35]. Researchers observed that CPAP therapy is effective in both systemic [36] and pulmonary hypertension [27] induced by OSAS. It is also shown to increase baroreceptor sensitivity [16], reduce renal RAAS activity [20], and improve endothelial function appraised by flow-mediated vasodilatation process [37] in OSAS patients with high cardiovascular risk by reduction of oxidative stress after long-term therapy.

Antihypertensive drugs

Moderate and severe OSAS patients with hypertension who develop intolerance to CPAP therapy are advised to administer antihypertensive drugs to prevent hypertension-induced target organ damage. Twenty-four hours of BP control must be provided both for nocturnal and persistent hypertension by selected daytime or nighttime doses of antihypertensives [38]. Because of inadequate evidence, there is no consensus regarding which antihypertensive drugs or which combinations should be involved in treatment protocol of OSAS-related hypertension.

Upper airway surgery

Surgical approach for OSAS is a promising option for the patients who have failed or could not tolerate CPAP therapy. The surgery basically aims to reduce or if possible, remove the obstructions in the upper airway (nasopharynx, oropharynx, or hypopharynx). The novel surgical procedures include reconstruction of nasal bones or cartilages, uvulopalatal flap (UPF), uvulopalatopharyngoplasty (removing excess tissue from palates and pharynx), laser-assisted uvulopalatoplasty, palatal implants, mandibular osteotomy, tongue reduction procedures (radiofrequency tissue reduction or reduction glossectomy), hyoid myotomy suspension, maxillomandibular advancement (enlarges retrolingual airway), adenoidectomy, tonsillectomy

etc.) [35,39]. Adenotonsillectomy is the most common first-line therapy for children with OSAS, for it improves respiratory parameters with high success rates, as measured by polysomnography [40]. In adults, reconstructive surgeries are considered Phase-1 surgeries and maxillomandibular advancement is considered Phase-2. The success rates of Phase-1 and 2 surgeries are reportedly 50-60% and 90%, respectively [41]. Resuli [42] investigated the effects of upper airway surgery on adults diagnosed with OSAS-related persistent hypertension. He evaluated 42 patients who had undergone uvulopalatopharyngoplasty (UPPP) for the treatment of mild and moderate OSAS in the 6th postoperative month and reported a significant decrease in arterial BP levels and the doses of antihypertensive drugs needed for BP control.

Conclusion

OSAS is frequently associated with a group of cardiovascular diseases including secondary hypertension. Although they have common etiological factors, such as older age, male sex, obesity, and smoking, OSAS seems to be an independent cause of hypertension. Growing number of cardiovascular morbidities is a frequent problem worldwide, and treatment of OSAS can reverse the effects of related hypertension. Therefore, early diagnosis and treatment of this combined pathology is gaining importance.

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