OBSTRUCTIVE SLEEP APNEA AS A RISK FACTOR FOR SYSTEMIC ARTERIAL HYPERTENSION

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Abstract
Obstructive sleep apnea (OSA) is a prevalent sleep disorder that impacts a considerable proportion of people around the world, and is often associated with other health conditions including obesity, diabetes and cardiovascular diseases. OSA is an important risk factor for developing hypertension as it leads to cyclical oxygen desaturation, sympathetic hyperactivity, poor sleep quality, frequent microarousals and daytime drowsiness. This review aims to present updated knowledge of the relationship and pathogenic association between sleep apnea and hypertension.
Keywords: *obstructive sleep apnea, systemic arterial hypertension, continuous positive airway pressure.*

Rezumat
Sindromul de apnee de somn este o boală a somnului cu o prevalență crescută, ce are un impact semnificativ asupra unui număr mare de persoane la nivel mondial, fiind frecvent asociat cu alte patologii precum obezitatea, diabetul sau bolile cardiovasculare. Sindromul de apnee de somn este un factor de risc important în dezvoltarea hipertensiunii arteriale, determinând desaturare ciclică în oxigen, hiperactivitate simpatică, calitate scăzută a somnului și somnolență diurnă. Acest review își propune să prezinte date actuale referitoare la relația și patogenia dintre apneea de somn și hipertensiunea arterială.
Cuvinte cheie: *sindrom de apnee de somn, hipertensiune arterială sistemică, presiune pozitivă continuă în căile aeriene.*

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Introduction

Obstructive sleep apnea (OSA) is distinguished by recurrent and intermittent upper airway obstruction episodes that occur during sleep. These episodes involve either complete (apnea) or partial (hypopnea) obstruction of airflow and occur more than five times per hour resulting in cyclical oxygen desaturation, sympathetic hyperactivity, poor sleep quality, frequent microarousals and daytime drowsiness[1]. The apnea-hypopnea index (AHI) is a metric used to assess the severity of obstructive sleeping. It categorises OSA into three levels: mild (ASHI 5-10 events/hour), moderate (AHI 15-30 events/hour), and severe (AHI over 30 events/hour). OSA is associated with male gender, advanced age, and obesity, with obesity being the sole significant modifiable risk factor. Within a cohort trial involving 690 participants, a ten percent increase in body weight was linked to an almost 32% elevation in AHI. Furthermore, even moderate weight management proved to be successful in decreasing the occurrence of sleep apneas[2].

Obstructive sleep apnea (OSA) impacts a significant proportion of the worldwide population, diminishes their quality of life, and heightens the likelihood of accidents occurring during the day and in the job. Nearly 1 billion people worldwide are estimated to have OSA. Around 425 million individuals aged 30 to 69 suffer from moderate to severe OSA, which is characterised by experiencing 15 or more episodes per hour[3]. According to reports, the prevalence of obstructive sleep apnea in the United States is estimated to be 25-30% among men and 9-17% among women. OSA prevalence varies among different ethnic groups being more common in Hispanic, Black, and Asian populations compared to other racial or ethnic groups[4].

OSA is acknowledged as a distinct risk factor for cardiovascular disease and is linked to coronary artery disease, arrhythmias, heart failure, and high blood pressure. It is also associated with metabolic disorders which themselves are closely associated with cardiovascular pathology[5].

The identification of individuals with obstructive sleep apnea who are most susceptible to hypertension can be achieved by the measurement of oxygen desaturation rate (ODR). The term "ODR" refers to the change in the percentage of pulse oxyhemoglobin saturation (SpO2) per second that occurs after an episode of apnea or hypopnea[6]. In a clinical experiment conducted in 2020, a total of 102 individuals diagnosed with severe OSA were involved. The trial findings indicated a significant association between rapid ODRs and the severity of both essential and resistant hypertension. In the fast ODR group was

registered a significantly higher systolic blood pressure than in the slower ODR group (while awake systolic blood pressure was 149.9±18.3 vs 131.8±15.6 mmHg; while asleep: 149.6±19.9 vs 128.7±15.6 mmHg; both P<0.001). In addition to that fast ODR correlates with higher prevalence of essential hypertension compared to slow ODR (74.0% vs. 26.9%, P<0.001)[6].

OSA and hypertension frequently coexist in many individuals and one condition heightens the likelihood of the other. Both are associated with stroke, heart disease and premature death. In a study from 2018 assessing OSA prevalence in 215 patients already diagnosed with hypertension, 81,9% were found with new onset of OSA[7]. Another research that used polysomnography data from 304 individuals diagnosed with hypertension but without a preexisting diagnosis of obstructive sleep apnea revealed that hypertension is linked to diminished sleep effectiveness and quality, reduced average and minimum oxygen saturation during episodes of apnea, elevated AHI, and an increased oxygen desaturation index. The latter is defined as the frequency of apneic events per hour that result in a reduction of oxygen saturation by at least 4% from the initial level[8]. In a study from 2020 with 4.500 individuals with OSA was concluded that even mild OSA increase by 78% the probability of developing hypertension in comparison to control individuals without OSA[9].

OSA was recognized as an identifiable cause of hypertension by The Join National Committee on High Blood Pressure in 2003[10]. Although there is a strong correlation between obstructive sleep apnea and hypertension, around 80% of middle-aged persons with moderate to severe OSA remain undetected. This underdiagnosis can likely be attributed to inadequate screening methods and the difficulty associated with polysomnography[11]. The estimated prevalence of OSA varies by gender: 6-19% among females, 13–33% among males, and 90% among geriatric men[12].

Mechanisms of Disease

The pathophysiology starts with reduced or stopped airflow to the lungs causing transient hypoxia and hypercapnia. During normal breathing, when inhaling, the diaphragm contracts and creates negative intrathoracic pressure which help draw air into the lungs, reducing the pressure within the thoracic cavity. Oromyopharyngeal obstruction is characterised by persistent diaphragmatic contraction, an elevation in negative intrathoracic pressure, and the formation of a pathological transmural pressure gradient with the intravascular compartment, specifically within the thoracic blood vessels. Vasodilation occurs in the blood vessels as a consequence of the pressure gradient, leading to a reduction in both intravascular pressure and right atrial filling pressure. Furthermore, stimulation of endothelial baroreceptors results in the transmission of general visceral afferent signals to the nucleus tractus solitarius, which is situated in the ventral medulla. By stimulating sympathetic nervous activity (SNA), heart rate, renin-angiotensin activity, and blood pressure are all increased[13]. The SNA plays a crucial role in regulating blood pressure and it preferentially increases diastolic blood pressure while systolic blood pressure elevation is caused by atherosclerotic, noncompliant arteries. Obesity and AOS stimulate SNA, therefore increase morning diastolic blood pressure[14]. In time, chronic elevated blood pressure leads to vascular

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dysfunction and insensitive baroreceptors which will further inhibit the reflex dipping phenomenon.

In healthy individuals blood pressure naturally lowers at night by around 10 to 20%. This phenomenon is referred to as “blood pressure dipping" and it is part of the circadian rhythm helping the body rest and recover during sleep[15]. The dipping phenomenon can be observed during sleep, when the patients are lying in a horizontal position and it involves changes in fluid distribution. Fluids in the legs shift in a rostral direction increasing carotid intravascular fluid volume. The carotid baroreceptors are triggered and reflexively reduce the activity of SNA, leading to a nocturnal decrease or dip in blood pressure. However, individuals with severe OSA have blood pressure dips of less than 10%, called a "nondipping" blood pressure pattern because the elevated SNA activity secondary to the obstruction of the upper airways can antagonize the natural dipping phenomenon, causing elevations in the intravascular pressure[16]. The risk for cardiovascular problems increases in individuals with nondipping blood pressure pattern. Many OSA patients experience a sudden and pronounced elevation of their blood pressure upon waking, which can increase the risk of cardiovascular events such as heart attacks or strokes, particularly in those with underlying hypertension[17]. OSA doesn't just impact blood pressure at night but as the severity of sleep apnea increases, daytime blood pressure tends to rise.

The severity of OSA is linked to body mass index and metabolic syndrome and these two correlate with hypertension. Gut dysbiosis found in metabolic syndrome may play a role in OSA. OSA leads to increased nocturnal awakenings, causing sleep fragmentation, energy expenditure, daytime sleepiness and fatigue. In light of this, individuals may encounter a need for energy-dense food items that possess elevated levels of fat, carbs, and salt, all of which exert an influence on the composition of the gut microbiome. Dietary habits together with chronic hypoxia may lead to a change in the composition of the gut microbiome stimulating the growth of foreign microbials within the gut. Neo-colonization within the gut may lead to immune derangements which could exacerbate OSA severity[18].

The change in gut microbiome exerts an endocrine effect by the way of gut-brain axis and alters the respiratory drive and mood. In a 2019 study on animals analyzing consequences of comorbid OSA and a diet high in salt used to simulate hypertension, it was shown that Lactobacillus rhamnosus colonies (the probiotics that are beneficial to gut microbioma) were in lower quantity in the rats exposed to high salt diet and apnea. In addition to this, proinflammatory citokines

like IFN gamma in the blood were increased in the animals exposed to high salt diet and apnea while anti inflammatory citokine levels TGFβ-1was reduced. The cytokine imbalance was rectified when the experimental animals were replenished with Lactobacillus rhamnosus colonies[19].

In OSA there is an upregulation of the inflammatory mediators as a consequence of chronic hypoxia, endothelial damage and gut dysbiosis. Based on a meta-analysis conducted in 2015, it was observed that individuals diagnosed with OSA exhibit elevated levels of inflammatory markers and carotid-femoral pulse wave velocities, which serve as indicators of arterial stiffness, as compared to patients without OSA [20].

In OSA the recurring upper airway collapse leads to intermittent hypoxia which stimulate the release of renin from the kidneys, further activating the renin-angiotensin aldosterone system (RAAS). A meta-analysis from 2016 found that individuals with OSA have higher plasma levels of angiotensin II than in controls and elevated levels of aldosterone, specifically in patients with hypertension[21]. High levels of aldosterone increase fluid retention causing edema of the nasopharyngeal tissue which narrows the upper airway, further exacerbating OSA[22].

The 2016 update by the Endocrine Society to primary hyperaldosteronism screening guidelines, which includes all patients with concomitant hypertension and OSA, reflects the recognition of the potential interplay between these conditions and their impact on health.

Treatment of OSA associated with hypertension involves a multifaced approach aimed at addressing both conditions simultaneously to improve overall health. Antihypertensive medications play a crucial role in managing blood pressure among individuals diagnosed with hypertension. However, in cases where OSA is the primary cause of hypertension, patients may derive greater benefits from therapies that specifically target the correction of nocturnal apneic episodes. However, it is important to note that antihypertensive drugs, such as ACE inhibitors, can significantly contribute to enhancing blood pressure regulation in these particular individuals[23].

CPAP therapy is a highly effective treatment for OSA by delivering continuous stream of air into the distal alveoli of the respiratory system, helping to maintain alveolar patency. The benefits of CPAP therapy extend beyond alleviating OSA symptoms and can have positive effects on cardiovascular health, including reducing arterial stiffness, lowering hypertension and improving vascular inflammation. In long-term CPAP therapy on average the variable reduction in systolic and diastolic blood pressure ranges from 2.0 to 2.5 mmHg and 1.5 to 2.0 mmHg while using 24-h blood pressure monitoring. A decrease in systolic blood pressure of 2-3 mmHg is linked to a mortality reduction of approximately 4-8%[24]. It is crucial that individuals with hypertension and sleep apnea collaborate with healthcare professionals in order to address both conditions comprehensively. Effective management of sleep apnea can reduce the risk of complications associated with the condition and improve cardiovascular health as a whole.

Conclusions

Obstructive sleep apnea and hypertension are frequently comorbid conditions having interconnected pathophysiology and both have been associated with stroke, heart disease and premature death. The identification of one condition elevates the

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likelihood of obtaining a diagnosis for the other. Early diagnosis and management of obstructive sleep apnea leads to improved outcomes in the management of hypertension, morbidity, and mortality.

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