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REVIEW ARTICLE

Cardiovascular diseases associated with obstructive sleep apnea syndrome

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Summary

Obstructive Sleep Apnea (OSA) is a syndrome characterized by repeated episodes of breathing cessation during sleep, which can be partial (hypopneas) or complete (apneas). Intermittent hypoxia is the fundamental pathophysiological mechanism in the development of all associated diseases with obstructive sleep apnea. OSA is linked to various forms of cardiovascular diseases, and their association is correlated with poorer health outcomes. It is present in as much as 40% to 60% of patients with pre-existing cardiovascular diseases, making the causal relationship between cardiovascular diseases and obstructive sleep apnea the focus of this article.

Keywords: obstructive sleep apnea, cardiovascular diseases, intermittent hypoxemia

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INTRODUCTION

Obstructive sleep apnea (OSA) is a syndrome characterized by recurrent episodes of partial or complete collapse of the upper airways during sleep. At the moment of collapse, the airflow through the airways is reduced or completely absent despite continuous efforts to inhale (1).

The most likely reasons for the collapse of the airways include the anatomy of the upper airways, the ability of the dilator muscles of the upper airways to respond to respiratory challenges during sleep, the tendency to wake up from increased respiratory drive during sleep (arousal threshold), and the stability of the breathing control system. The consequence of reduced airflow through the airways is inadequate alveolar ventilation, leading to poor gas exchange and increased activity of the sympathetic nervous system (1,2).

Snoring and interruptions in breathing during sleep lead to excessive daytime sleepiness and a lack of concentration which are characteristic features of patients with obstructive sleep apnea.

Obstructive sleep apnea is a serious condition associated with various metabolic disorders linked to increased mortality. Furthermore, there is evidence indicating that it represents an independent risk factor for a range of adverse cardiovascular outcomes (3). Cardiovascular diseases (CVD) are widely prevalent in the general population and constitute a leading cause of mortality. Therefore, significant attention is given to risk factors influencing their development and subsequent prevention (4). It is estimated to affect 34% of men and 17% of women in the general population, and 40% to 60% of patients with CVD (5).

Mechanisms linking OSA and CVD are not yet fully elucidated. A spectrum of different factors is involved, such as increased sympathetic activity, changes in intrathoracic pressure, and oxidative stress. One piece of evidence supporting a causal relationship between OSA and CVD is the alterations in blood pressure values and the improvement in left ventricular systolic function after continuous positive airway pressure (CPAP) therapy (6).

PATHOPHYSIOLOGY

As previously mentioned, intermittent hypoxia during the night is the fundamental pathophysiological mechanism in the development of associated diseases in patients with this syndrome. One of the main pathophysiological mechanisms of cardiovascular diseases in OSA is sympathetic activation in response to intermittent ischemia, driven by increased activity of chemoreceptors at the carotid bodies. This subsequently influences the development of an imbalance in myocardial oxygen demand and supply (7).

Additionally, increased oxidative stress is one of the most commonly described mechanisms responsible for the development of cardiovascular consequences. In normal conditions, there is an equilibrium between free radicals and antioxidants, and disrupting this balance leads to a disturbance known as oxidative stress.

Oxidative stress exerts its harmful effects in multiple ways, either by activating NADPH oxidase and synthesizing superoxide, which impacts the reduction of nitric oxide (NO), or by increasing the oxidation of biological compounds such as lipids, proteins, and DNA, or by reducing the activity of antioxidant enzymes (8).

NO is the primary vasodilator synthesized in the endothelium and it possesses abundant vasoprotective properties, including the inhibition of platelet aggregation and the expression of adhesion molecules. Due to its clear and well-known effects, the consequences of NO deficiency primarily involve elevated blood pressure values.

In patients with OSA, elevated levels of 8-isoprostane, compounds similar to prostaglandins, have been observed. The formation of isoprostanes involves free radicals as catalyzing agents in the reaction. Isoprostanes are compounds that enhance vasoconstrictor tone, thereby increasing the likelihood of developing arterial hypertension in patients with OSA (7). Systemic inflammation and its effects are crucial aspects in patients with OSA. In addition to everything mentioned earlier, intermittent hypoxia also induces the activation of inflammatory cells and the release of inflammatory mediators.

Vascular endothelium can be damaged by various stressors, including free oxygen radicals, blood pressure force, circulating cholesterol, or fatty acids. Endothelial injury stimulates the expression of leukocyte adhesion molecules and endothelial adhesion molecules, initiating the well-known process of atherosclerotic plaque formation, which is a prerequisite for the development of atherosclerosis (8).

A significant number of patients with OSA have metabolic syndrome, especially those who are obese. Elevated levels of triglycerides along with high LDL cholesterol values carry a high cardiovascular risk, primarily due to the atherosclerotic process. Studies have also shown that endogenous cholesterol synthesis is increased in obese individuals with OSA (9). Insufficient activity of the lipoprotein lipase enzyme is considered responsible for elevated LDL cholesterol levels. The activity of this enzyme is under the control of insulin, cortisol, and adrenaline. Therefore, it is crucial to emphasize the role of OSA in insulin resistance (10,11).

CARDIOVASCULAR DISEASES AND OBSTRUCTIVE SLEEP APNEA

From everything previously stated, we can conclude that unregulated blood pressure values are a hallmark in patients with OSA and are present in about 50% of patients.

What is characteristic are hypertensive episodes that occur during the night with the absence of the morning physiological blood pressure drop, otherwise known as non-dipper hypertension. They are often poorly controlled with standard antihypertensive therapy unless the syndrome itself is adequately treated. Up to 30% of hypertensive individuals may suffer from unrecognized OSA. The prevalence of hypertensive crises in patients with coexisting OSA and hypertension is as high as 15.7% (12,13).

In addition to the various etiologies previously described, one of the more serious consequences in patients with OSA is the development of manifest heart failure (3). As previously mentioned in the text, a characteristic feature of OSA is the interruptions in breathing during sleep, which occur despite the patient's inspiratory effort. At the moment of effort, there is a drop in intrathoracic pressure, leading to hemodynamic consequences. The decrease in intrathoracic pressure increases the pressure in the left ventricle, raising afterload and causing distension of the right ventricle. This, in turn, shifts the interventricular septum to the left, affecting the filling of the left ventricle and ultimately contributing to a reduction in stroke volume (3,14).

The combination of increased afterload on the left ventricle and a faster heart rate due to heightened sympathetic activity leads to a mismatch between myocardial oxygen supply and demand. This acute condition predisposes the patient to cardiac ischemia and arrhythmias, and chronically it can result in left ventricular hypertrophy and the development of heart failure (14).

Increased sympathetic tone occurs during each episode of upper airway obstruction and remains present even during waking moments in patients with OSA. Sympathetic discharges can provoke abnormal electrical activity in the atria. In addition to acute mechanisms occurring during each obstructive event, OSA can lead to cardiac remodeling, which, in turn, increases the susceptibility to cardiac arrhythmias and, of course, the possibility of sudden cardiac death as the most severe complication (15).

In severe forms of OSA, the frequency of arrhythmias can be as high as 50%. The most common are recurrent atrial fibrillation, nonsustained ventricular tachycardia (VT), sinus arrest, second-degree AV block, and premature ventricular contractions (PVCs). It is important to note that bradyarrhythmia is a common type of arrhythmia in patients with OSA and it is a consequence of increased vagal tone. A European multicenter study showed a high prevalence of obstructive sleep apnea syndrome, approximately 60%, among patients with implanted pacemakers, regardless of pacing indications (16).

It is crucial to emphasize that the occurrence of coronary heart disease and sudden cardiac death is more common in patients with OSA compared to the general population. It is characteristic that patients with OSA who die suddenly most often pass away while sleeping between 10 PM and 6 AM, in contrast to other patients who typically experience sudden death in the early morning hours (15,17).

DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA SYNDROME

To prevent and timely treat the described consequences before the onset of fatal complications, it is essential to promptly diagnose obstructive sleep apnea. The gold standard for diagnosing this syndrome is polysomnography, which precisely quantifies the extent of respiratory and sleep disorders.

To diagnose obstructive sleep apnea, a patient must experience more than 5 respiratory interruptions per hour, accompanied by desaturation and lasting for at least 10 seconds. Depending on the number of respiratory interruptions during sleep, whether they are partial (hypopneas) or complete (apneas), OSA is classified as mild (AHI 5-15/h), moderate (AHI 15-30/h), or severe (AHI over 30/h). To facilitate the diagnostic process and assess the severity of obstructive sleep disease, several clinical questionnaires have been developed, such as the STOP-BANG questionnaire, Epworth Sleepiness Scale, and Berlin questionnaire (18).

TREATMENT

The treatment of obstructive sleep apnea is complex and includes positional therapy, behavioral therapy, intraoral prosthetic systems, surgical treatment, as well as positive pressure therapy using CPAP and BIPAP devices. The choice of therapeutic modality depends on several factors, primarily the severity of symptoms assessed through clinical questionnaires, the patient's comorbidities, and, of course, the degree of diagnosed OSA. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP) therapy is undoubtedly considered the gold standard for treating OSA and represents the first-line therapy for patients with moderate to severe OSA (19).

Prominent daytime sleepiness and nighttime symptoms tend to diminish after a short period of consistent CPAP use. After 3-6 months of continuous treatment, patients often experience improvements in memory and attention. Some studies provide evidence that CPAP treatment has a positive impact on cardiovascular outcomes. CPAP therapy significantly lowers diastolic and systolic blood pressure, thereby reducing the incidence of fatal cardiovascular events. In addition, insulin resistance and altered lipid profiles in the serum are closely linked to OSA. Although the effect of CPAP on metabolic changes is widely researched, the results are still inconclusive. Inflammatory responses, which significantly contribute to the atherosclerotic process, increasing cardiovascular

and cerebrovascular morbidity, are proven to be significantly reduced with CPAP treatment (20).

Taken together, these data indicate that CPAP is extremely effective in controlling the symptoms and consequences of OSA. Very few unwanted effects have been recorded, and they are mainly associated with discomfort from wearing the mask. It is crucial to note that the effectiveness of CPAP strictly depends on its consistent use, and recurrence of symptoms occurs within 1-3 days of discontinuing the treatment.

In addition to treating the underlying cause, in this case, obstructive sleep apnea, it is necessary to treat the consequences with the goal of reducing cardiovascular risk. Statin therapy and its benefits in preventing cardiovascular diseases are unquestionable. However, evidence regarding the positive effects of lipid-lowering therapy in patients with OSA is controversial. Various multicenter studies have been conducted, but significant improvements in endothelial function after 12 weeks of atorvastatin use in patients with severe OSA have not been observed. It is evident that statin therapy has improved blood pressure values, potentially impacting overall cardiovascular risk (9).

In clinical practice, PCSK9 inhibitors, along with statins, have been shown to reduce cardiovascular risk in patients with stable atherosclerotic cardiovascular disease or recent acute coronary syndrome. As a relatively new and insufficiently studied biomarker, the regulation of PCSK9 in OSA is still poorly understood (21).

In recent years, the effects of mesenchymal stem cells have been studied due to their potent regenerative, pro-angiogenic, and immunomodulatory properties. As known, repetitive hypoxia induces an inflammatory response, which is a precondition for the development of atherosclerosis. Studies on animal models have been conducted, and the results show that mesenchymal stem cells effectively alleviate vascular injuries, inflammation, and fibrosis caused by OSA. It is crucial to emphasize that their effectiveness needs to be demonstrated in clinical studies (22).

CONCLUSION

Obstructive sleep apnea is a syndrome associated with a significant number of comorbidities and is a crucial factor in their development. It is important to emphasize that this syndrome is not synonymous with snoring but it is a significant independent factor for the development of cardiovascular diseases, which can have a fatal outcome if not treated in a timely manner.

The authors contributed equally to this work.

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KARDIOVASKULARNE BOLESTI UDRUŽENE SA OPSTRUKTIVNOM BOLESTI SPAVANJA

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Sažetak

Opstruktivna apneja u snu (OSA) je sindrom koji karakterišu ponavljajuće epizode prekida disanja tokom spavanja pri čemu prekidi mogu biti delimični (hipopneje) ili potpuni (apneje). Intermitentna hipoksija je osnovni patofiziološki mehanizam u razvoju svih udruženih bolesti sa opstruktivnom apnejom u snu. OSA je povezana sa različitim oblicima kardiovaskularnih bolesti, a njihova udruženost je povezana sa lošijim zdravstvenim ishodom. Prisutna je kod čak 40% do 60% pacijenata sa već postojećim kardiovaskularnim oboljenjima zbog čega je tema ovog rada upravo uzročno posledična veza kardiovaskularnih bolesti i opstruktivne apneje u snu.

Ključne reči: opstruktivna apneja u snu, kardivaskularne bolesti, intermitenta hipoksemija

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