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What is the relationship between Obstructive Sleep Apnoea and cardiovascular disease? Pathophysiology and therapeutic strategies: A review of the literature

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ABSTRACT

Obstructive sleep apnoea (OSA) is a usual sleep disorder affecting millions of people worldwide. This condition is characteristic of recurrent episodes of upper airway obstruction during sleep. This condition results in intermittent hypoxia and also sleep fragmentation. Due to OSA, there is a range of adverse health outcomes, including chronic fatigue, daytime sleepiness, depression, and an increased cardiovascular risk. Cardiovascular diseases (CVD) include hypertension, coronary artery disease (CAD), myocardial infarction, stroke, arrhythmias, and other diseases. This syndrome can be potentially life-threatening. The pathophysiological mechanisms linking OSA to CVD are multifactorial, including but not limited to increased sympathetic activity, chronic inflammation, oxidative stress, and endothelial dysfunction, which is a part of the discussion in our review. The processes mentioned contribute to the development and progression of atherosclerosis, coronary heart disease, and heart failure. In addition, this review examines the efficacy of different therapeutic approaches for treating sleep apnoea. A considerable body of evidence from many studies indicates that the treatment of OSA has a two-fold effect: it alleviates the severity of apnoea but also reduces the risk of cardiovascular disease. Continuous positive airway pressure (CPAP) is the most important aspect of treating sleep apnoea, particularly in cases of moderate to severe severity. CPAP is an effective method for reducing disease severity, lowering blood pressure, and improving sleep quality. Therefore, the treatment of OSA is crucial in the prevention and treatment of cardiovascular diseases.

Keywords: Obstructive sleep apnoea, cardiovascular disease, heart failure, inflammation

1. INTRODUCTION

Obstructive sleep apnoea (OSA) is a breathing disorder that occurs during sleep. It leads to repeated episodes of complete (apnea) or partial (hypopnea) closure of the upper airway (Eckert and Malhotra, 2008). Apnoea is the full airflow suspension for a minimum of 10 seconds. This results in intermittent episodes of apnea or inadequate ventilation, precipitating a decline in blood oxygen levels and frequent awakenings from sleep. In 2023, researchers collected data on the prevalence of obstructive sleep apnea worldwide. The prevalence was estimated to be 54% (De-Araujo-Dantas et al., 2023). The prevalence of OSA increases with age and is also higher in individuals who are overweight or obese and have type 2 diabetes, hypertension, or upper airway abnormalities.

Obstructive sleep apnoea has proven to cause many adverse health effects, including chronic fatigue, daytime sleepiness, and depression. There is a positive correlation between obstructive sleep apnoea and an elevated risk of hypertension, myocardial infarction, stroke, arrhythmias, and many other diseases. OSA affects quality of life and is associated with a higher risk of premature death. The overnight polysomnogram is the most commonly used method for diagnosing OSA, but not the only one (Peppard et al., 2013; Punjabi, 2008). The severity of OSA can be quantified using the apnoea-hypopnoea index (AHI) which is the number of apnoeas and hypopnoeas and apnoeas per hour of sleep.

The severity classification is as follows: AHI 5.0-14.9 events per hour stands for mild OSA, AHI 15.0-29.9 events per hour for moderate OSA, and at least 30.0 events per hour for severe OSA (Peker et al., 2023). Cardiovascular disease (CVD) is a cause of hospitalization and mortality worldwide. In 2019 WHO reported that CVDs were responsible for 32% of deaths worldwide. Researchers confirmed the association between OSA and CVD by numerous studies. In this review, we will summarise the relationship between these two conditions. As the treatment of OBS is an essential aspect of cardiovascular disease prevention and therapy, the article will also focus on the above topic.

2. METHODOLOGY

The following paper offers a comprehensive analysis of the existing literature on the subject retrieved from the PubMed and Google Scholar scientific databases from January 2000 to May 2024. The research included meta-analyses, randomized controlled trials, and systematic reviews, with inclusion criteria based on publication date, topic relevance, and keywords. To identify pertinent articles, the search terms were employed including: "obstructive sleep apnoea", "cardiovascular disease", "coronary artery disease", and "heart failure".

3. RESULT AND DISCUSSION

Numerous articles were collected from the data set using keywords and then subjected to a title and abstract screening process. Ultimately, the comprehensive analysis of results and discussion includes 37 articles. The data analyzed pertained to the relationship between obstructive sleep apnoea and cardiovascular disease, comprising 19 articles. A total of 18 articles presented various treatment options. The following subsections present a summary of the information collected.

Association of obstructive sleep apnoea with acute/chronic coronary artery disease

The etiology of cardiovascular disease (CVD) associated with obstructive sleep apnoea remains incompletely understood. Researchers have shown that an increase in sympathetic activity, alterations in coagulation pathways, chronic systemic inflammatory processes, oxidative stress, and endothelial dysregulation may be essential factors in this context. Activation of a sympathetic nervous system represents a critical pathogenetic element in the development of CVD, particularly in the context of heart failure and atrial fibrillation. Research papers demonstrated that in patients with OBS, an increase in blood and urine catecholamine levels is related to the acuteness of the disease. Furthermore, healthy individuals exposed to intermittent hypoxia activate the sympathetic nervous system. Additionally, animal studies have highlighted the importance of the sympathetic nervous system in the metabolic and cardiovascular consequences associated with intermittent hypoxia (Arnaud et al., 2020).

Another mechanism that is relevant to the pathogenesis of CVD is chronic low-grade inflammation. Research papers have demonstrated that in patients with OSA, intermittent hypoxia stimulates the activation of inflammatory pathways, including the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the hypoxia-inducible factor 1 (HIF-1). Activating

inflammatory pathways results in elevated levels of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin 8 (IL-8). Researchers have also demonstrated that elevated levels of these cytokines lead to an increased risk of developing coronary heart disease. Increasing pro-inflammatory cytokines leads to an elevation in C-reactive protein (CRP) levels. CRP is a member of the acute-phase protein family and has a role in the immune response. CRP possesses pro-atherosclerotic properties, including the induction of adhesion molecule expression, cytokine secretion, and a reduction in NO production.

Moreover, evidence indicates that it can activate macrophages and complement. CRP represents a potential biomarker that scientists can employ in the clinical setting to ascertain cardiovascular risk. The relationship between interleukin-6 (IL-6) levels and OSA remains inconclusive due to discrepancies in the findings of various studies (Vitulano et al., 2013). Studies have demonstrated that the activation of the transcription factor HIF-1 can have harmful effects on the cardiovascular system. HIF-1 is an oxygen-sensitive transcription factor. It is present in all cells of the body. Hypoxia blocks the degradation of HIF-1 and leads to an increase in its concentration. Activation of this factor leads to increased production of endothelin-1, which contributes to increased blood pressure and cardiac damage. Endothelins have mitogenic, procreative, and atherogenic effects.

Studies in mice and preliminary clinical trials indicate that this mechanism is not the only factor contributing to the cardiometabolic consequences of OSA. Further research studies are needed to fully understand the role of HIF-1 in OSA (Belaidi et al., 2009). Another pathogenetic element of OSA and CVD is oxidative stress. ROS can come from exogenous or endogenous sources. Exogenous sources include, for example, air pollution, smoking, poor diet, and radiation exposure. Also, intermittent hypoxemia followed by reoxygenation can lead to the production of reactive oxygen species. ROS (Reactive Oxygen Species), which accumulate in the body as a result of the intermittent hypoxemia-reoxygenation associated with OSA, can induce oxidative stress, leading to the activation of NF-κB, a key regulator of inflammation that, as we know from the paragraphs above, plays a role in generalized chronic inflammation.

This activation results in increased expression of adhesion molecules (VCAM-1, E-selectin, and ICAM-1), contributing to endothelial damage and the development of atherosclerosis. Excess ROS in the body also leads to peroxidation of cell membranes, protein degradation, and DNA mutations, resulting in cellular damage to, for example, cardiomyocytes. Additionally, sleep disturbances associated with OSA can lead to vascular endothelial dysfunction. Oxidative stress and endothelial dysfunction together worsen vascular health, increasing the risk of acute coronary syndrome and other cardiovascular complications. Additionally, ROS can instigate inflammatory responses, resulting in the overproduction of pro-inflammatory cytokines, including IL-6 TNF-α, CRP, and others. It exacerbates endothelial dysfunction and promotes the development of atherosclerosis (Li and Ren, 2022).

Numerous studies have shown an association between OSA and ischaemic heart disease. We selected several studies describing this association. The first study assessed the incidence of nocturnal myocardial ischemia in patients with OSA and coronary artery disease. A total of 226 patients - 132 men and 94 women - were included in the study. Patients underwent coronary angiography and additionally had overnight sleep monitoring and Holter recording. As many as 59% of patients showed ST-segment depression, with 31% of these cases occurring at night. Research studies found an association between respiratory failure and ischemia in 12% of patients, with a higher prevalence observed in men and those with more severe respiratory failure. Importantly, scientists most commonly observed nocturnal ischemia after a series of respiratory events (Mooe et al., 2000).

Another study analyzed the correlation between OSA and heart failure and the incidence of coronary heart disease as well as heart failure. In this study, researchers followed patients for 8.7 years. The study included 1,927 men and 2,495 women. OSA was identified as a significant predictor of coronary heart disease (CHD) only in men aged 40-70 years, showing a 68% higher risk of coronary heart disease in those with AHI ≥30. In addition, OSA increased the risk of heart failure in men by 58% but had no such association in women. OSA is associated with an increased risk of heart failure in men, but the evidence regarding its association with coronary heart disease is inconclusive (Gottlieb et al., 2010). Other studies have assessed the impact of OSA on short- and long-term prediction in patients with acute coronary syndrome.

The first study evaluating the effect of obstructive sleep apnoea on severity and short-term prognosis in patients with acute coronary syndrome included 213 patients with OSA and 218 controls. The results demonstrated that patients with OSA exhibited elevated levels of troponin, a protein released by the damaged heart muscle, along with a higher prevalence of vascular disease and prolonged hospitalization. Additionally, researchers found a correlation between OSA and higher body mass index and hypertension. The study demonstrated that OSA can have a deleterious impact on the short-term prognosis of affected individuals (Barbé et al., 2015). The second study assessed long-term prognosis, which was similarly unfavorable for patients with OSA and acute coronary syndrome.

The study included a total of 529 patients. The findings revealed that patients with moderate to severe OSA exhibited elevated rates of hypertension, prolonged hospitalization, and an augmented probability of major cardiovascular incidents when compared to the control group (Jia et al., 2018). The above studies indicate a strong association between OSA and coronary heart disease. Further research on this issue is needed. Understanding the mechanisms linking OSA and coronary artery disease may contribute to developing more effective therapies for coronary artery disease in the future. In the context of patient care for those with cardiovascular disease, it is beneficial to ascertain whether or not OSA is present or to rule it out.

Association of obstructive sleep apnoea with heart failure

Obstructive sleep apnoea is a usual condition in patients with heart failure - it appears both with reduced left ventricular ejection fraction and preserved ejection fraction. Obstructive sleep apnoea has many consequences, including myocardial hypoxia, chronic inflammation, consequent oxidative stress, and excessive sympathetic activity. The above factors lead to progressive left ventricular dysfunction (Javaheri et al., 2020). In addition, fluctuations in intrathoracic pressure result in increased preload and afterload as well as decreased left ventricular filling. This results in the activation of the renin-angiotensin-aldosterone (RAA) system, which subsequently induces myocardial remodeling (Gleeson and McNicholas, 2022). The occurrence of sleep disorders in patients with heart failure (HF) is considerable, with figures ranging from 40 to 60 percent. Obstructive sleep apnoea accounts for approximately one-third of cases (Yeghiazarians et al., 2021).

Episodes of shallow breathing and apnoea cause changes in arterial blood gasometry and negative chest pressure changes. Furthermore, patients with heart failure (HF) and the presence of sleep-disordered breathing (SDB) have a poorer prognosis, are hospitalized more frequently, and also have a higher mortality rate compared to patients with HF alone. In addition, the diagnosis of OSA in patients with heart failure requires careful nocturnal monitoring because patients with both OSA and HF have less typical symptoms than patients with OSA alone (Lévy et al., 2022). A 2018 cohort study using nationwide databases from Denmark between 2000 and 2012 observed higher incidence rates of HF in patients with untreated sleep apnoea compared to patients treated with CPAP therapy in a population over 60 years of age (Holt et al., 2018). The Mendelian randomization (MR) trial from 2023 describing the impact of OSA on cardiovascular disease (CVD) highlights the possible role of apolipoprotein B (ApoB) as a mediator between OSA and heart failure.

This study aimed to demonstrate a causal relationship between CVD (including HF) and OSA in the general population. The Mendelian randomized (MR) analysis employed genetic variants derived from published genome-wide association studies (GWAS). Genetic variants are not affected by confounding factors such as body mass index, alcohol consumption, education, or nicotine dependence. Additionally, the role of circulating metabolites as possible mediators were investigated: Apolipoprotein AI, apolipoprotein B, serum total cholesterol, HDL cholesterol, and LDL cholesterol. The results suggest an adverse causal effect of OSA on heart failure. Additionally, ApoB may act as a mediator in the development of heart failure in patients with OSA. The analysis showed a mediating effect of Apo B of 9%. The phenomenon requires further study and provides an opportunity to understand better the potential causal relationship between OSA and HF (Li et al., 2023).

Therapeutic options

According to research studies, there are many therapeutic options for treating OSA. Depending on the chosen method, we can observe various effects. This chapter will present an overview of therapeutic options for the treatment of OSA with a focus on their effectiveness. The different therapeutic techniques are collated and presented in (Table 1). The treatment of obstructive sleep apnea has a significant impact on the risk of cardiovascular events. Based on scientific publications, we presented the most productive treatment options for each condition below.

Table 1 Therapeutic options for the treatment of OSA.

Therapeutic method	The mechanism of action	Treatment Efficiency in OSA
Lifestyle changes and weight loss - for all patients, regardless of the severity of	It is recommended to avoid the use of sedative and hypnotic medications, avoid sleeping in a prone position,	A longitudinal study in the Wisconsin Sleep Cohort showed that a 10% weight gain predicted a

the disease.	abstain from alcohol consumption during evening hours, quit smoking, and weight loss.	32% rise in AHI; while a 10% weight loss was related to a 26% reduction in AHI (Peppard et al., 2000).
CPAP - is the basis for OSA treatment, especially for patients with moderate to severe disease.	Continuous positive airway pressure (CPAP) is administered nightly via a nasal mask to keep the upper airway open.	The treatment has been demonstrated to reduce disease severity, somnolence, blood pressure, and the risk of motor vehicle accidents, and improves sleep quality (Patil et al., 2019).
Oral appliances (for example tongue-retaining devices and mandibular advancement devices) - for patients intolerant of CPAP with mild to moderate OSA.	Increase the upper airway volume and reduce pharyngeal collapsibility.	The treatment has been demonstrated to reduce sleepiness and AHI but is less effective than CPAP (Sharples et al., 2016). It has also been shown to reduce SBP and DBP (Bratton et al., 2015).
Upper airway surgery - for patients with significant findings in the laryngological examination or as a supplement to CPAP therapy.	For instance, surgical procedures such as uvulopalatopharyngoplasty and septoplasty are utilized for the correction of nasal septum deformities. In contrast, tonsillectomy is performed for the removal of the tonsils.	A small randomized controlled trial showed that uvulopalatopharyngoplasty was associated with a reduction in blood pressure in patients with resistant hypertension (Fehrm et al., 2017).
Hypoglossal nerve stimulation - for patients intolerant of CPAP with moderate to severe OSA.	The neurostimulator is implanted subcutaneously during a surgical procedure. It stimulates the hypoglossal nerve and prevents the collapse of the airways during sleep.	Decreases AHI, improving quality of life (Strollo et al., 2014; Costantino et al., 2020).

Hypertension

OSA frequently coexists with hypertension, primarily resistant hypertension, where up to 80% of patients may have OSA (Logan et al., 2019). The treatment of OSA, predominantly through CPAP, has resulted in a reduction in blood pressure. A meta-analysis showed a drop in systolic blood pressure (SBP) by approximately 2-3 mmHg and in diastolic blood pressure (DBP) by about 2-2.5 mmHg, with a more meaningful reduction observed during nocturnal hours (Fava et al., 2014). Other treatment methods, such as oral appliances, have also shown efficiency in reducing BP. A meta-analysis demonstrated a reduction of approximately 2-3 mmHg in SBP, DBP, and MAP (Iftikhar et al., 2013). Hypertension is a significant risk factor for cardiovascular disease, so its control is essential for preventing complications such as myocardial infarction and stroke.

The prevention of secondary cardiovascular disorders

In a meta-analysis from 2023, researchers demonstrated that the consistent utilization of CPAP (≥4 hours per day) in patients with OSA and concomitant coronary artery disease resulted in a reduced incidence of secondary cardiovascular events, including heart failure, myocardial infarction, and stroke. The researchers demonstrated the above effects particularly in the long-term follow-up period (Sánchez-de-la-Torre et al., 2023).

Heart failure

In heart failure, OSA can lead to worsening of symptoms. During CPAP therapy, patients with heart failure have demonstrated frequent improvement in the left ventricular function, as evidenced by an elevated ejection fraction and superior clinical outcomes. The

MACH study (Multicenter Obstructive Sleep Apnea and Cardiac Function Heart Failure Study) demonstrated that CPAP therapy has a significant increase in LVEF in patients with heart failure and OSA. This improvement was related to reduced heart failure symptoms and better blood pressure control (Polecka et al., 2023). Also, the CANPAP study (Canadian Positive Airway Pressure Trial) showed that patients using CPAP experienced an improvement in LVEF by several percentage points compared to the control group. However, it did not prove a valid impact on patient survival (Bradley et al., 2005).

Atrial fibrillation

OSA is related to a raised risk of arrhythmias, including atrial fibrillation, as a consequence of the pathophysiology of OSA, which can result in atrial remodeling and fibrosis. The treatment of OSA, primarily with CPAP, may result in a reduction of atrial fibrillation and reduce the risk of developing cardiovascular complications. A small-scale study demonstrated a decrease in heart rate variability during the initial night of treatment, irrespective of gender or weight (Kufoy et al., 2012). Furthermore, patients with atrial fibrillation and OSA, after CPAP therapy, exhibited a significantly reduced risk of atrial fibrillation return after catheter ablation with pulmonary vein isolation and a diminished likelihood of developing permanent atrial fibrillation compared to patients who did not use CPAP treatment (Trongtorsak et al., 2024).

Other Arrhythmias

CPAP treatment in patients with OSA can have a sensible effect on multiple types of arrhythmias, not just atrial fibrillation. A cohort study showed an association between the severity of OSA and the appearance of arrhythmias. It also showed that three months of CPAP therapy diminish the number of arrhythmic episodes (Varga et al., 2020). OSA has been demonstrated to increase the risk of sudden cardiac death (SCD), primarily through the induction of ventricular arrhythmias (Gami et al., 2013). Researchers have shown that CPAP treatment reduces this risk by stabilizing heart rhythm and reducing episodes of hypoxia (Domaradzki et al., 2022).

4. CONCLUSION

Obstructive sleep apnea is a common condition that affects a significant proportion of the global population. By causing chronic fatigue and insomnia, the disease significantly reduces the quality of life. The condition increases the risk of CVD, such as myocardial infarction, hypertension, arrhythmias, and heart failure. The above diseases can lead to premature death in patients, which is why prompt recognition and effective treatment of the disease is so important. OSA therapy, mainly through treatment with continuous positive airway pressure, has the effect of reducing episodes of apnoea and hypopnoea.

In addition, CPAP improves sleep quality, headaches, and chronic daytime fatigue. Treatment of OSA has a beneficial effect on the cardiovascular system, reduces the risk of serious events, and improves the overall prognosis of patients with OBS. Identifying patients with OSA is extremely important as it can prevent many adverse health effects. Further research is needed to develop the most appropriate and least disruptive therapies for these patients.

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Author's Contributions

Agata Pisklak: Conceptualization; software; resources; investigation; data curation; writing - rough preparation; supervision.
Joanna Sykuła: Methodology; resources; writing - rough preparation; visualization.
Natalia Zalewska: Investigation; writing - rough preparation; writing - review and editing.
Kinga Filipek: Formal analysis; resources; writing - review and editing.

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Informed consent

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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