

Wijata Aleksandra, Wydeheft Lidia, Janiak Michał, Fronc Kamila, Kędziora-Kornatowska Kornelia. The effect of obstructive sleep apnea on the cardiovascular system. *Journal of Education, Health and Sport*. 2022;12(6):39-50. eISSN 2391-8306. DOI <https://dx.doi.org/10.12775/JEHS.2022.12.06.003> <https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.06.003> <https://zenodo.org/record/6492257>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przystosowane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 13.04.2022. Revised: 20.04.2022. Accepted: 26.04.2022.

The effect of obstructive sleep apnea on the cardiovascular system

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Key words: obstructive sleep apnea; cardiovascular disease; atrial fibrillation; hypertension;

Abstract

Introduction: Obstructive Sleep Apnea is a disease entity that affects many aspects of life, but is often overlooked and underdiagnosed. OSA is defined as episodes of apnea-hypopnea that disturbs not only sleep, but also daytime functioning. Symptoms can be divided into night symptoms (not breathing, snoring, gasping, fragmented sleep) and daytime symptoms (fatigue, low concentration, morning headaches, decreased libido). Moreover, OSA through many mechanisms affects the cardiovascular system and leads to its dysfunction.

Purpose: The aim of this study is to draw attention to the often underdiagnosed disease entity, which is OSA, which, if left untreated, may lead to serious complications.

Material and methods: In 2022, the PubMed and Google Scholar databases were searched using the following keywords: OSA, apnea, cardiovascular disorders, arrhythmias and heart disease. Works in English with the most recent data have been selected.

Summary: OSA is strongly associated with cardiovascular disorders, moreover, in both cases, we find similar risk factors for these disorders. A correlation has been demonstrated between OSA and atrial fibrillation, hypertension, and arrhythmias. On the other hand, OSA is still underdiagnosed and more research is needed to understand the correlation between these diseases.

Introduction

Obstructive Sleep Apnea (OSA) is a common problem, which is connected with many illnesses, especially with obesity, hipercholesterolemia, diabetes mellitus type 2, cardiovascular diseases [1], depression and also posttraumatic stress disorder [2]. OSA is categorized by apnea-hypopnea index(AHI) as mild when 5-15 episodes of apnea-hypopnea appear, moderate when there are more than 15 to 30 events of AHI and severe: more than 30 of AHI per hour [3]. It occurs during sleep and reveals as episodic upper airway narrowing and obstruction and it is associated with arousals and oxygen desaturation [4]. Patients with OSA have specific symptoms during sleeping such as snoring, gasping, not breathing, fragmented sleep and during the day they feel fatigued, have morning headaches, low concentration, decreased libido and feel unrefreshed despite a long time of sleeping [4]. OSA refers to 14% of men and 5% of women in the United States and it occurs more often when people are older. There are also other risk factors such as obesity, male gender, smoking, use of alcohol, supine sleeping position and structural changes such as facia elongation and mandibular hypoplasia [5]. The average patient with OSA is obese man between ages about 45 to about 65 or postmenopausal female with loud snoring and somnolence during the day and to state if the patient has OSA could be used a STOP-BANG questionnaire [5,6]. This questionnaire considers snoring, tiredness, observed apnea, blood pressure, Body Mass Index (more than 35), age (more than 50 years old), neck circumference (greater than 40 cm) and gender (male) and if there are three or more positive responses, the patient should be evaluated as high risk of OSA[6]. An untreated or undiagnosed OSA could contribute to risky drowsy driving episodes and increased risk of mortality, incident stroke and cardiovascular diseases [4,7,8]. There are many treatment options depending on the cause and heaviness of OSA from weight loss, behavioral modification to continuous positive airway pressure and surgical methods [9].

There is a strong connection between OSA and heart dysfunction. Actually patients with OSA more often have coronary arteriosclerosis, which could be induced by activating proinflammatory factors. They also have ventricular hypertrophy, diastolic and systolic dysfunction and heart failure caused by intermittent hypoxia, the negative thoracic pressure and activation of sympathetic nervous system [10]. Furthermore, in OSA there are incidents of hypoxia and hypercapnia, then oxygenation which could induce atrial fibrillation [11]. Those mechanisms and oxidative stress, endothelial dysfunction and activation of the renin-angiotensin-aldosterone system occur in populations with OSA and hypertension [12]. Research shows that both in the general population and among healthcare professionals awareness is low on OSA [13,14], which contributes to rare diagnoses and treatment. Moreover, cardiovascular diseases are the most related to mortality and morbidity because of OS [15]. Therefore, there will be presented cardiovascular diseases relative to OSA and methods of treatment, based on the updates.

Effect of obstructive sleep apnea on arrhythmias, with particular emphasis on atrial fibrillation

AF (atrial fibrillation) is the most frequent kind of persistent arrhythmia, affecting over 33.5 million people worldwide. OSA is present in 21-74 percent of individuals with AF [16]. Sleep apnea is more common in males than in women across the world [17]. However, because OSA and AF have many of the same risk factors, the existence of one may encourage the development of another. As a result, it's unclear if this link is direct or mediated by common risk factors. Age and hypertension, were revealed to have a major role in the connection between AF and OSA in one meta-analysis. Both AF and OSA are linked to these elements in different ways. Although toddlers and teenagers can get OSA, the condition is more common in adults and becomes more prevalent as they become older [18]. Several studies have indicated the elevated risk of AF in patients with OSA, including the Sleep Heart Health Study, which compared 228 patients with severe OSA to 338 patients without OSA, and Gami et al retrospective study of 3,542 patients, which found that OSA is a significant factor of the incidence of AF. According to these research, the frequency of OSA in patients with AF is greater than in the general population. Guilleminault et al. used polysomnography plus 24-hour Holter monitoring to examine 400 individuals with severe OSA in one of the first and biggest investigations. They discovered that such atrial arrhythmias were just detectable during sleep but not while the individuals were up, suggesting that OSA and the arrhythmias are linked. Becker et al. evaluated 239 individuals with OSA utilizing polysomnography & 24-hour Holter monitoring in observational research (with no control group) and found that 7.5 percent of these patients had severe bradyarrhythmias. They also discovered that the incidence of bradyarrhythmias was highly linked to the severity of OSA and the level of nocturnal desaturations [16]. OSA has direct and indirect effects on the growth of cardiac arrhythmias. The acute physiologic alterations that occur as a result of airway collapse in sleep, including the emergence of hypoxemia with hypercapnia, alterations in sympathetic and parasympathetic tone, and variations in thoracic pressure, are all direct impacts of OSA on arrhythmia development. OSA influences the structure of the heart indirectly and is a predisposing factor of structural heart disease. The development of cardiovascular disease, such as hypertension, heart failure, and coronary artery disease, that create the underlying substrate for arrhythmia development, is one of the indirect impacts. Whilst atrial fibrillation is by far the most prevalent arrhythmia linked to OSA [19]. OSA is characterized by hypopneic episodes and apneic caused by a repeated halt in breathing caused by repetitive airway collapse. For 10 seconds or longer, an apneic episode is defined as a 90% drop in flow with the existence of breathing effort [16]. Hypopnea is defined as a decrease in airflow of 50% or more for at least 10 seconds, with an oxygen desaturation of at minimum 4% [19]. OSA is linked to both parasympathetic and sympathetic activation during the early stages of apnea and later stages of apnea [16]. OSA is linked to an increase in sympathetic activity, which leads to additional tachycardia, peripheral vasoconstriction, and water and salt retention, as well as renin-angiotensin-aldosterone system activation (RAAS). OSA has been linked to an increase in circulating inflammatory markers, and neurohumoral activation, specifically the circulating RAAS paired with a generation of reactive oxygen species, has been reported in individuals who may experience electrical remodeling and atrial structure [20]. Higher intrathoracic negative pressure induced by forced inspiration in answer to blocked airways, on the other hand, activates the vagus nerve, but hypoxemia in the setting of OSA enhances carotid body activity [16]. Obstructed inspirations result in considerable intrathoracic pressure differences, which produce alterations in the heart's transmural pressure, causing atrial strain [20]. When these cues are combined, they can cause a brief rise in parasympathetic activity. Due to the elevated vagal tone caused by nocturnal hypoxemia, bradycardia and conduction rhythm abnormalities are more likely. Following apneic episodes,

arousal is triggered by sympathetic discharge and a reduction in vagal tone, leading to an increase in heart rate [16]. OSA induces hypoxia and hypercapnia on a regular basis, which activates the chemoreflex and increases sympathetic nerve activity, resulting in tachycardia and elevated blood pressure, especially towards the conclusion of apneic crises [20]. Repetitive hypoxia is also expected to enhance reactive oxygen species and change potassium regulation in sleep, affecting heart tissue's automaticity [19]. Tachycardia and hypertension increase myocardial oxygen demand, while hypoxia reduces myocardial oxygen supply, resulting in repeated myocardial ischemia during sleeping, that causes atrial and ventricular fibrosis, ventricular arrhythmias and atrial, and sudden cardiac death [20]. The creation of apneic episodes repeatedly in mouse models of OSA has been found to have direct impacts on connexin protein regulation, atrial fibrous tissue composition, and structural alterations, including slower atrial conduction [19]. Other idea that links atrial arrhythmias to OSA is that heightened vascular inflammation caused by OSA may predispose people to AF [16]. Increased inflammatory mediators such as IL-1, IL-6, TNF, interferon-, and vascular endothelial growth factor have been associated to sleep disturbance in adults .These mediators have also been linked to atrial fibrosis and AF events in the past [21]. OSA is linked to an increase in atherosclerotic cardiovascular disease, as well as congestive heart failure and the progression of coronary events.

OSA-related cardiac damage has been linked to a number of causes, neurohumoral activation, involving systemic inflammation, and chronic atrial dilatation caused by frequent variations in intrathoracic pressure, as well as numerous comorbidities including obesity and hypertension [20]. The Mueller maneuver is used to simulate OSA.

Increases in left ventricular (LV) end-systolic volumes, lower cardiac function, and sudden swings on left atrial volumes owing to mural stress on the more elastic left atrial wall are all effects of the these intrathoracic pressure fluctuations, according to this investigation.

The Mueller maneuver resulted in an increase in both the LV contraction load and the LV relaxation coefficient. The discovery that severe OSA is related with ventricular diastolic failure in a dose-dependent manner may be due to these pathophysiologic alterations [19]. Smoking, a sedentary lifestyle, obesity, OSA, and high blood pressure are all modifiable risk factors that are known to promote architectural and electrical atrial modification. OSA is one of them, and it is a substantial risk factor for the development of AF. Medical history (e.g., snoring, witnessing apneas, waking up with a choking sensation, and excessive daytime tiredness) and physical assessment may indicate OSA [20]. The most commonly used tools are:

1. the Epworth sleepiness scale, which assesses the occurrence of sleepiness on a four-point Linkert scale
2. the Epworth sleepiness scale, which assesses the incidence and severity of sleepiness on a four-point Linkert scale
3. the Epworth sleepiness scale, that evaluates the tendency to fall asleep in some situations
4. The Berlin questionnaire evaluates snoring behavior, wake-time sleepiness or fatigue, and a history of obesity and/or hypertension
5. the STOP-BANG questionnaire evaluates tiredness, snoring, higher blood pressure, identified apneas, neck circumference, Body Mass Index (BMI), and sexual identity to calculate a score to determine if sleep disordered breathing is present;

Finally, the NoSAS seeks to determine the severity of sleep apnea by examining five criteria [22]. The STOPBANG checklist seems to have the greatest precision for detecting OSA out of all of them. The Epworth sleepiness scale (ESS), an eight-item questionnaire given during a clinical visit, can help determine whether substantial OSA symptoms are present. While the ESS scale is not exclusive to drowsiness induced by sleep apnea, it has

been well verified in the OSA patients and is a good indicator of symptom severity. When OSA is highly suspected following screening, a laboratory-based polysomnogram (PSG) or a home sleep apnea test is used to confirm or rule out the diagnosis (HSAT). The apnea hypopnea index (AHI), which assesses the number of times a patient stops breathing (apnea) or has a substantial decrease in airflow (hypopnea) per hour of sleep time, is the most widely reported indicator of OSA severity.

The risk of an arrhythmia was 18 times higher during such period of respiratory disruption compared to regular breathing during sleep, according to a retrospective study of nightly polysomnograms from the Sleep Heart Health Study [19]. Despite the fact that several research have shown a link among OSA, atrial bradyarrhythmias and SCD. However, there is inadequate information about the link between among OSA and atrial arrhythmias [16]. Despite the fact that OSA is common in AF patients, hospital death and cardiovascular outcomes like as cardiac arrest, stroke, or severe hemorrhage were similar in AF patients with and without OSA, with no significant variations in length of stay. OSA is known to reduce the efficacy of both pharmaceutical and catheter-based pulmonary vein isolation (PVI) anti-arrhythmic therapy techniques in AF patients [23]. Aside from medicines, direct current cardioversion and RFA, CPAP therapy, which may be advantageous for people with AF, might be a therapeutic option [24]. Continuous positive airway pressure (CPAP) therapy was found to significantly reduce the occurrence of paroxysmal AF in OSA patients. Furthermore, multiple meta-analyses found that treating OSA with CPAP might increase the efficacy of AF therapies, reduce the incidence of AF recurrence, improve atrial conduction, and avoid atrial remodeling [25].

Hypertension and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is strongly linked to hypertension (HTN) which plays a big role, since it has been established that nocturnal hypertension is a significant risk factor for cardiovascular disease (CVD) [26,27]. Individuals with hypertension have a 40% prevalence of OSA, which climbs to 90% in patients with resistant hypertension (r-HTN) [28].

It has also been demonstrated that Ambulatory Blood Pressure Monitoring (ABPM) outperforms clinic measurement in forecasting risk of cardiovascular events, the Dublin Outcome Study investigated both clinic and ABPM data from 5292 individuals and discovered that nighttime blood pressure was the single most powerful indicator of cardiovascular risk, with a 10 mmHg increase in mean nocturnal SBP associated with a 21% rise in cardiovascular mortality [29].

Hypertension Mechanisms in Obstructive Sleep Apnea

Through the pathways of obesity, sympathetic activation, intermittent hypoxia and inflammation [Figure 1.], the transient physiological changes that occur during apnea promote nocturnal high blood pressure, which may lead to the development of chronic daytime hypertension (HTN) [30,31].

OSA and HTN have complicated and multivariate physiological interactions. The pathogenesis begins with restricted airflow into the lungs, resulting in temporary hypoxia and hypercapnia (Fig. 1). These repeated blood gas abnormalities cause sympathetic overactivity, leading to night arousals, disrupted sleep, and blood pressure spikes [31,32]. The initial shock of hypoxia and sympathetic overactivity leads to plenty of molecular changes that exacerbate HTN.

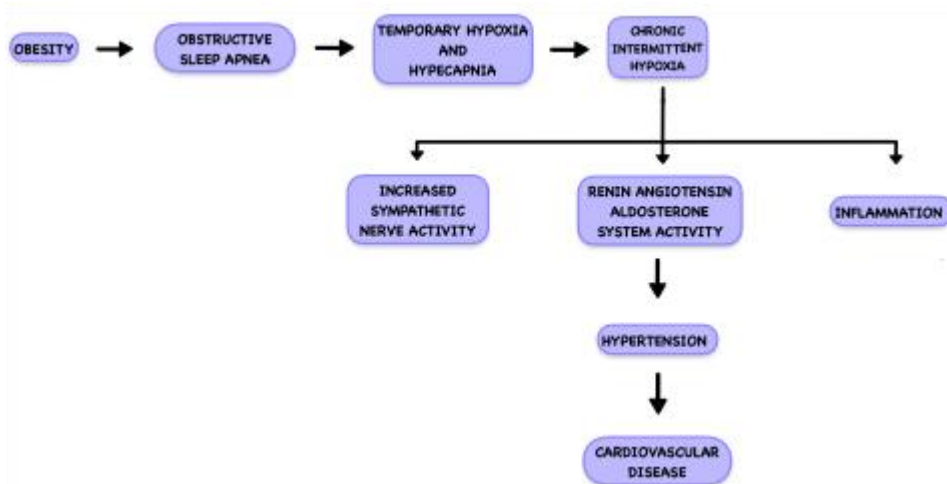


Figure 1. Pathogenesis of cardiovascular disease in obstructive sleep apnea.

Intermittent Hypoxia and Sympathetic Nervous System Activity

The sympathetic overactivity that occurs with the most of sleep disorders is a known predictor for the development of the elevated blood pressure [32].

During normal sleep, particularly non-rapid-eye-movement sleep phase (NREM) (which accounts for around 80% of total sleep duration), sympathetic activity declines and parasympathetic activity rises, resulting in reduced blood pressure (BP) and heart rate [33]. Rapid-eye-movement sleep (REM) is the complete opposite and is marked by transitory increases in sympathetic nerve activity, HR, and blood pressure. However, REM accounts for just around 20% of overall sleep time, therefore, during most physiological sleep, there is increased parasympathetic and reduced sympathetic activity, which contributes to normal nocturnal "dips" in blood pressure and heart rate [34].

On the other hand chronic intermittent hypoxia (CIH) seems to be the most common pathological symptom of OSA and is thought to be a distinct risk factor for CVD [35]. Recent research has linked its connection with CIH-related cardiometabolic diseases [36,37]. Sympathetic activation in OSA appears to be significantly connected to chemoreflex activation caused by CIH. Hypoxic stimulation of the carotid body results in an increase in sympathetic activity, ventilation, HR, and blood pressure. CIH has been demonstrated to cause long-term increases in sympathetic activity through long-term stimulation [34]. Furthermore, the meta-analysis, which identified 14 microneurographic studies, have revealed that even in the absence of additional cardiometabolic disorders, OSA has significant sympathetic activation, as seen by the muscle sympathetic nerve activity (MSNA) and heart rate behavior [12]. A sustained rise in sympathetic drive gradually causes an elevation in vascular resistance and vascular remodeling, both of which influence the documented increase in blood pressure[38].

Renine-Angiotensine-Aldosterone System

The sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) have a significant connection. Renin release from the kidney is carefully regulated by renal sympathetic nerve activity [39]. RAAS activation is a well-known mechanism that leads to hypertension. Renin in the RAAS transforms angiotensin to angiotensin I, which is then transformed to angiotensin II by angiotensin-converting-enzyme (ACE) [40]. When AngII binds to the AngII receptor type 1 (AT1R), blood pressure rises. Increased renin and aldosterone levels in the proximal tubules cause hypertension, and suppression of ACE,

AngII, or AT1 can reduce blood pressure [41]. Furthermore, oxidative stress or sympathetic reactivation of the mineralocorticoid receptor, an aldosterone-dependent transcription factor, has been related to resistant hypertension. As a result, blocking the mineralocorticoid receptor can reduce blood pressure [41].

Knowing that both OSA and RAAS activation are common in individuals with resistant hypertension, various investigations have been conducted to determine if OSA impacts the RAAS and therefore promotes hypertension. Some researchers have linked OSA to an excess of aldosterone and its blockade as an effective adjunctive therapy for OSA [42,43].

According to another studies, it can be seen that plasma AngII concentrations and the vasoconstrictor response to ANG-II are all higher in OSA patients [44].

The RAAS capacity to control peripheral resistance and blood volume, as well as its tendency to be triggered by intermittent hypoxia makes it a conceivable mechanism via which OSA might contribute to the development of hypertension [45].

Furthermore, the research conducted at the University of Calgary on ten healthy male subjects found a substantial rise in arterial pressure following exposure to isocapnic intermittent hypoxia in healthy individuals. The rise in blood pressure was prevented by blocking the AT1R, also suggesting that the renin-angiotensin system plays an essential part in the pathogenesis of hypertension associated with intermittent hypoxia caused by OSA [46]

Inflammation

Inflammatory indicators such as high sensitivity CRP, interleukin-6, interleukin-8, TNF alpha, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 are elevated in OSA patients [34]. The meta-analysis research indicated that OSA patients had greater levels of systemic inflammatory markers than control individuals [47].

Obesity and Sleep Apnea

The link between obesity and the development and exacerbation of OSA is widely recognized [48]. Moreover, obesity and OSA are intricately linked, because excess weight exacerbates several of the major metabolic and cardiovascular complications of OSA. Obesity is recognized as an exacerbating factor for OSA in published recommendations, and weight loss was included as an additional therapy approach [49].

Excess weight is so widespread in OSA that every hypertensive patient with a BMI more than 27 kg/m² should be suspected of having OSA. These patients should therefore be extensively questioned on the signs of OSA such as snoring, observed apnea, uneven breathing while sleeping, restless sleeping, and persistent morning tiredness [50].

However, as new evidence indicates, the association between OSA and obesity seems to be more complicated. Even though there is solid evidence that obesity, particularly visceral obesity, predisposes to OSA and that reducing weight improves OSA, current research suggests that OSA can induce weight increase [51,52].

Previous discussion regarding if OSA is a pathophysiologic component in high blood pressure has centered mostly on the substantial link between OSA and obesity. Since obesity is acknowledged to play a significant role in OSA, people with OSA might be at higher risk for weight gain, and OSA therapy may lower visceral fat. Now it seems that the possible causative relationship between OSA and hypertension includes both the obesity-hypertension relation as well as an independent involvement of OSA in chronic BP rise [50].

Available Treatment

Continuous positive airway pressure (CPAP) has been shown to reduce nocturnal and daytime blood pressure in OSA patients with hypertension [50].

The use of CPAP results in considerable improvement in the apnea-hypopnea index due to pneumatic splinting of the upper airway. Lowering the apnea-hypopnea index is associated with improvements in OSA clinical features such as daytime drowsiness and disrupted cognition and mood [34]. Secondary causes of hypertension should be identified and treated in people with resistant hypertension to assist the manage of blood pressure and minimize cardiovascular risk. Treating OSA with CPAP throughout sleep can lower BP in individuals with masked HTN, persistent HTN, and especially resistant HTN [53]. In patients receiving CPAP therapy, interventional trials indicated significant improvement in symptoms related with OSA, such as fatigue, snoring, morning headaches, and in decrease blood pressure. Furthermore, in a study of forty-four patients with hypertension and severe OSA, effective CPAP for three weeks led to a major reduction in office BP, ambulatory BP monitoring, central BP, and augmentation index, as well as an improvement in arterial stiffness parameters, such as carotid-femoral pulse wave velocity and arterial stiffness index. Although more research with a greater number of participants is required to validate these findings [54].

Discussion

This present shows that OSA is strongly related to cardiovascular diseases. Actually, it's clarified what OSA is and what mechanisms have an influence on changes that arise in the cardiovascular system. There were presented potential diseases and factors like obesity, RAAS activation and their connection with OSA, atrial fibrillation and hypertension. There were similar analyses (16), (17) which focus on heart and OSA and there are similar conclusions [55,56].

There is a correlation between OSA and AF, however there are some barriers in analyzing data because of OSA underdiagnosis and it is a problem to estimate real connexion OSA and AF [57]. There were also presented mechanisms of how AF and other rhythm disturbances occur in OSA. The autonomic nervous system impacts arrhythmogenesis and this statement is continued(19) [58]. Moreover, in both AF as well as hypertension it was described inflammation and inflammatory factors. It was discussed briefly what tools are used to determined severity of OSA, but there are also reports which state that for instance AHI is not enough to diagnosed OSA and there should be more parameters taken into account like desaturation during ventilatory disturbance and burden of hypoxemia [59]. Furthermore, there is a connection between OSA and hypertension and its complex pathogenesis. Actually there are evidences that OSA, hypertension and obesity are associated(21) [60]. But there are also reports that OSA and hypertension are independently related, excluding factors such as age and Body Mass Index(22) [61].

There were also promising methods of treatment using CPAP. There are positive results in reducing symptoms of OSA as well as hypertension and episodes of AF. In addition, studies show new methods of curing OSA by stimulating the hypoglossal nerve, but more research is needed (23),(24) [62,63]. Moreover, there are also simple methods of reducing negative effects of OSA like quitting alcohol, positional therapy, smoking cessation and weight loss (23) [62].

Conclusions

OSA is correlated with cardiovascular diseases. There is multi-faceted pathogenesis of the association of cardiac arrhythmias and hypertension with OSA. More frequent diagnosis of OSA could help assess the coexistence of cardiovascular disease with OSA. There are tools that can help determine the risk of OSA. There are effective methods of using CPAP that improve the quality of life of people with OSA and reduce the frequency of AF

episodes and improve blood pressure parameters. More research is needed to understand the association of OSA with arrhythmias and hypertension.

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