Association Between Obstructive Sleep Apnea and Hypertension

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ABSTRACT

Hypertension is growing more prevalent in patients with obstructive sleep apnea (OSA) than in the general population. Because of the linked association between OSA and hypertension, patients are at an increased risk for stroke, heart failure, and premature death. The proposed study will explore the bidirectional relationship between OSA and hypertension, and the epidemiologic factors that are responsible for their correlation. The project will examine current methods regarding the treatment of high blood pressure in OSA patients, and it will discover other mechanisms that may be promising for treatment and abolishing apneas. The expected results of the project will allow healthcare professionals to have a better understanding of the link from OSA to hypertension and the preferred route of treating OSA so that hypertension and its related morbidities can be prevented. All patients that are currently diagnosed with obstructive sleep apnea and have hypertension, as well as those with OSA who may be at risk for developing hypertension, will benefit from the findings of this project.

Keywords: hypertension, obstructive sleep apnea, blood pressure

CURRENT RESEARCH

Obstructive sleep apnea (OSA) is a sleeping disorder in which individuals experience episodes of complete or partial upper airflow obstruction during sleep due to periodic cessation of breathing (apnea) and closure of the throat (Hou et al., 2018). Individuals with OSA may experience interrupted sleep with frequent awakenings and loud snoring. According to Harvard Medical School (2019), the apneic episodes usually last between 10 and 30 seconds and can happen hundreds of times each night in very severe cases. People with untreated sleep apnea are more likely to develop high blood pressure, also known as hypertension. Hypertension is defined by the American Heart Association as the force of blood flowing through the blood vessels being at a consistently high level (≥140 mm Hg systolic or ≥90 mm Hg diastolic). Hypertension is the leading modifiable cause of death worldwide and affects 75 million adults in the US (Carnethon & Johnson, 2019). The goal of this review is to describe the current findings on the bidirectional relationship between OSA and hypertension and mechanisms available in treating OSA and its effects on blood pressure. Although collected data and treatments are available for OSA requiring blood pressure reduction, the treatments that are currently used need to be better understood and more new strategies are critically needed. There are scarce therapeutic options for treatment and many unanswered questions that pose future challenges, such as the role that continuous positive airway pressure therapy can play in the incidence of cardiovascular events (Oscullo et al., 2019). Creating a path for more consistent research and larger clinical trials is one of the only ways to make this happen. More and more OSA patients are in need for treatment of hypertension. Without treatment, patients are stuck in a pathophysiological cycle that leads to an increase in cardiovascular and cerebrovascular risk and diseases (Marrone & Bonsignore, 2018). Obstructive sleep apnea needs prompt diagnosis and treatment in order to prevent hypertension,

which will help address the growing cardiovascular morbidity and mortality experienced all around the globe (Ahmad et al., 2017).

METHODS

The first step that this project undertook was conducting a review of relevant current research in the main subject area of OSA and hypertension. Examining the prevalence of hypertension in OSA patients allowed for further investigation of the pathophysiology of OSA and exploration of epidemiological factors and mechanisms responsible for its causation. Once the evidence was collected and determination of which methods of current treatment for hypertension in OSA patients is most effective, knowledge gathered from the original research was taken to draw new conclusions, report on the original findings, and discuss the outcomes.

Databases such as PubMed, MedlinePlus, Google Scholar, and OU Library were used to search for relevant studies published up to 2021. The exhaustive search strategy used the following keywords: “obstructive sleep apnea”, “obstructive sleep apnea syndrome”, “sleep apnea”, “sleep disordered breathing”, “OSA”, “OSAS”, “hypertension”, and “HTN”, as well as a combination of these keywords. Thirty peer-reviewed journals and studies were procured and then examined according to the relationship between OSA and hypertension. Articles were then reviewed for potential treatment methods related to the two coinciding conditions. Reviewing the title, abstract, and full text of the publications to determine the suitability for inclusion, eligible studies include: 1) studies conducted on human populations; 2) studies conducted to investigate the relationships between OSA and hypertension; 3) case-control studies and cohort studies; and 4) studies published in English. Once the primary studies were deemed as eligible, they were compiled for interpretation and the data was extracted and analyzed. A handful of the collected articles have compiled data for a sample of patients with OSA and hypertension. Each participant

included in these samples were required to have blood pressure values listed. The individuals within the samples all have various treatment methods including no treatment, treatment with a continuous positive airway pressure (CPAP) machine, antihypertensive drugs, upper airway surgery, oral appliances, pharmacological treatment, and lifestyle modifications. Based on the blood pressure values of individuals in the sample receiving various treatments, a systematic review was carried out to discover the best treatment method available in reducing blood pressure in OSA patients.

LITERATURE REVIEW

BLOOD PRESSURE VALUES AND BODY REGULATION

Before looking into the mechanisms of high blood pressure and how OSA is linked to higher blood pressure values, first it is important to understand what is classified as a normal blood pressure and how it can be regulated. Blood pressure is the pressure exerted by blood on the walls of a blood vessel which helps push blood throughout the body ("Facts About Hypertension," 2021). Systolic blood pressure (the first number in a blood pressure reading) measures the amount of pressure that blood exerts on artery walls while the heart is beating. Diastolic blood pressure (the second number in a blood pressure reading) designates how much pressure the blood exerts against artery walls while the heart is at rest between beats. The five blood pressure ranges as recognized by the American Heart Association are: normal, elevated, hypertension stage 1, hypertension stage 2, and hypertensive crisis ("What is High Blood Pressure," 2016). A normal blood pressure is a blood pressure value equal to or less than 120/80 mm Hg; 120/80 mm Hg being the optimal blood pressure value. An elevated blood pressure is when the readings consistently range from 120-129 systolic and fewer than 80 mm Hg diastolic.

Individuals with elevated blood pressure are likely to develop high blood pressure unless other measures are taken to help control the condition. Hypertension Stage 1 is when blood pressure regularly ranges from 130-139 systolic or 80-89 mm Hg diastolic. At this stage of high blood pressure, doctors often advocate lifestyle changes and may also consider prescribing blood pressure medication. Hypertension Stage 2 is when blood pressure is consistently at 140/90 mm Hg or higher. Doctors most often prescribe a combination of blood pressure medications and lifestyle changes in hypertension stage 2. If blood pressure readings exceed 180/120 mm Hg, it is known as hypertensive crisis. The hypertensive crisis stage of high blood pressure requires medical attention immediately ("What is High Blood Pressure," 2016).

Typically, more attention is given to systolic blood pressure as a major risk factor for cardiovascular disease for people over 50 ("What is High Blood Pressure," 2016). In the majority of people, systolic blood pressure steadily elevates with age due to long-term buildup of plaque, increasing stiffness of large arteries, and a higher incidence of cardiac and vascular disease (Boutouyrie & Laurent, 2020). However, either an elevated systolic or an elevated diastolic blood pressure reading can be used to make a diagnosis of high blood pressure, not just the systolic reading. According to recent studies and the American Heart Association, "The risk of death from ischemic heart disease and stroke doubles with every 20 mm Hg systolic or 10 mm Hg diastolic increase among people from age 40 to 89," (2016). Many factors can affect blood pressure, such as hormones, stress (triggering a decrease in the diameter of the blood vessels), exercise, eating, and even sitting to standing. The size of blood vessels, action of smooth muscle, fluid pressure of blood, and one-way valves all regulate the flow of blood throughout the body (Boutouyrie & Laurent, 2020). Blood pressure is calculated as: *Flow x Resistance.* Cardiac

output, peripheral resistance, and changes to the blood viscosity and length of the blood vessels all play a role in resistance to blood flow.

Short-Term Regulation of Blood Pressure

The autonomic nervous system (ANS) controls the short-term regulation of blood pressure. Changes in blood pressure are detected by baroreceptors which are a form of mechanoreceptor that are activated upon the stretching of a vessel (Phillips & O'Driscoll, 2013). Increased arterial pressure stretches the walls of the blood vessel, causing the baroreceptors to be triggered. These baroreceptors then feed back to the ANS where action is taken to reduce the heart rate via the efferent parasympathetic fibers. This overall response reduces the blood pressure. Decreased arterial pressure is also detected by baroreceptors, which trigger a sympathetic response (Ahmad et al., 2017). This stimulates an increase in heart rate and contractility of the heart, leading to increased blood pressure. Baroreceptors do not regulate long term blood pressure because baroreceptors reset once a more adequate blood pressure is re-established.

Long-Term Regulation of Blood Pressure

There are several physiological mechanisms that regulate blood pressure in the long-term, first of which is called the renin-angiotensin-aldosterone system (RAAS). Renin is a peptide hormone released by the granular cells in the kidney in response to sympathetic stimulation and decreased blood flow to the kidneys (Panahi et al., 2021). Renin facilitates the conversion of angiotensinogen to angiotensin I which is then converted to angiotensin II. Angiotensin II is a vasoconstrictor that acts directly on the kidney to increase sodium reabsorption as well as promotes the release of aldosterone (Jehan et al., 2020). Aldosterone promotes salt and water retention and the electrochemical gradient for movement of sodium ions, leading to more sodium

collection in the kidney tissue. This leads to decreased water excretion and thus increased blood volume and blood pressure. The second mechanism by which blood pressure is regulated is by the Anti-Diuretic Hormone (ADH). This is usually in response to thirst or an increased plasma osmolarity (Wolk et al., 2003). ADH stimulates sodium reabsorption which increases water reabsorption thus increasing plasma volume and decreasing osmolarity, overall increasing blood pressure. Other factors that can affect long-term regulation of blood pressure are natriuretic peptides such as atrial natriuretic peptide and prostaglandins.

Cardiovascular Risk and Blood pressure During Sleep

For healthy individuals, sleep is associated with a 10 to 15% reduction in systolic and diastolic blood pressure compared to wakefulness. This reduction, known as "blood pressure dipping", coincides with sympathetic withdrawal and successive parasympathetic predominance that occurs when transitioning from wake to non-rapid eye movement (NREM) sleep (Ahmad et al., 2017). As compared to wakefulness, NREM sleep is associated with lower blood pressure, heart rate, and cardiac output. Rapid eye movement (REM) sleep, on the other hand, is interrupted by transient surges in heart rate and blood pressure (Ahmad et al., 2017). Sleep-related blood pressure dipping is important for cardiovascular health and diminished nocturnal dipping is a strong independent predictor of cardiovascular risk. In the Ohasama study of 1464 individuals, nighttime, as well as daytime blood pressure measured by 24 hour ambulatory blood pressure monitoring, were linearly related with stroke risk (Phillips & O'Driscoll, 2013). The Dublin Outcome Study, measuring both clinic and ambulatory blood pressure monitoring in 5292 individuals, demonstrated that a 10 mmHg increase in mean nighttime systolic blood pressure is associated with a 21% increase in cardiovascular mortality (Phillips & O'Driscoll, 2013). The measurement of nighttime blood pressure is particularly

important in people who are taking antihypertensive medication because in these individuals, daytime systolic blood pressure loses its predictive value for fatal/nonfatal cardiovascular events. Conversely, nighttime systolic blood pressure predicts mortality and nonfatal events no matter what the treatment status is. In the context of this review, we use ambulatory blood pressure monitoring for prognostic values in OSA patients because they typically have raised nocturnal blood pressures.

EPIDEMIOLOGY OF OSA AND HYPERTENSION

The overall estimated prevalence of OSA is in the range of 15 to 24% of all adults, with certain subgroups of the population bearing a greater risk over others (Ahmad et al., 2017). The prevalence of OSA varies among different populations and age groups, but the number continues to rise as other risk factors increase. This increase in prevalence of OSA has been linked to increased rates of obesity and other risk factors such as older age, male sex, craniofacial abnormalities, and ethnicity (Zhang & si, 2012). Furthermore, Ahmad et al. (2017) discusses how the sleep disorder affects about 25% of men and 23% of women between the ages of 30 and 70. Data from the National Health and Nutrition Examination Survey (NHANES) using the US population revealed that the prevalence of OSA in 2007–2010 compared with 1988–1994 increased by 14–55%, varying based on the subgroup analyzed (Salman et al., 2020). A joint scientific statement from the American Heart Association and the American College of Cardiology pointed out that 85% or more individuals with clinically significant OSA have not been diagnosed; this means that those who are diagnosed only represent the tip of the iceberg of OSA prevalence. The prevalence of hypertension is estimated at about 1.2 billion people worldwide, a staggering 26% of the globe's population (Jehan et al., 2020). The World Health

Organization reports that only 1 in 5 adults have their hypertension under control and less than half of adults with hypertension are actually diagnosed and treated ("Hypertension," 2021). As we look more closely at the prevalence within the United States, we learn that nearly half of adults in the United States, or 116 million people, have hypertension ("Facts About Hypertension," 2021). The increased prevalence of OSA in hypertension populations as well as hypertension in OSA populations has been a driving factor for determining the direction of causality (Phillips & O'Driscoll, 2013).

Prevalence of OSA in Hypertension

There is a bidirectional relationship between OSA and hypertension, which is supported by overwhelming epidemiologic evidence. Not only does OSA make patients susceptible to developing hypertension, but there is also a greater incidence of OSA in hypertensive patients. In the Vitoria Sleep Cohort Study, a sample of 1180 subjects, aged 30 to 70 years old for 7.5 years, showed a positive correlation between incident hypertension and elevated sleep disordered breathing; participants with hypertension exhibited a greater risk of OSA while compared to the participants in the control group (Ahmad, 2017; Jehan, 2020). Although it is an underestimate due to the fact that OSA is underdiagnosed, Ahmad et al. (2017) states that the prevalence of OSA in hypertensive individuals is around 30% to 50%. In a study with 99 hypertensive patients, 56% of the patients had OSA and it was also shown that the severity of OSA depended on the magnitude of high blood pressure; among African Americans, patients with family history of hypertension complained more of the severity they experienced in relation to their OSA as compared to a current diagnosis of hypertension in an individual with no family history of hypertension (Jehan et al., 2020). In a different study with 301 Canadian patients who also had congestive heart failure (CHF), those with comorbid OSA had almost 3 times greater systolic

blood pressure than those without OSA. This is problematic because as previously explained, an increase in systolic blood pressure is directly associated with the severity of OSA, even in patients treated medically with CHF (Jehan et al., 2020).

Prevalence of Hypertension in OSA

Systolic blood pressure is shown to be significantly higher in patients with OSA than in patients without OSA, indicating a high prevalence of systolic hypertension in patients with OSA (Zhang & si, 2012). The high prevalence of hypertension in individuals with OSA is well established, and according to Ahmad et al. (2017), the prevalence of hypertension in OSA patients is calculated between 30 and 70%. In a cross-sectional study of 2677 individuals, for every episode of apnea per hour of sleep the odds of hypertension increased by 1% (Salman et al., 2020). Likewise, in the Wisconsin Sleep Cohort, there was a linear increase in blood pressure as severity of sleep apnea increased; allowing these findings to be independent of age, sex, and BMI. The data revealed a 9/5 mmHg and 9/4 mmHg greater daytime and nighttime blood pressure in individuals with OSA over the group without OSA (Phillips & O'Driscoll, 2013). In the Sleep Heart Health Study, cohort of 6132 patients, the prevalence of hypertension was found to be 59% for mild, 62% for moderate, and 67% in severe sleep apnea; however, the results of this study were not statistically significant after accounting for BMI (Ahmad et al., 2017). Nonetheless, combined meta-analytic results across prospective studies estimate an increased risk of hypertension by 48% among individuals with OSA (Salman et al., 2020).

Risk Factors of OSA: Obesity, Sex, Age, Ethnicity

Among the various risk factors for OSA, obesity is one of the most important factors for the manifestation and progression of this breathing disorder. Several cross-sectional studies have found an association between increased body weight and the risk of OSA. Sleep apnea exists in

about 40% of obese individuals, and around 70% of OSA patients are obese. Moreover, in a population-based study, with sample size of 690 randomly selected Wisconsin residents, a 10% weight gain was associated with an increase in the development of sleep apnea by 6 times the normal amount (Wolk et al., 2003). Patients who have OSA are found to have craniofacial differences than individual who do not have the disorder; OSA patients tend to have smaller pharyngeal airways, lower placement of the hyoid bone, larger volume of soft tissue around the upper airways, and larger volume of the pharyngeal wall. When awake, patients with OSA are able to maintain a patent airway by increasing upper airway muscle activity. However, during sleep, upper airway muscles relax and contribute to airway obstruction (Hou et al., 2018). OSA can occur across a number of individuals with varying body sizes, but many of the previously discussed anatomic abnormalities occur more frequently in individuals who are obese and those with large neck girth. Correspondingly, in various other case-control studies, OSA patients who experienced weight loss led to a significant reduction in apnea frequency. It is, however, still unclear about the exact mechanisms which underlie the effects of obesity on the risk of OSA.

Just as obesity increases the risk for OSA, sleep apnea may predispose to weight gain and obesity. Individuals who have been newly diagnosed with OSA have a history of excessive recent weight gain in the period just prior to OSA diagnosis (Wolk et al., 2003). The mechanisms of this association are not solely due to one variable, they are multifactorial. The relation may be caused by changes in patients' lifestyle or endocrine dysregulation. An etiologic link between OSA and body mass is strengthened by the evidence that chronic CPAP therapy has been shown to decrease body fat and visceral fat accumulation in patients with OSA (Wolk et al., 2003). In experimental models, leptin (a protein product of the human obese gene), has been found to influence sleep architecture and upper airway resistance. Leptin is produced by adipose tissue

that affects satiety and plays a role in metabolic regulation such as glucose and fatty acid metabolism; it suppresses appetite and increases energy expenditure, resulting in weight loss. Obese individuals have high leptin levels, however, their obesity persists because of a resistance to the appetite suppressant known as leptin resistance (Wolk et al., 2003). Patients with OSA tend to have elevated levels of leptin, showing a positive correlation between leptin levels and OSA severity. Furthermore, Phillips et al. (2013) found that leptin levels were higher in 32 obese men with OSA as compared to 32 controlled individuals without OSA. This insinuates that OSA plays into leptin resistance and presence of leptin resistance in individuals with obesity and OSA likely impedes losing weight; contributing to worsening of OSA. Male patients with OSA have leptin levels that are 50% higher compared with similarly controlled subjects that do not have sleep disordered breathing (Wolk et al., 2003). It appears that there is a reciprocal relation between OSA and obesity that triggers a feed-forward mechanism, where each condition mutually enhances progression and severity. Obesity and hypertension are also intimately connected, so an obese patient with OSA is put at an even higher risk of developing hypertension due to the combined effects of obesity and OSA.

OSA is prevalent in the general population, but even greater severity and higher prevalence is noted specifically in males; affecting them 8 to 10 times more than females (Ahmad et al., 2017). Heightened male predominance of OSA remains somewhat equivocal but can allegedly be explained by factors such as fat distribution, upper airway and craniofacial anatomy, and hormonal variation (Ahmad et al., 2017). A study performed by the Sleep Laboratory Respiratory Medicine Unit, Royal Infirmary of Edinburgh showed via MRI that men usually have more fat deposition in the neck as opposed to women; this increased fat deposition consequently puts men at a higher risk of airway collapse (Panahi et al., 2021). Men’s airways

also tend to be longer than women's, putting men at a higher risk of pharyngeal collapse. Panahi et al. (2021) explains that the prevalence difference in respect to gender is hypothesized to be due to sex hormones during fertile age (which disappear after menopause) and influence the prevalence and severity of OSA in older females. Similarly, as for gender playing a role in hypertension, studies have shown that men have higher levels of hypertension consistently compared to women of the same age group (Correa et al., 2017).

Age is another risk factor for OSA, and older aged individuals are at a higher risk than are younger individuals. The SHIP-Trend study, analyzing the prevalence of OSA in 1280 participants, found that aging steadily increased the prevalence of apnea-hypopnea index (AHI) in women and men starting at the age of 50 (Panahi et al., 2021). A study examined by Zhang & si (2012) yielded similar results, showing that in individuals 65 years or older, the prevalence of OSA is 2 to 3 times higher than in middle-aged individuals. The hypothesized mechanism of how age influences OSA prevalence is decreased genioglossus reflexes to negative pressure, thus impairing dilator muscle′s ability to compensate for pharyngeal collapse (Panahi et al., 2021). Pharyngeal collapsibility and increased pharyngeal resistance independent of body mass index and gender, involves the dysfunction of muscles surrounding the parapharyngeal area during sleep. The United Nations report on World Population Aging in 2019 estimates that, "the proportion of the population over the age of 65 will increase from roughly 9% in 2019 to about 16.7% by the year 2050," (Panahi et al., 2021). This report indicates that an increase in the elderly population, alongside the expected increase in obesity, will result in an increased prevalence of OSA.

After explicating how obesity, sex, and age are potential risk factors for OSA, we now look at a final risk factor for OSA: ethnicity. Most clinical population-based studies on OSA

prevalence have been conducted in the United States, Europe, and Australia; but more recently, several studies have been undertaken in Asian countries to characterize the burden of OSA. The prevalence of OSA in Asians is comparable to that of European and American populations, however, the severity of OSA may differ by race. The prevalence of OSA was found to be approximately equal in Caucasians (30%) and African-Americans (32%), but the severity in the African-American population was higher (Zhang & si, 2012). In the Cleveland Family Study, African-Americans with OSA were, on average, younger than Caucasians with OSA. In addition, the association of body mass index with OSA had a stronger relationship in Caucasians than in African-Americans. A cross-sectional study of European (Caucasian) and New Zealand Maori (Polynesian) men showed that reductions in mandibular prognathism and wider nasal apertures represented major factors associated with OSA in Polynesian men, but in the Caucasian group, OSA was associated with a larger neck girth and reduced airway size (Zhang & si, 2012). Ethnicity is associated with hypertension prevalence and is a very important contributor to OSA prevalence. The New York Sleep Heart Health Study showed that in Japanese hypertensive patients, the prevalence of OSA was around 10%; around one-third of Western hypertensive participants. However, in the largest cross-sectional study in China (6132 participants), the prevalence of hypertension in patients with OSA was 56.2% (Zhang & si, 2012). The finding of the cross-sectional study being very comparable to Western countries.

MECHANISMS PROMOTING HYPERTENSION IN OSA

Sympathetic Activation

The pathophysiology of hypertension in OSA is complex because several anatomic and functional factors predispose patients to developing OSA. A mechanism by which OSA may

increase blood pressure is through acute and chronic increases in sympathetic activation. Increased parasympathetic and decreased parasympathetic activity occur during normal sleep and contribute to physiologic nocturnal dipping in heart rate and blood pressure (Panahi et al., 2021). In OSA, there are several pathophysiologic mechanisms that lead to an increase in sympathetic activity. Repetitive intermittent hypoxia as well as negative pressure are suspected to cause renal, adrenal, and peripheral chemoreceptor activation which generates an increase in circulating hormones such as angiotensin II, catecholamines, and renin. The increase of these hormones results in increased sympathetic nervous system activity (Panahi et al., 2021). In 1988, Hedner et al. measured muscle sympathetic nerve activity in patients with OSA and the results were as follows: during apneic events, OSA patients had progressively increasing sympathetic activity, revealing that patients with OSA have continuously elevated sympathetic activity even as they are awake (Gonzaga et al., 2015). The findings suggest that the effects of sympathetic drive continue into a wakeful state even after withdrawing from the hypoxic stimulus.

Accordingly, the severity of OSA is also positively correlated to urinary catecholamine levels. Numerous studies have reported obesity independent elevations in nocturnal as well as 24 hour urinary catecholamines in patients who have OSA (Phillips & O'Driscoll, 2013). It is this heightened and persistent sympathetic activity that leads to an increase in vascular resistance and vascular remodeling, which plays a role in the observed increase in blood pressure (Wolk et al., 2003). Animal and human studies have explored the role of sympathoactivation and subsequent elevation in blood pressure. Rats exposed to intermittent hypoxia for 8 hours/day over a period of 35 days showed an increase in mean blood pressure of 13.7 mmHg when compared to the controlled group (Phillips & O'Driscoll, 2013). Over a shorter period of time, human studies utilizing intermittent hypoxia have been able to show increases in blood pressure and

sympathetic activity. In these human studies, mean blood pressure increased by 4 mmHg in ten males exposed to intermittent hypoxia for 6 hours/day over a period of 4 days. Likewise, in twelve healthy subjects, intermittent hypoxia exposure of just two weeks increased systolic and diastolic blood pressure by 8mmHg systolic and 5 mmHg diastolic. This study suggests that sympathoactivation brought on by intermittent hypoxia likely contributes to elevation in blood pressure (Phillips & O'Driscoll, 2013).

Oxidative Stress

Alongside sympathetic activation, another noteworthy mechanism by which OSA may increase blood pressure is oxidative stress. Intermittent hypoxia in OSA also contributes to hypertension development by increasing oxidative stress. Oxidative stress is an imbalance between free radicals and antioxidants in the body and is a result from production of reactive oxygen species that limits circulating nitric oxide (NO) (Phillips & O'Driscoll, 2013). Decreased NO release from endothelial cells leads to vasoconstriction and promotes cardiovascular disease in patients with OSA. From these findings, several studies have documented OSA patients with increased markers of oxidative stress when compared to controls; lower nitrate and nitrite levels were found in the OSA group (Zhang & si, 2012).

Renin-Angiotensin System Activity

Activation of the renin-angiotensin-aldosterone system (RAAS) is another potential mechanism of hypertension in OSA because it is a complex hormone system that regulates blood pressure. Angiotensin II is a potent vasoconstrictor that also stimulates the secretion of the hormone aldosterone, altering sodium handling which results in fluid retention and increases blood pressure. One study reported that angiotensin II and aldosterone levels in 24 OSA patients were higher than the levels of 18 control subjects (Phillips & O'Driscoll, 2013). This suggests a

role for the RAAS in the pathophysiology of hypertension associated with OSA, although more studies are required to confirm these findings.

Endothelial Dysfunction

It was shown in an experimental model that intermittent hypoxia increases endothelial dysfunction. In a cohort of older adults, a statistically significant relationship between arterial diameter and the severity of hypoxia was uncovered. When OSA patients are juxtaposed with healthy controls, Gjørup et al. (2007) found that individuals with OSA had increased plasma levels of endothelin-1, which leads to higher severity of OSA and increased ambulatory blood pressure. A fundamental role in the development of atherosclerosis and hypertension is endothelial dysfunction, and it often precedes cardiovascular disease. Several studies have shown that successful treatment of OSA improves endothelial function (Ahmad et al., 2017). Furthermore, trials that utilize CPAP machines demonstrate improved endothelial function alongside the treatment of OSA.

Inflammation

OSA has been described as a low-grade chronic inflammatory disease because patients with OSA have higher circulating levels of inflammatory markers (Phillips & O'Driscoll, 2013). While systemic inflammation has been linked to hypertension, atherosclerosis, and cardiovascular disease, its role in OSA may be confounded by obesity. Circulating inflammatory markers such as interleukin-6 (IL6) and C-reactive protein (CRP) have been reported to be at higher levels in individuals with OSA. One study found elevated CRP and IL6 levels in OSA patients when compared with the control group, however, those OSA patients were also more obese (Zhang & si, 2012). Nevertheless, a large community study failed to detect an independent relationship between CRP and OSA after adjustment for BMI, suggesting that their association

may be primarily due to obesity. The evidence for increased levels of pro-inflammatory cytokine TNF-α provides a more solid foundation. Several studies have demonstrated that TNF-α circulating in patients with OSA are elevated as compared to controls, independent of obesity (Phillips & O'Driscoll, 2013).

TREATMENT OF OSA AND TREATMENT OF HYPERTENSION IN OSA PATIENTS

The main focus for the management of OSA is on the elimination of respiratory disorders during sleep (Marrone & Bonsignore, 2018). Treatment of OSA should be multidisciplinary, and objectives should include remission of symptoms and reduction of cardiovascular risk factors (Gonzaga et al., 2015). There are various approaches and treatment methods of OSA including treatment with a CPAP machine, antihypertensive drugs, upper airway surgery, oral appliances, pharmacological treatment, and lifestyle modifications. Taking a deeper look into each of these treatment methods, we will discover why they are used in OSA therapy and how they help eliminate or reduce OSA symptoms and risk factors.

CPAP Therapy

The first line of intervention in OSA treatment is CPAP therapy. A CPAP machine acts as a pneumatic splint, providing constant positive pressure into the airway through a nasal mask while still allowing for regular respirations (Panahi et al., 2021). As the gold-standard treatment of OSA, CPAP therapy has been observed to attenuate the nocturnal sympathetic surge and mediate acute reduction in nighttime blood pressure in OSA patients (Gonzaga et al., 2015). Numerous meta-analyses have demonstrated a mild decrease in blood pressure of about 1.3 to 3 mm Hg with CPAP. This modest blood pressure lowering effect of CPAP is significant nonetheless in improving cardiovascular and cerebrovascular conditions by decreasing mortality

by 6%–8% for stroke and 4%-5% for ischemic heart disease (Ahmad et al., 2017). In OSA patients who experienced nocturnal nondipping blood pressure, consistent use of CPAP led to the recovery of the nocturnal dipping pattern which helps improve cardiovascular morbidity and mortality since those with nocturnal rising blood pressure patterns have the greatest cardiovascular risk (Liu et al., 2016). These findings were validated by the HIPARCO Randomized Clinical Trial conducted in Spain, which showed higher dipping patterns in patients who received CPAP therapy as opposed to those who did not (35.9% dipping in CPAP group versus 21.6% in control). Another meta-analysis included 12 trials (572 patients) and reported a significant 1.69 mmHg decrease in mean blood pressure, with similar reductions in systolic and diastolic blood pressure (Zhang & si, 2012). The blood pressure lowering effect was also more pronounced in patients who used CPAP for at least 4 hours per night, with a drop of 1.3 mm Hg in blood pressure detected for each hour of CPAP therapy used. A randomized controlled trial was conducted, comparing the effect of therapeutic and subtherapeutic CPAP in patients with moderate to severe OSA. Substantial reductions in mean blood pressure (9.9 ± 11.4 mm Hg) and both nocturnal and daytime systolic and diastolic blood pressure (10 mm Hg approximately) were noted in the therapeutic CPAP group after an average treatment of 9 weeks, most likely owing to the length of the trial and treatment pressure used (Marrone & Bonsignore, 2018).

The magnitude of the drop in blood pressure is subject to various factors such as CPAP compliance, duration of treatment, use during REM sleep, baseline blood pressure, and severity of OSA. Not only does continuous use of CPAP therapy reduce systolic and diastolic blood pressure during sleep at night, but also during periods of wakefulness (Jehan et al., 2020). One study showed that when patients were removed from CPAP therapy for one-week, their OSA worsened and sympathetic activity increased (Phillips & O'Driscoll, 2013). CPAP therapy

improves hypertension in OSA patients and also reduces nocturnal sympathetic nerve traffic, decreases nocturnal blood pressure surges, improves cardiovascular prognosis in many OSA patients, increases quality of life, and decreases daytime drowsiness (Zhang & si, 2012). As regards to the effect of CPAP on blood pressure, although this is modest in hypertensive patients as a whole, it seems to be more substantial in patients with more severe OSA and in those with poorer control of their blood pressure levels (Oscullo et al., 2019).

Lifestyle Modifications

Since obesity is the single most important risk factor for OSA, even modest reductions in weight help attenuate the severity of both OSA and OSA induced hypertension. Weight loss is the most important goal for overweight patients with OSA because there is a direct correlation between increased neck fat deposition and OSA onset and progression (Ahmad et al., 2017). In 2019, a randomized controlled trial was conducted to examine the effectiveness of a weight-loss regimen and its effect on decreasing OSA severity in patients with severe OSA. It was concluded that OSA symptom severity decreased as weight loss increased, and the patients also saw decreased blood pressure and baroreflex sensitivity, cholesterol, biomarkers of inflammation, and blood glucose (Zhang & si, 2012). It is recommended that patients prevent/manage hypertension and reduce weight by using lifestyle modifications such as physical exercise and a low carbohydrate diet or DASH including diet features such as vegetables and fruit, low sodium intake, whole grains, and low-fat dairy products. These modifications are beneficial and help reduce LDL and HDL levels, as well as reduce inflammation (reduces inflammatory markers CRP, IL-6, and TNF-α) (Jehan et al., 2020). Positional therapy is when OSA patients sleep in a position other than on their back and it has been found to be useful in preventing airway collapse. Unfavorable airway geometry and limited functionality of muscles that dilate the airway are a

result of sleeping in a supine position. Ahmad et al. (2017) recommends the use of a pillow to prevent patients from sleeping in a supine position. Behavioral changes and lifestyle modifications should be made to correct predisposing or aggravating factors related to OSA.

Oral Appliances

Oral appliances, or mandibular advancement devices (MAD), are a recommended alternative treatment for OSA patients who cannot tolerate CPAP or have mild OSA. These applications change the position of the lower jaw and move it forward, preventing the upper airway from closing (Panahi et al., 2021). In both a systematic review and a meta-analysis of studies on CPAP and MAD, both treatment methods decreased blood pressure and there was no significant difference between the two and their outcomes. The meta-analysis of seven studies with 400 OSA patients observed that the average drop in systolic and diastolic blood pressure was reported to be 2.7 mm Hg (Ahmad et al., 2017). The systemic review by Okuno et al. expresses that although oral appliances have demonstrated good efficacy in patients with mild to severe levels of OSA, they are not effective in all patients. However, more recent data suggests that oral appliance therapy should be prescribed to OSA patients who are intolerant to CPAP therapy or prefer alternate therapy because oral appliances are noninferior and tend to have better compliance (Ahmad et al., 2017).

Upper Airway Surgery

There are typically two surgical options for OSA: tonsillectomy and uvulopalatopharyngoplasty (UPPP). UPPP widens the airway by removing a section of the soft palate, uvula, and tonsil; modified UPPP improves sleepiness, nocturnal respirations, and quality of life as well as lowering blood pressure significantly in patients with moderate to severe OSA (Panahi et al., 2021). Tonsillectomy and adenoidectomy are surgeries used to treat children with

OSA. Essentially, these surgical treatments are reserved for patients who do not respond well to CPAP or MAD (Panahi et al., 2021).

Antihypertensive Drugs

Antihypertensive drugs are used to treat hypertensive patients with mild to moderate OSA who do not need CPAP or those who cannot tolerate CPAP. There are no specific guidelines as to which class of antihypertensive medications should be used to treat hypertension in OSA patients, but aldosterone antagonists and Beta-blockers may be the best method for treatment due to certain pathophysiological mechanisms. ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists have a moderate antihypertensive effect in moderate OSA whereas aldosterone antagonists are more effective in severe OSA (Jehan et al., 2020). In a study, B-blockers (atenolol) significantly reduced nocturnal systolic and diastolic blood pressure more effectively than did calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers (Ahmad et al., 2017). However, the study showed no difference in daytime blood pressure and OSA severity between the different antihypertensive classes. Diuretics, especially spironolactone, have shown to be the most promising medication in helping to relieve pharyngeal edema, ultimately improving OSA severity and hypertension (Ahmad et al., 2017).

Pharmacological Treatment

Currently, there are no known pharmacological agents that are universally used, or FDA approved, for the treatment of OSA. At this time, FDA approved pharmacological agents are used strictly for symptom management, they are not used for disease management (Panahi et al., 2021). Trials studying the effectiveness of serotonergic drugs such as fluoxetine, paroxetine, trazodone, and mirtazapine have been conducted, however, none of them have proved to be successful in improving disease severity or management. Many patients remain untreated

because pharmacotherapeutic options for OSA and sleep apnea are limited (Phillips & O'Driscoll, 2013).

CONCLUSION

OSA is significantly prevalent worldwide and is underdiagnosed and undertreated. For over 40 years, the relationship between sleep apnea and cardiovascular diseases has been studied, unveiling a growing body of evidence of associated risk factors. 41% of the US population is projected to have some form of CVD by 2030 and therefore, possible coexisting OSA (Salman et al., 2020).There are many risk factors that contribute to OSA such as obesity, sex, age, and ethnicity. This condition can also increase one's risk of metabolic and cardiovascular diseases and increase mortality. Several pathophysiologic mechanisms contribute to the increased risk of hypertension and cardiovascular disease among individuals with OSA, having wide variation in individual susceptibility, including sympathetic activation, oxidative stress, endothelial dysfunction, renin-angiotensin system activity, and inflammation (Salman et al., 2020). Healthcare providers must be better familiarized with the epidemiology and pathophysiology of OSA for this condition to be better diagnosed and treated (Panahi et al., 2021).

Only after proper screening can the strain on the healthcare system caused by OSA and resulting comorbidities be reduced by appropriate treatment. The best treatment strategy for populations with OSA and hypertension likely involves combining OSA treatment with antihypertensive medication. This combination is likely to be more effective in lowering both nocturnal and daytime blood pressure than either treatment alone (Phillips & O'Driscoll, 2013). Other current first line therapies for the management of OSA and hypertension consist of weight loss, CPAP therapy, oral appliances, and surgical interventions such as tonsillectomy and

adenoidectomy in children to UPPP in adults (Ahmad, 2017; Panahi, 2021). The combination of CPAP therapy and weight loss has a great promise for cardiovascular risk reduction on OSA. However, future research is needed to identify ways to improve patient adherence to CPAP therapy and to clarify the relationship between CPAP and cardiovascular risk in an adequate adherence setting (Salman et al., 2020). Pharmacological treatment options are scarce and current FDA approved drugs are only for symptom management, not for the treatment of OSA (Ahmad et al. 2017). Future research should be directed at more clearly identifying factors that determine individual antihypertensive responses with OSA treatment and focus on reducing nocturnal hypoxia while minimizing patient burden (Salman et al., 2020). As more research becomes available, continued advancements in the field of medicine may lead to newer treatment modalities for patients with OSA (Ahmad et al., 2017). OSA requires prompt diagnosis and treatment in order to prevent hypertension, and developing strategies are essential to better address the pathogenesis of the condition. Improving the following areas will help address the growing cardiovascular morbidity and mortality experienced all around the world. (Gonzaga et al., 2015).

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