Obstructive Sleep Apnea and Hypertension

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Abstract
Obstructive sleep apnea is a common problem which is becoming more common due to the epidemic of obesity. This condition can lead to hypertension through a complex cascade involving the activation of several neurohumoral systems. Treatment of the obstructive sleep apnea often results in the improvement and sometimes the cure of the hypertension.

Categories: Cardiology, Internal Medicine
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Introduction And Background
Sleep apnea was actually well described by Charles Dickens in 1836 in his book, "The Posthumous Papers of the Pickwick Club". In this novel, a supporting character by the name of Joe, aka 'the fat boy', who constantly eats and falls asleep throughout the day. Dr. Burwell, et al. later coined the term 'Pickwickian Syndrome' in 1956 to describe their obese patient that fell asleep while playing poker. It was proposed that hypercapnia was the source of somnolence [1].

In 1965, Gastaut, Jung, and Kuhlo described the polysomnographic findings of sleep apnea. The syndrome had a high association with obesity, but in 1976 Guilleminault advocated for the use of the term 'sleep apnea syndrome' and 'obstructive sleep apnea' (OSA) in an effort to change the association from obesity since the syndrome can be seen in non-obese patients as well. Initial directed treatments for sleep apnea started in 1969 with tracheostomy procedures. In 1981 uvulopalatopharyngoplasty (UPPP) was performed for the treatment of OSA. The use of continuous positive airway pressure (CPAP) to treat OSA began in 1981 [2].

Recently, there has been interest in the relationship between OSA and resistant hypertension. This is hypertension that fails to meet target values despite the use of three anti-hypertensives. This paper will focus on the epidemiology of OSA, risk factors of OSA, the mechanism of hypertension development, relationship with aldosterone, and the treatment of OSA.

Review
Epidemiology
In North America, approximately 20% of the population has OSA, and 26% are at risk of developing OSA. OSA occurs most commonly in individuals between the age of 18 and 45 [3-4]. Men are three times more likely to have OSA than women [5]. There is also an increased prevalence in African-Americans.

How to cite this article
Risk factors

Risk factors for OSA include advancing age, male sex, obesity, and genetics [5]. These risk factors can lead to abnormalities in the airway, increasing pharyngeal dilator muscle dysfunction, lowering arousal threshold, increasing ventilator control instability, or reduced lung volumes [6]. There is an increased prevalence with advancing age. However, body mass index (BMI) tends to decrease with advancing age [7]. It is believed that the increased prevalence of OSA in the elderly is due to increased deposition of fat in the parapharyngeal area andlengthening of the soft palate [8]. Males are at increased risk of having OSA over women. Men have more parapharyngeal fat deposition [9]. Pre-menopausal women are at a decreased risk compared to postmenopausal women by a factor of four [10]. Hormone replacement therapy in postmenopausal women lowers the risk of OSA to that of premenopausal women [10]. Obesity is the most important risk factor associated with the prevalence of sleep apnea. The possible explanation for this is increased fat deposition in the pharynx. This narrows the airway. Central obesity has also been shown to reduce lung volume [5]. The reduction in lung volume increases the risk of upper airway collapsibility [11]. Individuals with a high BMI of 40 or greater have a sleep apnea prevalence between 40-90% [12]. Encouraging weight loss in patients can have drastic improvements in decreasing apnea episodes. A 10% reduction in weight can lead to almost a 25% decrease in apnea episodes [13].

Family history and genetics is considered a risk factor in the development of OSA. There is a relative risk of 1.5-2 for individuals with that have affected first-degree relatives [14]. This could be due the prevalence of obesity in some families, as well as similar craniofacial morphology that may be more susceptible to development of OSA. Some examples of craniofacial abnormalities that can alter upper airway movement include: macroglossia (enlarged tongue), micrognathia (mandibular hypoplasia), glossoptosis (downward displacement of tongue), and cleft palate [15]. Individuals of Chinese heritage have a high likelihood of having an inferiorly positioned hyoid bone and a retropositioned maxilla [16]. These characteristics are conducive to a more severe form of OSA. Individuals that smoke cigarettes are at an increased risk of developing OSA, with an odds ratio of 4.44 [17]. The inflammation that develops from smoking is believed to increase this collapsibility of the upper airway. Alcohol can relax the upper airway dilator muscles (leading to a narrower lumen), and due to its sedative effects can prolong the duration of each apnea episode [18].

Diagnosing sleep apnea

Patient’s with sleep apnea generally complain about daytime sleepiness, and are brought in because a significant other has witnessed loud snoring or cessation of breathing [19]. If a patient is suspected of having OSA, a sleep study or polysomnography should be performed in a sleep laboratory. If a patient is unable to go to a sleep lab, portable home monitors are an acceptable alternative for patients suspected of having moderate to severe OSA [20]. Ambulatory testing should not be performed in patients with comorbidities due to the possibility of affecting the study. For example, heart-failure predisposes patients to central sleep apnea [21].

The primary measurement that is used to classify patient with OSA is the apnea hypopnea index (AHI). The AHI is the number of absent or decreased respirations that one experiences in one hour. It is normal for individuals to have periods of apnea during rapid eye movement (REM) sleep, but this is usually brief (less than 10 seconds) and are not repetitive. Patients are asymptomatic. Mild cases are defined as having an AHI between 5-15 per hour [22]. Patients may have be asymptomatic or have some daytime sleepiness that does not interfere with life. Patients are encouraged to lose weight, abstain from alcohol, and use continuous positive airway pressure (CPAP). Moderate cases are defined as having an AHI between 15-50 per hour. Patients usually experience daytime sleepiness and can lead to disruptions in their daily life.
These disruptions include frequent nap taking, excessive caffeine use, or avoiding activities that require sustained attention, like long drives. These patients frequently have hypertension and should be screened. Patients respond well to CPAP [23]. Severe cases have an AHI of 30 or more events per hour, and have an oxygen saturation below 90% for more than 20% of total sleep. These patients have excessive daytime sleepiness, and this can interfere with activities of daily living. Patients are at risk of developing heart failure and should be treated urgently. Polycythemia is typically evident in these patients as well [24].

**Mechanism of hypertension in obstructive sleep apnea**

Individuals with OSA are at an increased risk for development of arterial hypertension, heart failure, and stroke [25-26]. It is believed that chronic intermittent hypoxia (CIH) leads to endothelial dysfunction, atherosclerosis and sympathetic activation, and oxidative stress [27-30]. This is summarized in Figure 1. Endothelial dysfunction leads to a decrease in vascular reactivity [31]. Nitric oxide (NO) is a vasoactive substance that is normally released by endothelial cells which causes vasodilation. In subjects with CIH, levels of nitric oxide were blunted in response to an acetylcholine infusion [32]. Additionally, with NO synthase inhibition, expected levels of vasoconstriction was not as high as expected. Individuals with endothelial dysfunction due to OSA has been shown to have increased levels of NFκB and decreased expression of nitric oxide synthase [33]. When individuals were treated with CPAP, levels of NFκB decreased and expression of NO synthase increased [33]. It was also found that treatment with the antioxidant enzyme superoxide dismutase resulted in restoration of vascular reactivity [34]. In vitro studies also suggest that xanthine oxidase (XO) plays a role in the endothelial dysfunction that occurs in muscular arteries because the XO inhibitor allopurinol restored vascular reactivity [35]. Endothelial dysfunction is also a precursor for the development of atherosclerosis. Atherosclerosis is an inflammatory process. Most patients with OSA are found to have elevated artery-intima media thickness [25, 29]. Other markers associated with atherosclerosis include arterial stiffness, plasma C-reactive protein, and catecholamines. After four months of treatment with CPAP, subjects in one study were found to have decreased C-reactive protein, decreased catecholamines, and a carotid intima-media thickness to values similar to healthy controls [33].

Arterial hypertension is the most common cardiovascular manifestation of OSA and is more common than pulmonary hypertension [23]. The higher the AHI, the higher odds ratio there is for the development of hypertension [23]. The major mechanism of vasoconstriction in CIH is believed to be due to the carotid chemoreflex. The carotid chemoreflex detects reductions in P02 and elevations of CO2. Afferent branches of the glossopharyngeal nerve goes to the cardiorespiratory centers in the medulla. Efferent branches of the vagus nerve allows for regulation of breathing and blood pressure. Decreased parasympathetic firing results in a higher sympathetic response: increased breathing and vasoconstriction. If the sympathetic nervous system is blocked, increases in blood pressure is blunted [36-37]. The carotid chemoreflex leads to an elevated sympathetic response, which activates the renin angiotensin II (Ang II) pathway. Ang II and HIF – α (hypoxia inducible factor) are believed to activate nicotinamide adenine dinucleotide phosphate-oxidase (NADPH Oxidase, NOX) and form reactive oxygen species (ROS). Mice with knocked out NOX prevented the development of arterial hypertension. Additionally, NOX gene transcription levels are upregulated in the carotid body in subjects exposed to CIH (Figure 1) [38].
Oxidative stress can also lead to heart failure. LV hypertrophy and a reduced ejection fraction were seen in animals subject to CIH [31]. LV function was found to be inversely related to levels of lipid peroxides [39]. NOX gene expression was found to be elevated in the myocardium of mice subjected to CIH, and mice that had NOX knocked out resulted in protection from LV dysfunction [40-42]. Treatment with allopurinol decreased LV dysfunction [42].

**Resistant hypertension**

Resistant hypertension is defined as hypertension that remains above target, despite the use of three anti-hypertensive pharmaceutical agents from different classes [43]. Often times, a fourth agent is needed. Resistant hypertension is estimated to occur in 12% of the treated hypertensive population [44]. Uncontrolled hypertension has medical implications, such as end organ damage and increased incidence of cardiovascular disease [45]. OSA is now considered a recognizable form of secondary hypertension [43]. The mechanism of hypertension in these individuals is multi-factorial as discussed earlier, but current understanding of this process indicates that intermittent hypoxia leads to increased sympathetic activation, systemic inflammation, and endothelial dysfunction [46]. It now appears that OSA may be the most common condition associated with resistant hypertension and treatment of OSA with CPAP leads to a reduction of BP [47-48]. In one clinical study, a group of individuals with resistant hypertension were divided in two groups. One group was given the standard of hypertensive treatment (control) and another group was given the same drugs with the addition of CPAP. Patients’ blood pressures were monitored with a 24-hour ambulatory system. At the end of six months, the patients with CPAP resulted in a significant decrease in awake blood pressure, but the nocturnal blood pressure did not significantly change. CPAP users that started with a blood pressure of 148.4±2.5/85.4±2.3 ended the study with a blood pressure of 141.9±3.3/80.9±2.7. This was a drop of (-6.5±3.3/-4.5±1.9) mmHg (p<0.05). The control group actually experienced an increase in blood pressure from (145.8±4.0/88.4±3.4) to (148.8±3.8/90.6±2.7) mmHg (p<0.05) [47]. In another study, the use of CPAP for one year was
recorded in patients with severe OSA. Patients with OSA were also divided between those with resistant hypertension and those with controlled hypertension. The use of CPAP resulted in a reduction in daytime BP in patients with resistant hypertension. This reduction was seen at six months of treatment and persisted after a year of treatment. A modest and statistically significant decrease in mean arterial pressure was seen (-4.4 mmHg, p<0.05). In 71% of patients with resistant hypertension, the use of CPAP resulted in decrease in either the number of antihypertensives used or a reduction in the dosage of drug use. Patients with severe OSA and controlled hypertension did not experience significant changes in decreasing their blood pressure or medication usage [49].

Elevated levels of aldosterone can be seen in 14% - 21% of patients with resistant hypertension. This is most commonly due to bilateral adrenal hyperplasia. Aldosterone increases sodium and water retention in the kidneys, but it has long been established that aldosterone plays a pro-inflammatory role in the cardiovascular and renal systems [50]. Elevated levels of aldosterone has also been shown to reduce the activity of nitric oxide, leading to decreased vasodilation [51]. Targeting aldosterone with a medium starting dose (25 mg/d) of spironolactone, patients with resistant hypertension had a mean reduction in BP of 22/10 mmHg [52]. OSA has been found in 83%-85% of patients with resistant hypertension and treatment with CPAP has shown to have an antihypertensive effect [49, 53-54]. At a study at the University of Alabama at Birmingham, researchers found that there is a positive and significant correlation between plasma aldosterone levels and the apnea-hypopnea index [54]. These results lead the authors of the study to conclude that hyperaldosteronism is responsible for the worsening of OSA. A possible mechanism that has been proposed is that the increase in fluid retention leads to fluid shifts in the extracellular space. Excess fluid in the neck area could lead to an increase in airway resistance and a lower threshold for airway collapse [55]. Patients with severe OSA and resistant hypertension were treated with spironolactone in an open-label study and showed a significant decrease in AHI, weight, and BP after eight weeks [56]. AHI decreased from 39.8 ± 19.5 to 22.0 ± 6.8 (p<0.001). Weight decreased from 243.0 ± 32.4 to 239.9 ± 29.4 (p = 0.03). Systolic blood pressure decreased from (145 ± 18) to (124 ± 16) mmHg (p<0.001). Diastolic blood pressure decreased from (81 ± 16) to (72 ± 9) mmHg (p = 0.04).

A surgical cure for the actual sleep apnea (i.e., achieving an AHI <5 is not common, vida infra), but a uvulopalatopharyngoplasty (UPPP) does appear to be effective in treating hypertension. In one study, six months after the surgery, 24-hour systolic blood pressure decreased from (160.8 ± 6.8) to (142.5 ± 7.3) mmHg. Daytime systolic blood pressure decreased from (170.5 ± 2.5) to (150.8 ± 7.6) mmHg. Night contraction decreased from (163.6 ± 10.5) decreased to (140.1 ± 6.4) mmHg. Diastolic blood pressure decreased from (100.8 ± 5.6 to 81.8 ± 7.4) mmHg. Mean arterial pressure decreased from 96.8 ± 7.5 to 93.7 ± 2.4 mmHg. Blood pressure changes were also statically significant (P < 0.05). Overall, the AHI improved from a median of 37.5 to 9.5 events per hour. The oxygen saturation also improved from 0.655 ± 0.114 to 0.860 ± 0.037. These changes were statistically significant (P value < 0.05). There was a correlation between the AHI improvement and the SaO2, systolic, and diastolic blood pressure changes (r > 0.80 and r(2) > 0.50). The UPPP procedure also allowed for a decrease in antihypertensive drug use from (3.6 ± 0.5) to (2.9 ± 0.5) in 63.8% of patients [57].

### Treatment of OSA

General health counseling should first take place. Proper nutrition, cessation of tobacco use, and decreasing alcohol consumption should be encouraged but generally have a minimal effect on overall prognosis [58]. Weight loss should be encouraged in all overweight individuals. In a meta-analysis studying the effects of weight loss on obstructive sleep apnea, 435 individuals with an initial AHI of 50.9 events/hour (range 10.1 - 91.4) were selected for a dietary weight loss program. Patients had a mean BMI reduction of 4.99 kg/m2 (95% confidence interval [CI], 4.0 - 5.9), resulting in an improvement of AHI to 34.5 events/hour (95% CI 26.5-42.9). This study
recommended that weight loss be seen as adjunct therapy [59]. Treatment of OSA should begin if a patient has an AHI of >5 and have comorbidities related to impaired sleep. This includes excessive daytime sleepiness, impaired cognition, or cardiovascular disease. If a patient has an AHI > 15 and doesn’t have any comorbidities related to impaired sleep, he should also be started on treatment [21, 60]. CPAP is the first line treatment in sleep apnea because it has been found to be best at decreasing AHI, increasing oxygen saturation, and increasing sleep efficiency [61]. However, in regards to the symptoms of excessive sleepiness, arousal index and sleep architecture CPAP as well as the use of an oral appliance is similar [62]. Patients generally prefer using an oral appliance, like a mandibular advancement splint, over the CPAP.

Surgery is another option for patients that fail conservative measures. Thorough surgical evaluation should be done to determine if there is an anatomical obstruction in the upper airway, like hypertrophied tonsils. There are many surgical options including: radiofrequency ablation, septoplasty, rhinoplasty, nasal turbinate reduction, nasal polypectomy, palatal advancement pharyngoplasty, tonsillectomy, adenoidectomy, palatal implants, partial glossectomy, lingual tonsillectomy, genioglossus advancement, uvulopalatopharyngoplasty, and maxillomandibular advancement [65]. If no specific anatomical abnormality can be found, a uvulopalatopharyngoplasty (UPPP) may be performed. This procedure involves the removal of the uvula, extra retrolingual tissue, and extra palatine tissue. A surgical cure, as defined as an AHI of <5, occurs between 16-25% of cases [64, 65]. The patients that had a cure were typically younger (35.9 ± 13.1 vs 44 ± 13.7 years; p=0.05), had a lower BMI (30.8 ± 6.5 vs 34.6 ± 6.6; p=0.05), and had less severe apnea (38.1 ± 33.6 vs 69.6 ± 32.8; p=0.004) [65]. Maxillomandibular advancement is another procedure that is gaining popularity, and is most associated with a reduction in AHI. It has a higher surgical cure rate than UPPP. Studies have shown a surgical cure rate of around 40% [66-68].

Conclusions
OSA is common disease that can greatly affect the functioning and productivity of patients. OSA can be properly managed, but requires physician’s recognition and patient education. OSA clearly also plays a role in hypertension, particularly resistant hypertension. Both CPAP and UPPP have been shown to augment blood pressure control.

Additional Information
Disclosures
Conflicts of interest: The authors have declared that no conflicts of interest exist.

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