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Obstructive Sleep Apnoea: A Risk Factor for Hypertension

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ABSTRACT

Obstructive Sleep Apnoea (OSA) is the most prevalent condition among sleep disordered breathing that leads to increased risk of cardiovascular (CV) and cerebrovascular morbidity and mortality. The most common comorbidity associated with OSA is systemic hypertension (HTN). Various epidemiological studies suggest a link between OSA and hypertension that involves complex interactions between various pathophysiological mechanisms and metabolic risk factors. OSA causes changes in normal physiological functions during nocturnal apneic episodes which in-turn lead to daytime hypertension. The widely accepted mechanisms by which the OSA contributes to the development of hypertension include sympathetic activation, inflammation, oxidative stress, and endothelial dysfunction. OSA and hypertension coexist in millions of people and both have been associated with heart disease, stroke, and premature death. Worldwide the prevalence of hypertension in OSA is estimated between 30 and 70%, thus setting it off as a major public health problem. Furthermore, not only has OSA been implicated in causing new hypertension but also it is said to promote resistant hypertension in already existent hypertensive patients, which may further grim the clinical and therapeutic outcomes. It is necessary to recognize the underlying OSA in-order to decrease the overall healthcare burden in terms of rigorous anti-hypertensive therapy instituted to OSA subjects. The review summarizes an up-to-date scenario of obstructive sleep apnoea as a cause of systemic hypertension and the overall cardiovascular risks.

Introduction

In 2010, the global age-standardized prevalence of hypertension in adults aged ≥20 years was reported 31.1%[1]. It is the major cause of cardiovascular mortality and morbidity among adults. The World Health Organization (WHO) has identified hypertension as one of the most important preventable causes of premature morbidity and mortality[2]. In 2014, the overall prevalence of hypertension in India was reported to be 29.8% of which 33% and 25% were urban and rural population respectively[3]. It is labeled as the third most common risk factor for the burden of diseases in South Asia[4]. From 2011-2014, nearly 30.4% of adults aged ≥20 years were reported to be hypertensive in USA alone[5]. According to the new guideline, published in November 2017 by The American Heart Association (AHA), hypertension is defined as a systolic blood pressure more than 130 mm Hg and diastolic blood pressure more than 80 mm Hg[6]. As per this report, the prevalence of hypertensive individuals is extremely high and previous studies most likely underestimate the prevalence in this context. On the other hand, obstructive sleep

apnoea (OSA), also known as obstructive sleep apnoea-hypopnea, is a disorder that involves repetitive episodes of complete or partial cessation of airflow (breathing) during sleep, due to collapse of the upper airway (Oropharyngeal tract) with a consequent decrease in oxygen saturation[7]. The airway collapse during sleep leads to fragmented sleep pattern. During the brief period of breathing obstruction, in severe OSA, intermittent hypoxia with bursts in sympathetic nerve activity occur. This sympathetic over activity results in increased heart rate and blood pressure (BP). The severity of OSA is determined by Apnoea-Hypopnoea-Index (AHI), which is defined as the total number of periods of breathing pauses per hour of sleep[8]. Different populations and age groups present a varying set of prevalence of OSA[9]. It is an emerging health problem, particularly in high income countries[10]. Its high disease burden is related to both the health care costs attributable to OSA alone and as an independent risk factor for cardiovascular, metabolic, and psychiatric disorders such as hypertension, stroke, diabetes, and depression which are global health priorities[11,12]. According to American Sleep Association,25 million adults in United States have OSA with nearly 9-21% of women and 24-31% of men[13]. Generally, 34% of men and 17.4% of women between the 30-70 years of age are expected to have an AHI≥5[14]. Various cross-sectional and longitudinal studies suggest an association between OSA and hypertension[15,16,17]. Also, resistant, chronic and long-standing hypertension is purportedly caused by untreated or underdiagnosed OSA[18,19].

A study by *Grote and colleagues* reported that the prevalence of hypertension was higher in patients with OSA and vice-versa[20]. Additionally, a study conducted in 709 subjects conferred a three-fold risk of being diagnosed with hypertension over a follow-up period of four-year in association with the presence of severe OSA at the enrollment of study[17]. Population-based cohorts find an increased prevalence and incidence of hypertension in adults with OSA, which remains significant after controlling important confounding factors such as obesity[21].

Normal Sleep Pattern And Blood Pressure

Sleep is a state of unconsciousness in which the brain is relatively more responsive to internal than external stimuli[22]. In healthy individuals, 10-15% reduction in systolic and diastolic blood pressure occurs during sleep compared to wakefulness[23]. This decrease in BP during sleep in normal individuals is referred to as “BP dipping” or “dipping pattern”. The dipping pattern is a physiological reaction in response to the sympathetic withdrawal and parasympathetic dominance occurring during transition from wakefulness to non-rapid eye movement (NREM) sleep[24]. The interaction between circadian rhythm and sleep-wake cycle causes diurnal variations in cardiovascular activity which is high during day and gradually decreases during night-time, as sleep sets in. During NREM sleep BP, heart rate, cardiac output, and systemic vascular resistance are lowered while during rapid eye movement (REM) sleep brief surges in sympathetic nerve (SN) activity, heart rate and BP occur[25]. Since REM sleep constitutes only 20% of total sleep cycle, an overall reduction in cardiovascular functions occur[25,26]. A less than 10% decrease in nocturnal dipping is referred to as non-dipping which is attributed to be the strong, independent predictor of cardiovascular risk[26].

Nocturnal BP Pattern In Patients With OSA

The alteration in the physiological nocturnal BP decrease (dipping pattern) occurs in patients with OSA, predisposing them to cardiovascular risks[27]. The night-time BP is an important indicator of overall cardiovascular risk as well as daytime BP[28]. The diminished/absence of nocturnal dipping makes the patients more liable of developing diseases like chronic kidney disease, hypertension, diabetes, resistant hypertension beside others. The subjects with OSA as compared to the normal subjects exhibit a high prevalence of unfavorable circadian pattern using 24 hour-Ambulatory blood pressure measurement (ABPM)[29]. A cross-sectional study, including 84 patients, concluded that fragmented sleep pattern (seen in OSA) is associated with the non-dipping pattern i.e. less BP decrease during sleep[30]. A similar prospective study conducted in 140 patients with hypertension found a higher dipping ratio (ratio between the mean nighttime BP and the mean daytime BP) in patients with OSA compared to individuals without OSA[31]. Another prospective cohort Ohasama study, including 1464 patients, reported that daytime BP measured by 24-hr ABPM was linearly related to stroke risk and 20% greater cardiovascular mortality is associated with every 5% deficiency in the normal decline in nocturnal BP[32]. A high nocturnal BP (SBP ≥120 mm Hg and/or DBP ≥70 mm Hg) is the most important predictor of cardiovascular[33] and cerebrovascular outcomes[34]. Thus, ABPM is a superior clinical measure for the determination of nighttime BP which is particularly important in patients taking anti-hypertensive medications because such subjects present normal daytime BP (masking the need for cardiovascular risk evaluation). The patients with OSA have a markedly raised nighttime BP making ABPM a strong prognostic test.

Pathophysiological Mechanisms Promoting Hypertension In OSA

There is an interplay of mechanisms that play a role in the development of hypertension in patients with OSA. The most agreed upon and acceptable mechanisms are:

Sympathetic activation

The most plausible mechanism by which OSA contributes to the elevation in BP is through acute (chronic in case of

long standing OSA) surges in SN activity. The outcome of these surges in SN activity manifest throughout the day as sustained effect in comparison to control subjects[35]. The repetitive episodes of hypoxemia and hypercapnia caused by reduced ventilation during airway obstruction elicit reflex changes in sympathetic and parasympathetic activity[36]. The derangements in chemo-reflex activity due to intermittent hypoxia along with elevated levels of catecholamine during daytime have been attributed to cause hypertension[37]. The micro arousals from sleep due to breathing cessation induce negative intrathoracic pressure and reduce the pulmonary stretch receptor activation[38]. These changes activate sympathetic response, causing rise in BP[39]. Both animal and human studies have exhibited the role of hypoxia on BP levels. In a canine model, four dogs were subjected to OSA induction and subsequently checked for daytime and nighttime BP during and after 1-3 months. The study concluded that OSA resulted increase in nighttime BP (mean ± SEM of 13±2.0 mm Hg) and eventually increased the daytime BP (15.7 ± 4.3 mm Hg)[40]. A human study comprising 12 healthy subjects has shown that the consistent 2-week intermittent hypoxia increases systolic BP by 8 mm Hg and diastolic BP by 5 mm Hg[41].

Inflammation

An inflammatory reaction occurs in response to repeated hypoxemic episodes during sleep in OSA. The oxygen desaturation followed by rapid re-saturation (characterized as intermittent hypoxia), sets off a cascade of responses in the body. The most noteworthy inflammatory biomarkers include interleukin-1 (IL-1), interleukin-8 (IL-8), high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), soluble intercellular adhesion molecules (sICAM), interleukin-6 (IL-6) and RANTES (Regulated on Activation, Normal T cells expressed and Secreted)[42]. Some of these biomarkers (especially CRP) are thought to be responsible for increased atherosclerotic risk, endothelial dysfunction and elevated BP[43]. The TNF-α levels in OSA show an independent association with oxygen desaturation index, thus supporting the role of intermittent hypoxia as a trigger to inflammatory response[44]. A recent study conducted in 80 patients with OSA and 40 controls concluded that the former group had elevated levels of hs-CRP, TNF-α and IL-6 and increased thickness of carotid-intima, promoting atherosclerotic lesions. A new biomarker, known as Pentraxin-3 was also shown to be increased in patients with OSA[45]**.** The other novel biomarkers discovered, having a role in developing hypertension in OSA include Nesfatin-1, Fibrinogen, and YKL-40 (also referred to as human cartilage glycoprotein)[42]. A study successfully demonstrated the protective effects of atorvastatin against deleterious effects of inflammation on cardiovascular consequences induced by chronic intermittent hypoxia using murine model[46].

Activation of the renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system (RAAS) has a well-established role to play in the development of hypertension. Firstly, Angiotensin is converted to Angiotensin I by renin which is further converted to Angiotensin II by angiotensin-converting-enzyme (ACE)[47]. An increase in BP is noted when Angiotensin II binds to its receptor 'Angiotensin II receptor type I' (AT1). Since Angiotensin II is a potent vasoconstrictor, it causes aldosterone secretion which results in fluid retention and hence BP elevation. In proximal tubules of kidney, the levels of renin and aldosterone have a direct elevating effect on BP, on the other hand, inhibition of ACE, Angiotensin II or AT1 lowers BP[48]. A study conducted in 325 newly hypertensive patients, found a high prevalence of primary aldosteronism and a positive correlation between severity of OSA and plasma renin activity in patients with OSA[49]. Another randomized controlled trial demonstrated that by blocking the Angiotensin II receptors the increase of BP from intermittent hypoxia can be prevented[50]. Yet another recent study suggests that OSA is associated with RAAS activation and OSA subjects have higher levels of Angiotensin II and aldosterone compared to control[51].

Oxidative stress

Oxidative stress is defined as an imbalance between anti-oxidant and pro-oxidant systems, resulting in excessive production of reactive oxygen species (ROS). Intermittent, hypoxia is the prime event that triggers oxidative changes. It is considered analogous to ischemia/reperfusion (I/R) because hypoxemia causes quick changes in the oxygenation of blood which serves as a nidus for the injury due to ROS production[52]. The blockade of NO synthase and subsequent reduced bioavailability of NO causes vasoconstriction which acts as an initiator of promoter of cardiovascular diseases in OSA. Oxidative stress results in enhanced release of superoxide by leucocytes, reduced bioavailability of nitric-oxide (NO), and reduced antioxidant capacity[53]. The other biomarkers that promote cardiovascular risks (particularly hypertension) include ROS production in peripheral neutrophils (provoked by intermittent hypoxia),[54] 8-isoprostane levels in blood[55] and 8-isoprostane in exhaled breath condensate[56].

Endothelial dysfunction

Endothelial dysfunction, resulting from intermittent hypoxia, is an early precursor to the development of atherosclerosis and hypertension preceding cardiovascular disease in OSA[57]. A normal vascular structure and function is maintained by endothelium through the release of mediators like NO, Angiotensin II and endothelin-1 (ET-1). Endothelial dysfunction occurs when the vasoconstrictor

mediators (Ang-II, ET-1) overpower vasodilator mediators (NO) causing arterial wall damage[58]. Hypoxia/reoxygenation associated with transient cessation of airflow in OSA affects NO production and promotes oxidative stress. This in-turn decreases the transcription and activation of endothelial nitric oxide synthase (eNOS) by suppressing its phosphorylation[59]. Among ROS, superoxide rapidly scavenges NO generating peroxynitrile (a toxic metabolite that nitrosylates tyrosine residues, forming nitrotyrosine[60]) in the microvascular walls of OSA subjects[61]. As endothelial oxidative stress increases and fewer cofactors are available for NO synthesis, eNOS preferentially promotes superoxide production that hastens NO degradation and reduces its availability causing a vicious cycle[59]. A study concluded that the patients with OSA and hypertension had prominent impairment of endothelial-dependent vasodilator capacity[62]. Thus, endothelial dysfunction and inhibition of NO production in OSA is implicated in the OSA-related hypertension[63].

Epidemiological Association Of OSA And Hypertension

Population and community-based studies indicate that patients with OSA exhibit a high prevalence of hypertension and vice-versa[64,16]. The two conditions co-exist in millions of people with OSA serving as a risk factor for hypertension[65]. OSA is a highly prevalent disorder in patients with systemic hypertension. A recent cross-sectional study conducted by *Muxfeldt and colleagues* at Brazil University Hospital concluded that 20%–40% of individuals with hypertension suffered from OSA. The levels were even higher in resistant hypertensive patients with 82.2% having OSA and 55.5% having severe/moderate OSA[66]. The prevalence of OSA in consonance with hypertension was nearly 64%[67]. A study by Demede and co-workers reported a 2.5-fold higher risk of OSA in patients with resistant hypertension in comparison to other hypertensive subjects[68]. A number of cross-sectional studies have accounted high prevalence of OSA in hypertension and vice-versa which may vary according to age[69], BMI[9], sex[70] etc. According to AHA and JNC 8 guidelines OSA is one of the most common secondary cause of hypertension[71]. Various epidemiological studies conducted so far confirm that OSA is a common secondary cause of hypertension. Table 1 gives an overview of studies conducted till date which also confirms the bidirectional association between hypertension and OSA.

Treatment Of OSA

The goals of treatment are to resolve signs and symptoms of OSA, improve sleep quality, and normalize the AHI and oxyhemoglobin saturation levels. OSA should be approached as a chronic disease requiring long-term, multidisciplinary management. There are medical, behavioral, and surgical options for the treatment of OSA. Numerous randomized trials have found that effective treatment of OSA [i.e. continuous positive airway pressure (CPAP) or mandibular advancement devices (MAD)] reduce systemic blood pressure, regardless of whether the patients are hypertensive at baseline, and thus proving a causal relationship[72].

Behavioral Approaches

Several behavioral approaches are recommended

Table 1: Population based studies on epidemiology of OSA in hypertension.

Authors	Number of Subjects (n)	Study design	Duration	Results
Peppard etal.2000[21]	709	Prospective population-based	4 years	Odds ratios for the presence of hypertension were 1.42 with an AHI of0.1 to 4.9 events/h at base line as compared with none, 2.03with an AHI of 5.0-14.9/h, and 2.89 with an AHI≥15.0/h.
Lavie et al. 2000[64]	2677	Population based cohort	10 years	36.5% with mild, 46% with moderate and 53.6% with severe OSA had hypertension
Nieto et al. 2000[16]	6132	Cross-sectional	3 years	43% with AHI <1.5/h, 53% with AHI 1.5-4.9/h, 59% with AHI 5-14.9/h and 67% with AHI ≥30/h had hypertension
Mubaril et al.2017[95]	258	Retrospective	1 year	36% had OSA with hypertension
Wali et al.2017[96]	346	Cross-sectional case-control	2 years	67.9% had OSA with an apnoea-hypopnea index (AHI) of ≥5
Arnardottir et al. 2016[97]	415	Prospective cohort	2 years	OSA with ≥5 AHI: 43.1%; AHI ≥5 to <15: 24.6%; AHI ≥15 to <30: 13.7%; ≥30 AHI: 4.8%
Shirani et al. 2016[98]	385	Cross-sectional	2 years	74.5% had hypertension with OSA
Heinzer et al. 2015[14]	3042	Population-based	4 years	71.9% had OSA with AHI ≥ 5; 36.1% with AHI ≥15; 14.5% with AHI ≥30
Min et al. 2015[99]	475	Retrospective	3 years	75.6% had OSA with hypertension and 87.7% had OSA with resistant hypertension
Tkacova et al. 2014 [100]	11,911	Prospective cohort	6 years	78% had AHI ≥5 events/h
Marin et al. 2012[17]	1889	Prospective cohort	17 years	37.3% had incident hypertension
Gonçalves et al. 2007 [101]	133	Case control	2 years	71% had OSA with resistant hypertension

to treat OSA which include avoidance of alcohol[73] and sedatives before sleep (they aggravate apnoea), avoiding supine sleep position,[74] and weight loss. Weight loss improves or eliminates apnoea in virtually all over-weight patients, as evident after surgically induced weight loss procedure[75].

Mechanical Measures

Mechanical measures include positive airway pressure with CPAP or bi-level positive airway pressure (Bi-PAP) device and oral appliance therapy. However, the first-line therapy used in most patients with obstructive sleep apnoea syndrome is nasal continuous positive airway pressure, commonly called nasal CPAP (nCPAP)[7].

1. Continuous positive airway pressure: It is generally administered through nose and is considered the gold standard treatment for OSA. Invented in 1983 by Dr. Sullivan, it is now recommended as the first choice treatment for patients with moderate to severe OSA[76]. The CPAP device consists of a blower unit that produces continuous positive-pressure airflow. This air flow is usually applied at the nose and is then directed through the upper airway. CPAP increases the lateral dimensions of the upper airway and thins the lateral pharyngeal walls, which are thicker in patients with OSA[77]. Effectively, CPAP works by pneumatically splinting the pharyngeal airway and thus substantially reducing or reversing the subjective and objective sleepiness associated with OSA[78]. CPAP significantly improves quality of life indices and normalizes blood pressure in hypertensive patients. Newer devices auto-titrate the lowest pressure required to keep the airway open eliminating the need for CPAP titration in the laboratory[79].

2. Bi-level positive airway pressure (Bi-PAP):Bi-PAP ventilation provides two different levels of pressure (higher during inhalation and lower during expiration) and can potentially treat OSA at a lower mean pressure than CPAP, at the same time improving lung ventilation via a pressure support[80]. It provides a valid alternative in patients intolerant to CPAP and in patients with associated hypoventilation or chronic obstructive pulmonary disease (COPD)[81].

3. Oral Appliances: These devices are designed to advance the mandible thereby pulling the tongue structure forward and opening the pharyngeal airway[82]. The success rate of these devices is generally 40-60% with a greater percentage of patients showing improvement in respiratory disturbance index[83]. The most commonly used oral appliances reduce upper airway collapse by advancing the mandible and thus are known as mandible advancement devices (MAD)[82].

Surgical Interventions

Surgical modes of therapy may be beneficial in selected patients but are not considered as primary therapy for OSA. This mode of treatment is most effective in patients having OSA because of a severe surgically correctable obstructing lesion in the upper airway, such as, tonsillar hypertrophy, adenoid hypertrophy, or craniofacial abnormalities[8].

1. Uvulopalatopharyngoplasty (UPPP):UPPP (conventional or laser assisted) is the most common procedure performed in patients with OSA. It involves the resection of redundant soft tissue in the upper airway (uvula: part of the soft palate and tissue excess in the oropharynx) and is usually performed with simultaneous tonsillectomy[84]. The success rate of UPPP ranges from 30% (performed alone) to 60% (performed with tonsillectomy). Nearly 20-30% of patients experience the side-effects like velopharyngeal insufficiency (up to one-third of patients), dry throat and swallowing difficulty[85].

2. Genioglossus advancement with hyoid myotomy (GAHM):The GAHM involves the repositioning of genioglossus anteriorly through an inferior mandibular osteotomy (genioglossus advancement). This maneuver places the pharyngeal muscles and the base of the tongue on tension and expands the airway. The hyoid is suspended to the superior edge of the larynx and fixed in this position, adding to the effect of genioglossus advancement[77].

3. Maxillomandibular advancement (MMA):It is obtained by osteotomy of the maxilla and mandibular. The advancement of the skeleton structures passively induces an anterior displacement of the soft palate and the tongue with a simultaneous widening of the pharyngeal space[86]. This procedure represents the most effective treatment after tracheotomy and has reported a mean reduction of 87% in AHI. MMA is an invasive treatment presenting an aesthetic sequelae and complications. Therefore, this approach is reserved for selected patients when other modalities fail, as in patients with craniofacial abnormalities[87].

4. Tracheostomy: This procedure relieves upper airway obstruction and its physiological consequences, thus representing the definitive treatment (virtually 100% effective) for OSA[88]. It is reserved for patients who do not respond to conservative treatment, in case of life-threatening arrhythmias or severe disability. It is a disfiguring procedure that decreases the patient's quality of life (QOL) with numerous adverse effects, such as, granuloma formation, speech difficulty, and stoma and airway infection[8].

5. Transoral robotic surgery: It was first introduced in March 2008 by Vicini and coworkers for the treatment of tongue base hypertrophy in OSA[89]. It is an effective treatment option for isolated retro lingual obstruction[90]. A study by Vicini et al. revised the 10-month polysomnography of 20 patients out of overall series of 44 operated cases. It was reported that a significant decrease of AHI occurs with success rate of 70%[91].

6. Hypoglossal nerve stimulation device: The electrical stimulation of the genioglossus muscle, the largest upper airway dilator muscle, causes tongue protrusion and stiffening of the anterior pharyngeal wall[92]. The first successful use of hypoglossal nerve stimulation to activate the genioglossus muscle was done by Schwartz and coworkers in 2001. A reduction in the severity of OSA in a small cohort of patients was reported[93]. The STAR trial is the largest ongoing clinical trial to assess sleep apnoea outcomes from hypoglossal nerve stimulation. The study outcomes have shown that improvements observed at one-year were sustained at the three-year follow-up mark. These include 78% reduction in AHI events, 80% reduction in oxygen desaturation events, high adherence to therapy and improvements in quality of life[94].

The other procedures including distraction osteogenesis, rapid maxillary expansion, and laser midline glossectomy, lingual plasty, nasal surgery (septoplasty, turbinectomy, and polypectomy) may be useful as adjuncts to above mentioned measures.

Conclusion

Various mechanisms have been proposed for the development of hypertension in patients with OSA. The mostly agreed upon mechanisms include sympathetic activation, inflammation, activation of RAAS, oxidative stress and endothelial dysfunction. OSA acts as an essential cause of secondary hypertension. There is a growing body of literature which suggests that treatment of OSA in hypertensive patients lowers BP and improves the overall quality of life. However, more studies in different populations are required to demonstrate the effect of OSA treatment on cardiovascular and cerebrovascular health of a patient. In suspected cases of OSA a screening test should be undertaken followed by treatment of implicit OSA. Also, all cases of resistant hypertension should be screened for OSA and antihypertensive treatment should be combined with the treatment of OSA, wherever plausible. Thus, the issues of cardiovascular morbidity and mortality associated with OSA and hypertension can be addressed.

Conflict Of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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