Obstructive Sleep Apnea and Cardiovascular Disease - An Asian Perspective

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Abstract

Obstructive Sleep Apnea (OSA) is a chronic condition in which there is repetitive partial or complete collapse of pharynx during sleep. OSA is the most common sleep-related breathing disorder, and is increasingly being recognized as an important risk factor in cardiovascular diseases. OSA is prevalent in Asian populations despite lower prevalence of obesity as compared to Caucasian counterparts, suggesting possible differences in pathophysiology. There is increasing evidence that the effect of OSA on cardiovascular diseases is significant in the Asian population and is associated with poorer outcomes. In this review article, we look at OSA particularly in the Asian context, as well as examine the correlation between OSA and cardiovascular disease.

Keywords: Asians, cardiovascular disease, OSA, arrhythmias, heart failure, CPAP

Introduction

Obstructive sleep apnea (OSA) is a chronic condition in which there is repetitive partial or complete collapse of pharynx during sleep. OSA is the most common sleep-related breathing disorder, and is increasingly being recognized as an important risk factor in cardiovascular diseases.[¹] In this review article, we look at OSA, particularly in the Asian context, as well as the correlation between OSA and cardiovascular disease.

OSA is defined by having five or more predominantly obstructive respiratory events per hour of sleep, together with symptoms such as sleepiness, waking up with breath holding, snoring, or having comorbidities of medical or psychiatric disorders (hypertension, coronary artery disease, stroke, congestive cardiac failure, atrial fibrillation [AF], Type 2 diabetes mellitus, cognitive dysfunction, or mood disorder).[²] Alternatively, a frequency of 1.5 or more predominantly obstructive respiratory events per hour of sleep, even in the absence of associated symptoms or comorbidities, also satisfies the criteria of OSA.[³] Obstructive respiratory events can be demonstrated on polysomnography or derived from out-of-center sleep testing. The number of apneas and hypopneas on sleep studies is quantified as the apnea-hypopnea index (AHI).

Prevalence of OSA

Epidemiological studies from the United States show that of those now aged between 30 and 70 years, approximately 13% of men and 6% of women have OSA with an AHI ≥15 events per hour demonstrated on formal polysomnography.[³] The prevalence of OSA in Asian adults is less clear. A systematic review of the literature states that OSA prevalence in Asia ranged from 3.7% to 97.3%.[⁴] This large range in prevalence varies with how investigators define OSA. In this systematic review, 732 articles on OSA prevalence in Asia were identified, of which 24 were eligible for in-depth review. Of these 24 articles, 10 studies used various sleep questionnaires to evaluate prevalence, and 14 used instrumental sleep monitoring and/or full polysomnography assessment. The systematic review has acknowledged that since the studies were of different methodological quality, tested different populations and many countries lack any epidemiologic data, it is particularly difficult to extrapolate the data to the global OSA prevalence in Asia. Based on its results, the estimated prevalence of OSA is around 7% in Hong Kong and 13.74% for OSA in India.[⁴] The rates are similar to Caucasian counterparts despite the general impression that Asians are less obese. Asians can develop OSA at lower body mass index (BMI).[⁵] More

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severe OSA is found in Asians when compared to Caucasians of similar BMI. Asians have a greater body fat content at similar BMI compared to Caucasians. Parapharyngeal fat deposition can result in a reduction in caliber and a change in shape of the upper airway promoting collapsibility.

Craniofacial shape has been recognized as an important contributor to OSA risk. Skeletal features implicated are maxillary-mandibular shape, inferior hyoid position, and small cranial base. Soft tissue features implicated are the size of the tongue, soft palate, tonsils, pharyngeal walls, and parapharyngeal fat pads. Studies suggest that skeletal restriction such as shorter cranial base, difference in length, and positioning of maxilla and mandible predicts OSA in Asians. An inferiorly positioned hyoid and an extended cranio cervical angle are also risk factors.

Male gender, older age, a higher BMI and waist-to-hip ratio, greater neck circumference, arterial hypertension, smoking, snoring, and a higher Epworth sleepiness scale score were related to OSA in Asians. Interestingly, a population-based study found that the risks of OSA may be different between different ethnic groups within the Asian population.

The Singapore Health Study 2012 was a national cross-sectional study in a multiethnic population. Of those sampled, 30.5% had AHI ≥15 events per hour and 91.0% were previously undiagnosed. The most common symptoms of OSA are snoring and excessive daytime sleepiness. However, these symptoms may be regarded as common by patients depending on cultural context and they may not seek medical attention for it.

Pathophysiology of OSA

OSA includes repetitive hypopneas, cyclical apneas, excessive hypoventilation, or a combination of these induced through pharyngeal collapse to the point of ventilatory constraint. During sleep, it is a physiological phenomenon to have reduced tonic activation of upper airway dilator musculature, leading to increased airway compliance and an enhanced collapsibility. However, OSA patients have more susceptible and collapsible airways.

Pathogenesis of OSA is thought to be a complex interaction of unfavorable pharyngeal anatomical compromise, upper airway dilator muscle dysfunction, reduced end-expiratory lung volume, and upper airway edema. There are multiple upper airway dilator muscles, the largest being the genioglossus. These muscles receive input from the respiratory pattern generating neurons, chemoreceptors, and negative pressure receptors in the airway. Patients with highly compromised upper airways tend to develop complete obstruction, leading to apnea. Accumulation of arterial carbon dioxide during apnea will trigger ventilator efforts and transient cortical arousal.

Cardiovascular Consequences of OSA

There are several mechanisms in OSA that contributes to the pathogenesis of a range of cardiovascular consequences.

When the airway is occluded, there is a sudden increase in negative intrathoracic pressure, which, in turn, increases the left ventricular transmural pressure and wall stress, increases cardiac afterload, resulting in myocardial oxygen supply-demand mismatch. To avoid asphyxia, there is arousal from sleep, which raises sympathetic activity during sleep, causing a surge in heart rate and blood pressure (BP). This hemodynamic impact has been described to be equivalent to minute by minute bolus administration of a pressor agent throughout the night, continuing over several years. In addition, there is evidence that longstanding OSA causes oxidative stress, triggers a pro-inflammatory state and endothelial dysfunction and insulin resistance, which stiffens conduit arteries, and accelerates atherosclerosis.

Hypertension

OSA and hypertension frequently coexist. This is hypothesized by the heightened sympathetic activity and inflammatory state in OSA. Clinical observations show that 24 h urinary catecholamine excretion is increased in individuals with sleep-disordered breathing. OSA is now recognized as the most common secondary cause of hypertension. Recent meta-analysis suggests that OSA confers a significant association with both essential and resistant hypertension, even after controlling for potential confounding factors. A dose effect is demonstrated, whereby the risk of hypertension is proportionate to the number of apneic episodes. Caucasians with OSA seem to suffer more from uncontrolled hypertension, with a pooled odds ratio (OR) of the causal association of 4.406, as compared to Asians with pooled OR of 2.460.

Ischemic Heart Disease

A recent systematic literature review analyzed three prospective works that followed 5067 patients, of which 53.5% had different degrees of untreated OSA diagnosed by polysomnography. All the studies found an association between OSA and fatal and non-fatal cardiovascular outcomes. In Singapore, up to 66% of patients who were admitted with acute myocardial infarction were found to have previously undiagnosed OSA. This may be mediated by the association between OSA and multiple vascular risk factors, pro-inflammatory state with endothelial dysfunction, as well as dyslipidemia. Although a clear causal relationship of OSA and dyslipidemia is yet to be demonstrated, there is increasing evidence that chronic intermittent hypoxia that occurs in OSA is possibly the root cause of the dyslipidemia through the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species, peroxidation of lipids, and sympathetic system dysfunction. Meta-regression analysis pooling data from 18,116 patients showed significantly greater levels of plasma low-density lipoproteins, total cholesterol, and triglycerides in those with OSA, while high-density lipoprotein cholesterol concentrations were lower. A prospective Singaporean study examined atheroma volumes in patients with angiographically proven coronary artery disease and found that moderate-to-
severe OSA was independently associated with a larger total atheroma volume in the target coronary artery.[16]

In a meta-analysis of studies done in Asian and Caucasian cohorts including patients who underwent percutaneous coronary intervention (PCI), there is increased risk of major cardiovascular event (MACE), including all-cause or cardiovascular death, myocardial infarction, stroke, repeat revascularization, or heart failure (HF).[27] One of the studies in this meta-analysis was from Singapore, which showed that patients who underwent PCI for ST-elevation myocardial infarction have a lower event-free survival at 18 months if they have severe OSA.[28]

Heart Failure

Sleep-related breathing disorders, including obstructive and central sleep apnea, often coexist with HF. This is postulated to be due to a bidirectional relationship between sleep apnea and HF. Confluence of intermittent hypoxia, elevated sympathetic activity, and reduced intrathoracic pressure promotes HF development. Rostral shift of fluid into peripherally structures in HF also worsens OSA.[13] Epidemiology reported prevalence’s of 37–53% of chronic HF patients to have OSA.[29,30] In the sleep health study (SHHS), risk–adjusted prevalence of HF with baseline OSA and an AHI ≥11 increased 2.38-fold relative to those without OSA.[31] In patients with HF, OSA confers an increased risk of death independently known risk factors.[32]

There are limited data in Asia that looks at the prevalence and association of HF with OSA.

Arrhythmias

OSA is involved in multiple arrhythmogenic mechanisms. Apnea and hypoxia predispose to vagally mediated bradycardic responses and atria-ventricular blocks during sleep.[15] There are also exaggerated intrathoracic pressure oscillations which distend the atria and cause increased cardiac wall stress.[33] Several cross-sectional and case–control studies found significantly increased the prevalence of AF and other arrhythmias in OSA patients, with up to 4-fold higher odds between OSA and AF.[34,36] In a large arrhythmia-free clinical cohort with suspected OSA, nocturnal hypoxemia was independently associated with increased hazard of incident hospitalized AF by 77%.[36] Patients with untreated OSA have a higher risk of the recurrence of AF after successful cardioversion compared to treated OSA patients and those without OSA.[35] Most studies on the relationship of cardiac arrhythmias and OSA were predominantly done in the Western population. The first large study in Southeast Asia that explored the relationship between OSA and cardiac arrhythmias showed increased the prevalence of cardiac arrhythmias among Asian patients with OSA as opposed to those who had primary snoring.[38] However, the prevalence of arrhythmias in OSA patients in this Asian study (8% of OSA patients) is far lower than that of Western counterparts (up to 49% of OSA patients).[39,40]

Postulated mechanisms for this include ethnic variations in atrial size, atrial electrophysiological parameters, and cardiac calcium ion channels.[41] Further, Asian studies should be conducted to ascertain if ethnicity affects arrhythmogenesis in OSA patients.

Cerebrovascular Disease

Large prospective cohort studies suggest that OSA increases the risk for stroke, after adjusting for confounding risk factors including hypertension.[42-45] The risk of ischemic stroke is reported to increase by 6% with every unit increase in baseline AHI from 5 to 25.[42] A study of patients with acute stroke demonstrated that obstructive apnea persisted despite neurologic recovery, suggesting that the OSA may have predated the development of stroke.[46] Among those who survive stroke, OSA is associated significantly with a lower cognitive and functional status.[47] Data from Taiwan report sleep apnea as a risk factor for stroke, with women at a higher risk than men, and younger women at higher risk than older women.[48] This is contrary to findings of the meta-analysis that suggests males with OSA are at significantly higher risk than women to develop stroke.[46]

Continuous Positive Airway Pressure Therapy (CPAP) Treatment and its Impact on Cardiovascular Outcomes

CPAP is known as the first line and mainstay therapy for adults with OSA. The CPAP machine generates a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure, hence, preventing upper airway collapse. With evidence to suggest causal relationship between OSA and cardiovascular disease, there is a need to review if CPAP therapy can reduce cardiovascular morbidity and mortality.

With regard to hypertension, a meta-analysis of randomized controlled trials showed that CPAP reduces systolic BP (SBP), diastolic BP (DBP), and nocturnal BP in patients with OSA.[49] Mean net change in SBP for those treated with CPAP compared with control was −2.46 mmHg (95% confidence interval (CI): −3.81 to −1.09); mean net change in DBP was −1.74 mmHg (95% CI: −2.95 to −0.53), and mean net change in mean arterial pressure was −2.22 mmHg (95% CI: −4.33 to −0.10). Similar improvements in BP were seen in OSA patients who had resistant hypertension. After CPAP, 24 h ambulatory SBP and DBP were −4.78 mmHg (95% CI: −6.53 to −3.03) and −2.95 mmHg (95% CI: −5.37 to −0.53), respectively. CPAP was also associated with reduction in nocturnal DBP (−1.53 mmHg, 95% CI, −3.07 to −0.00).[50]

When looking at cardiovascular events as a whole, there are multiple observational studies to suggest that CPAP may reduce the risk of fatal and non-fatal cardiovascular events and CPAP in OSA patients.[31-34] The sleep apnea cardiovascular endpoints (SAVE) study is a randomized multicenter trial which recruited patients with cardiovascular disease and moderate-to-severe OSA from China and Western countries.[51] Patients were randomized to CPAP versus usual care. Primary endpoint was a composite of
death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, HF, or transient ischemic attack. Patients using CPAP reported less daytime sleepiness and improved quality of life as expected. However, it did not show to have statistically significant benefit on primary composite endpoints, despite reducing AHI from 29 to 3.7 events per hour per night. A concern was that on average, patients assigned to the CPAP arm used it for about 3.3 h instead of ideal 4 h or more, and there is a possibility that increased adherence may improve treatment benefit. When a subgroup analysis was performed for patients who were adherent to CPAP therapy, it showed a lower risk of stroke in patients who were adherent. Despite that, the CPAP adherence achieved in the SAVE trial is likely to reflect “real world” clinical experience where CPAP is used 3–3.5 h per night on average.[58]

A meta-analysis of 10 randomized trials of patients with OSA, compared with no treatment or sham, also showed that CPAP did not result in a reduction in the risk of MACEs (acute coronary events, stroke, or vascular death) or all-cause death.[59] Plausible reasons for these findings include non-adherence to therapy and short follow-up duration of most trials giving insufficient time for CPAP to have affected vascular outcomes.[60] Poor adherence was common to all large clinical trials with cardiovascular endpoints.[13]

Barriers to CPAP Therapy

Non-adherence to CPAP is a major issue limiting its benefits.[51,55] Adherence is defined as using CPAP >4 h per night on >70% of nights, as this is the minimum duration required to experience reduction in daytime somnolence and neurocognitive function. There is a high rate of CPAP rejection in Singaporean patients with OSA.[57] The overall non-adherence rate in studies done in a time frame of 20 years was 34.1% with no improvement over the years.[58] Cost of therapy, discomfort with mask and difficulty breathing through the nose, insomnia, and other psychosocial factors are associated with non-adherence.[49] Individualized strategies to improve adherence rates should be employed.[50]

Other Treatments

Alternative treatments for OSA include oral appliances and surgical therapy. Oral appliances work by increasing the dimensions of the upper airway, hence, reducing its collapsibility, and maintaining patency. Patients consider them to be a more acceptable treatment modality compared to CPAP,[60] as they are quiet, portable and do not require a power source.[61] A large randomized trial comparing CPAP and oral appliances demonstrated CPAP to be superior in terms of AHI reduction, but self-reported compliance with oral appliance treatment was higher.[62] There are data to suggest that oral appliances can reduce awake mean SBP and DBPs, with the peak effect (approximately 3 mmHg) noted during the late sleeping period and early morning.[63] However, there are currently no randomized trials comparing cardiovascular morbidity between CPAP and oral appliance treatment,[62,64] and comparative efficacy data with long-term follow-up for cardiovascular endpoints are lacking.[62]

Upper airway surgery as the treatment for OSA is generally considered for patients who have failed CPAP or oral appliances therapy and appears to be most effective in those with a surgically correctable lesion obstructing the upper airway.[65] Surgical outcomes depend on the pattern of upper airway obstruction.[66] Surgical treatment seems to improve outcomes such as snoring and daytime sleepiness in patients appropriately selected, but there is limited evidence on improving cardiovascular outcomes.[67] Higher level evidence with outcome measures that evaluate treatment effectiveness will be necessary to advance the field; however, it is acknowledged that there are methodological challenges, particularly in the field of surgery.[12,67]

Conclusion

OSA is prevalent in Asian populations despite the lower prevalence of obesity as compared to Caucasian counterparts. There is increasing evidence that the effect of OSA on cardiovascular diseases is significant in the Asian population and is associated with poorer outcomes. Most studies investigating the impact of CPAP and alternative OSA treatment options are from the Western population. Further, research on OSA treatment and its impact on cardiovascular outcomes, particularly in the Asian context, is essential. Given that, craniofacial features play a key role in Asian OSA, there could be a larger role for surgical treatment as well.

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