



## OBSTRUCTIVE SLEEP APNEA(OSA) AS A RISK FACTOR FOR STROKE

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### ABSTRACT

Modern medicine has been able to disentangle some of the phenomena that disturb sleep. Among the most notable offenders is sleep apnea which has gained prominence in the past few decades. It is being proposed as one of the potentially modifiable risk factors for vascular diseases including stroke. Obstructive Sleep Apnea (OSA) is a common co-morbid condition in stroke patients which is a sleep breathing disorder characterized by recurrent and intermittent hypoxia with continued respiratory effort against a closed glottis. Currently, medical researches deem that the mechanism that OSAS impacts and aggravates ischemic stroke may include following factors, like oxidative stress, sympathetic excitation, metabolic disorder, increase of blood pressure, and abnormal hemodynamics. Though case-control and cohort studies demonstrate an inferential relationship between OSA and cerebrovascular ischemic events via common risk factors, several studies have recently asserted that untreated OSA is an independent risk factor for stroke. This review article focuses on the clinical evidence linking obstructive sleep apnea and stroke and on the specific mechanisms perpetuating stroke risk in this population.

**Keywords:** Obstructive Sleep apnea syndromes(OSAS); Stroke; Homeostasis, polysomnography, atrial - fibrillation; cardiovascular disease; hypertension; dyslipidemia

## INTRODUCTION

Stroke is the second leading cause of death worldwide and the leading cause of long-term disability. The vast majority of strokes are ischemic and it results from a transient or permanent reduction in cerebral blood flow to a specific territory of brain [1,2]. Identification and active modification of risk factors, as well as progress in acute stroke care, underlie the improvements in stroke statistics. Modifiable risk factors like: high blood pressure, hyperlipidemia, diabetes, smoking, physical inactivity, and unhealthy diet are responsible for 90% of the risk of stroke [3,4]. However, stroke incidence has not dropped significantly in young adults, and is still soaring in low and middle income countries [5,6]. Insufficient modification of the established risk factors, or the ongoing effects of under-recognized risks, might explain the high global burden of stroke. Recently, the role of obstructive sleep apnea pathology in the development of stroke has been highlighted by experimental and observational studies [7]. Several cross-sectional analyses have shown an increase in the risk of stroke with sleep-disordered breathing. Besides, a study of patients with acute stroke demonstrated that obstructive apnea persisted despite neurologic recovery, suggesting that the obstructive sleep apnea syndrome may have predated the development of stroke. We therefore hypothesized that patients with the syndrome have an increased risk of stroke or death from any cause that is independent of other cerebrovascular risk factors [8].

### **Obstructive Sleep Apnea Syndrome(Osas):**

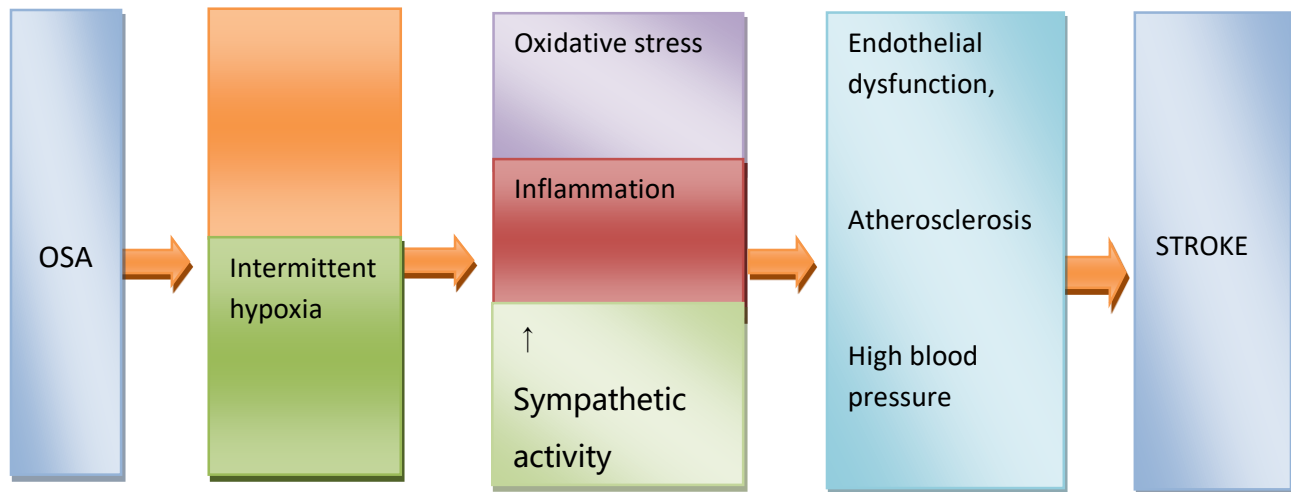
Obstructive sleep Apnea (OSA) is defined by the American Thoracic Society (ATS) as ‘a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns. [9] When the number of apneas exceeds five per hour of sleep (apnea index, AI >5) the obstructive sleep apnea syndrome (OSAS) is usually diagnosed. The prevalence of moderate-to-severe OSA in the adult general population is 9% to 14% in men and 4% to 7% in women [10].

### **Initial Observations Regarding Link Between Osa and Stroke:**

The link between OSA and stroke was first described in a 1985 case report of a 34-year-old man with an acute stroke diagnosed with severe OSA [11]. There was a subsequent retrospective case series in 1991 which found a prevalence of OSA in stroke patients of 72%, 53% and 30% when using apnea-hypopnea index (AHI) of 10, 20 and 30 respectively [12]. The prevalence of stroke is strongly associated with OSA; particularly, the severity of OSA which plays a significant role in the development of stroke [10]. Stroke incidence has been increasing with the severity of OSA with time [13]. OSA is highly prevalent in stroke patients who are not treated with adequate CPAP treatment [14,15]. In a study conducted in Japan, researchers noticed a difference between patients with OSA and the control group. Patients with OSA showed silent cerebral infarction (SCI). Severe OSA, which occurs when the Apnea Hypopnea Index (AHI)  $\geq 15$ , shows higher prevalence of silent cerebrovascular lesions on MRI compared to less severe and moderate OSA [16]. The first evidence of a link between OSA and stroke was from a series of case-control and cross-sectional analyses of epidemiological studies using snoring as a surrogate marker for OSA. These reported increased prevalence and incidence of strokes in snorers [17–21]. In the largest of these prospective studies, 71,779 women were followed for 8 years

during which 398 strokes were documented. Habitual snoring increased the adjusted odds ratio of stroke by 1.33 (95% CI, 1.06–1.67) [22]. More recently, the Sleep Heart Health Study also examined the relationship between untreated OSA and incident stroke in 5422 subjects without prior stroke over an 8-year period. 193 subjects suffered an ischemic stroke, with an overall incidence of 4.4 strokes per 1000 person/years in men and 4.5 strokes per 1000 years in women. In men, there was an almost 3-fold increased risk of stroke in those with an obstructive AHI 25. Furthermore, for every one-unit increase in the obstructive AHI in men there was a 6% increase in stroke risk. In women, the increased stroke risk was not observed until the obstructive AHI was 25. This also demonstrated a significant association between severe OSA and ischemic stroke [23].

**Mechanism of Osa Contributing to The Development of Stroke:**



In OSA apneic/hypoxemic episodes initiate the process of inflammation and there is a cascade of inflammatory markers such as IL-1, IL-6, TNF  $\alpha$ , and interferon  $\gamma$ . These inflammatory markers damage the endothelial lining of the blood vessels, and this will cause increased aggregation of platelets that lead to further oxidative stress and vascular endothelial damage. This repetitive oxidative stress and vascular damage in OSA patients can cause CVD and stroke [24]. In a study of 50 non-obese subjects with stroke and OSA there were increased IL-6 levels compared to a control group. The IL-6 levels were independently correlated with the oxygen desaturation index and low oxygen saturation, but not with the AHI. This also suggests inflammation as an important unifying mechanism between OSA and stroke [25,26]. The nocturnal cyclic intermittent hypoxia of OSA activates systemic inflammation, oxidative stress and metabolic dysfunction which are potential precursors of endothelial dysfunction and atherosclerosis [27].

In OSA patients not only apneic/hypoxemic episodes cause oxidative stress and inflammatory damage to the blood vessels, but sympathetic system stimulation also releases catecholamines, and increased blood pressure which leads to platelet aggregation and further damage to the vascular endothelium and eventually progress to CVD and stroke [28]. There is a dual effect of these apneic/hypoxic episodes; they not only stimulate the sympathetic system, but also depress the parasympathetic pathway. This inhibition also helps in the release of inflammatory markers, causing more oxygen desaturation, platelet aggregation, and endothelial

damage[29,30,31].The sympathetic system activation is also responsible for hypertension, tachycardia, and myocardial wall dysfunction and damage.Because of these apneic/hypoxemic episodes in OSA patients, the activation of a sympathetic system and the beginning of the release of inflammatory markers predispose the patient to a stronger risk of CVD and stroke[32].

### **Experimental and Observational Findings:**

An independent association between the two conditions was supported by large scale epidemiological studies including the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study [33]. In these studies, OSA with an apnea-hypopnea index (AHI)  $\geq 20$ /hr or  $>11$ /hr was related to prevalent stroke, with an OR of 4.31 (95% CI, 1.31 to 14.15) and 1.58 (95% CI, 1.02 to 2.46), respectively, when adjusted for age, sex, weight, blood pressure, smoking, and other confounders. In the Sleep Heart Health Study (n=5,422; stroke incidence, 4.4 per 1,000 person years), men with moderate-to-severe OSA (AHI  $>19$ /hr), but not women, had a higher risk for ischemic stroke during follow-up (median, 8.7 years; HR, 2.86; 95% CI, 1.1 to 7.4) [33,34,35]. Case reports and series suggest a high prevalence of OSA in subjects with TIA (62%–69%) [36,37,38]. A recent study has shown that OSA occurs in 43% of patients with acute TIAs, persists in the majority of cases at 90 days and is associated with a higher vascular event rate when untreated [39]. Contradicting this is a matched case-control study which failed to show any significant difference in the frequency of OSA between the control and TIA groups [40]. While there are conflicting reports regarding OSA in TIA patients, the majority of the studies show an increased prevalence in this population suggesting the pre-existence of OSA in stroke patients [41,42].

Prospective observational studies of clinic-based cohorts, assessing composite cardiovascular events as a primary endpoint, also suggested a role for OSA in the development of stroke [37,43]. Peker et al. reported an independent association of OSA with cardiovascular events in a small community sample of men (age, 30 to 69 years old; n=182) free from prevalent cardiovascular diseases, hypertension, and diabetes. During the 7-year follow-up, the OR for people with OSA having cardiovascular diseases (including stroke) was 4.9 (95% CI, 1.8 to 13.6), and effective treatment of OSA significantly reduced the risk (OR, 0.1; 95% CI, 0.0 to 0.7) [37]. One prospective longitudinal study examining the elderly (age 70–100) shows that patients with severe OSA (AHI $\geq 30$ ) demonstrated higher incidence of stroke compared to patients without OSA.23 Stroke patients with OSA have a worse prognosis, experiencing a more prolonged hospitalization and spending more time in rehabilitation [44]. Summarizing the observational findings, prospective studies largely support a causal relationship between OSA and stroke. Recent systematic meta-analyses reported that OSA was significantly associated with incident stroke (OR, 2.24; 95% CI, 1.57 to 3.19) (relative risk [RR], 2.02; 95% CI, 1.40 to 2.10) [45,46].

### **SUMMARY**

In summary, the epidemiology evidence suggests a significant relationship between OSA and stroke and there are multiple pathophysiological pathways by which OSA may predispose to stroke [47]. Possible mechanisms include acute hemodynamic changes during episodes of apnea, decreased cerebral blood flow paradoxical embolization, hypercoagulability, hypoxia-related cerebral ischemia, and atherosclerosis

[48,49,50]. Strategies for comprehensive acute, chronic and preventive care of stroke should be complemented with evaluation for the presence or absence of OSA [51]. In conclusion, the obstructive sleep apnea syndrome is significantly associated with the risk of stroke or death from any cause, and this association is independent of other risk factors, including hypertension. Increased severity of the syndrome is associated with an incremental increase in the risk of this composite outcome [52].

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