Obstructive sleep apnea (OSA) is a prevalent disease and has been increasingly recognized as an independent risk factor for hypertension, diabetes, cardiovascular disease, and stroke. Stroke is a frequent disease, a second leading cause of death worldwide which generates high healthcare costs. Recent studies suggest that sleep apnea is common after stroke with the prevalence of 50-94%. OSA is emerging as one of the important risk factors for stroke.

Untreated OSA contributes to poor stroke outcome and also is a risk factor for subsequent cardiovascular diseases including recurrent stroke. Treating sleep apnea improves recovery from stroke and decreases cardiovascular morbidity & mortality.

Nonetheless, the under-diagnosis of OSA in stroke patients is still common. Considering that typical symptoms of OSA are not often found in stroke, as well as none of the predictors regarding stroke characteristics can identify the presence of sleep apnea in stroke patients. These findings support the implementation of routine OSA screening in stroke patients.

Obstructive sleep apnea (OSA), the most common form of sleep disordered breathing (SDB), is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) airway obstruction during sleep despite respiratory effort resulting in repeated arousals, sleep fragmentation and hypoxia during sleep. Classic symptoms of OSA include snoring, witnessed apnea, choking during sleep, excessive daytime sleepiness or fatigue. OSA is common in the general adult population and may occur in up to 24% of men and 9% of women. It becomes more prevalent with increasing age; approximately 70% of older men and 56% of older women. Regarding underlying diseases, its prevalence seems to be even higher among patients with neurological diseases such as Parkinson’s disease, Alzheimer’s disease, myotonic dystrophy, epilepsy as well as stroke.

OSA is common after stroke, and stroke appears to be more common in those with OSA. Moreover, there are shared risk factors for both. So the question remains, stroke causes sleep apnea, or sleep apnea leads to stroke, or are they both caused by the same risk factors? This is important because it may have implications for prevention, acute treatment, and rehabilitation of patients with acute stroke. There is actually extensive research over the past 2 decades. In this review, the accumulating evidence of sleep apnea and stroke is summarized, regarding prevalence, predictors, causative relationship, and consequences of untreated OSA in stroke patients as well as possible mechanisms responsible for OSA leading to stroke.
Case Report

A 52-year-old male was transferred to the Bangkok Hospital Pattaya from an outside hospital for evaluation of recurrent transient ischemic attacks (TIAs) and acute ischemic stroke. He has presented to an outside hospital one day prior with acute onset weakness and numbness of left upper and lower extremities. Initial computed tomography of the brain was performed which failed to reveal any evidence of cerebral infarction or hemorrhage. His past medical history was significant for hypertension, hypercholesterolemia and recurrent TIAs. One year prior to his current presentation, the patient had a transient episode of right-sided numbness and slight weakness on the right for two hours and six months ago the patient had reported an episode of left-sided weakness and numbness lasting for four hours for which he has been treated in the outside hospital. He denied regular alcohol drinking, tobacco or illicit drug use. His medication included Diovan, Prevacid, Crestor and Aspirin. After the second episode of TIA, Aspirin was subsequently switched to Plavix.

On initial presentation at our hospital, the patient had a blood pressure of 130/82 mmHg, heart rate of 80 beats per minute, respiratory rate of 14 per minute and oxygen saturation of 98% at room air. His body mass index (BMI) was 28. His lungs were clear to auscultation. Cardiac auscultation did not reveal any murmurs or gallops. Neurological examination was significant for left facial palsy as well as grade 4/5 weakness of the left upper and lower extremities. He was then admitted to the stroke unit of our hospital. Magnetic resonance imaging of the brain was performed which revealed acute infarction in the right thalamus. Even though all of the symptoms had completely recovered within 8 hours after admission, we had tried to identify the mechanism of stroke and recurrent TIAs in his case by various tests. Magnetic resonance imaging of the carotid and intracranial arteries were unremarkable. Ultrasonography of bilateral carotid arteries and transcranial doppler ultrasound (TCD) were reported to be normal. Trans-esophageal echocardiogram with bubble test was unremarkable for intracardiac mass, valvular defects and patent foramen ovale (PFO). There was mild left ventricular hypertrophy and left ventricular ejection fraction was 74%. Routine laboratory work up including of fasting blood sugar, protein C, protein S and antithrombin III were normal. Cholesterol was 140 and LDL was 60mg/dL.

At this point, we were aware that sleep apnea was one of the risk factors of stroke. Based on sleep history collected from the patient and his wife, there was no history of typical clinical features of OSA such as loud snoring, witnessed apneas or excessive daytime sleepiness. However, he mentioned occasional morning headaches which usually resolved within 2-3 hours after waking which could be one of the manifestations of sleep apnea. An ear nose throat examination revealed normal uvula and tonsils. Friedman tongue position was grade II. A polysomnogram was done which revealed severe obstructive sleep apnea associated with severe oxygen desaturation to the nadir of 64%. The apnea-hypopnea index (AHI) was 70. Apnea was defined as an episode of > 90% reduction in amplitude of the nasal pressure signal lasting > 10 seconds. The hypopnea definition was > 50% reduction in amplitude for > 10 seconds associated with an arousal or > 3% oxygen desaturation. The total number of apneic and hypopneic episodes per hour of sleep represented the AHI. The diagnosis of sleep apnea was made when an AHI ≥ 5. Sleep apnea severity was defined as mild: AHI 5 - <15, moderate: AHI 15 - < 30 and severe: AHI > 30. CPAP titration study was also performed which revealed that at the CPAP setting of 10 cmH2O, the AHI was normalized and oxygen saturation was maintained at or above 95%. After using CPAP, the patient felt more refreshed in the morning and no longer had morning headache. Moreover, after the regular use of CPAP during sleep for 2 years, without any change in medication, he had no further episode of recurrent stroke or TIA.

Prevalence of sleep apnea following stroke

Several studies have reported that sleep apnea is common after stroke with the prevalence of 50-94% from the first day to 5 weeks after acute stroke or TIA.3-16 One study revealed the sleep apnea prevalence of 62% during the first night after cerebral infarction (62%).9 Recently, a meta-analysis of 29 studies of sleep apnea in stroke patients revealed that the frequency of sleep apnea (determined by apnea-hypopnea index: AHI > 5) was 72%.17 The prevalence was reported to be 61% among ischemic stroke, 71% among hemorrhagic stroke and 52% in TIA. However, this prevalence was possibly underestimated given that most studies excluded patients with severe medical conditions and who were unable to sign informed consent.

Furthermore, there were several important limitations to these studies, for example, patient selection (age, gender, BMI), the criteria diagnosis of SDB regarding the AHI cut-off, various types of polysomnogram (PSG) monitoring, and co-existing cardiovascular diseases.

OSA as a risk factor of stroke

Treatment of stroke include antiplatelet, thrombolysis, anticoagulants for patients with cardiac embolism, statin, blood pressure control, glucose control in patients with diabetes mellitus, carotid endarterectomy or stenting in patients with significant ipsilateral carotid stenosis along with lifestyle changes. Considering that despite aggressive treatment of stroke, up to 43% of stroke patients will have a progression of neurological deficit, with 87% occurring within the first 48 hours and the relative reduction in the risk of recurrent stroke is not greater than 10 to 30%, reflecting that these traditional risk factors do not fully
explain the occurrence of stroke.\textsuperscript{18,19} A better understanding of the risk factors for stroke is warranted in order to develop additional preventive strategies. In this sense, sleep apnea is being increasingly recognized as an important risk factor for stroke.

Initially, several articles focused on snoring. They demonstrated that snoring was an independent risk of stroke even when adjusted for confounding factors.\textsuperscript{20-25} There was a two-fold increase in relative risk for the combined outcome of stroke and ischemic heart disease in habitual snorers versus nonsnorers.\textsuperscript{26} Later, when the AHI was used as a gold standard for OSA diagnosis, several large prospective studies had demonstrated that OSA increases the risk of stroke independently of known risk factors and the strength of the increase in the risk of stroke in OSA is similar to that of the traditional risk factors of stroke, such as hypertension, hypercholesterolemia and smoking.\textsuperscript{3,5,6,8}

The relationship between OSA and stroke is complex. There are shared risk factors that may lead to a high co-occurrence of these disorders. Additionally, OSA may be an independent risk factor for stroke, as it is thought to promote atherosclerosis due to repeated hypoxemia, and also may promote hypercoagulability through platelet activation. Conversely, OSA or CSA (central sleep apnea) can be a consequence after stroke, in other words, stroke may be a risk factor for OSA/CSA. There is evidence suggesting that OSA is likely to be a risk factor for stroke. First, several prospective studies demonstrated that sleep apnea had preceded stroke. Secondly, if sleep apnea were the result of stroke, the prevalence of sleep apnea in stroke would be expected to exceed the prevalence in TIA given that there is no lasting neurological damage in TIA. But recent studies showed that the prevalence of sleep apnea was the same in both stroke and TIA. This suggests that sleep apnea is likely to have preceded stroke. Thirdly, likewise, if sleep apnea were the consequence of stroke, it would likely improve following stroke, as do other stroke-related symptoms. Nonetheless, a study of patients with acute stroke demonstrated that sleep apnea persisted despite neurologic recovery, suggesting that it may have occurred before the development of stroke. And lastly, the lack of association between different stroke locations and prevalence of sleep apnea favor sleep apnea causing stroke given that if stroke is the cause of sleep apnea, sleep apnea may be more prevalent in brainstem stroke which can affect respiratory neurons.

As mentioned above, several large prospective studies have demonstrated that OSA (defined as AHI ≥ 5) increases the risk of stroke independent of known risk factors. Marin et al. recruited more than 1,000 male OSA patients from sleep lab compared with simple snorers, and healthy men, matched for age and BMI. After a mean follow-up of 10.1 years, patients with untreated severe OSA had a higher incidence of cardiovascular events including stroke than patients with mild to moderate OSA and OSA of any severity treated with CPAP, snorers, and healthy controls. And severe OSA had 3-fold increase in the risk of cardiovascular events and death from cardiovascular events including stroke compared to controls after adjusting for potential confounders; hypertension, diabetes, cardiovascular diseases, lipid disorders, smoking status.\textsuperscript{27} Another prospective study stratified over 1,000 patients admitted to a sleep laboratory into groups with an AHI ≥ 5 or < 5 and followed up over 6 years. OSA was found in 68% and was associated with a stepwise increased in the risk for stroke, TIA and death from any cause even when adjusted for confounding factors (such as age, gender, BMI, HT diabetes, AF, hyperlipidemia, and smoking habits). The risk of stroke or death in patients in the most severe quartile of sleep apnea (AHI > 36) was three times that in the controls and even the mild OSA increased the risk almost 2 times.\textsuperscript{28} However, the major limitation of these 2 studies is that vascular risk was examined in patients who came to see doctors with some sleep complaints, and therefore their risk profile may not represent the general population. There are some population-based studies which overcame this limitation. The Wisconsin sleep cohort, which followed up 1,500 persons, initial age of 48±8 years, over 18 years, found that SDB patients (defined as AHI ≥ 5) had an increased risk for overall and cardiovascular mortality including stroke when compared with those without sleep apnea after adjustment for age, sex, BMI, smoking, and hypercholesterolemia.\textsuperscript{29} Moreover, the mortality increased with the severity of sleep apnea in which severe sleep apnea (AHI ≥ 30) have an increased risk for overall (OR 3.8) and cardiovascular mortality (OR 5.2) when compared with those without sleep apnea. Most studies focused on a middle-aged population, whereas it is well-known that the greatest incidence of stroke is found in older people. So Munoz recruited an elderly population aged from 70 to 100 years old, stroke-free at baseline, and followed up for 6 years. The subjects with severe sleep apnea without CPAP treatment had an increased risk of first-ever ischemic stroke by 2.5 fold independent of known confounding factors.\textsuperscript{30}

Recently, the Sleep Heart Health Study which is an 8 year-follow-up of prospective data from a large community based cohort of 5,422 enrolled patients of middle-aged and older adults, which specifically addressed stroke as an endpoint rather than a composite endpoint as had been reported before, provided compelling evidence that in men, stroke risk increases across the mild to severe range of AHI.\textsuperscript{31} Moreover, men with moderate to severe OSA had an almost 3 fold increase risk of ischemic stroke. In the mild to moderate range (AHI 5-25), the risk of stroke increased 6% with every unit increase in AHI. Moreover the effect size for stroke for AHI levels in the upper quartile (AHI > 20) was comparable to that for a 10-year increase in age or atrial fibrillation. However, in women, the increased risk was observed at an AHI > 25.
Mechanisms of OSA leading to stroke

There are two major types of stroke: hemorrhagic stroke and ischemic stroke which accounts for 80% of all stroke. Determining the causes of stroke does influence choices for management. The causes of stroke include embolism from the heart, aorta, or paradoxical via PFO, small vessel occlusion, extracranially or intracranially large-artery atherosclerosis or coagulation abnormalities.

OSA may directly or indirectly increase the risk of stroke by increasing the odds of developing risk factors for stroke (for example hypertension and diabetes mellitus) or provokes cardiac arrhythmias. In clinical practice, OSA and hypertension (HTN) are tightly linked. HTN was observed in more than 50% of patients with OSA and conversely 25% of HTN patients had OSA. The prevalence of OSA was particularly higher in patients with drug-resistant HTN found in up to 83%. OSA is an independent risk factor for hypertension and AHI is an independent predictor of HTN. Adults with AHI of 15 or more had three times the risk of developing HTN in the next 4 yrs. The risk increased with a higher AHI. Moreover, even mild OSA increased risk of HTN. Among OSA patients, the risk of developing diabetes was increased by 5.5-fold and there was some evidence that OSA has been shown to be 2 times higher in OSA patients than in controls (27 vs. 15%) suggesting that the shunt may be open from right to left during brief Valsalva effect at the termination of sleep apneas.

Another possible mechanism for increased risk of stroke among OSA patients is linked to Patent Foramen Ovale (PFO). PFO reopening or increased shunt while straining can cause paradoxical embolization leading to ischemic stroke. The prevalence of PFO by TCD has been shown to be 2 times higher in OSA patients than controls (27 vs. 15%) suggesting that the shunt may be open from right to left during brief Valsalva effect at the termination of sleep apneas.

Types of sleep apneas in acute stroke patients

The most common form of sleep apnea in stroke patients is OSA. However, central sleep apnea (CSA) and Cheyne-Stokes breathing (CSB) may be present in up to 7%. The contribution of brain damage to the pathophysiology of OSA and CSA in stroke remains poorly understood. In one study, from the acute (within 72 hours) to the subacute (at 3 months) phase of stroke, sleep apnea tended to improve, but this was due to an improvement in central apneas not in OSA in which more than half of patients still exhibited an AHI > 10. These results suggested that OSA likely exists prior to the stroke; on the other hand CSA or CSB is a consequence of stroke. The presence of bilateral strokes, heart failure, and profound disturbances of consciousness, traditionally described in stroke patients with CSB, is not always necessary.

OSA and outcome of stroke

Previous studies have reported that almost half of stroke patients will have a neurological progression. This typically occurs early after stroke onset, with almost 90% occurring within the first 48 hours despite standard treatment. This may, in part, be due to uncorrected factors including sleep apnea which could contribute to poor stroke outcome and also be a risk factor for subsequent cardiovascular diseases including recurrent stroke.
Short term outcomes of stroke with sleep apnea includes an early neurological worsening, more depression, delirium and longer hospitalization.55,56 Long term outcomes include a poorer clinical outcome of stroke and a higher mortality rate.3,52,54 One study even showed that the mortality risk increased 5% for each additional unit of AH1.54

**Significance of treating OSA post-stroke**

Treatment strategies of OSA in stroke patients include prevention, early recognition and treatment of aspiration pneumonia along with avoidance of alcohol and sedative-hypnotic drugs, which may all negatively affect breathing during sleep. Side sleeping position can also improve OSA.57 Continuous positive airway pressure (CPAP) should be prescribed for patients with OSA and oxygen/adaptive servo-ventilator (ASV) in patients with CSA and CSB.

Treatment of sleep apnea in acute stroke patients is important. CPAP has been shown to improve stroke recovery, subjective well-being and mood in stroke patients.55 Based on the blood pressure-lowering effects of CPAP, treatment of sleep apnea may lead to a stroke risk reduction of 20%.58 Furthermore, CPAP reduced cardiovascular events after stroke and reduced 5-year mortality from stroke and all-cause mortality in severe sleep apnea (defined as an AH1 > 20 in this study) compared to patients intolerant to CPAP.59,60 There was evidence that CPAP decreased the level of surrogate markers of vascular diseases, reversed the inflammatory changes and endothelial dysfunction.61-63 Moreover, the CPAP treatment decreased carotid intima-media thickness (IMT), a validated marker of atherosclerosis.64

**Predictors of OSA in stroke**

Given that sleep apnea has been identified as a risk factor of stroke (JNC7) and contributes to poor stroke outcome, exploring the predictors of sleep apnea in stroke is clinically compelling. Among several studies,4,5 apart from some traditional OSA risk factors (high BMI and neck circumference), nothing can predict stroke patients likely to have sleep apnea. Most patients did not have the typical clinical features of OSA (excessive daytime sleepiness, snoring, nocturnal choking or un-refreshed sleep). Thus, approximately 30% of stroke patients with severe OSA would be missed if only clinical history of typical symptoms of sleep apnea alone were used for screening. Moreover, sleep apnea was not related to infarct volume or neurologic severity. A recent meta-analysis of 29 studies of stroke and sleep apnea57 revealed that a significant number of patients will be missed if sleep history alone is used for screening given that > 25% of sleep apnea patients did not snore while > 50% of those without sleep apnea did snore. Sleep apnea was more common in male patients and there was a trend toward increasing frequency of AH1 > 10 with increasing age but not with increasing BMI. Moreover, the frequency of sleep apnea was not significantly related to any stroke characteristics including stroke types (61% in ischemic stroke, 71% in hemorrhagic stroke, 52% in TIA), locations (83% in brain stem stroke and 73% in hemispheric stroke) or timing of sleep study after stroke onset (within 1 week, 1-4 weeks, > 4 weeks). Sleep apnea was more common in those with recurrent strokes and stroke of unknown etiology. The reason why the patients with an unknown cause of stroke had increased rate of sleep apnea could be that sleep apnea may be responsible for the cause in some of these patients. One study showed the high prevalence of nocturia in OSA and demonstrated that nocturia was an independent predictor for severe OSA in ischemic stroke.65 This association between OSA and nocturia has further been confirmed by the significant improvement of nocturia after CPAP treatment.66

**Conclusions**

In conclusion, the prevalence of SDB, particularly OSA, is very high in patients with acute stroke. OSA appears to be an independent risk factor for stroke, and, conversely, stroke is a risk factor for OSA, CSA and CSB. Untreated OSA contributes to worse outcomes of stroke and is also a risk factor for coronary artery disease, arrhythmia and recurrent stroke. Patients with acute stroke with co-morbid OSA should certainly be treated with CPAP which can improve recovery from stroke and decrease cardiovascular morbidity & mortality.

At the present time, there are no guidelines whether stroke patients should be routinely screened for the presence of OSA. Thus, OSA is still under-diagnosed among stroke patients. This review supports that OSA should be viewed as an important modifiable risk factor for stroke and the systematic screening of OSA in all stroke patients is needed given its high prevalence, its implications for acute treatment and rehabilitation as well as prevention of further cardiovascular diseases and recurrent stroke. Further well-designed prospective studies are needed to determine the clinical effect of CPAP on stroke and cardiovascular outcome.
References


