Ann Natl Acad Med Sci (India), **49(3&4):** 169-176, 2013

Sleep and Stroke

M.V. Padma Srivastava
Department of Neurology
All-India Institute of Medical Sciences, New Delhi

ABSTRACT

Circadian variations in conjunction with sleep-related heart rhythm changes and sleep disordered breathing (SDB) are contributing risk factors for stroke. Strong scientific evidence now exists indicating that SDB contributes to systemic hypertension, a prominent risk factor for stroke, and compelling circumstantial evidence is present suggesting that SDB raises the risk for development of stroke through other circulatory mechanisms as well. Preliminary evidence indicates that post-stroke patients have a higher prevalence of SDB, which is likely to compromise their rehabilitation outcomes. Since SDB is modifiable with the application of CPAP and other treatment modalities, there is practical value in investigating patients at risk of stroke or post stroke for presence of SDB. Successful application of CPAP or BiPAP therapy may improve the outcome in both instances.

Key words : Sleep, Stroke, SDB, CPAP

Correspondence : Prof. M.V. Padma Srivastava, Department of Neurology, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi – 110029. E-mail: vasanthapadma123@gmail.com

Most strokes occur as a result of the concerted action of risk factors, prominent among which are age, hypertension, ischemic heart disease, diabetes and smoking. The awareness of new risk factors provides the opportunity to activate more preventive measures. Such is the case with obstructive sleep apnea (OSA). The role of sleep apnea disorder in circulatory alteration and vascular injury is a recently developed concept.

Circadian Variations Influential in Circulatory and Vascular Phenomena :

Many physiological systems directly involved in functions of the circulatory system are affected by the circadian rhythm and interact in a chain of events with far-reaching ramifications. Such are the endocrine secretions, thermoregulation, renal functions, respiratory control, heart rhythm, hematologic parameters, immune system and drug metabolism.

Plasma catecholamine levels rise from 6 AM to noon in parallel with an increase in heart rate and blood pressure. Fibrinolytic activity is reduced in the mornings while platelet aggregability is elevated. These phenomenons have been linked to increased vascular morbidity during morning hours.

A number of studies have shown that stroke onset is more common between 6 AM and non during the 24 hour cycle; the most critical period occurs 1 hour after awakening. Several factors have been proposed as possibly influential in this cyclical occurrence, including cortisol rhythm, hemodynamic variability, increased platelet aggregability, changes in blood viscosity and decreased fibrinolytic activity (1).

Snoring :

Pathologic snoring can be described as the habitual harsh and loud vibratory sound produced by respiratory effort in the sleeping individual. Most individuals past middle age are snorers, but of importance to the clinician should be habitual, unabating, intensely loud snoring that is disturbing to others. Habitual snoring has been associated with arterial hypertension, ischemic heart disease and stroke. Sleep Disordered Breathing (SDB) can have serious cardiovascular and cerebrovascular consequences.

SDB and Stroke :

Abundant circumstantial evidence points to a causal association between SDB and stroke. Vascular risk factors, such as systemic hypertension, provide a slowly evolving indirect link to stroke in untreated SDB patients, while heart disease in any of its forms, as is widely appreciated, is a more direct pathway, if not a trigger, for stroke.

Sleep disordered breathing is a rubric under which OSA, snoring, upper airway resistance syndrome and central hypoventilation/apnea are included. OSA is the most common form of SDB and is

characterized by intermittent and repetitive episodes of partial or complete obstruction of the upper airway, accompanied by elevated airway resistance leading to apneas and hypopnoeas during sleep, both of which cause intermittent hypoxemia (2).

Epidemiology of OSA :

Sleep apnea is a common disorder, affecting up to 20% of the general population according to some reports. With two of the greatest risk factors for OSA being age and obesity, the prevalence should increase with time as the population ages and waistlines bulge. Sleep apnea severity is measured by the apnea-hypopnea index (AHI). The AHI is a measure of the number of apneas, complete cessation of airflow and the number of hypopneas, reduction in airflow with desaturation or arousal, per hour of sleep. An AHI > 5 events/hour with symptoms of daytime somnolence, snoring or waking with gasping or choking or an AHI > 15 events/hour regardless of symptoms is considered diagnostic of OSA. The prevalence of sleep apnea is high in stroke patients – estimated to be between 50% and 70%. The most common type of sleep-disordered breathing found after stroke or transient ischemic attacks (TIA) is OSA. It may predate the stroke, worsen during the acute stage and persist after the acute phase (2,3,4,5).

OSA and Stroke: Shared risk factors vs independent association :

The relationship between OSA and stroke is a complex one with shared risk factors as well as a likely independent association. Several studies have established OSA as a strong risk factor for hypertension, one of the leading risk factors for stroke. Studies have linked OSA to other major stroke risk factors, including insulin resistance, coronary artery disease, heart failure, and arrhythmias. Individuals with OSA have a fourfold increased risk of atrial fibrillation and a two to three fold higher risk of other complex arrhythmias, even after adjustment for potential confounders. Sleep apnea has also been suggested as an independent risk factor for stroke. Postulated mechanisms of OSA as an independent risk factor for stroke include tachyarrhythmias related to sympathetic activation; impaired cerebral hemodynamics as a consequence of blood pressure fluctuations; enhanced inflammation and oxidative stress associated with hypoxemia, including evidence for OSA activating nuclear factor kappa-B-mediated inflammatory pathways leading to systemic inflammation; promotion of atherosclerosis and thrombosis; abnormal coagulation markers, including plasma fibrinogen levels and platelet reactivity and increased right-to-left shunting through a patent foramen ovale (2,3,4,5,6,7,8).

Various studies also support casual association between hypertension

and OSA. The autonomic and hemodynamic responses of OSA lead to acute surges in heart rate and blood pressure. Sleep heart health study demonstrated that sustained diurnal hypertension is a consequence of chronic OSA. The relative risk of hypertension in severe OSA (AHI> 30) compared with the mildest category (AHI < 1.5) in this study was 1.37 (95%, CI: 1.03-1.83), and the odds for hypertension increased with AHI in a dose-response manner. Another compelling evidence for OSA leading to hypertension is available from Wisconsin sleep cohort study, in which even after adjusting for baseline hypertension, age, gender, BMI, weekly cigarette and alcohol consumption, the risk of developing hypertension in people with an AHI of > 15 remained higher compared with those without OSA. Treatment of OSA with CPAP (Continue Positive Airway Pressure), compared to sham CPAP, reduced the hypertension, which further supports an association between OSA and hypertension. OSA may raise the systemic blood pressure significantly and thus can be one of the most important mechanism by which OSA leads to cerebrovascular morbidity (2,3,4,5,6,7,8).

Mechanism of interaction between OSA and normal blood pressure leading to hypertension has been studied and it is observed that patients with OSA have considerably higher sympathetic activity compared with controls, even during wakefulness. A modification caused in renal physiology in the form of an augmentation of the rennin-angiotensin system in chronic OSA-induced hypoxia has also been forwarded as an explanation for the genesis of hypertension in OSA. OSA is also been implicated in contributing to medically refractory hypertension.

The cardiac response to apnea consists of reduction of stroke volume, decreased heart rate and reduced cardiac output. These changes occur in convergence with progressive oxyhemoglobin desaturation and in prolonged apneas, with gradual hypercapnia. In patients with advanced SDB, cardiac arrhythmias, which are more abundant in older patients, appear when the oxyhemoglobin saturation falls below 65%. REM sleep is a most vulnerable time of the night for subjects with cardiovascular and cerebrovascular risk factors since cerebral blood flow normally increases and cardiac rhythm variability is at a maximum in this stage. In SDB, REM sleep related atonia of dilator oropharyngeal muscles and loss of respiratory drive dependency on chemoreceptor reflex activity result in more prolonged episodes of obstructive apnea. In consequence, the accompanying hypoxemia is more profound and the cardiac rhythm changes are more prominent, creating a dissociation between an increasing demand and a progressively faltering supply of blood flow to the brain. (2-11)

TIA and silent infarctions may also occur at night while individuals are asleep, but proof is still missing. The most compelling circumstantial evidence that SDB affects cerebral hemodynamic

mechanisms comes from studies investigating cerebral blood flow velocities with ultrasound techniques in the middle cerebral artery (MCA) territory in patients with SDB. During the apnea event, significant reduction in MCA blood flow velocity occurs that correlates with the duration of the apnea that correlates with the duration of the apnea rather than with the depth of oxyhemoglobin desaturation. These intracranial hemodynamic changes occurring repeatedly night after night in patients with marginal circulatory reserve may contribute to a raise in the risk of stroke. (2-11)

Acute Stroke and Sleep :

Inversion of the sleep-wake rhythm is commonly observed in the days that follow a large hemispheric stroke and is manifested by agitation during the night and lethargy during the day. The early presence of REM sleep and normal sleep cycles is a good prognostic sign. Location and extent of the stroke determine the type of sleep-related alteration. Neuronal centers controlling respiratory drive, pharyngeal motility, and some sleep functions are located in anatomic proximity in the tegmentum of the pontomedullary junction. Vascular injury to the respiratory centers in the lateral medullary syndrome may precipitate SDB. Other patterns of respiratory dysfunction noted with infratentorial lesions include apneusis or apnea during sustained inspiration, nonobstructive, obstructive and mixed apneas and failure of automatic breathing (so called Ondine's Curse). Sleep apnea events of the obstructive or non obstructive varieties with oxyhemoglobin desaturations may require administration of oxygen through a nasal cannula (12-16).

Patients with mesencephalic or paramedian thalamic lesions may exhibit excessive daytime somnolence as a result of loss of alerting mechanisms due to damage to reticular activating pathways and nuclei rather than development of OSA as such. Patients with hemispheric infarction demonstrate reduction of REM sleep during the acute stage proportional to the severity of neurologic deficit. In bilateral hemispheric lesions, Cheyne-Stokes respiration may be observed.

The reported frequency of OSA in stroke patients varies between 30% and 80%. In recent meta- analysis of ischemic or hemorrhagic stroke and TIA patients, the frequency of SDB with AHI of >5 was 72 %, and with an AHI of >20 was 38%, it was reconfirmed by a previously reported higher prevalence of SDB (AHI>10) in men compared with women (65% vs. 48%; p-0.001), and also a higher percentage of SDB (AHI>10) in patients with recurrent stroke than initial stroke (74% vs. 57%; p-0.013). Patients with cardio embolic strokes had a lower percentage of SDB compared with patients with strokes due to unknown etiologies (15,16).

OSA as a predictor of poor outcome after stroke :

If sleep apnea increases the risk of stroke, either directly or indirectly,

untreated patients with co-morbid OSA may have worse functional outcomes and higher mortality after acute stroke. Several observational studies suggest that OSA is a predictor of poor functional outcome after stroke, increasing the likelihood of dependency, and poststroke mortality. Potential mechanisms of OSA contributing to poor neurologic recovery include direct effects of reduced cerebral blood flow and modulation of blood pressure and oxygen saturation associated with apneic episodes, resulting in further neurologic injury due to a compromise in perfusion to the ischemic penumbra. In the subacute setting of the recovering stroke patient, untreated OSA can also cause impaired cognitive function, decreased concentration and excessive daytime sleepiness, prolonging hospitalizations and compromising rehabilitation participation. (17,18,19)

Diagnosis of OSA after Stroke :

Randomized trials of CPAP after stroke suggest identifying OSA may be best accomplished with portable devices. The Sleep Apnea Treatment After Stroke (SATS) trial proposed screening with full polysomnography (PSG), but switched to portable monitoring early in the study sue to intolerance and logistical challenges of coordinating an in-laboratory PSG during the acute stroke period.

Treatment of OSA after Stroke :

Treatment with CPAP has the unique potential to improve the recovery from stroke and to reduce the risk of recurrent stroke both indirectly through better control of multiple modifiable risk factors and directly through a variety of proposed mechanisms. It is an effective treatment for OSA, reducing OSA-associated hypertension, atrial fibrillation, cardiovascular morbidity and mortality, exclusive of stroke, and reducing daytime somnolence. CPAP provides a constant, positive pressure to the airway throughout the respiratory cycle, serving to open the upper airways to prevent narrowing or collapse. The impact of early treatment of OSA with CPAP on neurologic recovery after stroke is just beginning to be studied. Preliminary randomized trials of CPAP therapy after ischemic stroke have shown an improvement in stroke impairment scales, depressive symptoms, motor recovery, sleepiness, and the time until the appearance of cardiovascular events. Other randomized trials have shown no difference. Although results across the studies appear inconsistent, a few conclusions may guide neurologists to initiate CPAP in a stroke patient with OSA. The studies that have shown increased CPAP adherence have demonstrated greater improvements in stroke symptom recovery, while those limited by poor recruitment or adherence have been underpowered to show any significant CPAP benefit (17,18,19).

Treatment with CPAP may also reduce the risk of recurrent stroke in patients with OSA directly. An observational study suggested that treating stroke patients with CPAP prevented recurrent stroke. Stroke

patients with moderate to severe sleep apnea (AHI> 20 events/hour) who did not tolerate CPAP showed an increased adjusted incidence of nonfatal cardiovascular events, especially for new ischemic stroke, during a 7-year follow-up period (hazard ratio 2.897; 95% CI 1.11-7.71) compared to those who tolerated CPAP and compared to patients with mild disease (AHI 10-19 events/hour) or without OSA (AHI< 10 events/hour).

Conclusions :

1. Evidence that sleep apnea is a risk factor for stroke is strong and its prevalence among stroke survivors is high. After stroke, OSA may be an underappreciated risk factor for both poor functional outcome and stroke recurrence.
2. Until better evidence accumulates, providers are left having to decide how aggressively to pursue a diagnosis of OSA and treatment with CPAP in patients who have had a stroke.
3. Current studies suggest that treatment with CPAP may be beneficial in patients after stroke.

REFERENCES

1. Argentino C, Toni D, Rasura M et al. (1980). Circadian variation in the frequency of ischemic stroke. *Stroke* **21**: 387 – 389.
2. Bassetti C, Aldrich M (1998). Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep* **22**: 217 – 223.
3. Dyken ME, Somers VK, Yamada et al. (1996). Investigating the relationship between stroke and obstructive sleep apnea. *Stroke* **27**: 401 – 407.
4. Nieto FJ, Young TB, Lind BK et al. (2000). Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* **283**: 1829 – 1836.

is a potential mechanism increasing stroke risk. *Eur J Neurol* **16**: 283- 284.

12. Bassetti C, Mathis J, Gugger M et al. (1996). Hypersomnia following paramedian thalamic stroke: a report of 12 patients. *Ann Neurol* **39**: 471 – 480.

13. Culebras A (1998). REM-sleep related diaphragmatic insufficiency. *Neurology* **150(suppl 4)**: 393- 394.

14. Vingerhoets F, Bogousslavsky J (1994). Respiratory dysfunction in stroke. *Clin Chest Med* **15**: 729 – 737.

15. Iranzo A, Santameria J, Berenguer J, Sanchez M, Chamorro A (2002). Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction. *Neurology* **58**: 911-916.

16. Kepplinger J, Barlinn K, Albright KC et al. (2012). Early sleep apnea screening in a stroke unit is feasible in patients with acute cerebral ischemia. *J Neurol* (Epub ahead of print).

17. Barlinn K, Alexandrov AV (2011). Sleep-disordered breathing and arterial blood flow steal represent linked therapeutic targets in cerebral ischemia. *Int J Stroke* **6**: 40-41.

18. Martinez-Garcia MA, Soler-Cataluna JJ, Ejarque-Martinez L et al. (2009). Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5 year follow-up study. *Am J Respir Crit Care Med* **180**: 36 – 41.

19. Minnerup J, Ritter MA, Wersching H et al. (2012). Continuous positive airway pressure ventilation for acute ischemic stroke: a randomized feasibility study. *Stroke* **43**: 1137 – 1139.