Sleep, Ageing and Stroke- Newer Directions in Management of Stroke

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Abstract
Stroke is a serious health problem and is chiefly a disorder of the elderly population. Several modifiable and non-modifiable risk factors have been studied. The association of sleep disorders and stroke is exciting. Obstructive sleep apnea (OSA) which is now considered a systemic disease significantly increases the risk of stroke and death from any cause and the increase is independent of other risk factors including hypertension. There is high prevalence of OSA in the elderly. OSA affects the cerebral hemodynamics adversely. There appears to be a bi-directional relation between sleep disordered breathing (SDB) and cerebrovascular accidents. Strokes can themselves generate SDB. The presence of OSA in stroke patients is associated with poor outcome. Cyclical hypoxia and sympathetic stimulation has deleterious effects on cardiovascular, cerebrovascular and metabolic functions. The effects are particularly important in existing ischemic brain injury. Use of continuous positive pressure in OSA patients is rewarding. We propose that feeding through Ryle's tube may compromise with the patency of pharynx during sleep times and therefore this must be considered in management guidelines for stroke.

Introduction
Stroke is a serious health problem since it is the third most common cause of death in the world after ischemic heart disease and all types of cancer combined. Cerebrovascular diseases (CVD) have considerable morbidity and mortality. Stroke is often a crippling disease and it poses a major socioeconomic challenge in the occupational and neurorehabilitational programmes of the “stroke survivors”. Worldwide, about 20 million people suffer from stroke each year, 5 million will die as a consequence and 15 million will survive; of those, who survive, 5 million will be disabled by their stroke. In India the prevalence rates (or estimates) for completed strokes for different zones is North India (Kashmir) 143/100,000 persons; for West India (Mumbai) - 245/100,000; for South India (Vellore) - 64/100,000 and for East India (Assam) 270/100,000 respectively. Studies have shown that incidence of stroke rises with advancing age, the maximum being in the age band of 41-70 years. Cardiovascular disorders including diabetes (Diabetes is a cardiovascular disease) are major risk factors for stroke. Cardiovascular disease contribution has increased from 25.5% in 1990 to 30.2 for all causes of mortality in India. The prevalence of coronary artery disease (CAD) in India has been reported to have increased from 1.05% in 1962 to 12% in urban areas. Also there has been a steady increase in the prevalence of diabetes in India. Modifiable risk factors for stroke include hypertension, heart disease (heart failure, atrial fibrillation), diabetes, hyperlipidemia, smoking, excess alcohol consumption, polycythemia and oral contraceptives. All these have been studied well and find place in the prevention and management of strokes. Sleep which is essential for life and for physical, mental and emotional well being must be of good quality and quantity. Sleep disorders as a risk factor for the development of cardiovascular disorders and diabetes is now being recognized. Sleep disorders also affect metabolic pathways. Obstructive sleep apnea (OSA) is a risk factor for hypertension, ischemic heart disease, diabetes and strokes.

Peppard et al in a prospective study of the association between sleep disordered breathing and hypertension found a dose-response association between sleep-disordered breathing at base line and the presence of hypertension four years later that was independent of known confounding factors. They concluded that sleep-disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population. Shahar et al examined the cross sectional association between sleep disordered breathing and self reported cardiovascular disease (CVD) in 6,424 free living individuals who underwent overnight unattended polysomnography at home. Mild to moderate disordered breathing during sleep was highly prevalent in the sample. The finding were compatible with modest to moderate effects of sleep disordered breathing on heterogeneous manifestations of CVD within a range of apneahypopnea index values that are considered normal or mildly elevated.

OSA is a systemic disease and can even affect retina which is the highest oxygen consuming part of the body. Identification of sleep apnea as a risk factor and as a consequence of stroke has been in focus recently. Management of sleep apnea is highly rewarding.

Sleep, Brain and Cardiovascular system-Studies using positron emission tomography have demonstrated that there is a significant decrease in cerebral blood flow during slow wave sleep compared to waking in the brainstem (including midbrain, pons, hypothalamus, basal forebrain and basal ganglia) and in the cortex. However cerebral blood flow is increased during REM sleep in the brain stem and limbic areas but decreased in frontal cortex. The cerebral blood fluctuations result from changes in vascular resistance. Also these fluctuations are independent of systemic hemodynamic changes. (The regulation of cerebral circulation during the sleep wake cycle aims to finely match the blood flow to the metabolic needs of brain activity at a regional level (flow metabolism
Sleep has a close relation to cardiovascular system both scientifically and emotionally. Cardiac functions in sleep are under control of autonomic nervous system activity, which in turn is dictated by brain states. NREM sleep is associated with relative cardiac and autonomic stability. There is also a functional co-ordinated activity between cardiac and respiratory variables. However in REM sleep there is cardiac bound sympathetic and parasympathetic activity which results in significant surges and pauses in heart rhythm. It is expected that these changes have a potential to affect cardiac function particularly coronary blood flow and cardiac stability. Sleep is not a protected state in subjects suffering from cardiac and respiratory disease.  

### Sleep Disorders, Ageing and Cardiometabolic Consequences

#### A. Sleep Disordered Breathing

There is a increased prevalence of cardiovascular disorders viz hypertension, IHD, stroke increase with advancing age. Also sleep patterns change both subjectively and polysomnographically with ageing. Elderly subjects suffer from sleep problems too often. Sleep disordered breathing (SDB) is one of the common sleep disorders in the elderly. SDB is a spectrum of disorders consisting of snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central or mixed. Obstructive sleep apnea (OSA) often goes unrecognized due to poor awareness. Habitual snoring and excessive daytime sleepiness are two prominent symptoms of the disorder. The other nocturnal symptoms witnessed apneas, choking, dyspnea (can be mistaken for dyspnea of cardiac origin) restlessness manifested by frequent change of posture, nocturia, gastroesophageal reflux, diaphoresis and drooling. Daytime symptoms includes sleepiness (excessive daytime sleepiness can result in vehicular and industrial accidents), fatigue, morning headaches, poor concentration, decreased attention, depression, decreased dexterity and personality changes. Subjects of OSA often exhibit mood swings. Although obesity is risk factor for development of OSA it is not uncommon to observe OSA in low and normal body weight subjects due to anatomical factors - narrow upper airway or pharyngeal weakness. OSA is characterized by repeated pharyngeal collapse in sleep resulting in cyclical hypoxemia, sympathetic stimulation coupled with release of stress hormones and endothelin. (There is normally parasympathetic dominance in slow wave sleep). These events impose a significant burden on the cardiovascular and metabolic systems and are also detrimental to brain circulation.

It is clear that snoring increases with age at least up to age of 70 years. After the age of 80 years snoring prevalence appears to decline. Snoring is evident when a group of subjects sleep together. This is commonly seen in sleeper coaches of railway trains where we can identify 4 loud snorers in each coach. In India Udwadia et al. reported habitual snoring in 26% of the study population (middle aged urban Indian men) and the estimated prevalence of SDB was 19.5% and that of obstructive sleep apnea hypopnea syndrome (SDB with daytime hypersomnolence) was 7.5%. Young et al. reported that 4% of men and 2% of women in a middle-aged North American population had symptoms of OSA and an apnea hypopnea index of greater that 5 events per hour of sleep. This signifies that approximately 5 – 10 million Americans are affected. Several studies show the prevalence of sleep disordered breathing increases with age ranging from 5% to 15% in middle aged adults to approximately 24% in community dwelling adults. Also polysomnography demonstrates that obstructive events predominate rather than central or mixed events. Therefore several elderly subjects suffer from obstructive sleep apnea. Based on data sleep apnea appears to be two different disorders:

1. Age related, manifesting in middle age.
2. Age dependent, manifesting in old age.

The longer you live the more chances of developing sleep apnea. OSA which develops in adults usually continues and can be seen in older adults Also there are several disorders which are also age dependent, like diabetes, atherosclerosis, hypertension and others. It must be appreciated that obstructive sleep apnea (OSA) is a risk factor for the developing hypertension, ischemic heart disease, diabetes, stroke. Also strokes can worsen the severity of OSA. Snoring predicts the onset of diabetes. Sleep apnea is an independent risk factor for metabolic syndrome. Patients suffering from these disorders need to be screened for SDB. Idiopathic cardiomyopathy and congestive heart failure has been reported in patients with obstructive sleep apnea. There is a close association between sleep, aging and metabolic syndrome.

Management of OSA by continuous positive airway pressure has proved highly effective in decreasing the number of episodes of airway obstruction and also improve or completely abolish clinical symptoms and adverse physiological consequences of sleep apnea. Positive airway pressure remains the initial medical treatment of choice for OSA, since it not only treats OSA but also has beneficial effects in associated disorders viz. hypertension ischemic heart disease, diabetes, and stroke.

#### B. Ageing, Upper Airway and Oxidative Stress

Martin et al. have demonstrated that upper airway size decreases with increasing age in both men and women and that men have greater upper airway collapsibility in lying down compared to sitting than women. Several studies suggest obstructive sleep apnea (OSA) is associated with oxidative stress. Oxidative stress aggravates ageing.

#### C. Upper Airway and Cardiovascular Disease

Although obesity is a strong risk factor development of OSA it is not always necessary for an OSA subject to be obese. Ip and colleagues observed in a study involving Chinese office workers from Hong Kong that obesity was relatively uncommon in subjects suffering from obstructive sleep apnea hypopnea syndrome (OSAHS). She postulated that craniofacial features could exist in her study population contributing to upper airway narrowing and high prevalence of OSAHS. The anatomical factors which promote upper airway narrowing are retreved chin, retracted mandible, inferiorly positioned hyoid bone and macroglossia. OSA is possibly an anatomical disease. Low body weight and normal body weight subjects can also suffer from OSA. Sleep disordered breathing begins quite early in life. This may be manifested by snoring but the sleep...
difficulty may be overcome by sleeping in prone position particularly in subjects who have macroglossia. Sleeping prone enlarges the airway due to gravitational reasons. The presence of SDB in young adults is a significant contributory factor for the development of cardiometabolic disorders (vide supra) in adult life particularly in genetically prone subjects. Sleep loss itself results in obesity and impaired glucose tolerance and diabetes.21

D. Sleep Deprivation and Cardiovascular events.

Chronic sleep deprivation (CSD) is associated with cardiovascular events. Irwin et al35 has recently concluded that sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response. A modest amount of sleep loss also alters molecular processes that drive cellular immune activation and induce inflammatory cytokines; mapping the dynamics of sleep loss on molecular signaling pathways has implications for understanding the role of sleep in altering immune cell physiologic characteristics. Intervention that target sleep might constitute new strategies to constrain inflammation with effects on inflammatory disease risk. CSD causes an autonomic imbalance and decreases intracellular magnesium which could be associated with chronic sleep deprivation induced cardiovascular events.36 CSD in young healthy volunteers has been reported to increase levels of proinflammatory cytokines decrease parasympathetic and increase sympathetic tone, increase blood pressure, increases cortisol levels as well as elevate insulin and blood glucose levels.37 Sleep deprivation also induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.38 This only adds to the problem in individuals who are obese. Sleep apnea patients usually suffer from REM sleep deprivation.

Sleep Disturbances and Stroke

More than 50% of stroke patients have breathing disturbances which is more during sleep than wakefulness.39 It is interesting to note that supratentorial strokes are often associated with Cheyne Stokes respiration while infratentorial strokes with OSA, central hyperventilation, central apnea, apneustic breathing and ataxic breathing. Also different breathing disturbances can be seen in different stages of sleep. OSA and CSR can coexist in the Modern Life Style

Genetic Factor Diet

Stress Obesity

Insulin Resistance Hyperinsulinemia

Sleep Deprivation

Sleep Disordered Breathing

Apneic Activity

Cyclical Hypoxia

Sympathetic Stimulation
Cyclical Hypertension, Stress Hormones
Catecholamine, Cortisol Release

Increased Intracranial Pressure
Decreased Cerebral Perfusion Pressure

Metabolic Errors
Insulin Resistance

Hypertension IHD

Altered Insulin Action and Disposal

Insulin Resistance

Hyperinsulinemia

Modern Life Style

Insulin Resistance

Hyperinsulinemia

Anatomical Factors
(Macroglossia, Retruded Chin, Others)

Sleep Fragmentation
Arousals, Nocturia, Insomnia

Stress

Apneic Activity

Cyclical Hypoxia

Sympathetic Stimulation
Cyclical Hypertension, Stress Hormones
Catecholamine, Cortisol Release

Increased Intracranial Pressure
Decreased Cerebral Perfusion Pressure

Metabolic Errors
Insulin Resistance

Hypertension IHD

Altered Insulin Action and Disposal

Insulin Resistance

Hyperinsulinemia

Insulin Resistance

Hyperinsulinemia

Flow Chart
Highlighting the Path Taken by Nocturnal Events in Sleep Disordered Breathing Culminating in Stroke, Cardiovascular and Metabolic Consequences.
same patient. All these phenomena can result in hypoxia which has deleterious effects on the ischaemic brain which is not yet irreversibly damaged. Also breathing disturbances also carry the risk of development of complications like pulmonary aspirations particularly in patients with brain stem stroke eg. Wallenberg’s syndrome. The presence of OSA in stroke patients is associated with poor outcome. Other sleep changes after stroke principally include hypersomnia and insomnia. Hypersomnia in which there is reduced latency to sleep can be passive or active. Passive hypersomnia results in deficient arousal while in active hypersomnia there is increased production of sleep. Sleep deprivation (common in patients admitted in ICU), medications, associated medical disorders like chronic obstructive pulmonary disease, heart failure may also cause hypersomnia. Parasomnias like REM sleep behavior disorder, periodic limb movement disorder, hallucinations and dreaming can also occur. Alterations in sleep architecture after stroke have also been observed. It is important to appreciate that sleep disorders can hamper the physical and mental recovery from acute brain damage.

Society in general has held the view that snoring is a sign of sound sleep. In literal terms sound sleep needs to be differentiated from healthy sleep. About one third of strokes occur apparently during sleep and only snoring was significantly associated with stroke in sleep. Sleep related breathing disorders affect cerebral haemodynamics adversely. There is greater than 50% reduction in central blood flow during apneic and hypopneic events. This reduction is related to the duration of hypopnea and degree of oxygen desaturation. There appears to be a bi-directional relationship between cerebrovascular accidents and sleep disorders. Sleep disorders increase the risk of stroke or death from any cause and the increase is independent of other risk factors including hypertension. Habitual snoring has been associated with increased risk of strokes. Freidlander et al observed that persons with OSA syndrome are more likely to manifest calcified atheromas on their panoramic radiographs than age matched controls. Also type 2 diabetes was significantly more prevalent in individuals with both OSA syndrome and calcified atheromas. The factors which contribute to the development of stroke or TIA in a patient of OSA are nocturnal desaturations, autonomic instability and increase in intracranial pressure which reduces the cerebral perfusion pressure. Elevated catecholamine levels in OSA also promote thrombosis (see flow chart). These events are prominent in REM sleep. Untreated OSA patients have more strokes, stroke morbidity and mortality than those who are treated. It is to be noted that strokes themselves may generate sleep disordered breathing. There is high prevalence of OSA syndrome in patients with acute stroke. Turkington et al observed that the severity of upper airway obstruction appears to be associated with worse functional outcome following stroke, increasing the likelihood of death and dependency. Longer respiratory events appear to have a greater effect. These data suggest that long term outcome might be improved by reducing upper airway obstruction.

**Use of CPAP**

Recently, in a study it has been concluded that CPAP treatment during 18 months in patients with AH1 >/=20 afforded significant protection against new vascular events after ischemic stroke. Studies have shown that usage of CPAP in stroke patients who have OSA is highly rewarding. Broadley et al studied in the prevalence and association of OSA and the safety and tolerability of early treatment with nasal CPAP (nCPAP) in a cohort of stroke patients. They observed that portable diagnostic system for detecting OSA in acute stroke was well accepted and early treatment with nCPAP was effective and well tolerated. Wessendorf et al also reported favourable outcomes with use of nCPAP. The strong association of OSA and stroke justifies the use of polysomnogram in the diagnostic evaluation of stroke and transient ischemic attacks. However CPAP may be difficult to use in patients who are delirious and have severe cognitive impairment.

**Nutrition, Ryle’s Tube and Sleep Apnea (suggested hypothesis)**

Nutritional care of stroke patients may require feeding through Ryle’s tube. Although this is a standard method to provide nutrition but this mechanism for feeding may compromise pharyngeal lumen thereby aggravating OSA. Also restless patients are administered sedatives which also aggravates hypotonia of pharyngeal muscles. OSA patients would definitely require Continuous Positive Airway Pressure (CPAP) support. Ryle’s tube may hinder the application of CPAP but modern medicine and masks can overcome this hurdle and Ryle’s tube removal is not necessary.

**Conclusions**

Stroke and sleep apnea bear a close relationship. With the available data it would be wise to detect OSA in patients of stroke. Strategies in stroke management must include polysomnogram. Treatment of OSA is highly rewarding since it corrects the basic defect –cyclical hypoxia and accompanying cardiovascular and metabolic consequences.

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