Sleep and Stroke

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ABSTRACT

Sleep affects brain function and may contribute to vascular cerebral pathology through a diversity of direct and indirect mechanisms. Circadian rhythm investigation shows increased incidence of stroke between 6 AM and 12 noon. Risk factors for stroke such as high blood pressure, ischemic heart disease, and diabetes are modified by sleep and sleep apnea. Epidemiological studies have shown a dose-response relationship between the severity of sleep apnea and the odds ratio for development of systemic hypertension. There is now evidence of a causal relationship between sleep apnea and stroke. Following stroke, both in the acute and chronic stages, patients have a high prevalence of sleep apnea that reduces the potential for rehabilitation, further increases the risk of secondary stroke, and heightens mortality. Successful correction of sleep apnea with noninvasive positive airway pressure ventilation lowers mean blood pressure, and indirectly lowers the risk of stroke. Unfortunately, patients with stroke tolerate positive noninvasive ventilation poorly, and other means of correcting sleep apnea need to be investigated.

KEYWORDS: Sleep apnea, stroke, positive noninvasive ventilation, hypertension, cardiovascular disease

Circadian variations that appear in consonance with sleep or sleep-related disorders may alter vascular function to the point of creating risk or provoking injury to the brain.^{1,2} The concept of an association between sleep and stroke comes primordially from the notion that sleep-disordered breathing, generically known as sleep apnea, is a risk factor for primary and secondary stroke. Much of this notion is derived from evidence implicating sleep apnea in the precipitation or aggravation of systemic hypertension and heart disease,³ both of which are established major risk factors for stroke. The prevalence of clinically significant sleep apnea in the general population has been estimated at 4% in men and 2% in women.⁴ Other mechanisms of sleep-related stroke risk include blood pressure swings in sleep, sleep apnea-related reduction of cerebral blood flow, changes in cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, prothrombotic coagulation

shifts, proinflammatory states, and increased platelet aggregation in sleep.

CIRCADIAN VARIATIONS AND STROKE

Various studies in different parts of the world have shown that the incidence of stroke peaks at the end of nocturnal sleep between 6:00 AM and 12:00 noon.^{1,2} The most critical period is one hour after awakening, whereas the least likely time for stroke occurrence is the late evening before midnight. Sympathetic activity decreases in non-rapid eye movement (NREM) sleep; parasympathetic activity tends to predominate, accounting for a reduction of heart rate, blood pressure, cardiac output, peripheral vascular resistance, and respiratory frequency. REM sleep is characterized by variability in the activity of both the sympathetic and parasympathetic systems with phasic oscillations and surges that result in a net

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Clinical Sleep Neurology; Guest Editor, Alon Y. Avidan, M.D., M.P.H. *Semin Neurol* 2009;29:438–445. Copyright © 2009 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. DOI 10.1055/s-0029-1237121. ISSN 0271-8235.

increased parasympathetic tone and decreased sympathetic influence. In REM sleep, heart rate and arterial blood pressure variability are observed, while cerebral cortical and spinal blood flow increase. Fibrinolytic activity diminishes in the mornings,⁵ while platelet aggregability increases.⁶ These phenomena have been linked to augmented vascular morbidity during morning hours. The administration of aspirin fails to modify the circadian pattern of onset of stroke in the morning, suggesting that circadian-mediated hemodynamic factors are more important than rheologic and thrombotic factors.

SLEEP AND CONVENTIONAL MAJOR RISK FACTORS FOR STROKE

Blood Pressure Changes

Blood pressure (BP) levels and sleep are intimately linked. Physiologic and pathologic variations in BP are commonly observed in sleep. Certain BP variations are dependent on sleep stages; for instance, BP dips 10 to 15% in NREM sleep and is variable in REM sleep. Experimentally, NREM sleep can precipitate severe myocardial ischemia in a region of the heart supplied by coronary stenosis.⁷ Low blood pressure at night in vulnerable patients with altered vasomotor reflexes who take vasoactive medications has been implicated as a contributing factor in the development of thrombotic stroke.⁸ Absence of nocturnal blood pressure dipping, extreme dipping, or reversed dipping have been associated with increased prevalence of silent cerebral infarctions and strokes in older hypertensive patients.⁹ Deep and less-fragmented sleep is associated with more blood pressure dipping in normal subjects.¹⁰ Conversely, blood pressure normally surges in the morning.¹¹ Morning hypertension is considered a strong independent predictor for future clinical stroke events in elderly hypertensive patients.¹² Poor sleep quality is associated with prehypertension in healthy adolescents. The association is not explained by socioeconomic status, obesity, sleep apnea, or known comorbidities, suggesting that inadequate sleep quality is the critical factor associated with elevated blood pressure.¹³

Diabetes

Experimentally induced sleep deprivation in young men is associated with glucose intolerance, as well as with other alterations of endocrine function and metabolic regulation.¹⁴ Chronic inflammation has been proposed as one of the mechanisms linking sleep disturbances and new onset diabetes.¹⁵ New provocative research has linked sleep duration and diabetes type II.¹⁶ The authors examined the association between sleep duration and abnormal glucose tolerance, among 1336 men and

1434 women in Finland, aged 45 to 74 years. Oral glucose tolerance tests and sleep questionnaires were undertaken by all participants. The authors found an independent association between abnormal sleeping times and type 2 diabetes in middle-aged women. Even after adjustments for age, body mass index, sleep apnea probability, smoking, physical activity, and psychoactive medication, sleep duration of 6 hours or less or 8 hours or longer was independently associated with type 2 diabetes in women but not in men. The study was observational and limited by a low recruitment rate (62%), only one measurement of blood glucose, and a self-reported questionnaire with polysomnographic confirmation. Nonetheless, the study provides strong indications of a link between sleep alterations and diabetes.

Several other studies have shown a relationship between sleep alteration and diabetes type II both in men¹⁷ and in women.¹⁸ In the Nurses Health Study of women, both increased (>8 hours) and decreased (<6 hours) sleep times were associated with increased risk of diabetes. The adjusted OR of the incidence of diabetes was 1.18 for women sleeping less than 5 hours and 1.29 if sleeping more than 9 hours per night. Restricted sleep in healthy volunteers can lower glucose tolerance and increase sympathetic tone, both of which are risk factors for the development of insulin resistance.¹⁹

SLEEP-RELATED FACTORS INCREASING THE RISK OF VASCULAR DISEASE

Snoring

Pathologic snoring is the habitual harsh and loud vibratory sound produced by respiratory effort in the sleeping individual. Most persons past middle age exhibit some form of snoring, but only habitual, sustained, intensely loud snoring that is disturbing to others should be of importance to the clinician. Snoring of these characteristics is frequently a marker of obstructive sleep apnea disorder. Habitual snoring was associated in early studies with arterial hypertension,²⁰ ischemic heart disease,²¹ and stroke.²² Epidemiologic studies have suggested that habitual snoring is a risk factor for brain infarction²³ independent of confounding factors, such as hypertension, ischemic heart disease, obesity, and age. The association of snoring with obstructive sleep apnea disorder reinforces its weight as a risk factor. More recently, habitual snoring has been independently associated with hypertension in men and women. Kim et al²⁴ studied 2730 men and 2723 women without obesity and hypertension at the time of their initial examinations. All participants were reevaluated after an interval of 2 years. Hypertension was defined on the basis of blood pressure equal or higher than 140/90 mm Hg or the use of antihypertensive medications. Habitual snorers were defined as those who snored at least 4 days per week.

The authors found that habitual snoring was independently associated with hypertension in men and women with odds ratios of 1.49-fold and 1.56-fold at 2 years, respectively. Their results support the notion that habitual snoring is an important predisposing factor for development of high blood pressure, even for nonobese adults. The act of snoring implies great effort and force in the process of breathing. It is generally associated with arousals in the upper respiratory disturbance syndrome and with profound negative intrathoracic pressures that alter the hemodynamic function of the heart and may contribute to the risk of vascular disease.

Sleep Apnea

The hemodynamic consequences of sleep apnea and the pathophysiologic link between snoring and obstructive apneas were initially described in Italy by Lugaresi and coworkers²⁵ and Coccagna and collaborators.²⁶ Sleep apnea may directly or indirectly increase the risk of stroke by increasing the odds of developing risk factors for stroke (i.e., high blood pressure) or aggravating comorbidities triggering stroke (i.e., atrial fibrillation). Other less well-assessed risk factors in sleep apnea are patent foramen ovale, impaired vascular endothelial function, accelerated atherogenesis, prothrombotic coagulation shifts, proinflammatory states, and increased platelet aggregation. But it was not until recently that direct evidence was uncovered of the link between sleep apnea and vascular events including stroke.

SLEEP APNEA AND HYPERTENSION

Transient elevations of systemic blood pressure reaching 200/100 mm Hg lasting a few seconds have been recorded in the recovery phase from apnea. This phenomenon has been attributed to the arousal that terminates the apnea event. The arousal is characterized polygraphically by a change in electroencephalogram (EEG) morphology and an enhancement of muscle tone that facilitates oropharyngeal dilator muscle function, a phenomenon responsible for overcoming the obstruction to air flow. Microneurography, a technique that evaluates autonomic discharges in nerves, has shown surges in sympathetic activity in association with arousals explaining the occurrence of blood pressure elevations and acceleration of the heart rate. Repeated bouts of hypertension night after night in patients with untreated sleep apnea may eventually lead to sustained hypertension through unknown mechanisms.²⁷

Convincing evidence of an association between sleep apnea and sustained systemic hypertension, defined as a resting systolic pressure of 140 mm Hg and a diastolic pressure of 90 mm Hg or more, has been obtained. Results from the large community-based Sleep Heart Health Study²⁸ indicate a dose-response relationship between sleep-disordered breathing and hyperten-

sion. The study was conducted between 1995 and 1998 and included a total of 6132 subjects from which the apnea-hypopnea index (AHI) and other measures of disturbed sleep, including arousal index and percentage of sleep time below 90% oxygen saturation, were obtained by unattended home polysomnography. The odds ratio for development of hypertension comparing the highest category of AHI (>30/h) with the lowest category of AHI (<1.5/h) was 1.37 (CI 1.03–1.83), even after adjustment for confounding variables that included obesity and neck circumference. The adjusted odds of hypertension increased steadily with AHI values of 15/h to 20/h and higher, surpassing odds ratios of 2 for very high AHI values. A similar relation was obtained using as the reference parameter oxygen saturation measurements of 90% or less. Controlling for body mass index (BMI) diminished the strength of the association between sleep-disordered breathing and hypertension, suggesting that sleep apnea may be one of the intermediary mechanisms between obesity and hypertension.

The association between sleep apnea and hypertension was confirmed by the Wisconsin Sleep Cohort study²⁹ and the Toronto study.³⁰ In both investigations a dose-response relationship was uncovered between sleep-disordered breathing and hypertension, even after adjustment for confounding factors.

Morbidly obese patients with globular abdomens that challenge the mechanical activity of the diaphragm, the only functional respiratory muscle in REM sleep, exhibit the most profound oxygen desaturations in this stage in association with apnea events and arousals.³¹ The correlation between abdominal obesity and REM sleep-related apnea events and desaturations may explain, at least in part, the observed epidemiologic link between abdominal obesity and hypertension.³²

SLEEP APNEA AND HEART DISEASE

Sleep apnea provokes cardiac dysrhythmias when there is concomitant cardiac or respiratory comorbidity.³³ Patients with advanced sleep apnea may exhibit cardiac arrhythmias, such as atrioventricular block and atrial fibrillation, particularly when the oxyhemoglobin saturation falls below 65%.³⁴ Chronic and paroxysmal atrial fibrillation have been associated with sleep apnea.^{35–37} A high prevalence of sleep apnea is found in relatively young patients (56 ± 12 years) with both paroxysmal and persistent atrial fibrillation with normal left ventricular function,³⁸ leading to the recommendation that relatively young individuals with atrial fibrillation should be investigated for the presence of sleep apnea. Obesity and the magnitude of nocturnal oxygen desaturation, which is an important pathophysiologic consequence of obstructive sleep apnea, are independent risk factors for atrial fibrillation in individuals <65 years of age.³⁹

In an earlier study,⁴⁰ the authors reported episodes of asystole lasting up to 9 seconds during phasic REM sleep in otherwise asymptomatic healthy young adults. They hypothesized that bursts of parasympathetic tone during phasic REM sleep reduced heart rate and played an important role in inducing asystole, a phenomenon that might be linked to unexplained sudden nocturnal death in vulnerable patients. Periods of asystole in REM sleep are of particular concern in patients with sleep apnea.⁴¹

In a study by Marin et al,⁴² the effect of obstructive sleep apnea as a cardiovascular risk factor was investigated. The authors compared incidence of fatal and nonfatal cardiovascular events (myocardial infarction and stroke) in simple snorers, patients with untreated obstructive sleep apnea, patients treated with continuous positive airway pressure (CPAP), and healthy men. The presence and severity of the disorder was determined with full polysomnography. Participants were followed-up for a mean of 10.1 years (SD 1.6) and CPAP compliance was checked with a built-in meter. Multivariate analysis, adjusted for potential confounders, showed that untreated severe obstructive sleep apnea significantly increased the risk of fatal (OR 2.87, 95% CI 1.17–7.51) and nonfatal (OR 3.17, 95% CI 1.12–7.51) cardiovascular events compared with healthy participants, and suggested that CPAP treatment reduced the risk.

Sleep apnea is significantly associated with the risk of stroke among patients with coronary artery disease who are being evaluated for coronary intervention.⁴³ The presence of patent foramen ovale (PFO) was studied with a transcranial Doppler technique in 78 consecutive patients with sleep apnea, and the results were compared with those obtained in age-matched controls.⁴⁴ Twenty-seven percent of sleep apnea patients and 15% of control subjects had PFO. The authors concluded that the prevalence of patent foramen ovale is statistically higher ($p < 0.05$) in patients with sleep apnea, and suggested that the shunt may be open from right to left during brief Valsalva effects at the termination of sleep apneas. They hypothesized that patients with PFO have a higher risk of stroke due to paradoxical embolization.

SLEEP APNEA AND CEREBRAL HEMODYNAMIC DYSFUNCTION

Cerebral blood flow studies have shown that during the apnea event there is significant reduction in middle cerebral artery blood flow velocity.⁴⁵ The drop correlates with the duration of the apnea rather than with the depth of oxyhemoglobin desaturation. The phenomenon suggests that hemodynamic disturbances consequent to thoracic negative pressures during obstructive apneas determine a reduction of cerebral blood flow. Intracranial hemodynamic changes occurring repeat-

edly night after night in patients with marginal circulatory reserve may contribute to raise the risk of stroke, in particular in patients with significant sleep apnea disorder.⁴⁶

When the cerebral circulation is compromised, hemodynamic changes may act as triggers of irreversible ischemic changes in regions with poor hemodynamic reserve, particularly borderzone areas and terminal artery territories. Preliminary studies of auditory event-related potentials in patients with treated sleep apnea found no improvement in abnormal P3 wave latencies,⁴⁷ suggesting permanent structural changes in the white matter of the hemispheres, likely as a result of ischemia.

Healthy young children with apparently mild sleep-disordered breathing have potentially reversible cerebral hemodynamic and neurobehavioral changes following adenotonsillectomy, suggesting normalization of middle cerebral artery blood flow as measured with transcranial Doppler techniques.^{48,49}

SLEEP APNEA AND STROKE

The specific risk of stroke or death in sleep apnea was investigated by Yaggi et al.⁵⁰ In their study, the risk of stroke or death of any cause in patients with sleep apnea with a mean apnea/hypopnea index (AHI) of 35/hour was expressed by a hazards ratio of 2.24 (95% CI 1.30–3.86). The increased risk was independent of other risk factors including hypertension. Increased severity of sleep apnea was associated with an incremental risk of stroke and death.

A causal association between sleep apnea and stroke was reinforced with recent work. In a study of 394 men aged 70 to 100 years,⁵¹ the authors concluded that severe obstructive sleep apnea/hypopnea (defined as AHI ≥ 30 /hour) increases the risk of ischemic stroke in an elderly male noninstitutionalized population, independent of known confounding factors. In a prospective analysis of 1,189 subjects from the general population,⁵² the authors found that sleep-disordered breathing with an AHI of 20 or greater was associated with an increased risk of suffering a first-ever stroke over the next 4 years (unadjusted OR 4.31; 95% CI 1.31–14.15; $p = 0.02$). After adjustment for age, sex, and BMI, the odds ratio was still elevated, but was no longer significant (3.08; 95% CI 0.74–12.81; $p = 0.12$). In a cross-sectional analysis of 1,475 individuals, the same authors found that subjects with an AHI of 20/hour or greater had increased odds for stroke (OR 4.33; 95% CI 1.32–14.24; $p = 0.02$) compared with those without sleep-disordered breathing (AHI < 5) after adjustment for known confounding factors. The authors concluded that there is a strong association between moderate to severe sleep-disordered breathing and stroke, independent of confounding factors.

REM sleep is a most vulnerable time of the night because cerebral blood flow normally increases and

cardiac rhythm variability is at a maximum. In sleep apnea patients, 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 more prominent, creating dissociation between an increasing demand and a progressively faltering supply of blood flow to the brain.³¹

There is some clinical evidence that small vessel disease and leukoaraiosis are worse in subjects with sleep apnea disorder. A higher prevalence of sleep apnea has been reported in patients with multi-infarct dementia compared with patients with Alzheimer's disease or control individuals of similar age.⁵³ An association between sleep apnea and lacunar strokes has been reported.⁵⁴ These observations support the hypothesis that brain regions with poor hemodynamic reserve are preferentially affected in sleep apnea, and coincide with reports of permanent alteration of auditory-event related potentials in these patients. The observations also suggest that early therapeutic intervention in sleep apnea is desirable.

Whether sleep apnea precedes the onset of stroke, occurs as a consequence of it, or both, remains an unresolved issue. In a polysomnographic study of patients 9 days poststroke or posttransient ischemic attack (TIA),⁵⁵ the authors found a respiratory disturbance index of 10/hour or more in 62.5% of subjects as opposed to 12.5% of controls. These results indicate that sleep apnea is common in the acute stages of stroke, but also suggest that sleep apnea may precede the onset of stroke, since TIA patients have a similar prevalence.

Acute Stroke and Sleep

Sleep apnea is frequent during the first 24 hours following stroke.⁵⁶ In a polysomnographic study of 50 patients with acute hemispheric ischemic stroke, the authors found a sleep apnea prevalence of 62%. Neurologic but not functional worsening was associated with the presence of sleep apnea. The study also showed a correlation between severity of sleep apnea and sleep-related onset of stroke. Bassetti et al⁵⁷ found that sleep apnea is common, particularly in elderly stroke men with diabetes, nighttime stroke onset, and macroangiopathy as cause of stroke. They also found that sleep apnea improves after the acute phase, is associated with an increased poststroke mortality, and can be treated with CPAP in a small percentage of patients. Other authors⁵⁸ have found that the severity of upper airway obstruction appears to be associated with a worse functional outcome following stroke, increasing the likelihood of death and dependency, and that longer respiratory events appear to have a greater effect.

Inversion of the sleep-wake rhythm may be observed in the days that follow a large hemispheric stroke and is manifested by agitation during the night and lethargy during the day, conditions that may be misinterpreted as signs of neurologic deterioration. The early presence of normal sleep cycles and generation of REM sleep are good prognostic signs.⁵⁹ Location and extent of the stroke determines the type of sleep-related alteration. Respiratory dysfunction noted with infratentorial lesions include apneusis or apnea during sustained inspiration, nonobstructive, obstructive and mixed apneas, and failure of automatic breathing (Ondine's curse).⁶⁰ In bilateral hemispheric lesions, Cheyne-Stokes respiration may be observed.⁶⁰ The identification of clinically significant sleep apnea in patients with acute stroke is feasible with unattended stroke unit-based polysomnography or portable diagnostic systems.⁶¹ Sleep apnea events of the obstructive or nonobstructive varieties with oxyhemoglobin desaturations may require administration of oxygen through a nasal cannula or application of noninvasive positive airway pressure ventilation.

A study of sleep positions in patients with acute stroke showed that the vast majority of sleep time was spent supine. The majority (63%) of subjects spent no time asleep in any of the nonsupine positions (prone, left, right). Given the high prevalence of supine sleep identified, positional therapy for acute stroke patients with sleep apnea may be warranted.⁶²

Recent transcranial Doppler studies in patients with acute stroke suggest the possibility to detect and quantify cerebral steal in real-time, a phenomenon that describes recurrent hemodynamic and neurologic changes with persisting arterial occlusions attributable to cerebral blood flow steal from ischemic to non-affected brain regions. This condition has been termed the reversed Robin Hood syndrome.⁶³ If the steal is confirmed as the cause of neurologic worsening, reversed Robin Hood syndrome may identify a target group for blood pressure augmentation and noninvasive ventilatory correction in stroke patients. The condition may be particularly severe in patients with sleep apnea and stroke.

Treatment of Sleep Apnea with Noninvasive Positive Airway Pressure Ventilation in Patients with Vascular Risk Factors or Stroke

The treatment of sleep apnea has shifted from the early tracheotomies to the modern application of noninvasive continuous positive airway pressure (CPAP) ventilation, bilevel positive airway pressure ventilation, and more recently automatic control of airway pressure delivery with auto-CPAP devices. Successful treatment of sleep apnea reduces systemic hypertension and by inference the risk of stroke.^{64,65}

Noninvasive ventilation reverses sleep-related desaturation of oxygen and hypercapnia in patients with acute stroke. It is also useful for management of congestive heart failure and Cheyne–Stokes respirations. Unfortunately, the data relative to acute stroke patients is not conclusive, albeit highly suggestive of a favorable effect.⁵⁷

STROKE REHABILITATION AND SLEEP

The prevalence of sleep-disordered breathing is high during the rehabilitation period following stroke. In an overnight study with continuous computerized oxymetry and polysomnography in selected cases,⁶⁶ the authors found that 19% of patients had more than 100 desaturation events on the night of recording. Patients with 10 episodes or more of desaturation per hour of sleep had significantly lower Barthel Index scores on discharge and at 3 months and 12 months poststroke. Mortality was associated with oxymetry variables, indicating increased percentage of time spent below 90% saturation. The study suggested that oxymetry values compatible with sleep apnea in patients in rehabilitation from stroke were associated with worse functional outcome and higher mortality rates.

Other studies^{67–69} have pointed out repeatedly that patients poststroke have a high prevalence of sleep-disordered breathing (71%,⁶⁹ 77%⁶⁸) and that optimal rehabilitation potential and even survival may be compromised. Patients with stroke and obstructive sleep apnea had an increased risk of early death in the study by Sahlin et al.⁷⁰ Patients were followed for up to 10 years, and central sleep apnea was excluded as a risk factor. The risk of death was higher among patients with obstructive sleep apnea than controls (adjusted HR 1.76; 95% CI 1.05–2.95; $p = 0.03$) and was independent of age, sex, BMI, smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination score, and Barthel Index.

Sleep apnea reduces motivation and decreases cognitive capacity while increasing the risk of stroke and death. The application of noninvasive positive airway pressure ventilation offers a window of opportunity to patients with sleep apnea to increase the rehabilitation potential poststroke. Unfortunately, CPAP compliance has not been good in patients recovering from stroke, and beneficial effects have not been confirmed.⁷¹ Subject dropout was related to difficulties with CPAP usage, facial weakness, motor impairment, and discomfort with usage of full-face mask. In the study by Palombini et al,⁷² the majority of sleep apnea stroke patients rejected CPAP treatment. The authors concluded that better education and support of patients and families, and special training sessions in rehabilitation services, will be needed to improve compliance.

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