Sleep-Related Breathing Disorders and Risk of Stroke

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Background—Stroke and sleep-related breathing disorders are both common and are associated with significant morbidity and mortality. Several recent large epidemiological studies have shown a strong association between these 2 disorders independent of known risk factors for stroke. This article will outline the scientific basis for this relationship and suggest sleep-related breathing disorders as modifiable risk factors for stroke.

Summary of Review—Several studies have shown a characteristic circadian rhythmicity in stroke. We have discussed the influence of normal sleep states as well as the effect of sleep-related breathing disorders on cerebral hemodynamics. The hemodynamic, metabolic, and hematologic changes during sleep-related breathing disorders in the form of decreased cerebral perfusion and increased coagulability are possible pathogenetic mechanisms for stroke. There are accumulating lines of evidence that sleep apnea disorder may indeed cause diurnal hypertension. However, the increased risk of stroke in patients with sleep-related breathing disorders appears to be independent of coexisting hypertension; the presence of hypertension would increase the risk even further. Furthermore, several studies have documented high prevalence of sleep apnea disorders in patients with transient ischemic attacks and stroke.

Conclusions—Sleep-related breathing disorder appears to contribute as a risk factor for stroke through hemodynamic and hematologic changes. Because of the high prevalence of sleep apnea disorder in this population, patients with transient ischemic attacks and stroke should undergo evaluation for these disorders.

Key Words: cerebrovascular disorders • risk factors • sleep apnea syndromes • snoring • stroke

Stroke is the third leading cause of death in the United States, after coronary heart disease and cancer. There are approximately 600 000 cases of stroke each year; of these, >150 000 are fatal.1 There are >3 million stroke patients alive in the United States, and the cost of acute and long-term care for such patients is approximately $30 billion per year.2 A diurnal variation in the onset of ischemic stroke has been reported in several studies.3–5 In the largest series, stroke symptoms were present on awakening in 331 (31%) of 1075 patients.5 In another study, 54% of individuals with stroke had its onset in sleep.6 In those patients who developed symptoms of stroke onset during wakefulness, the highest frequency was observed after rising and during morning hours. The relation between the onset of stroke symptoms and the time of day may relate to the underlying pathophysiology of stroke. Intracerebral hemorrhage, subarachnoid hemorrhage, and embolic infarction often occur during daily activities, whereas atherothrombotic brain infarctions often have their onset during sleep or the early morning hours (Figure 1).3,7

Sleep-related breathing disorders have been recognized as important health problems with high morbidity.8–11 Sleep-related breathing disorders are composed of habitual snoring, increased upper airway resistance syndrome, periodic breathing, and sleep apnea disorder. Obstructive sleep apnea is defined as cessation of airflow due to collapse of the upper airway for at least 10 seconds. Hypopnea is defined as >50% reduction in air flow rate with >4% oxygen desaturation. Significant sleep apnea disorder is present when there are >5 episodes of apnea or hypopnea per hour of sleep (respiratory disturbance index [RDI]).12 However, a clinically significant condition is considered to be present when there are >10 events of apneas or hypopneas per hour of sleep. Obstructive sleep apnea syndrome is a condition characterized by repetitive obstruction of the upper airway often resulting in oxygen desaturation and arousals from sleep. The majority of patients suffer from excessive daytime sleepiness and tiredness with neuropsychological dysfunction in the form of poor work performance, memory impairment, and, at times, mood disorders.13–16 Many patients with obstructive sleep apnea disorder suffer from concurrent cardiovascular and cerebrovascular disease.17–23 Recent clinical studies have shown a strong association between sleep-related breathing disorders and stroke. These studies report high prevalence of obstructive sleep apnea in patients with recent stroke.6,22,24,25 In the United States, the prevalence of obstructive sleep apnea disorder, defined as having >5 respiratory events per hour, has been estimated to be 9% to 15% for men and 4% to 9% for women between the ages of 30 and 60 years.9 Obstructive sleep apnea syndrome is relatively common, affecting 2% to 4% of the adult population.9,26 For approximately 31 million

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Americans aged 65 years and older, sleep apnea is estimated in >7 million of them, with 46% at a moderate or severe level. To place the disorder in perspective, in the adult population sleep apnea is more common than diabetes mellitus and asthma.

In this review we consider the effect of sleep on cerebral hemodynamics in normal individuals and pathogenetic mechanisms involved in compromised cerebral perfusion in patients with sleep-related breathing disorders.

Cerebral Hemodynamics During Normal Sleep

Cerebral circulation, like most other vascular beds (eg, coronary and skeletal muscle) but in contrast to some other vascular beds (renal and cutaneous), is characterized by “coupling” of changes in metabolism and blood flow. Changes in perfusion pressure produce marked changes in cerebrovascular resistance and therefore contribute to maintenance of relatively constant levels of blood flow over a wide range of pressures. Mechanisms that mediate autoregulation of cerebral blood vessels may include myogenic responses, metabolic factors, neural mechanisms, and activation of potassium channels. Sleep state has a profound effect on cerebral hemodynamics. Several studies, using a variety of methods that include transcranial Doppler ultrasonography, $^{133}$Xe inhalation, and single-photon emission CT, have shown 5% to 28% reduction in cerebral blood flow during non–rapid eye movement (REM) sleep and 4% to 41% increase in REM sleep compared with wakefulness in normal persons. Changes in cerebral blood flow parallel changes in the brain metabolic rate and oxygen consumption in both non-REM and REM sleep. The exception to this is during transition to and from sleep. These changes in cerebral blood flow are independent of extracerebral hemodynamic factors.

Effect of Aging on Cerebral Blood Flow

Several cross-sectional studies have demonstrated an age-related reduction in regional cerebral blood flow in the range of 20% to 24% in normal aging individuals (Figure 2). This reduction in regional blood flow has been attributed to age-related brain atrophy and increased cerebral vascular resistance secondary to cerebral arteriosclerosis. The mechanism underlying this change has been attributed to altered endothelium function. Relaxation of the basilar artery in humans and cerebral arterioles and the carotid artery in rats in response to endothelium-dependent agonists is impaired with aging. Deposits of β-amyloid in brain and cerebral vessels are seen in aging individuals. Recent data suggest that β-amyloid may impair endothelium-dependent relaxation by generation of superoxide anion. Similarly, impairment of vasoconstrictor responses to several stimuli has been reported in the human basilar artery. The age-related decline in cerebral blood flow as well as the alterations during sleep may predispose the brain to compromised blood supply during sleep.
Cerebral Hemodynamics in Sleep-Related Breathing Disorders

Several studies have shown large fluctuations in cerebral blood flow during and after apnea. One of the first studies, using the $^{13}$Xe inhalation method, showed decreased regional cerebral blood flow in patients with obstructive sleep apnea disorder during the awake state compared with normal subjects and significantly greater reductions in regional cerebral blood flow, particularly in brain stem–cerebellum regions, during non-REM sleep. Simultaneous monitoring of intracranial pressure, intra-arterial blood pressure, and central venous pressure in patients with obstructive sleep apnea disorder while awake and during sleep-induced apnea demonstrated a marked increase in intracranial pressure and a decrease in cerebral perfusion pressure during obstructive apneas. Although there was some degree of vasodilation due to hypercapnia and hypoxia during apneic episodes, cerebral perfusion pressure decreased by approximately 11.2 ± 7.8 mm Hg from baseline. The magnitude of increased intracranial pressure was linearly related to the duration of apneas. Abnormalities of cerebral vascular response to hypercapnia have been found in patients with sleep apnea during wakefulness, suggesting impaired cerebral autoregulation. The rise of common carotid blood flow with increasing CO$_2$ was attenuated in the patients, while carotid resistance increased instead of falling, as it did in normal subjects. Using transcranial Doppler ultrasonography during sleep, Fischer et al demonstrated 15% and 20% reductions, respectively, in mean and systolic cerebral blood flow velocities of the middle cerebral artery in a group of patients with sleep apnea disorder compared with control subjects. Balfours and Franklin showed an initial increase of 15% in cerebral blood flow velocity immediately after termination of obstructive sleep apnea, followed by a 23% reduction compared with baseline values. Similarly, Netzer et al demonstrated >50% reduction in the cerebral blood flow in obstructive apneas and hypopneas compared with central apneas. The reduction in cerebral blood flow was related to the duration of apneas and the degree of oxygen desaturation.

The fluctuation in cerebral blood flow closely correlated with arterial blood pressure, indicating that cerebral autoregulation is insufficient to protect the brain from rapid systemic pressure changes in obstructive sleep apnea. Patients with obstructive sleep apnea disorder have diminished cerebral vasodilator reserve, which can further impair the ability of cerebral vessels to adapt to the metabolic needs of the brain. This abnormality is corrected with the treatment of sleep apnea with continuous positive airway pressure, suggesting a functional impairment as opposed to structural changes in cerebral hemodynamics due to sleep apnea. The cerebral underperfusion during the apneic events is associated with cerebral oxygen desaturation on near-infrared spectroscopy, suggesting cerebral ischemia during apneas.

Snoring and Sleep Apnea as Risk Factors for Stroke

There are several lines of evidence from cross-sectional and case-control studies that suggest a strong association between sleep-related breathing disorders and cerebrovascular disease. A number of epidemiological studies have shown increased risk of stroke in habitual snorers and those with obstructive sleep apnea disorder (Table 1). In a case-control study by Partinen and Palomaki, the relative risk of stroke was 10.3 (95% CI, 3.5 to 30.1) compared with nonsnorers. In a similar study, Neau et al demonstrated a 3.37 (95% CI, 1.52 to 7.59) relative risk of stroke in 133 individuals with a mean age of 60.6 years after adjusting for known risk factors. The association between snoring and brain infarction was found among all patient subgroups with strokes of probable cardiogenic and atherothrombotic origin and among those with infarction in the
carotid and vertebrobasilar territories. The strength of the association (estimated relative risk) was in the same order of magnitude as seen with other stroke risk factors such as hypertension (95% CI, 4.0 to 5.0), cardiac disease (95% CI, 2.0 to 4.0), smoking (95% CI, 1.5 to 2.9), diabetes mellitus (95% CI, 1.5 to 3.0), and hyperlipidemia (95% CI, 1.0 to 2.0). In addition, risk of stroke is further enhanced because of the high prevalence of hypertension in the population with sleep-related breathing disorders. In a recent cross-sectional study by Nieto and colleagues, as part of the Sleep Heart Health Study, mean systolic and diastolic blood pressure as well as the prevalence of hypertension increased significantly with increasing severity of sleep-related breathing disorder. The odds ratio for hypertension, in a comparison of the highest category of RDI (>30 per hour) with the lowest category of RDI (<1.5 per hour), and after adjustment for demographics and anthropometric variables as well as smoking and alcohol intake, was 1.37 (95% CI, 1.03 to 1.83; \( P = 0.005 \)). Associations of hypertension with RDI were seen in both sexes, older and younger ages, all ethnic groups, and among normal-weight and obese individuals.22 In a recent prospective study by Peppard et al, 1189 participants underwent overnight polysomnography; 709 were restudied after 4 years to determine the effect of sleep apnea disorder on the cardiovascular system. They found a dose-response relationship between sleep-related breathing disorder at baseline and the presence of hypertension 4 years later that was independent of other known risk factors for hypertension. The adjusted odds ratios were (in reference to baseline RDI of zero) 1.42 (95% CI, 1.13 to 1.78) for RDI 0.1 to 4.9 events per hour, 2.03 (95% CI, 1.29 to 3.17) for RDI 5.0 to 14.9 events per hour, and 2.89 (95% CI, 1.46 to 5.64) for RDI \( \geq 15.0 \) events per hour. These data show that the presence of sleep-related breathing disorder at baseline was predictive of development of hypertension 4 years later, independent of other confounding factors. It should be noted from the aforementioned studies that the risk of stroke from sleep-related breathing disorders is independent of coexisting hypertension. The presence of hypertension further enhances the risk.

### Increased Prevalence of Sleep Apnea in Patients With Transient Ischemic Attack and Stroke

The strong association between sleep apnea disorder and stroke is further supported by a number of studies examining the prevalence of sleep apnea in patients with recent stroke or transient ischemic attacks. Mohsenin and Valor demonstrated a high prevalence of obstructive sleep apnea disorder (80%) in a group of patients recovering from hemispheric stroke without a previous history of sleep apnea compared with age-matched patients with similar frequency of hypertension and smoking without stroke. A subsequent study by Dyken et al showed a similar result in which 77% of men and 64% of women with stroke had obstructive sleep apnea disorder compared with age-matched controls with a prevalence of sleep apnea disorder of 23% (\( P = 0.01 \)) in men and 14% (\( P = 0.01 \)) in women without stroke. In a larger study of 128 patients with transient ischemic attack and stroke, Bassetti and Aldrich found obstructive sleep apnea in 62.5% of the patients compared with 12.5% in the normal control group. They observed a high frequency of obstructive sleep apnea disorder in patients with transient ischemic attack, suggesting preexisting obstructive sleep apnea disorder before cerebrovascular events rather than as a consequence of it. This latter observation strongly supports the role of sleep apnea as an independent risk factor for cerebrovascular accident (Table 2).

Regardless of whether sleep apnea disorder precedes or follows a stroke, it is associated with poor functional outcome in survivors and higher mortality after 1 year compared with those patients with stroke but without sleep apnea disorder. The high prevalence of sleep apnea disorder and poor functional outcome in stroke should prompt physicians to evaluate patients for underlying sleep-related breathing disorders.

### Mechanisms of Transient Ischemic Attack and Stroke in Sleep-Related Breathing Disorders

There are several pathophysiological mechanisms that may underlie the diurnal development of stroke. The alteration of cerebral hemodynamics, hypoxemia, and dysfunction of cerebral autoregulation appear to be the main mechanisms of cerebral ischemia in patients with sleep-related breathing disorders. Marked episodic elevation of cerebrospinal fluid pressure seen during nocturnal sleep in patients with obstructive sleep apnea may further compromise the cerebral blood flow. The decrease in arterial blood pressure (secondary to more negative intrathoracic pressure) and gradual rise in intracranial pressure during apnea result in decreased cerebral perfusion pressure. Pronounced cerebral blood flow velocity changes during apneic episodes and the concomitant alterations of vessel wall tension might lead to chronic strain on the brain vessels and formation of atherosclerosis. Another important factor that increases the risk of thromboembolic stroke is enhanced platelet aggregability.
during sleep and immediately after rising. Platelets from normal men show increased responsiveness to epinephrine and adenosine diphosphate with enhanced aggregability between 6 AM and 9 AM. Platelet aggregation, both spontaneous and after activation, is significantly enhanced in patients with severe obstructive sleep apnea during the night compared with normal individuals. The abnormality reverses with treatment of sleep apnea with 1 night of treatment with norepinephrine and epinephrine levels. Increased plasma catecholamine concentrations have been shown in patients with obstructive sleep apnea. Likewise, increased platelet aggregability during early morning hours has been shown to increase the risk of myocardial infarction and sudden death. Elevated plasma fibrinogen level is believed to be associated with increased risk of stroke and other vascular events. Plasma fibrinogen has been shown to be elevated in patients with stroke and sleep apnea disorder. In the same study the investigators found a correlation between severity of coexisting sleep apnea disorder and fibrinogen level in patients with stroke. Taken together, the combination of cerebral hypoperfusion and hypercoagulability in sleep apnea disorder is possibly the main pathophysiological mechanism for increased risk of stroke in this population.

Evaluation of Sleep-Related Breathing Disorders

Patients with transient ischemic attacks and stroke should undergo a thorough sleep history interview and physical examination. The most common presentation of sleep apnea disorder is excessive daytime sleepiness and unrefreshing sleep. Many patients describe falling asleep during socially inappropriate occasions. Intermittent snoring with breath holding terminated by loud snorts and body movements is a typical feature that patients may not be able to report about themselves. A detailed history from a bed partner, when there is one, is of crucial importance. Other related complaints include restless sleep, choking or coughing during sleep, nocturia, and headaches. Physical examination of the upper airways may disclose a deviated nasal septum or swollen turbinates, retrognathia, an enlarged tongue, a hypertrophic uvula, a redundant soft palate, or paralyzed vocal cords. In view of the high prevalence of sleep apnea disorder and nonspecificity of symptoms in the setting of stroke, every patient should undergo polysomnography. Likewise, patients with transient ischemic attacks should also be evaluated for sleep-related breathing disorders. Treatment of sleep apnea disorder has been shown to improve the quality of life, lower blood pressure, and improve sleep quality and daytime symptoms.

In summary, sleep-related breathing disorders are strongly associated with increased risk of stroke independent of known risk factors. The mechanisms underlying this increased risk of stroke are multifactorial and include reduction in cerebral blood flow, altered cerebral autoregulation, and increased platelet aggregation and plasma fibrinogen level. Since sleep-related breathing disorders are treatable, patients with stroke and transient ischemic attacks should be investigated for these conditions.
To breathe regularly and smoothly at night is not only socially correct but also healthy. Individuals who snore with trepidation and have lapses in their respiratory rhythm while asleep may be at increased risk of suffering a stroke, as Mohsenin points out in the preceding article.

The role of disruptive snoring and sleep apnea disorder, or sleep-disordered breathing (SDB), in circulatory alteration and vascular injury is a concept of recent development. Evidence of an association between SDB and sustained systemic hypertension, has become available recently. Results from the large community-based Sleep Heart Health Study indicate that there is a dose-response relationship between SDB and hypertension. The adjusted odds of hypertension increased steadily with apnea-hypopnea index (AHI) values of 15/h to 20/h and higher measured at home, surpassing odds ratios of 2 for very high AHI values. In a similar prospective study of SDB and hypertension, the Wisconsin Sleep Cohort Study showed that the odds ratio for developing hypertension at 4 years for subjects with a baseline AHI of 5/h to 14.9/h was 2.03, while for subjects with AHI of ≥15/h the odds ratio was 2.89.

These epidemiological, community-based studies fail to reveal the mechanisms that drive the blood pressure up in patients with significant SDB. Powerful negative intrathoracic pressures generated during the apnea event disturb the hemodynamics of the heart. Arousals at the termination of the apnea episode enhance sympathetic activity, and the repeated occurrence of these changes night after night perpetuates blood pressure elevations. Successful treatment of SDB may reduce systemic hypertension. In an early study, application of nasal continuous positive air pressure (nCPAP) to 14 patients with established SDB reduced the mean blood pressure after 8 weeks of treatment. More recently, Pankow et al showed that after 4 to 6 months of nCPAP treatment, 24-hour blood pressure measurements fell from 142/91 to 134/84 in hypertensive patients.

Hypertension is not the only potential complication of SDB. Netzer et al showed that during the apnea event there is a significant reduction in middle cerebral artery (MCA) blood flow velocity that correlates with the duration of the apnea. Intracranial hemodynamic changes in patients with marginal circulatory reserve may contribute to raise the risk of stroke.

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 facilitate prolonged episodes of obstructive apnea. Morbidly obese patients with globular abdomens and a mechanically disadvantaged diaphragm, the only functional respiratory muscle in REM sleep, exhibit very prolonged apnea events during REM sleep. In consequence, the accompanying hypoxemia is more profound and the cardiac rhythm changes more prominent, creating a divorce between an increasing demand and a progressively faltering supply of oxygenated blood flow to the brain. When the cerebral circulation is compromised, regions with poor hemodynamic reserve, particularly borderzone areas and terminal artery territories, will suffer the most damage. Preliminary studies of auditory event-related potentials in patients with treated SDB found no improvement in abnormal P3 wave latencies, which suggests that permanent structural changes in the white matter of the hemispheres were likely the result of ischemia.

Several recent studies point out that after acute stroke, patients have a high prevalence of SDB. In the study by Good et al, 19% of patients had a mean of >100 desaturation events 13 days after stroke. Follow-up evaluations showed that poor oximetry measures during rehabilitation correlated with worse functional outcome and higher mortality. Studies have confirmed that poststroke patients have an unexpectedly high prevalence of SDB. All emphasize that the rehabilitation potential and even survival may be compromised, because SDB reduces motivation and decreases cognitive capacity while increasing the risk of recurrent stroke and death.

These considerations would be academic were it not for the well-established fact that SDB is correctable. The application of positive-pressure breathing treatment modalities may reduce the risk of hypertension and stroke in patients with SDB and improve the rehabilitation potential of patients after stroke. However, the results of clinical studies showing that successful correction of SDB in patients at risk of stroke and in poststroke patients will improve functional, neurological, and mortality outcomes are still pending. These are clear research goals for the immediate future.

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