Sleep-disordered breathing and stroke

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Care-charming Sleep, thou easer of all woes, Brother to Death, sweetly thyself dispose. John Fletcher (1579–1625), The Tragedy of Valentianin (V, ii).

It is fascinating to consider that something as basic as the way we breath during sleep is associated with conditions that account for several of the leading causes of mortality in adults in this country: hypertension, cardiovascular, and cerebrovascular disease. When considered separately from other cardiovascular diseases, stroke ranks as the third leading cause of death, and it is the leading cause of serious long-term disability [1]. Stroke constitutes several different types of cerebrovascular disease: ischemic stroke, embolic stroke, transient ischemic attack (TIA), and hemorrhagic stroke. There are currently few effective therapies for stroke, so understanding underlying pathophysiologies, promoting preventative behaviors, and developing novel therapeutic approaches for the treatment of stroke are of crucial importance.

Like stroke, sleep-disordered breathing is highly prevalent [2] and constitutes a spectrum of diseases: primary snoring, upper airway resistance syndrome, obstructive sleep apnea (OSA), central sleep apnea, and obesity-hypoventilation syndrome. The high prevalence of stroke and sleep apnea could cause an overlap of these two diseases just by chance alone. There are several reasons to suspect a direct relationship between stroke and sleep-disordered breathing, however. In the authors’ clinical experience, apneic spells and snoring are frequently observed on the stroke rehabilitation service. Patients who suffer from cerebral infarction often complain of diffuse cerebral symptoms and cognitive problems, such as impaired memory, inability to concentrate, emotional instability, and excessive daytime sleepiness [3]. In large part, these symptoms have been attributed to structural damage to brain tissue; however, many of these symptoms are also pervasive in patients with sleep-disordered breathing [4]. There are several overlapping risk factors and consequences of both diseases, such as gender, age, hypertension, obesity, smoking, and alcohol use. Finally, some of the physiologic consequences of OSA, such as cyclic oxygen desaturations and labile blood pressure, are known to be poorly tolerated in patients with stroke.

Identifying and treating underlying sleep-disordered breathing ultimately may represent a novel management strategy for reducing the large morbidity and mortality burden of stroke. Over the past decade, the understanding of the strength of the association between sleep-disordered breathing and stroke has grown considerably, as has the understanding of the physiologic, autonomic, humoral, and vascular consequences of this breathing disorder. Several challenging questions persist with respect to any causal inference between sleep-disordered breathing and stroke, however: What is the temporal relationship between sleep apnea and stroke? In other words, does sleep-disordered breathing cause stroke, or does stroke cause sleep disordered-breathing? Is sleep-disordered breathing an independent risk factor for the development of stroke in the setting of confounding overlapping risk factors, or is the association with stroke simply mediated by higher levels of cardio-

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vascular risk factors in patients with sleep-disordered breathing? Does the presence of sleep-disordered breathing influence the morbidity or mortality from stroke, and does treatment of sleep disordered breathing influence this risk?

The primary objective of this article is to explore these questions by critically reviewing the current literature. First, epidemiologic studies about the relationship between sleep-disordered breathing and stroke are analyzed with respect to issues regarding the strength of the association, temporal relationship, dose-response relationship, and consistency of the association using different study designs and different populations. Subsequently, the biologic plausibility of the relationship is explored by reviewing studies that examine the pathophysiology of sleep-disordered breathing and stroke focusing on cerebral hemodynamic and humoral mechanisms.

**Epidemiologic studies**

Several studies have sought to determine the presence and extent of a causal interaction between sleep-disordered breathing and stroke independent of frequently coexisting and potentially confounding variables common to both conditions. Established modifiable risk factors for stroke include hypertension, hypercholesterolemia, smoking, and diabetes for atherosclerotic cerebrovascular disease; atrial fibrillation and myocardial infarction for cardiogenic embolism; and hypertension for intracerebral hemorrhage. Established risk factors for sleep-disordered breathing include excess body weight, age, gender, estrogen depletion, smoking, and alcohol. To complicate matters further, the adjustment for potential confounding factors is open to criticism, because these factors may be on the causal pathway of the relationship between OSA and stroke. This applies especially to hypertension, because removal of its effect might overadjust the apparent risk and negate a true cause-effect relationship between sleep-disordered breathing and stroke.

An investigation from the Sleep Heart Health Study, a cohort of 6440 men and women over age 40, explored the associations between sleep-disordered breathing and cardiovascular risk factors and found that the respiratory disturbance index (RDI, the number of apneas and hypopneas per hour sleep) was cross sectionally associated with age, body-mass index (BMI), waist-to-hip ratio, hypertension, diabetes, and lipid levels [5]. This risk factor pattern of hypertension, diabetes, and hypertriglyceridemia is commonly seen in people who are obese, and the multivariate models in this study suggest that the degree of obesity, age, and gender explain most of the elevation in these cardiovascular risk factors, with the exception of hypertension. The presence of an independent association of the RDI with hypertension suggests that it may be in the causal pathway. As discussed elsewhere in this issue, because of the acute and profound effects of sleep-disordered breathing on vascular tone, hypertension is believed to be a major mechanism by which sleep-disordered breathing might influence future cardiovascular and cerebrovascular disease risk [5].

**Snoring and stroke**

Early epidemiologic studies that examined the relationship between sleep-disordered breathing and cerebrovascular disease used self-reported snoring as the primary exposure variable. Self-reported “habitual snoring,” usually defined as subjects who snore “often” or “always,” is a sensitive measure of true heavy snorers based on all night recordings [6]. The specificity is low, however, with many patients being misclassified as snorers. The consequence of such misclassification is the reduction of a potential relationship and bias toward the null hypothesis.

Despite this failing, most of these studies clearly show an association between snoring and stroke (Table 1) and demonstrate that the strength of this association is on the same order of magnitude as traditional risk factors for stroke, such as hypertension, smoking, cardiac arrhythmia, and hypercholesterolemia. Even when adjusted for confounding risk factors such as obesity, hypertension, age, and gender, an independent association remained between snoring and stroke. The designs of these initial studies were predominantly case control or cross-sectional [7–12] and were subject to criticism with respect to recall bias and establishing the temporal relationship between stroke and sleep-disordered breathing, because snoring and sleep apnea can be consequences of stroke [13].

More convincing evidence comes from several large, prospective studies that seemed to corroborate these case-control and cross-sectional studies. In an early cohort study exclusively of men that used a Finnish nationwide registry, there was a twofold increase in the relative risk for the combined outcome of stroke and ischemic heart disease in habitual snorers compared with non-snorers [14]. A smaller but still significant positive association (relative risk = 1.33) between regular snoring and the combined cardiovascular outcome of stroke and ischemic heart disease was seen exclusively in women in the Nurses Heath Study [15]. In this large cohort, the age-adjusted relative risk for stroke alone in regular
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of subjects</th>
<th>Exposure assessment</th>
<th>Disease assessment</th>
<th>Confounding assessment</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partinen [9]</td>
<td>Case control</td>
<td>50</td>
<td>Personal interview, habitual snoring</td>
<td>Stroke patients admitted to hospital, neurologic exam, CT/MRI</td>
<td>Age, BMI</td>
<td>10.3 (3.5–30.1)</td>
</tr>
<tr>
<td>Koskenvuo [14]</td>
<td>Cohort, 3-year follow-up</td>
<td>4388</td>
<td>Mailed questionnaire, habitual snoring</td>
<td>Finish registry, death, ischemic heart disease, stroke</td>
<td>Age, BMI, hypertension, smoking, alcohol</td>
<td>2.08 (1.5–3.77)</td>
</tr>
<tr>
<td>Spriggs [11,12]</td>
<td>Case control</td>
<td>400</td>
<td>Personal interview, regular snoring</td>
<td>Stroke patients admitted to hospital, neurologic exam, CT/MRI</td>
<td>Age, gender</td>
<td>3.2 (2.3–4.4)</td>
</tr>
<tr>
<td>Palomaki [8]</td>
<td>Case control</td>
<td>177</td>
<td>Standardized questionnaire, habitual snoring</td>
<td>Stroke patients admitted to hospital, neurologic exam, CT/MRI</td>
<td>Age, gender, alcohol, hypertension, ischemic heart disease</td>
<td>2.13 (1.29–3.52)</td>
</tr>
<tr>
<td>Smirne [10]</td>
<td>Case control</td>
<td>330</td>
<td>Personal interview, habitual snoring</td>
<td>Stroke patients admitted to hospital, Neurologic exam, CT/MRI</td>
<td>Age, gender, BMI, diabetes, dyslipidemia, smoking, alcohol, hypertension</td>
<td>1.86 (1.2–2.87)</td>
</tr>
<tr>
<td>Jennum [63]</td>
<td>Cohort 6-year follow-up</td>
<td>804</td>
<td>Personal interview, habitual snoring</td>
<td>Cardiovascular outcome based on Danish Health Registry</td>
<td>Hypertension, BMI, diabetes, smoking, alcohol, hyperlipidemia, catecholamines</td>
<td>1.26 (1.3–6.8)</td>
</tr>
<tr>
<td>Neau [7]</td>
<td>Case control</td>
<td>133</td>
<td>Personal interview, habitual snoring</td>
<td>Stroke patients admitted to hospital, Neurologic exam, CT/MRI</td>
<td>Gender, age, hypertension, obesity, cardiac arrhythmia</td>
<td>2.9 (1.3–6.8)</td>
</tr>
<tr>
<td>Hu [15]</td>
<td>Cohort 8-year follow-up (Nurses Health Study)</td>
<td>71,779</td>
<td>Mailed questionnaire, regular snoring</td>
<td>Follow-up questionnaire to determine cardiovascular outcome confirmed by medical record review</td>
<td>Smoking, age, BMI, alcohol, physical activity, menopausal status, family history of myocardial infarction, diabetes, high cholesterol</td>
<td>1.33 (1.06–1.67)</td>
</tr>
</tbody>
</table>
snores was 1.88 (1.62–2.53), which became non-significant when adjusted for BMI and other cardiovascular covariates.

These initial studies of the association between snoring and stroke on balance supported a positive association and served to raise some important methodologic issues. First, if hypertension is on the intermediate causal pathway between sleep-disordered breathing and stroke, should it be adjusted for and considered a confounder? Second, self-reported habitual snoring may not be a reliable measurement of true snoring. Although self-reported habitual snorers seemed to be true heavy snorers when validated against overnight recordings, a large percentage of self-reported never-snorers were not aware of their snoring, which resulted in exposure misclassification and bias toward the null hypothesis [6]. The presumed mechanism for the association between snoring and stroke is that snoring serves as a marker for OSA. Although heavy snoring invariably accompanies sleep apnea [16], most snorers do not have sleep apnea. In some of the case-control studies discussed previously [8,17], the authors attempted to identify within their populations those snoring subjects more likely to have OSA by identifying snorers who also have apneas, excessive daytime sleepiness, and obesity. The addition of these potential markers for OSA increased the odds ratio in these studies.

A different approach to assessing exposure to sleep-disordered breathing occurred in a study that used data from the First National Health and Nutrition Examination Survey (NHANES I) cohort [18]. Instead of self-reported snoring, other clues to pre-existing OSA were used: self-reported sleep duration and daytime somnolence. Sleep duration and symptoms of daytime somnolence were significantly associated with the development of stroke and coronary heart disease adjusted for potential confounding cardiovascular risk factors. Although these symptoms are assumed to serve as markers for sleep apnea, the validity of this assumption is questionable, and it is conceivable that these symptoms of increased sleep duration and daytime somnolence serve as general markers of disease and disability.

Sleep apnea and stroke (the temporal relationship)

Several studies have used overnight polysomnography to define OSA more precisely in an attempt to sort out whether it is the minority of patients with OSA who account for the apparent increased risk of sleep-disordered breathing with stroke (Table 2). These studies have focused on OSA as a risk factor for the development of stroke and as an outcome and consequence of stroke.

A study by one of the authors (V.M.) in 1995 of ten patients who were recovering from hemispheric stroke revealed a high prevalence (80%) of OSA compared with age- and BMI-matched controls with similar frequency of hypertension and smoking without stroke [19]. The mean RDI for the control and stroke group was 3 and 52 events per hour, respectively. Predominantly obstructive events were found in seven patients. Because none of the study subjects had a previous history of significant snoring, apnea, obesity, hypersonmolence, or neurologic impairment, the conclusion was that OSA might be a sequela of stroke. It is known that repeated upper airway obstruction in patients with OSA occurs as a consequence of reduction in pharyngeal muscle tone during sleep. The pharyngeal muscles may be affected in stroke; neurologic dysphagia has been demonstrated in 30% to 40% of patients admitted to the hospital with unilateral hemispheric stroke [20,21].

A subsequent case-control study of consecutively admitted inpatients with stroke [22] speculated that the hypoxia and hemodynamic responses in OSA may have predisposed to the development of stroke rather than the other way around. This study compared the polysomnograms of 27 healthy age- and gender-matched controls recruited from the local population to 24 inpatients with recent stroke confirmed by neurologic examination and imaging studies of the brain. Overall, OSA was diagnosed in 19% of the controls and 71% of the stroke patients. The mean lowest oxygen saturation level was 91% in the control group and 85% in the stroke group, and the mean RDI was 4 events per hour for controls and 26 events per hour for stroke patients. Once again, predominantly obstructive apneas were found as opposed to central or Cheyne-Stokes respirations. 4 stroke patients were reevaluated at 5 months with polysomnography, and they demonstrated OSA on reevaluation. The 4-year mortality rate for patients with stroke was 21%, and all patients with stroke who died (of various causes) had OSA. These findings led the authors to propose that OSA predisposes patients to stroke.

Although case-control studies generally are efficient study designs for evaluating strength of association, they have a significant limitation in their ability to establish the temporal course in a cause-effect relationship. When comparing hospitalized inpatients to healthy community-dwelling controls, a selection bias known as Berkson’s Bias may distort the actual association in that patients who are admitted to the hospital or rehabilitation unit also may have
<table>
<thead>
<tr>
<th>Study date</th>
<th>Study design</th>
<th>No. stroke/controls no.</th>
<th>Mean RDI</th>
<th>Study population</th>
<th>Confounding assessment</th>
<th>Prevalence sleep apnea in stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohsenin [19]</td>
<td>Case control</td>
<td>10/10</td>
<td>52</td>
<td>Predominantly hemispheric stroke in a rehabilitation unit</td>
<td>Age, BMI, hypertension, smoking</td>
<td>80% with RDI ≥20</td>
</tr>
<tr>
<td>Good [34]</td>
<td>Descriptive</td>
<td>47 (19 underwent polysomnography)</td>
<td>NA</td>
<td>Rehabilitation patients recently hospitalized for stroke</td>
<td>NA</td>
<td>32% had ≥10 desaturation events/h based on computerized overnight oximetry</td>
</tr>
<tr>
<td>Dyken [22]</td>
<td>Case control</td>
<td>24/19</td>
<td>26</td>
<td>Recently hospitalized for stroke</td>
<td>Age, gender</td>
<td>71% with RDI ≥10</td>
</tr>
<tr>
<td>Bassetti [24]</td>
<td>Case control</td>
<td>128/25 (80 underwent polysomnography)</td>
<td>28</td>
<td>Inpatients with stroke and TIA</td>
<td>Age, BMI, diabetes, severity of stroke</td>
<td>63% with RDI ≥10</td>
</tr>
<tr>
<td>Parra [28]</td>
<td>Descriptive</td>
<td>161</td>
<td>21</td>
<td>Inpatients with stroke and TIA</td>
<td>NA</td>
<td>71% with RDI ≥10 (acute phase)¹</td>
</tr>
<tr>
<td>Shahar [23]</td>
<td>Cross-sectional (Sleep Heart Health Study)</td>
<td>6424 (see text)</td>
<td>NA (see text)</td>
<td>Assembled from several ongoing population based studies of cardiovascular disease in the United States</td>
<td>Age, race, gender, smoking, diabetes, hypertension, BMI, cholesterol</td>
<td>61% with RDI ≥10 (stable phase)</td>
</tr>
</tbody>
</table>

¹ “Acute phase” after admission and “stable phase” indicate >3 months later.
pathology in addition to the stroke (ie, OSA), which increases the chance of admission.

Perhaps the strongest epidemiologic evidence demonstrating the association between sleep-disordered breathing and cerebrovascular disease comes from the initial results of the Sleep Heart Health Study [23]. This study explored the cross-sectional association between sleep-disordered breathing and prevalent self-reported cardiovascular disease (myocardial infarction, angina, coronary revascularization procedures, heart failure, or stroke) in a large cohort of 6424 individuals who underwent overnight polysomnography at home. By comparing the upper apnea-hypopnea index (AHI) severity quartile (>11) to the lower AHI severity quartile (0–1.3), the most parsimonious logistic regression model revealed an odds ratio of 1.58 (1.02–2.46) for the association of stroke with sleep-disordered breathing adjusted for age, race, sex, smoking status, self-reported diabetes, total cholesterol, and HDL lipoprotein cholesterol. Unlike coronary heart disease and congestive heart failure, in which much of the risk associated with sleep-disordered breathing came from mild sleep apnea (RDI < 10), there seemed to be an incremental increase in risk of stroke associated with increasing AHI severity (Fig. 1). Support of this finding is limited, however, by the small number of subjects at higher AHI severity in this population-based study. Hypoxemia seemed to explain 10% to 40% of the AHI effect, and sleep fragmentation per se, as measured by the arousal index, was not associated with cardiovascular disease in these data. If the associations observed in this study are causal, it seems that even a modestly elevated risk of stroke coupled with the high prevalence of mild/moderate sleep-disordered breathing will have considerable public health implication.

Cross-sectional associations might reflect reverse causal pathways, whereas sleep-disordered breathing has been the consequence rather than the cause of stroke. The direction of this arrow of causation ultimately can be determined definitively only by analysis of incident cerebrovascular disease events, and it awaits the results of future prospective follow-up studies. To the authors’ knowledge no study has investigated prospectively the relationship between polysomnographic indices of sleep-disordered breathing and stroke, several investigations have taken creative approaches to gaining insight into this temporal relationship.

One study that provided some insight into the causal pathway of stroke and OSA was a retrospective cohort study of patients who were diagnosed with OSA by using polysomnography in the 1970s before the availability of continuous positive airway pressure (CPAP), when the only known aggressive therapy for OSA consisted of tracheostomy [17]. 7 years of follow-up was provided on 198 patients, of whom 71 received tracheostomy (considered “effective treatment”) and 127 received “conservative treatment” that consisted of recommended weight loss (the only alternative). Any new hypertension, myocardial infarction, or stroke that occurred since the original polysomnography was considered the main vascular morbidity outcome. Despite the fact that at study entry the tracheostomy group included more patients with a history of hypertension, myocardial infarction, or stroke, the conservatively treated group presented with significantly more vascular morbidity.

Patients with TIA potentially represent another unique opportunity to delineate the directionality of the cause-effect relationship between OSA and cerebrovascular disease. TIA represents an intermediate stage of disease in the natural history of ischemic stroke, and by definition, patients with TIA have no residual neuromuscular side effects, which makes the causal pathway of TIA leading to OSA less plausible. Demonstrating an increased prevalence of OSA among cases of TIA bolsters the theory that OSA leads to the ultimate development of ischemic stroke rather than the other way around. In follow-up studies of patients with acute TIA or ischemic stroke [24,25] researchers demonstrated a similar elevated frequency and severity of OSA. In one of these studies [24], adequate polysomnography was performed in 80 subjects (stroke = 48, TIA = 32) and the prevalence

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Fig. 1. Predicted log odds (a measure of risk) of stroke as a function of AHI. AHI indicates the number of apneas and hypopneas per hour of sleep. The histogram is adapted from regression of the log odds of stroke. (From Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19; with permission.)
and severity of OSA were compared in patients with stroke, TIA and “normal” healthy controls from the Michigan Alcohol Research Center. Stroke and TIA patients differed significantly from normal controls in measurements of AHI, maximal apnea duration, and minimal oxygen saturation. Stroke and TIA patients also were similar in all variables considered, including habitual snoring, AHI, maximal apnea duration, mean apnea duration, and minimal oxygen saturation.

Although the face validity of these studies of TIA and OSA is high with respect to clarifying the temporal relationship between OSA and cerebrovascular disease, there are several limitations with respect to internal and external validity. Most importantly, patients with TIA may represent a heterogeneous group of individuals. Symptoms of TIA, a clinical diagnosis, are mimicked by multiple other disease entities, which may result in disease misclassification. Strictly defining and validating the definition of TIA for clinical research is of the utmost importance. Because the traditional definition of TIA requires the resolution of signs and symptoms within a 24-hour period, generally it has been assumed that TIAs leave no residual damage. Cerebral infarctions have been demonstrated by neuroimaging techniques in 5% to 10% of patients with clinically defined TIA, however [26], and some estimates of unrecognized infarctions by CT (32%) and MRI (77%) are even higher [27].

Another approach used to gain some insight into the temporal relationship between sleep-disordered breathing and stroke prospectively followed 161 consecutive patients with first-ever stroke or TIA admitted to a stroke unit [28]. TIA was strictly defined according to the National Institute of Neurologic Disease and Stroke classification [29]. In this study, previously validated portable respiratory recordings were performed within 48 to 72 hours after admission (acute phase) and subsequently after 3 months (stable phase). The important findings of this study included lack of significant differences in OSA severity according to stroke subtype (TIA, ischemic stroke, or hemorrhagic stroke) or brain parenchymatous location. The study also found that the frequency of obstructive apneas did not significantly decline from the period immediately after stroke to 3 months later. Because there were no significant differences in obstructive apneas between baseline and 3 months later or between different stroke subtypes and locations, the findings led the authors to conclude that obstructive events seem to be a condition predating the development of cerebrovascular disease and they act as a risk factor for rather than a consequence of cerebrovascular disease.

Sleep-disordered breathing and hypertension

Further evidence in support of the causal pathway of sleep-disordered breathing leading to stroke comes from recent large cross-sectional and cohort studies in support of OSA being an independent risk factor for the development of hypertension. From the Sleep Heart Health Study [30], sleep-disordered breathing was associated with prevalent hypertension even after controlling for potential confounders, such as age, gender, BMI (and other measures of adiposity), alcohol, and smoking. The relative risk for the highest category of AHI (>30/hour) compared with the lowest category (<1.5/hour) was 1.37 (95% CI, 1.03–1.83). Overall, the odds of hypertension seemed to increase with increases in AHI in a dose-response fashion.

More compelling data that lends support to the evidence of a causal role of sleep-disordered breathing in hypertension comes from the prospective findings of the Wisconsin Sleep Cohort Study [31]. The presence of sleep-disordered breathing at baseline was accompanied by a substantially increased risk for future hypertension at 4 years of follow-up. Even after adjusting for baseline hypertension status, age, gender, BMI, waist and neck circumference, and weekly alcohol and cigarette use, the risk was elevated, with an odds ratio of 2.89 (95% CI, 1.46–5.64) for subjects with an AHI of more than 15/hour compared with patients without any nocturnal apnea. It should be noted that for many of the aforementioned studies (see Tables 1, 2), the risk of stroke from sleep-disordered breathing was independent of coexisting hypertension. The presence of hypertension further enhances the risk.

Functional outcome after stroke

Previous studies reported that up to 43% of stroke patients will have a progression of their neurologic deficit [32,33]. Regardless of whether OSA precedes or follows stroke, it is associated with unfavorable clinical outcomes after stroke, including early neurologic worsening, delirium, depressed mood, poor functional status, and impaired cognition [12,34–36]. In one study [34], the functional status, as assessed by the Barthel Index (a multifaceted scale that measures mobility and activities of daily living), in patients with stroke and OSA was significantly lower compared with patients with stroke but no evidence of sleep-disordered breathing at discharge and 3 and 12 months (Fig. 2). Death at 1 year was negatively correlated with percentage of time spent at less than 90% SaO2. Whether sleep-disordered breathing is an independent predictor of poor functional outcome or
simply a marker for more severe stroke is not clear from this study.

Predictors of upper airway obstruction in stroke

Typical OSA-type risk factors, such as elevated BMI and neck circumference, seem to be the best predictors of the development of upper airway obstruction in acute stroke. Limb weakness also seemed to be an independent predictor of OSA in acute stroke, but other stroke characteristics, such as severity and subtype, do not seem to be associated with the development of upper airway obstruction [37]. Of clinical relevance in this study was that most of the sleep-disordered breathing occurred while the subjects were supine. Whether simple maneuvers targeted at preventing upper airway obstruction, such as position therapy, may improve outcomes in acute stroke remains an important unanswered question.

Continuous positive airway pressure treatment trials

Two CPAP treatment trials of patients who exhibit sleep-disordered breathing after stroke recently were published and have provided insight into whether sleep-disordered breathing is truly an independent cause of worse outcome after stroke and the effectiveness and acceptance of CPAP [12,34,35,38]. Although the trials only reflect short-term use of CPAP, the results are encouraging because they demonstrated beneficial effects and comparable compliance rates to OSA patients without stroke. In one trial [39], although not randomized, there was a significant reduction in nocturnal blood pressure (8 mm Hg) after 10 days of treatment in comparing CPAP-compliant and CPAP-noncompliant patients. There was improvement in subjective well-being (although this later finding is based on less well-validated neuropsychiatric testing). In a logistic regression model, aphasia and the severity of motor disability as quantified by the Barthel index were significant negative predictors of acceptance of CPAP.

The second CPAP study was a randomized treatment trial [38], and although it was not double-blinded, it demonstrated that depressive symptoms are reduced in patients who are treated with nasal CPAP at 7 and 28 days compared with controls who are not treated. There was no significant improvement in delirium, activities of daily living, or cognitive functioning. Compliance was lower in this study (approximately 50%), perhaps partly related to the fact that this was an older population.

Overall, the primary acceptance of CPAP (at least in the first treatment study) seems comparable to patients with OSA without stroke, and CPAP seems to exert a beneficial influence in terms of well-being, hypertension, and depression. Long-term compliance is not certain, however, especially in a population of patients with more functional and cognitive disability. As suggested elsewhere [40], bearing in mind that

Fig. 2. The Barthel Index (BI) scores on admission and discharge and 3- and 12-month follow-up for patients with sleep-disordered breathing (OSA group) compared with other stroke patients without sleep-disordered breathing. Lower BI scores indicate worse cognitive impairment and activity of daily living impairment. (From Good DC, Henkle IQ, Gelber D, et al. Sleep-disordered breathing and poor functional outcome after stroke. Stroke 1996;27:252-9; with permission.)
obstructive apneas result in recurrent hypoxemia and cerebral blood flow fluctuations that could damage the area of the ischemic penumbra, one possible argument in favor of CPAP treatment is to prevent stroke recurrence. Patients with TIA or minor non-disabling stroke may represent an important target group for CPAP treatment for secondary prophylaxis because they may be a younger and more compliant group with fewer deficits.

Circadian variation in ischemic events

The relation between the time of stroke symptoms and the time of day may relate to the underlying pathophysiology of stroke. Early studies of the timing of acute stroke indicated that acute strokes tend to occur either during the evening hours or during sleep, and many afflicted patients reported awakening with new neurologic deficits [41–43]. A metaanalysis of 11,816 strokes revealed that similar to myocardial infarction and sudden cardiac death, a “morning excess” of all types of stroke (including TIA) is seen between 6:00 AM and 12:00 PM and is significantly higher than would be expected by chance (Fig. 3) [44].

It is of interest that the most prolonged rapid eye movement (REM) sleep period occurs in close temporal proximity to this circadian preference for ischemic stroke (the early morning hours). Specifically, during REM sleep there are significant hemodynamic changes [45] with increases in cerebral blood flow [46] and blood pressures, which can reach near-normal waking levels [47]. The early morning hours are associated with decreased fibrinolytic activity [48], increased platelet aggregability, and peak levels of catecholamines [49].

As is described in the following sections, many of these same autonomic, hemodynamic, and physiologic mechanisms are heightened in patients with OSA.

Mechanism studies

During sleep in OSA, repetitive episodes of airway occlusion with resulting hypoxemia, hypercapnia, and significant changes in intrathoracic pressure elicit a wide variety of autonomic, hemodynamic, humoral, and vascular perturbations that serve as plausible biologic mechanisms whereby OSA may cause stroke (Table 3). Large variations in intrathoracic pressure with nadirs during inspiratory effort increase the filling of the right heart and cause a leftward shift of the interventricular septum [50]. The resulting reduction of stroke volume is one probable cause of the decreased arterial pressure seen early during apnea. Changes in autonomic activity influence blood pressure variability by vasoconstriction, with increased levels of circulating catecholamines and increased endothelin-1 production (a potent vasoconstrictor) likely contributing to diurnal hypertension [51]. Impaired endothelial function and accelerated atherogenesis, which may theoretically result from the repetitive hypoxia and pressure surges, are also evident in patients with OSA. Finally, altered cerebral blood flow, fluctuations in intracranial pressure, impaired cerebrovascular autoregulation combined with increased platelet aggregability, increased fibrinogen, and increased plasma homocysteine levels are also likely contributory mechanisms.

Because autonomic mechanisms that contribute to diurnal hypertension are discussed elsewhere in this issue, the following discussion of physiologic mech-
Mechanisms that regulate blood flow are broadly categorized as local (intrinsic) control and neural or hormonal (extrinsic) control (ie, sympathetic innervation). The cerebral circulation is controlled almost entirely by local control mechanisms. Many circulating vasoactive substances do not affect the cerebral circulation because their large molecular size prevents them from crossing the blood-brain barrier.

Mechanisms for the local control of blood flow include autoregulation, active hyperemia, and reactive hyperemia. Autoregulation is the maintenance of constant blood flow to an organ in the face of changing arterial pressure [52,53]. For example, if arterial pressure in a cerebral artery suddenly decreases, an attempt is made to maintain constant blood flow through this artery by the immediate compensatory dilation of cerebral arterioles decreasing the resistance of the cerebral vasculature and keeping flow constant in the face of decreased pressure. Active hyperemia is the concept that blood flow to an organ is proportional to its metabolic activity. For example, if metabolic activity increases as a result of strenuous activity, then blood flow increases proportionately to meet the increased metabolic demand. Finally, reactive hyperemia is an increase in blood flow in response to or as a reaction to a prior period of decreased blood flow. For example, reactive hyperemia is the increase in blood flow to an organ that follows a period of arterial occlusion. During the occlusion, an oxygen “debt” is accumulated. The longer the period of occlusion, the greater the oxygen debt and the greater the subsequent increase in blood flow above the preocclusion levels. The increase in blood flow continues until the oxygen debt is “repaid.” In the cerebral circulation the major vasoactive metabolites are CO₂ and H⁺. In addition to these local control mechanisms, mechanical effects, such as changes in intracranial pressure, can cause changes in cerebral blood flow.

Sleep state has a profound effect on cerebral hemodynamics. Multiple studies using various methods, including transcranial Doppler ultrasonography [54], Xe inhalation, and single photon emission testing, have shown a 5% to 28% reduction in cerebral blood flow during non-REM sleep and a 4% to 41% increase in REM sleep compared with wakefulness in normal persons [46,54–61].

Intracranial hemodynamics in sleep apnea

Individual episodes of sleep apnea are accompanied by marked episodic elevations of cerebrospinal fluid pressure and decreases in SaO₂ (Fig. 4) [62]. Cerebrospinal fluid pressure in patients with OSA was monitored via a pressure transducer and a plastic tube inserted into the subarachnoid space at the lumbar level. Another study that invasively monitored radial artery pressure, central venous pressure, and intracranial pressure (ICP) [63] confirmed the previous findings and demonstrated that values of ICP were also elevated in patients with OSA even while awake. ICP increases further during sleep, and there was a strong correlation between duration of apnea and ICP elevations. These increases in ICP were attributed to (1) increases in central venous pressure, which causes an increase in cerebral vascular volume, (2) increased systemic arterial pressure, which causes an increase in cerebral perfusion pressure, and (3) hypoxic and hypercapnic cerebral vasodilation, which causes an increase of the intracranial blood volume. It was suggested that these ICP elevations may be of importance in understanding the cerebral symptoms in patients with sleep apnea, such as morning headache and cognitive impairment. The mechanical effects of increased ICP may impede cerebral blood flow and predispose to cerebral ischemia.
Several recent studies have attempted to gain insight into the regulation of cerebral flow during sleep by measuring middle cerebral artery blood flow velocities noninvasively using transcranial Doppler. One study [64] revealed that the overall cerebral blood flow velocities in patients with sleep apnea were significantly reduced during all phases of sleep compared with control subjects with no polysomnographic evidence of sleep apnea. They postulated that this may be caused by impaired autoregulatory and active/reactive hyperemic mechanisms in patients with OSA given that PCO2 was noted to rise in these patients. Of therapeutic interest is that impairment of cerebrovascular reactivity to elevated CO2 in patients with OSA may be reversed by treatment with nasal CPAP [55].

Another study [65] that examined more specifically cerebral blood flow velocity in direct relation to individual obstructive apneic events demonstrated a biphasic pattern with a concomitant increase in mean arterial pressure and cerebral blood flow velocity during early apnea followed by a subsequent decrease of almost 25% below baseline after apnea termination. The authors suggested that the period immediately after the apneas, after the resumption of ventilation in combination with hypoxemia, potentially would make individuals with OSA vulnerable to nocturnal cerebral ischemia.

Obstructive apneas and hypopneas compared with central apneas lead much more frequently to a reduction in cerebral blood flow, and the longer the obstructive event the greater the likelihood for a reduction in blood flow [66]. The relationship between airway obstruction and decreased perfusion of the middle cerebral artery was attributed to the negative intrathoracic pressure generated by the increased respiratory effort against an obstructed airway. Increased time of obstruction could lead to the development of a high cardiac preload, lower cardiac afterload, activation of carotid body receptors, and vasodilation by increasing arterial carbon dioxide and decreasing oxygenation, all of which can contribute to a reduction in cerebral blood flow.

**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 [67,68]. This reduction in regional blood flow has been attributed to age-related brain atrophy and increased cerebral vascular resistance secondary to cerebral arteriosclerosis [68]. The mechanism underlying this change is attributed to altered endothelium function. Relaxation of the basilar artery in humans [69] and cerebral arterioles [70] and the
carotid artery in rats [71] 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. This impaired endothelium-dependent relaxation has been attributed to degradation of nitric oxide by generation of reactive oxygen species in the vessel wall [71]. Similar impairment of vasoconstrictor responses to several stimuli has been reported in the human basilar artery [69]. These age-related changes in cerebral blood flow and the alterations during normal sleep may predispose the brain to compromised blood supply during sleep.

**Humoral mechanisms**

In addition to physiologic mechanisms that alter cerebral blood flow and contribute to hypoperfusion, several humoral mechanisms may contribute to increased hypercoagulability in patients with sleep-disordered breathing and predispose to ischemic and thromboembolic stroke. Elevated plasma fibrinogen levels are believed to be associated with increased risk of stroke and other cardiovascular events [72–77]. Plasma fibrinogen is an acute-phase protein that is synthesized in the liver and is intrinsically involved in coagulation. It enhances thrombosis and atherosclerosis by effects on platelet aggregation, blood vessel wall, and endothelial cell injury [78,79].

Patients with OSA have been shown to have increased morning levels of fibrinogen [80]; therefore, elevated fibrinogen levels may be one mechanism that links OSA to stroke. Further evidence of the association between OSA and increased fibrinogen levels and stroke comes from a cross-sectional study of 113 stroke patients who underwent neurologic rehabilitation. Fibrinogen level was positively correlated to RDI and length of respiratory events and negatively correlated with oxygen desaturation during sleep [81]. As suggested elsewhere [82], given the cross-sectional nature of this latter study, it is not clear whether the higher fibrinogen levels are a reflection of the acute-phase reaction to the stroke insult, with stroke being worse and fibrinogen levels being higher in patients with preexisting OSA. Alternatively, could airway inflammation associated with OSA induce increases in plasma fibrinogen? Although it is widely held that BMI and other measures of obesity may be determinants of fibrinogen [83], this study showed that OSA, not BMI, was independently associated with increased fibrinogen. Whether fibrinogen is simply a marker for stroke is yet to be determined, but it is provocative to consider it as a potential intermediate step of the pathophysiologic pathway between OSA and stroke. Further studies that explore the effects of fibrinogen with treatment for sleep apnea should prove informative.

Increases in platelet reactivity have been associated with increased risk of cardiovascular event and death [84–87]. The ability of aspirin, a recognized inhibitor of platelet function, to prevent stroke, myocardial infarction, and death can be interpreted as additional evidence linking platelets to these disorders. It also has been demonstrated that platelet aggregability increases significantly during the period from 6:00 AM to 9:00 AM, which is temporally related to rising plasma catecholamine levels and the circadian period. This period has the highest risk for cardiovascular/cerebrovascular events and sudden cardiac death [49] (see Fig. 3). A small prospective study of men who underwent polysomnography for suspected sleep apnea demonstrated significantly increased spontaneous platelet activation and aggregation in patients with OSA compared with controls without OSA [88]. Although no relationship could be established between the level of spontaneous platelet activation and specific markers of sleep-disordered breathing, a second important finding of the study was a reduction of platelet reactivity after the application of CPAP. The authors speculated that the mechanisms for increased platelet reactivity in patients with OSA are possibly the cyclic hypoxemia, hypercarbia, and catecholamine surges that are part of OSA, which also have been reported to cause enhanced platelet reactivity [89–91]. Several other humoral factors associated with cardiovascular morbidity and mortality have been demonstrated to be increased in patients with OSA, including plasma homocysteine [92], circulating endothelin-1 (a potent vasoconstrictor) [93,94], vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and L-selectin [95].

A last mechanism whereby OSA may increase the risk of stroke relates to it being provocative of right-to-left shunting through a patent foramen ovale [96]. The increased right heart pressure–associated apneic events may serve to increase the exposure time of right-to-left shunting through a patent foramen ovale, which increases the risk of paradoxic embolism. Patients with sleep apnea may have an increased prevalence of patent foramen ovale [97].

Taken together, cerebral hypoperfusion, sympathetic activation, hypertension, hypercoagulability, hypoxemia, endothelial impairment, and right-to-left shunting via patent foramen ovale all likely have a role in pathogenesis of cerebrovascular disease in patients with sleep-disordered breathing.
References


Summary

Sleep-related breathing disorders are strongly associated with increased risk of stroke independent of known risk factors. The direction of causation favors sleep-disordered breathing leading to stroke rather than the other way around, although definitive proof of this awaits the results of prospective cohort studies. If causal, even a moderately elevated risk of stroke coupled with the high prevalence of sleep-disordered breathing could have significant public health implications. The relationship between sleep-disordered breathing and stroke risk factors is complex, and likely part of the risk for cerebrovascular events is because of higher cardiovascular risk factors in patients with increased RDI. The mechanisms underlying this increased risk of stroke are multifactorial and include reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, thrombosis, and paradoxic embolism. Because of the effects of sleep-disordered breathing on vascular tone, hypertension is believed to be a major mechanism by which sleep-disordered breathing might influence risk of stroke. Because sleep-related breathing disorders are treatable, patients with stroke/TIA should undergo investigation, with a thorough sleep history interview, physical examination, and polysomnography. Treatment of sleep apnea has been shown to improve quality of life, lower blood pressure, improve sleep quality, improve neurocognitive functioning, and decrease symptoms of excessive daytime sleepiness. Further treatment trials are needed to determine whether treatment improves outcome after stroke and whether treatment may serve as secondary prophylaxis and modify the risk of recurrent stroke or death.


[62] Sugita Y, Susami I, Yoshio T, et al. Marked episodic elevation of cerebral spinal fluid pressure during nocturnal sleep in patients with sleep apnea hypopornia syn-


