

Sleep Apnea and Stroke

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Abstract Clinical evidence has established that sleep apnea is a risk factor for stroke. Patients with stroke have a high prevalence of sleep apnea that may have preceded or developed as a result of the stroke. Well-established concurrent stroke risk factors for stroke like hypertension and atrial fibrillation respond favorably to the successful treatment of sleep apnea. The gold standard diagnosis of sleep apnea is obtained in the sleep laboratory, but unattended polysomnography is gaining acceptance. Positive airway pressure (PAP) (continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) applications are the gold-standard treatment of sleep apnea. Suggestive evidence indicates that stroke occurrence or recurrence may be reduced with treatment of sleep apnea.

Keywords Obstructive sleep apnea · Central sleep apnea · Acute stroke · Ischemic stroke · Hypertension · Atrial fibrillation · Patent foramen ovale · Hypoxia · Cerebral small vessel disease · Cognitive dysfunction · Autonomic dysregulation · Arousal response · Pro-inflammatory risk factors · Cerebral hemodynamic changes · Polysomnography · CPAP · BiPAP

Introduction

Growing evidence over the past 20 years has shown that there is an intimate relationship between sleep apnea, in particular the more common obstructive form, and cerebrovascular disease. In fact, obstructive sleep apnea is now recognized as an

independent risk factor for stroke, acting in concert with other major risk factors such as hypertension, diabetes, and ischemic heart disease. Furthermore, sleep apnea may be present at the time of the acute stroke, causing neurological deterioration if severe. In the post-stroke rehabilitation period, sleep apnea is also very common and, when of moderate or severe intensity, sleep apnea may modify the course of the rehabilitation process. Clinical signs and symptoms of sleep-related breathing disorders are not reliable in patients with stroke, and diagnostic sleep testing with polysomnography or unattended sleep testing is required to make the diagnosis. Clinical trials have demonstrated that treatment of sleep apnea with positive airway pressure (PAP) significantly reduces apneas, arousals, and oxygen desaturations during sleep, but data in stroke patients are more limited. Overall, obstructive sleep apnea responds satisfactorily to PAP applications and should be treated despite the fact that strong evidence of the clinical impact of sleep apnea management in cerebrovascular disease is still lacking.

Clinical Evidence

Risk of Stroke

Prospective cohort studies suggest that obstructive sleep apnea (OSA) increases the risk of stroke. Confidence in the evidence is supported by the findings of a large effect and a dose-response gradient (i.e., correlation between the severity of OSA and the risk for stroke). Yaggi et al. [1] found that the risk of stroke or death of any cause in patients with severe sleep apnea (mean apnea/hypopnea index (AHI) of 35/h) had a hazards ratio of 2.24 (95 % confidence interval [CI] 1.30–3.86). The increased risk of stroke was independent of other risk factors including hypertension, while increased severity of sleep apnea was associated with an incremental risk of

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stroke and death. Muñoz et al. [2] found that severe OSA (defined in their study as $AHI \geq 30/h$) increased the risk of ischemic stroke in an elderly male, noninstitutionalized population, independently of known confounding factors. Arzt et al. [3] in a prospective analysis of 1189 subjects from the general population found that sleep-disordered breathing ($AHI \geq 20/h$) was associated with an increased risk of a first-ever stroke over the subsequent 4 years (unadjusted odds ratio 4.31; 95 % CI 1.31–14.15; $p=0.02$). After adjustment for age, sex, and body mass index, the odds ratio was still elevated, but was no longer significant (3.08; 95 % CI 0.74–12.81; $p=0.12$). The same authors found in a cross-sectional analysis of 1475 individuals that subjects with an AHI of $\geq 20/h$ had increased odds for stroke (odds ratio 4.33; 95 % CI 1.32–14.24; $p=0.02$) compared with those without sleep apnea ($AHI < 5$) after adjustment for known confounding factors concluding that there is a strong association between moderate to severe OSA and stroke, independent of confounding factors.

The Sleep Heart Health Study [4•] offered the highest quality data in men. This was a prospective cohort study that followed 5422 individuals without a history of stroke for a median of 8.7 years. Men with an index ($AHI > 19.1/h$) in the highest quartile were more likely to have an ischemic stroke than men whose index was in the lowest quartile ($AHI < 4.1/h$), even after adjustment for potential confounders (adjusted hazard ratio [HR] 2.86; 95 % CI 1.10–7.39). A similar effect was not found among women, although the study was limited by small numbers. Nonetheless, in women, stroke risk increased when there was an $AHI \geq 25$ events/h.

Other studies suggest that women with OSA may have an even higher risk of stroke. In one large observational study using a universal insurance claims database in Taiwan, women were at higher risk than men, and younger women were at higher risk than older women [5•]. The incidence of stroke in patients with sleep apnea confirmed with polysomnography ($n=29,961$) was 52 per 10,000 person-years for males and 62 per 10,000 person-years for females; in controls, the incidence was 41 per 10,000 person-years for males and 37 per 10,000 person-years for females. In women with sleep apnea, the magnitude of the risk of stroke decreased with age (adjusted HR 4.9 for subgroup aged 20 to 35 years; HR 1.6 for subgroup aged 36 to 50 years; HR 1.4 for subgroup aged 51 to 65 years). While the pathophysiology behind this finding could not be determined by the study, the higher risk in women of child-bearing age provides support for the recognition and treatment of OSA during pregnancy [6•].

Acute Stroke

Vasomotor reactivity may be altered in patients with acute stroke. Alexandrov et al. [7•] reported the presence of intracranial blood flow steal in response to vasodilatory stimuli like

carbon dioxide elevations in patients with sleep apnea and stroke; they termed this phenomenon reversed Robin Hood syndrome (RRHS). The syndrome might play an important role in clinical deterioration after an acute stroke. Such observations have led to the notion that noninvasive ventilatory correction in patients with acute stroke and sleep apnea might have a beneficial effect on brain perfusion.

Small Vessel Disease and Cognitive Impairment

Clinical evidence suggests that moderate to severe obstructive sleep apnea (OSA) is a risk factor for development of cognitive impairment. Sleep apnea may lead to cognitive dysfunction through the effects of chronic hypoxia and sympathetic stress associated with small vessel disease in the brain, causing white matter ischemia and lacunar strokes. In a recent publication, Yaffe et al. [8•] reported that elderly women with OSA develop cognitive deficits when compared to age-matched controls. The authors concluded that cognitive decline correlated with hypoxemia rather than with fragmentation of sleep architecture caused by apneas and hypopneas.

Cognitive impairment may be the result of cerebral subcortical small vessel disease [9] that is expressed as white matter change or leukoaraiosis and silent infarctions. These conditions are increasingly found in patients with sleep apnea. Kim et al. [10] investigated 503 individuals (mean \pm SD, age 59.63 ± 7.48 years) with polysomnography. White matter disease was identified with brain magnetic resonance imaging (MRI) in 199 individuals (39.56 %). Multivariate logistic regression analyses revealed that OSA (>15 AHI) was significantly associated with the presence of white matter changes (odds ratio [OR] 2.08; 95 %, confidence interval [CI] 1.05–4.13) compared with no OSA. Additional adjustment of hypertension to the model did not alter the significance of the association. The authors hypothesized that OSA mediates white matter changes and concluded that moderate to severe OSA is an independent risk factor for white matter changes in middle-aged and older individuals.

In another study, Cho et al. [11] investigated the presence of silent cerebral infarctions (SCI) in individuals with OSA. The authors recruited 746 participants (252 men and 494 women) aged 50–79 years. Subjects underwent polysomnography and brain MRI. Moderate to severe OSA was defined by $AHI \geq 15$. Compared with subjects free of OSA, individuals with moderate to severe OSA were more likely to have a positive association with SCI (odds ratio [OR] 2.44; 95 % confidence interval [CI] 1.03–5.80) and with lacunar infarction (OR 3.48; 95 % CI 1.31–9.23) in the age ≥ 65 -year group.

Although the cause of subcortical small vessel disease in patients with OSA is not clear, there is supportive evidence that intermittent nocturnal hypoxia in patients with moderate to severe OSA may contribute to ischemic damage in the

cerebral periventricular territory of long penetrating terminal arteries [12].

Intermittent hypoxia adds ischemic burden to this vascular borderzone territory with blood flow that may be already precarious as a result of diabetes with vascular autonomic dysregulation and poorly controlled hypertension. Ischemic damage to the cerebral periventricular white matter disturbs the connections of the cortex with the thalamus leading to a form of subcortical dementia characterized by apathy, decreased executive functions, poor memory, and in advanced cases, difficulty walking and urinary incontinence (Binswanger's disease).

Treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) may lower cerebrovascular risk. However, CPAP applications will not modify structural lesions of the brain, and therefore, early diagnosis and treatment of OSA before structural brain damage ensues is strongly recommended, particularly in patients with other risk factors for stroke.

Mechanisms of Stroke in Sleep Apnea

Hypertension

Blood pressure tends to increase during daytime hours in patients with sleep apnea, along with variability in blood pressure values. Several studies clearly demonstrate a dose-dependent relationship between sleep apnea and hypertension [13, 14], particularly when the blood pressure fails to respond optimally to at least three antihypertensive medications [15]. Refractory hypertension is a well-known comorbidity of uncontrolled sleep apnea that may respond favorably to the successful application of CPAP [16]. Children with sleep apnea may also have abnormal blood pressure levels compared to children without sleep apnea [17].

Blood pressure values normally drop by 10–20 % during sleep relative to daytime values, a phenomenon known as “dipping.” Nondipping, defined as less than a 10 % drop in blood pressure during the night, is common in sleep apnea, increasing in prevalence as the severity of sleep apnea augments [18].

Autonomic Alterations in Sleep Apnea

Increases in sympathetic activity have been well documented during sleep in patients with clinically significant sleep apnea. Overactive sympathetic activity influences heart rate and blood pressure. Increased sympathetic activity is induced through a variety of different mechanisms, including chemoreflex stimulation by hypoxia and hypercapnia, baroreflexes, pulmonary afferents, the Mueller maneuver,

impairment in venous return to the heart, alterations in cardiac output, and the arousal response [19]. Sympathetic overactivity may be the critical link between sleep apnea and hypertension. Sleep apnea influences heart rate variability, not only during sleep but also during wakefulness. Compared to controls, normotensive sleep apnea patients have a higher heart rate at rest during wakefulness [20] and a higher blood pressure response to head-up tilt, suggesting sympathetic overactivity. Increase in sympathetic activity and autonomic imbalance are possible determinants of cardiovascular comorbidity and increased mortality risk in patients with sleep apnea. Treatment of sleep apnea with continuous positive airway pressure (CPAP) leads to a significant improvement of autonomic modulation and cardiovascular variability [21].

Arousal Response

The arousal response at the termination of untreated sleep apnea events may be the principal cause of elevations in sympathetic and parasympathetic activity, with significant variations in blood pressure and heart rhythm instability [22]. The arousal response is characterized polygraphically by a change in 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 [23].

Pro-inflammatory Risk Factors

Pro-inflammatory vascular risk factors, oxidative stress, and endothelial disease may be enhanced by sleep apnea. Repeated hypoxia may damage the endothelium and trigger the release of pro-inflammatory factors like plasma cytokines, tumor necrosis factor- α , and interleukin-6. Chronic intermittent hypoxia causes vascular dysfunction by increasing endothelin, augmenting neurovascular oxidative stress, decreasing vascular neuromuscular reserve, reducing vascular reactivity, and increasing susceptibility to injury [24]. A state of inflammation may be related to gestational hypertension [25] and to an increased risk for development of preeclampsia in obese women with sleep apnea [26].

Atrial Fibrillation

Clinical data have shown a strong relationship between sleep apnea and atrial fibrillation, and epidemiological studies suggest that sleep apnea is a risk factor for new-onset atrial

fibrillation. A large study evaluated 3542 patients without atrial fibrillation who underwent polysomnography and were followed for an average of 5 years [27]. Nocturnal oxygen desaturation predicted new-onset atrial fibrillation, in patients under 65 years of age. In another study of 424 patients undergoing ablation, sleep apnea more than doubled the risk of acute intra-procedural failure [28], while procedural failure may be predicted by sleep apnea and noncompliance with continuous positive airway pressure [29]. The effects of sleep apnea therapy on atrial fibrillation outcomes are largely unknown, and prospective randomized controlled trials will be necessary to clarify this issue.

Patent Foramen Ovale

In the general population, patent foramen ovale (PFO) occurs with a range of 10–30 % [30], depending on the diagnostic method. In one study, 27 % of sleep apnea patients and 15 % of control subjects had PFO ($p < 0.05$) [31], suggesting that nocturnal apneic-related shunting as a result of intra-thoracic negative pressures could augment the risk of paradoxical embolism and stroke. Should pulmonary hypertension develop as a result of nocturnal hypoxemia [32], the risk would increase.

In one prospective study, 335 patients with cerebrovascular ischemic events on waking were evaluated [33]. Two hundred two (60 %) had at least one long obstructive sleep apnea event lasting 20 s or more and 116 (35 %) a right-to-left shunt; 69 (21 %) had both. There were significantly more wake-up strokes/TIAs in subjects with right-to-left shunt plus long obstructive sleep apneas than in subjects without this association (27/69 vs. 70/266; OR 1.91 [95 % CI 1.08 to 3.38; $p = 0.03$]). No other risk factor was associated with an increase in the incidence of events on waking. The authors concluded that the combination of long obstructive sleep apneas and right-to-left shunt could be a potentially treatable risk factor for cerebrovascular ischemic events.

Cerebral Hemodynamic Changes

Cerebral blood flow studies have shown that during the apnea event, there is significant reduction in middle cerebral artery blood flow velocity [34]. The reduction correlates with duration of the apnea event rather than with depth of hypoxia. Intermittent intracranial hemodynamic changes night after night in patients with marginal blood flow reserve may increase the risk of stroke in patients with clinically significant sleep apnea disorder [35]. Profound intrathoracic negative pressures during obstructive apneas may determine a reduction of cerebral blood flow, while studies with near-infrared spectroscopy [36] have noted that cerebral hemodynamic autoregulatory mechanisms fail in the presence of frequent apneas (AHI > 30) and brain hypoxia.

In regions with poor hemodynamic reserve where cerebral circulation is compromised, particularly in borderzone areas and terminal artery territories, hemodynamic alterations may trigger irreversible ischemic changes. Studies of auditory event-related potentials in patients with treated sleep apnea [37] found no improvement in abnormal P3 wave latencies, suggesting permanent structural changes in the white matter of the hemispheres, likely the result of ischemia. A subsequent study showed that healthy children with sleep-disordered breathing exhibit cerebral hemodynamic and neurobehavioral changes that are potentially reversible following adenotonsillectomy, indicating normalization of middle cerebral artery blood flow as measured with transcranial Doppler techniques [38]. These studies suggest that successful control of sleep apnea may reduce the risk of permanent ischemic cerebral lesions.

Diagnosis

The diagnosis of sleep apnea requires formal testing with polysomnography. Sleep laboratory studies are generally not feasible during the acute stages of stroke, and unattended polysomnography may be considered.

Obstructive sleep apnea is defined by the presence of ≥ 5 predominantly obstructive respiratory events per hour of sleep (for laboratory polysomnography) or per hour of recording time (for unattended studies). Central sleep apnea is defined by the presence of ≥ 5 central apneas per hour of sleep if more than 50 % of the total number of apneas and hypopneas are central [39••]. In this article, sleep apnea is used as a generic term for both obstructive and central sleep apnea. Given the high prevalence of sleep apnea in patients with stroke or at risk of stroke, clinicians should maintain constant awareness and a low threshold for pursuing diagnostic testing. The 2014 American Heart Association/American Stroke Association guidelines for the prevention of stroke recommend screening for sleep apnea with polysomnography as part of secondary stroke prevention [40••]. The American Academy of Sleep Medicine clinical practice guidelines also recommend that patients with stroke or transient ischemic attack and symptoms or signs of sleep apnea undergo polysomnography [41].

Laboratory full-night or split-night polysomnography is the gold standard diagnostic test for sleep-related breathing disorders, but unattended sleep testing is rapidly becoming an acceptable alternative in compliant patients. As the condition evolves over weeks or months post-stroke, repeated laboratory tests to reevaluate sleep apnea may not be practical and unattended ambulatory studies may be the solution.

Management of Sleep Apnea in Patients with Stroke or at Risk of Stroke

Positive airway pressure applications, whether continuous (CPAP) or bilevel (BiPAP), decrease the frequency of nocturnal arousals and suppress acute blood pressure fluctuations. Controlled trials have established that CPAP treatment of patients with moderate to severe sleep apnea lowers blood pressure levels, primarily by stabilizing the sympathetic-vagal balance. In patients with drug-resistant hypertension, requiring three antihypertensive drugs or more for control of blood pressure, successful CPAP therapy of sleep apnea contributes to blood pressure reduction that is greater than what can be achieved with drugs alone [42]. A reduction in recurrence of atrial fibrillation has been observed in patients with sleep apnea when treated with CPAP [43].

Vasomotor reactivity may be altered in patients with acute stroke. Alexandrov et al. [7•] have reported the presence of intracranial blood flow steal in response to the vasodilatory stimuli of carbon dioxide elevations in patients with sleep apnea and stroke; they term this phenomenon reversed Robin Hood syndrome. The syndrome might play an important role in clinical deterioration after an acute stroke. Such observations have led to the notion that noninvasive ventilatory correction in patients with acute stroke and sleep apnea might have a beneficial effect on brain perfusion and stroke outcome.

Sleep Apnea Post-Stroke

After stroke, sleep apnea is common with a prevalence ranging between 50 and 75 % [44, 45]. Sleep apnea may precede or appear after stroke. Central sleep apneas predominate in the acute stroke phase, giving way to obstructive apneas in the chronic stages [46]; as the stroke condition evolves, sleep apnea may change in its intensity. Nonetheless, sleep apnea after stroke is associated with poor functional outcome, depressed mood, cognitive dysfunction, deteriorated ability to perform activities of daily living (ADL), as well as psychiatric and behavioral symptoms [47] and may be significantly and independently related to length of hospitalization [48, 49].

Results of the application of CPAP post-stroke have shown a beneficial effect, particularly with the use of auto-CPAP during the acute phases of stroke [50]. A favorable effect has also been shown on neurological and cognitive functions during the stable phase of stroke in a rehabilitation setting [51, 52•]. However, compliance with treatment needs to be resolved before CPAP treatment becomes generalized post-stroke.

Concluding Remarks

Sleep apnea and stroke are common disorders that intersect and worsen each other. Clinicians should maintain a high state of awareness and a low threshold for testing with polysomnography patients who are at risk of stroke because of concurrent risk factors or who have developed stroke and are receiving rehabilitation. PAP applications control sleep apnea and have a favorable effect on risk factors for stroke. Suggestive evidence indicates that stroke occurrence and recurrence may be reduced with PAP applications, and therefore, this form of treatment should be pursued in all patients with sleep apnea.

Compliance with Ethics Guidelines

Conflict of Interest Antonio Culebras has received payments from Medlink for manuscript preparation and royalties from UptoDate and Cambridge University Press, has stock options in Clinical Stroke Research, and has received paid travel expenses from the World Congress of Neurology.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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