

Sleep apnoea and stroke

Sameer Sharma,¹ Antonio Culebras²

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ABSTRACT

Sleep disorders have been known to physicians for a long time. In his famous aphorisms, Hippocrates said “Sleep or watchfulness exceeding that which is customary, augurs unfavorably”. Modern medicine has been able to disentangle some of the phenomena that disturb sleep. Among the most notable offenders is sleep apnoea that has gained prominence in the past few decades. It is being proposed as one of the potentially modifiable risk factors for vascular diseases including stroke. The pathological mechanisms linking sleep apnoea to vascular risk factors include hypoxia, cardiac arrhythmias, dysautonomia, impaired glucose tolerance, hypertension, dyslipidaemia and inflammation. In this article, we review literature linking sleep apnoea and stroke, including sleep apnoea as a risk factor for primary prevention with the potential to improve outcome after acute stroke and as a secondary risk factor, amenable to modification and hence vascular risk reduction.

INTRODUCTION

The first description of obstructive sleep apnoea (OSA) was provided not by a physician or scientist, but by Charles Dickens in a series of papers titled ‘The posthumous papers of the Pickwick club’ in 1836, in which he described an obese boy who had excessive daytime somnolence, loud snoring and probably right heart failure.¹ In 1889, Hill² observed that upper airway obstruction contributed to ‘stupidity’ in children. In 1965, Gastaut *et al*³ in France performed nocturnal polygraphy of respiratory pauses in patients with obesity, and 10 years later, Lugaresi⁴ in Italy associated nocturnal apnoeas with loud snoring. The term OSAS was first defined after the 1972 Rimini conference.⁵ Around the same time, the first sleep disorders centre was established in Stanford University, California. Upper airway surgery was used for treatment of snoring in 1964 and was later used for treatment of OSA in 1981 in Japan.⁶ During the same period, nasal positive airway pressure was introduced by Sullivan for its treatment in 1981 and soon became the treatment of choice.⁷

Sleep apnoea and/or habitual snoring began to be recognised as independent risk

factors for arterial hypertension (HTN),⁸ cardiac arrhythmias,⁹ coronary artery disease, myocardial infarction^{10–11} and ischaemic stroke¹² only during late 20th century. The same research also recognised that patients with untreated sleep apnoea had higher risk of cardiovascular morbidity compared with patients with treated sleep apnoea.¹³ Recently, population studies have suggested that sleep apnoea may be a risk factor for vascular dementia.¹⁴

Sleep-disordered breathing (SDB) involves both obstructive and central breathing disorders, Cheyne-Stokes breathing and central sleep apnoea belonging to the latter category. This article reviews the current literature describing the inter-relationship between sleep apnoea and stroke; both direct and indirect evidences are discussed. Literature review was carried out by using PubMed search with words ‘Sleep apnea’ AND ‘stroke’, and personal article collection of the corresponding author.

SLEEP APNOEA AS VASCULAR RISK FACTOR Sleep apnoea and autonomic nervous system

Understanding the effects of sleep apnoea on autonomic nervous system (ANS) is important for better understanding of the subsequent sections. The body’s biological clock—suprachiasmatic nucleus (SCN) has autonomous rhythmicity in its neuronal activity. The autonomic body functions modulated by SCN include sympathetic–parasympathetic balance,¹⁵ hepatic glucose production and insulin sensitivity.¹⁶

During sleep, physiological changes in respiratory and cardiovascular activity are predominantly sleep-cycle dependent and mediated by autonomic control.¹⁷ During NREM, there is an increase in parasympathetic activity while during REM sleep, there is a decrease in parasympathetic activity accounting for increase in cardiovascular activity during the latter.¹⁸ Any arousal during sleep results in an increase in respiratory and cardiovascular activity.¹⁷ The intrinsic rhythmicity increases heart rate and blood pressure with tilting of sympathetic–



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¹Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA

²Department of Neurology, SUNY Upstate Medical University, Syracuse, New York, USA

Correspondence to

Dr Antonio Culebras;
Aculebras@aol.com

parasympathetic balance towards the former immediately before waking, preparing the body for daily activities.¹⁹ The pathophysiological responses to OSA occur mainly in response to decrease in ion arterial oxygen tension and increase in arterial carbon dioxide tension. These provoke an increase in sympathetic nervous system activity causing peripheral vasoconstriction to divert blood flow to vital organs. At the same time, parasympathetic activity reduces myocardial activity and hence oxygen requirements. At the end of apnoeic episodes, there is an increase in blood pressure as myocardial function is restored. The vasoconstriction and changes in myocardial activity cause an increase in cardiac after load, while pulmonary vasoconstriction induced by hypoxia may contribute to right heart failure.^{17 20} Frequent and sustained episodes contribute to non-dipping of blood pressure at night¹⁷ and sensitisation of the hypoxic sensory response of carotid bodies which induces changes at genetic levels associated with increased oxidative stress.²¹ Microneurography has shown increased muscle sympathetic nervous activity at the termination of apnoeas in patients with OSA.²²

Use of CPAP improves sympathetic–parasympathetic balance in patients with moderate and severe sleep apnoea²³ and improves heart rate variability.²⁴ Increase in catecholamines has been found in urine and plasma in patients with OSA²⁵ which can be lowered with therapies.²⁶

In summary, patients with untreated sleep apnoea tend to have a heightened sympathetic activity and autonomic dysregulation which can benefit with management of OSA with either CPAP or tracheostomy.

Sleep apnoea and HTN

As discussed in an earlier section, there is increase in parasympathetic activity during slow-wave sleep, while sleep in general tends to have a parasympathetic predominance.²⁷ A direct effect of autonomic dysfunction of OSA on blood pressure is an increase in its variability.²⁸ There is evidence to suggest that this autonomic dysfunction extends into wakefulness.²⁹

In terms of its effect on nocturnal blood pressure, there is evidence of non-dipping blood pressure²⁹ in patients with OSA. Hla *et al*³⁰ studied the longitudinal association between SDB and incident non-dipping in 328 adults enrolled in the Wisconsin sleep cohort study, and found a dose–response increase in odds of systolic non-dipping with SDB. Non-dipping blood pressure itself is a well-known risk factor for cardiovascular disease.

In addition to non-dipping of blood pressure, there is ample evidence to suggest that OSA contributes to daytime HTN as well. Nieto *et al*³¹ did a cross-sectional analysis on 6132 participants enrolled in the multicentre Heart Health Study and found independent correlation between increasing severity of OSA and raised systolic and diastolic HTN. Peppard *et al*³² found a similar dose–response relationship between severity of SDB and

daytime HTN. Another large study conducted in Spain studied 1889 normotensive participants and found increase in risk of HTN in patients with OSA, which decreased in response to treatment with CPAP.³³

OSA also has significant interaction with treatability of HTN. A study by Logan *et al*³⁴ found a prevalence of sleep apnoea of 83% among participants with refractory HTN. Walia *et al*³⁵ analysed data from the HeartBEAT study and found that patients with OSA had a fourfold OR of having resistant HTN as compared with participants with moderate OSA. Walia *et al*³⁶ in their clinic-based effectiveness for blood pressure control study observed a significant reduction in blood pressure measures after treatment with CPAP in both groups containing participants with refractory and non-refractory HTN. Martinez-Garcia *et al*³⁷ in the HIPARCO randomised controlled trial (RCT) studied 194 patients with refractory HTN and apnoea–hypopnoea index (AHI) ≥ 15 . They found that CPAP treatment for 12 weeks was effective in reducing 24-hour mean and diastolic blood pressure, improving nocturnal blood pressure patterns. A meta-analysis of observational and RCTs by Ifikhar *et al*³⁸ examined the effects of CPAP treatment in patients with refractory HTN and OSA. They found a favourable reduction in blood pressure with CPAP treatment in their patients. The effect size was also found to be larger than reported in patients with OSA without resistant HTN.

In summary, OSA contributes to development of HTN, its refractoriness to medical therapy; treatment of OSA contributes to reduction in blood pressure.

Sleep apnoea and atrial fibrillation

Sleep apnoea has been linked to increase in prevalence, effect on treatment and aggravation of atrial fibrillation (AF) as described in this section. Prevalence of AF in patients with sleep apnoea has been found to be between 3% and 5% as compared with 1% in the general population.^{39 40} Moore *et al*⁴¹ studied patients undergoing cardiac bypass surgery with polysomnography for the diagnosis of sleep apnoea and found both AHI and O₂ desaturation index to be highly predictive of postoperative AF. The Sleep Heart Health Study found AF prevalence rates of 4.8% and 0.9% in participants with and without SDB. The same study also found the likelihood of arrhythmic events to be more common after hypopnoeic or apnoeic episodes.³⁹ Severity of sleep apnoea has also been shown to influence the prevalence of AF.⁴² Under-reporting of excessive daytime sleepiness and low EDSS scores is a possible contributory factor to underdiagnosis of sleep apnoea in these patients.^{43 44}

In patients undergoing management of AF who were followed up for 1 year, recurrence of AF was found to be present in 82% of the patients with untreated sleep apnoea compared with 42% in patients with treated sleep apnoea.⁴⁵ In another study, procedural failure of AF ablation was predicted by presence of sleep apnoea and non-compliance with CPAP.⁴⁶ The Outcomes

Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry found that participants with sleep apnoea were more likely to have more severe or disabling symptoms as compared with participants without OSA (22% vs 16%), and more likely to be receiving rhythm control therapy (35% vs 31%, respectively).⁴⁷ In a reverse association, studies have found favourable effect of treatment of AF on central sleep apnoea,⁴⁸ and a significant reduction in AHI in patients with SDB.⁴⁹

Various effects of sleep apnoea on pathophysiology of AF have been described. Increased negative intrathoracic pressure during apnoeic episodes of OSA increase cardiac vagal output that enhances AF inducibility. This effect can be prevented by vagotomy and atropine.⁵⁰ It has also been found to activate stretch-sensitive ion channels or fibrosis at anchoring regions of atria that are critical to AF induction.^{51 52}

Obesity and the magnitude of nocturnal oxygen desaturation are independent risk factors for AF in individuals <65 years of age⁵³ and OSA is a univariate predictor of AF (HR 2.18, 95% CI 1.34 to 3.54).⁵⁴

So, sleep apnoea not only increases the risk of AF, it also increases the refractoriness of AF to treatment. In addition, the treatment of AF has a positive beneficial effect on central sleep apnoea.

Sleep apnoea and stroke

While sleep apnoea has been shown to indirectly increase the risk of stroke by its effect on vascular risk factors as aforementioned, it has also been independently associated with increased risk of stroke.

In the landmark study by Yaggi *et al*,⁵⁵ investigators found an independent increase in risk of stroke and all-cause mortality with a HR of 2.24 in patients with AHI ≥ 35 /hour. This risk remained elevated despite controlling for traditional stroke risk factors such as HTN, AF, smoking status, diabetes and hyperlipidaemia. A study of 394 patients aged 70–100 years old found an AHI ≥ 30 associated with an increased risk of ischaemic stroke in an elderly non-institutionalised male population.⁵⁶ In a study of 1189 patients, AHI ≥ 20 was associated with an increase in the risk of having stroke over the next 4 years.⁵⁷ The Sleep Heart Health Study helped link sleep apnoea with stroke.⁵⁸ It found that men in the highest quartile of AHI (>19) had a HR of 2.86 for having stroke and even in the mild-moderate sleep apnoea category (AHI 5–25), each 1 unit increase in AHI increased the risk of stroke by 6%. In women, the same study found an increase in risk of stroke only in the severe sleep apnoea group (AHI >25). In a study by Marin *et al*,⁵⁹ severe OSA significantly increased the risk of fatal and non-fatal cardiovascular events while CPAP treatment reduced the risk. In the Wisconsin sleep cohort study, there was a significant, high cardiovascular mortality risk with untreated SDB, independent of age, sex and body mass index (BMI).⁶⁰ The American Heart Association recommends screening for OSA for stroke

prevention and suggests that treatment might be reasonable.⁶¹

In conclusion, the various effects of sleep apnoea/SDB on cardiovascular risk factors and stroke as a risk factor itself are now well documented and should be routinely identified as risk factor for stroke in clinical practice.

Management of sleep apnoea

In this section, we will summarise the current management of sleep apnoea without going into details, which can be found in the references listed.

Screening for sleep apnoea

The clinical symptoms of sleep apnoea may include snoring, witnessed episodes of apnoea by family members, history of awakenings associated with a sensation of choking, nocturia, morning headaches, palpitations due to difficult to control AF, refractory HTN and excessive daytime sleepiness. While any of the above should trigger a search for sleep apnoea, the authors believe that the first screening should ideally happen in a primary care setting similar to other vascular risk factors such as HTN and obesity, prior to development of complications of sleep apnoea.

The Epworth Sleepiness Scale (EPSS), Berlin apnoea questionnaire, STOP and STOP-Bang questionnaires are various clinical screening tools available. The Berlin apnoea questionnaire identifies patients at risk for OSA.⁶² STOP and STOP-Bang questionnaires have been studied and validated in presurgical patients.⁶³ The EPSS quantifies subjective measures of excessive daytime sleepiness⁶⁴ using a questionnaire format; the multiple sleep latency test (MSLT) can be used to objectively assess excessive daytime sleepiness.⁶⁵ Another in-hospital tool that may be used for screening of sleep apnoea in patients with stroke is continuous overnight oximetry which will be discussed under 'Sleep apnoea in the acute stroke' subsection below.

Diagnostic criteria

OSA falls under the category of SDB which also includes central sleep apnoea and Cheyne-Stokes breathing. Once sleep apnoea is suspected, the diagnostic gold standard is an overnight polysomnogram.⁶⁵ During polysomnography, various abnormal respiratory parameters have been defined and include the following:

1. Apnoea—cessation of airflow ≥ 10 s. (with or without respiratory effort).
2. Hypopnoea—a $\geq 30\%$ reduction in airflow for at least 10 s that is accompanied by either $\geq 3\%$ desaturation or an arousal.
3. Respiratory effort-related arousal (RERA): a partially obstructed breath that does not meet the criteria for hypopnoea but is associated with increased respiratory effort and arousal.
4. Flow-limited breath: a partially obstructed breath identified by flattened inspiratory flow shape.

Severity of OSA/hypopnoea (OSAHS) syndrome can be quantified using the following criteria:

1. AHI—number of apnoeas and hypopnoeas per hour of sleep.
2. Respiratory disturbance index—AHI+RERAs per hour of sleep.
3. Mild OSAHS—AHI 5–14/hour.
4. Moderate OSAHS—AHI 15–29/hour.
5. Severe OSAHS—AHI \geq 30/hour.

Therapies for sleep apnoea

Treatment includes a recommendation to lose weight. Most patients who lose weight have less severe apnoea, but it is difficult to predict the amount of improvement associated with loss of a specified amount of weight. Nonetheless, weight loss via intensive lifestyle interventions should be encouraged as a treatment for mild-to-moderate OSA.

Avoidance of precipitating factors, such as alcohol, smoking and hypnotic drugs is helpful. For patients in whom sleep apnoea occurs only when supine (positional OSA), training to avoid this sleeping position is often beneficial (positional therapy).

The cornerstone of therapy is positive airway pressure ventilation. The air pressure splint acts to maintain airway patency during sleep and ameliorate the effects of sleep apnoea. Various PAP modes that are used include CPAP, bilevel-PAP and autoPAP. Oral appliances that can be used to ameliorate mild-to-moderate OSA include tongue retaining devices and soft palate lifting devices. Surgical therapies may be used for definitive anatomical obstructions contributing to OSA. Mandibular repositioning devices have been used for patients with mild-to-moderate OSA with PAP intolerance.⁶⁶ Fully implantable hypoglossal nerve stimulating systems inducing electrical stimulation of the genioglossus muscle have been approved for nerve stimulation and prevention of pharyngeal collapse without arousing patients from sleep.⁶⁷

Sleep apnoea in acute stroke

Epidemiology of sleep apnoea in acute stroke

Respiratory changes are seen acutely after stroke and can be divided into sleep–wake cycle and SDB. The changes may vary with the location of the stroke. As mentioned in an earlier section, OSA is part of SDB which includes central sleep apnoea. About 50–70% of patients with stroke have SDB as defined by AHI \geq 10/hour with OSA being the most common pathology.⁶⁸ Some studies indicate that during the first 5 days post-stroke central sleep apnoea predominates.⁶⁹

The frequency of OSA itself has been reported to be between 38% when measured as AHI $>$ 20/hour to 72% when measured as AHI $>$ 5/hour in a meta-analysis performed by Johnson and Johnson only 7% of SDB was central apnoea. Males had a higher percentage of SDB (AHI $>$ 10) than females (65% vs 48%, respectively). Patients with recurrent strokes had higher percentage of SDB than patients with first stroke (74% vs 57%

respectively).⁷⁰ A small study involving patients in an acute stroke rehabilitation unit demonstrated AHI $>$ 10 in 91% of the studied population with a mean AHI of 32/hour.⁷¹ Worsening of OSA may also be found after acute stroke due to impairment of respiratory muscle coordination. In some studies, presence of dysphagia was found to predict the development of OSA in patients with acute stroke,⁷² while another suggests that presence of prestroke leucoencephalopathy predicts a more severe OSA.⁷³ BMI and neck circumference have also been found to predict the presence of OSA in post-stroke patients.⁷⁴

Screening patients with acute stroke for sleep apnoea

Concentrating on minimal requirements in a stroke population, a sleep apnoea assessment would require a system that monitors nasal airflow, and thoracic and abdominal respiratory muscles. A comprehensive polysomnogram would provide additional details regarding specific SDB, but is rarely available as an inpatient service even in many US hospitals with comprehensive stroke care capabilities. One of the oldest tools available for screening patients for sleep apnoea includes a continuous overnight oximetry recording. It is the modality that we recommend to ease the unavailability of other recording methods.

Overnight oximetry has been used for a very long time and can be found in the British Thoracic Society report in 1990 on diagnosis and treatment of sleep apnoea/hypopnoea syndrome.⁷⁵ A review published in *Chest* concluded overnight oximetry to be a cost-effective tool with substantial accuracy for screening OSA.⁷⁶ In a validation study, Wang and colleagues reported an accuracy of 87.33–87.77%, a sensitivity of 89.36–89.87% and area under the curve of 0.953–0.957 for the diagnosis of severe sleep apnoea in a patient population clinically suspected of having OSA. Validation parameters were slightly less impressive in the moderate-to-severe sleep apnoea category.⁷⁷

Studies comparing overnight oximetry to ambulatory PSG in patients with acute stroke are needed. It is anticipated that in-hospital ambulatory PSG will be of significantly greater clinical utility in patients admitted with acute ischaemic stroke suspected of having sleep apnoea.

Effect of treating sleep apnoea in patients with acute stroke on outcome

In addition to its effect on the cardiovascular system, an arterial blood flow steal phenomenon has been described in patients with acute stroke. The affected tissue in ischaemic stroke is supplied by maximally or nearly maximally dilated arterioles with decreased vasomotor reactivity of the blood vessels.⁷⁸ Studies have found severely impaired cerebral vasoreactivity and increased arterial stiffness in patients with PSG—confirmed severe OSA,⁷⁹ even during wakefulness.⁸⁰ During episodes of apnoea, development of hypercapnia results

in selective vasodilation of blood vessels supplying normal brain tissue, resulting in a steal phenomenon away from the ischaemic vasoparalysed region depriving it of critical oxygen. The term 'reverse Robin Hood syndrome' has been used for this phenomenon.⁸¹

Studies demonstrating the effect of positive airway pressure ventilation during acute stroke are not many and much needed. During the acute phase, SDB of variable degree has been found to be associated with an increased risk of neurological deterioration within 72 hours of acute stroke.⁸¹ This deterioration may occur even after improvement in stroke severity. In one study,⁸¹ neurological deterioration was independently predicted by sleep apnoea with an OR of 8.2. Another small study using BiPAP treatment initiated within 24 hours of acute stroke onset indicated a favourable effect.⁸²

Various non-randomised studies suggest that CPAP may improve mortality and prevent new vascular events after ischaemic stroke in patients with OSA.^{83–85} Both long-term survival and functional outcomes have been shown to be affected by presence of SDB.^{86–87} In an RCT by Parra *et al*,⁸⁸ neurological improvement at 1 month and length of time from stroke to first cardiovascular event were in favour of the CPAP treatment group which was started 3–6 months after acute stroke. Another RCT by Bravata *et al*⁸⁹ showed that treatment with CPAP had a potential benefit on cardiovascular events in patients with transient ischaemic attack. The downside is that poststroke patients tolerate poorly PAP treatments.⁹⁰

In summary, treatment of sleep apnoea may prevent acute neurological worsening, decrease neurological morbidity and improve long-term outcomes in patients with acute ischaemic stroke. More definitive studies are needed.

Evolution of sleep apnoea after acute stroke

SDB improves as the stroke evolves, although 50% of patients still exhibit an AHI \geq 10/hour after 3 months following the acute event. CSA has been reported in about 26% of patients with acute stroke which improves over time more rapidly than the obstructive events.⁸⁸ Another study suggests better improvement of SDB in haemorrhagic versus ischaemic strokes.⁹¹ Improvement in stroke symptoms probably plays a role in the resolution of symptoms after the acute phase of stroke. Indication for sleep apnoea therapies including positive airway pressure ventilation may require reassessment after the acute and subacute phases of stroke.

Sleep apnoea and vascular dementia

Increasingly, more studies are finding a link between sleep apnoea and cerebral white matter disease. Harbison *et al*⁷³ found the presence of prestroke cardiovascular and white matter disease to be associated with worse SDB. They concluded that either white matter is particularly sensitive to the hypoxia and cardiovascular effect of SDB, or white matter disease contributes to exacerbation of stroke

following SDB. Guarnieri *et al*⁹² found SDB to be more severe among patients with vascular dementia while no increased prevalence of the same was found in other dementia syndromes. Shin and colleagues found moderate-to-severe OSA as an independent risk factor for white matter changes in middle-aged and older individuals in Korea.¹⁴ Minoguchi *et al*⁹³ studied patients with moderate-to-severe OSA and found a higher prevalence of silent brain infarcts in patients with OSA compared with control participants. The biochemical markers for silent brain infarcts were also looked at and were found to respond favourably when patients were treated with nasal CPAP.⁹³ Another study found one out of four patients with newly diagnosed OSA had a severe and distinctive neuropsychological dysfunction mainly involving inductive and deductive thinking, and constructive ability. Some analogy with cognitive patterns of MID suggests that a mainly subcortical damage underlies this dysfunction.⁹⁴ Moderate-to-severe OSA may be a risk factor for development of vascular cognitive impairment as a result of cerebral subcortical small vessel disease.⁹⁵ In Yaffe *et al*⁹⁶ study, old women with OSA >15 AHI were more likely to develop cognitive impairment. Intermittent nocturnal hypoxia in patients with moderate-to-severe OSA contributes to ischaemic damage in the cerebral periventricular territory of long penetrating terminal arteries. Ischaemic damage to the cerebral periventricular white matter partially disconnects the frontal cortex with the thalamus leading to a form of subcortical dementia characterised by apathy, decreased executive functions, poor memory and in advanced cases difficulty walking and urinary incontinence. CPAP applications may delay onset of dementia.⁹⁷

While more definitive studies are needed to establish causality of sleep apnoea in the pathogenesis of vascular dementia, there seems to be a provocative association between the two.

CONCLUSION

Sleep apnoea causes pathological increase in sympathetic activity, contributing to autonomic dysregulation. This dysautonomia probably contributes to worsening of the cardiovascular risk profile in patients with sleep apnoea, and may be responsive to treatment with positive airway pressure ventilation and other sleep apnoea therapies. The worsening of cardiovascular profile is well known to increase the risk of stroke. Early diagnosis and treatment of sleep apnoea should reduce the risk of stroke. Sleep apnoea also contributes to the refractoriness of AF, HTN and diabetes to treatment. Untreated sleep apnoea can contribute to acute, subacute and long-term neurological deterioration in patients with acute stroke. Vascular dementia is another entity that may be associated with sleep apnoea.

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