Chapter 1

Overview of sleep and stroke

Antonio Culebras

Introduction

Even ancient physicians knew that when sleep faltered, health failed. In his famous Aphorisms, Hippocrates said "Sleep or watchfulness exceeding that which is customary, augurs unfavorably" [1]. Perhaps the statement is too general for today's usage but the concepts are immovable. Sleep is one of the pillars of health along with diet and exercise. When sleep is fragmented, not deep enough, or short in duration, a chain of events is released that leads to failing health [2]. Modern medicine has been able to disentangle some of the phenomena that disturb sleep and is beginning to foresee the consequences. Among the most notable offenders is sleep apnea, a highly prevalent disorder that incomprehensively became known just a half century ago. Sleep apnea is the term that we will use in this chapter for the generic denomination of all forms of sleep-related respiratory disturbance.

Sleep apnea alters sleep, night after night, and when so doing puts in motion a spectrum of adverse reactions that break down the physical and mental health of the individual and can lead to vascular disorders and death. The sleep apnea syndrome, that is sleep apnea with clinical consequences, occurs in 4% of adult men and 2% of adult women [3]. However, the prevalence of sleep apnea without specific complaints is as high as 24% in men and 9% in women in the general population [3]. In selected populations like the obese and the elderly, this value may be as high as 60% [4]. Furthermore, sleep apnea is not the only culprit. Recent research has unveiled some long-term vascular costs of restless legs syndrome, another prevalent condition that may disturb sleep, and is beginning to make inroads into the protracted outcomes of circadian dysrhythmias and primary insomnias.

In this book, *Sleep, Stroke and Cardiovascular Disease*, renowned authors write about the vascular consequences of altered sleep, focusing on sleep apnea, the most common and best-studied condition to date. In recent years, obstructive sleep apnea (OSA) has been identified as an independent risk factor for cardio- and cerebrovascular morbidity.

Proinflammatory risk factors

The litany of pathophysiological derangements caused by sleep apnea commences with Slava Berger and Lena Lavie's account of oxidative stress, proinflammatory vascular risk factors, and endothelial disease triggered by sleep apnea [Chapter 2]. The authors highlight the significance of oxidative stress and vascular inflammation in promoting endothelial disease and atherosclerosis in sleep apnea patients, with an emphasis on the contribution of these mechanisms to the development of cardiovascular morbidity and stroke.

Sleep, Stroke, and Cardiovascular Disease, ed. Antonio Culebras. Published by Cambridge University Press.

Inflammation and hypoxia are intertwined at the molecular, cellular, and clinical levels [5]. Repeated hypoxia may damage the endothelium and trigger the release of proinflammatory factors like plasma cytokines, tumor necrosis factor-alpha, 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 [6]. This state of inflammation may be related to gestational hypertension that develops in about 10% of all pregnancies [7,8] and to an increased risk for delivering preterm, small-for-gestational-age, and low birth-weight infants, along with a higher rate of preeclampsia and cesarean sections in women with sleep apnea [9].

Autonomic alterations in sleep apnea

Sleep apnea may also cause a significant increase in sympathetic activity during sleep, which in turn influences heart rate and blood pressure. Increased sympathetic activity appears to be induced through a variety of different mechanisms in sleep apnea, 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 possibly the arousal response [10]. According to Cortelli and Provini (Chapter 3), sympathetic overactivity appears to be the critical link between sleep apnea and the pathogenesis of hypertension. Sleep apnea influences heart rate variability, not only during sleep but also during wakefulness. Cortelli et al. [11] showed that normotensive sleep apnea patients have a higher heart rate at rest during wakefulness and a higher blood pressure response to head-up tilt than do controls, suggesting sympathetic overactivity. When performing cardiovascular reflex tests, sleep apnea patients show significantly lower values of respiratory arrhythmia and a greater decrease in heart rate induced by cold face testing, indicating normal or increased cardiac vagal efferent activity. An increase in sympathetic activity and autonomic imbalance are possible determinants of cardiovascular comorbidity and increased mortality risk in patients with sleep apnea [11,12]. Treatment of sleep apnea with continuous positive airway pressure (CPAP) leads to a significant improvement of autonomic modulation and cardiovascular variability [13].

Blood pressure

It is known that blood pressure values normally drop by 10%–20% during sleep compared to daytime values; this phenomenon is known as dipping [14]. Nondipping, defined as less than a 10% drop in blood pressure during the night, is common in sleep apnea, and rises in prevalence as the severity of sleep apnea increases [15], as described by Barot and Kushida in Chapter 4. Nondipping has been associated with a higher prevalence of small-vessel disease and stroke [16]. In addition, blood pressure during the day tends to increase in sleep apnea patients, along with variability in blood pressure values [17]. In fact, data from various large-scale population studies clearly demonstrate a dose-dependent relationship between sleep apnea and hypertension [18,19]. Cardiologists have learned to refer patients to a sleep center for evaluation of possible sleep apnea when the blood pressure fails to respond optimally to at least three antihypertensive medications. Refractory hypertension is thus a well-known comorbidity of uncontrolled sleep apnea [20] that responds favorably to the successful application of CPAP [21]. Even children with sleep apnea may have abnormal blood pressures compared to children without sleep apnea [22] to the point that signs of cardiac remodeling, proportionate to the degree of hypertension, have been observed on echocardiography [23].

Arousal response

Dyken et al. (Chapter 5) take it one step further and report evidence suggesting that untreated obstructive sleep apnea (OSA) is a significant health risk for the development of hypertension, cardiovascular disease, and stroke. This pathophysiological pathway is mediated by hypoxemia, hypercapnia, and simultaneous elevations in sympathetic and parasympathetic activity, with significant variations in blood pressure, tachycardia/bradycardia, and asystole. The arousal response at the termination of untreated sleep apnea events conjugates many of these phenomena and emerges as a principal link in the chain of events that lead to potentiation of stroke risk factors that cause stroke.

Atrial fibrillation

Atrial fibrillation has emerged as another associated factor increasing the risk of stroke in patients with sleep apnea. The prevalence of atrial fibrillation in the United States was estimated at 3.03 million persons in 2005 [24] and has been increasing as more individuals survive into old age [25]. Compelling data have shown a strong relationship between sleep apnea and atrial fibrillation, as described in Gami's chapter (Chapter 6). Epidemiological studies suggest that sleep apnea is a risk factor for new-onset atrial fibrillation, and that sleep apnea confers a poorer prognosis after atrial fibrillation interventions. 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

Patent foramen ovale (PFO) is very prevalent, and depending on the diagnostic method, it has been estimated to be within 10%–30% in the general population [26]. The association between PFO and sleep apnea is described by Forteza in Chapter 7. Several studies have reported the association between PFO and sleep apnea; 27% of sleep apnea patients and 15% of control subjects had PFO in one study [27]. The association of PFO and sleep apnea suggests that nocturnal apneic-related shunting from right to left through a PFO could increase the risk of paradoxical embolism and stroke. The risk increases further if pulmonary hypertension develops as a result of nocturnal hypoxemia [28]. In a study presented at the American Academy of Neurology meeting in 2011 [29], 339 consecutive stroke patients were studied. Stroke on awakening was found in 39% of patients with the association of sleep apnea and PFO, but stroke on awakening occurred in only 26% of patients if there was no association. The authors concluded that the association of sleep apnea and PFO should be considered a risk factor for stroke on awakening (OR=2.2 (CI, 1.2–3.9; P=0.01). Studies describing the association of sleep apnea and PFO are relatively few and disallow strong conclusions, at least for now. However, the evidence is suggestive and worthy of further exploration.

Stroke

Sleep apnea is also an independent risk factor for stroke. The specific risk of stroke or death in sleep apnea was investigated by Yaggi et al. [30]. In their study, the risk of stroke or death from any cause in patients with sleep apnea with a mean apnea/hypopnea index (AHI) of 35/h was expressed by a hazards ratio of 2.24 (95% CI, 1.30–3.86). The increased risk was independent of other risk factors including hypertension, while increased severity of sleep apnea was associated with an incremental risk of stroke and death.

A causal association between sleep apnea and stroke was also observed in a study in elderly individuals. Investigating 394 males aged 70–100 years, Muñoz et al. [31] found that severe obstructive sleep apnea/hypopnea (defined as an AHI of >30 events/h) increases the risk of ischemic stroke in an elderly male noninstitutionalized population, independent of known confounding factors. In another prospective analysis of 1189 subjects from the general population, Arzt et al. [32] found that sleep-disordered breathing with an AHI of 20 events/h or greater was associated with an increased risk of suffering a first-ever stroke over the next four years (unadjusted odds ratio, 4.31; 95% CI, 1.31–14.15; P=0.02). After adjustment for age, gender, 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). In a cross-sectional analysis of 1475 individuals, the same authors found that subjects with an AHI of 20 events/h or greater 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 events/h) after adjustment for known confounding factors. The authors concluded that there is a strong association between moderate to severe sleep-disordered breathing and stroke, independent of confounding factors. In the Sleep Heart Health Study [33], men in the highest AHI quartile (>19 events/hr) had an adjusted hazard ratio of stroke of 2.86 (95% CI, 1.1–7.4). In the mild to moderate range (AHI, 5–25 events/hr), each one-unit increase in AHI in men was estimated to increase stroke risk by 6% (95% CI, 2%–10%). In women, stroke risk increased when there was an AHI of >25 events/h.

Small-vessel disease and cognitive dysfunction

Sleep apnea may also lead to cognitive dysfunction from the effects of chronic hypoxia and sympathetic stress associated with small-vessel disease in the brain, white matter ischemia, and lacunar strokes. In Chapter 8, Román reports the observation of deleterious effects of OSA on cognitive functions demonstrated in patients referred to the Alzheimer and Dementia Clinic of the Methodist Neurological Institute in Houston, Texas (Román, unpublished data). Magnetic resonance imaging (MRI) of the brain showed that OSA was accompanied by varying intensities of cerebral small-vessel disease, appearing as periventricular hyperintensities of the white matter and lacunar strokes, which would correlate with the clinical picture of subcortical prefrontal dysfunction, sometimes mixed with features of Alzheimer's disease.

In a recent publication, Yaffe et al. [34] reported that elderly women affected by OSA develop cognitive deficits when compared to age-matched controls with normal sleep. The authors concluded that cognitive decline correlated with hypoxemia rather than with fragmentation of sleep architecture caused by apneas and hypopneas. Román, along with other authors, is hopeful that early recognition and treatment with CPAP may result in improvement of cognitive function [35] and prevention of dementia in patients with sleep apnea.

Cerebral hemodynamic changes

When the cerebral circulation is compromised, hemodynamic alterations may act as triggers of irreversible ischemic changes in regions with poor hemodynamic reserve, particularly borderzone areas and terminal artery territories. Preliminary studies of auditory event-related potentials in patients with treated sleep apnea [36] found no improvement in abnormal P3 wave latencies, suggesting permanent structural changes in the white matter of the hemispheres likely as a result of ischemia. On the other hand, healthy children with

mild sleep-disordered breathing [37] have cerebral hemodynamic and neurobehavioral changes that are potentially reversible following adenotonsillectomy, suggesting normalization of middle cerebral artery blood flow as measured with transcranial Doppler techniques [38].

Cerebral blood flow studies have shown that during the apnea event there is significant reduction in middle cerebral artery blood flow velocity [39,40]. The drop correlates with the duration of the apnea event rather than with the depth of oxyhemoglobin desaturation. The phenomenon suggests that hemodynamic disturbances caused by profound intrathoracic negative pressures during obstructive apneas determine a reduction of cerebral blood flow. Intracranial hemodynamic changes occurring repeatedly night after night in patients with marginal circulatory reserve may contribute to raising the risk of stroke, in particular in patients with significant sleep apnea disorder [41]. Using near-infrared spectroscopy (NIRS), Pizza et al. [42] observed that cerebral hemodynamic autoregulatory mechanisms fail with brain hypoxia in the presence of frequent apneas (AHI>30 events/h).

Acute stroke

Extending the concept of cerebral hemodynamic alterations in patients with sleep apnea, Barlinn and Alexandrov (Chapter 9) review the notions of altered vasomotor reactivity in patients with acute stroke. They report the occurrence of intracranial blood flow steal in response to changing vasodilatory stimuli like carbon dioxide elevations in patients with sleep apnea and stroke and propose that this phenomenon, termed reversed Robin Hood syndrome [43], might play a pivotal role in clinical deterioration after an acute stroke. These observations have led to the notion that noninvasive ventilatory correction in select acute stroke patients might have a beneficial effect on sleep apnea and brain perfusion and constitute a missing link in the pathogenesis of early neurological deterioration and stroke recurrence.

Continuous positive airway pressure treatment

The gold standard treatment of clinically significant sleep apnea is achieved with nightly applications of CPAP. Kohler and Stradling (Chapter 10) review the effects of CPAP treatment on stroke risk factor control and on stroke outcomes. The effect of CPAP on systemic blood pressure in patients with sleep apnea appears to depend on the severity of sleep-disordered breathing, daytime sleepiness, the extent of obesity, and the hours of nightly CPAP use. Continuous positive airway pressure treatment has been shown to decrease nocturnal arousal frequency and suppress acute blood pressure fluctuations. Randomized controlled trials have established that CPAP treatment of symptomatic patients with moderate to severe sleep apnea lowers blood pressure levels. The precise mechanism of this favorable effect remains to be identified, although there is suggestive evidence that CPAP reduces blood pressure primarily by stabilizing the sympathetic–vagal balance. Patients with drug resistant hypertension, requiring three antihypertensive drugs or more for control of blood pressure, should be screened for sleep apnea, because succesful CPAP therapy leads to significant blood pressure reductions that are greater than what can be achieved with drugs alone [44].

Continuous positive airway pressure therapy may have a favorable effect on atrial fibrillation recurrence. Preliminary observational studies have shown reduction in recurrence of atrial fibrillation following therapeutic procedures in patients treated with CPAP [45,46]. However, additional research is required to confirm this therapeutic action of CPAP.

The effect of CPAP on stroke recurrence remains to be established. It can be surmised that if CPAP exerts a favorable effect on controlling stroke risk factors, the occurrence or recurrence of stroke might be reduced. Preliminary evidence from several studies suggests that this is the case [47,48]; however, large randomized, controlled, and prospective studies need to be conducted to establish the favorable effect of CPAP on stroke occurrence.

Poststroke sleep apnea and rehabilitation

Several studies have shown that sleep apnea is common in patients after stroke [49–52]. This important observation and its implications for rehabilitation of patients following stroke is reviewed by Jafari and Mohsenin in Chapter 11. The prevalence of sleep apnea poststroke has a range of 50%–75%, depending on the study. Whether sleep apnea precedes the occurrence of stroke or appears poststroke remains a matter of debate. It may well be that both etiopathological mechanisms play a role. Sleep apnea may contribute to neurological deterioration during the acute stages of stroke and may worsen the rehabilitation outcome weeks and months after stroke occurrence. Some studies have shown that central sleep apneas predominate initially, giving way to obstructive apneas in the chronic stages following acute stroke [53].

The relationship of sleep apnea to poor functional outcome, delirium, depressed mood, cognitive functioning, ability to perform activities of daily living (ADL), as well as psychiatric and behavior symptoms has been studied in patients undergoing rehabilitation for stroke by several authors [54]. Some studies have shown that sleep apnea is significantly and independently related to functional impairment and length of hospitalization following stroke [55,56].

The feasibility and effectiveness of CPAP therapy, particularly auto-CPAP, in patients with sleep apnea and stroke have been investigated both in the acute and chronic phases [48,57,58]. Preliminary results show a beneficial effect of auto-CPAP during the acute phases of stroke [59] as well as on neurological and cognitive functions during the stable phase of stroke in a rehabilitation setting. However, compliance with treatment is a challenging proposition that needs to be resolved before this treatment becomes generalized.

Restless legs syndrome, periodic limb movements of sleep, and risk of stroke

Alterations of sleep other than those caused by sleep apnea may increase the risk of stroke. Emerging evidence suggests that restless legs syndrome (RLS) and its associated condition, periodic limb movements of sleep (PLMS), represent risk factors for cardio- and cerebrovascular disease, even leading to stroke [60–62]. This topic is reviewed in Chapter 12 by Federica Provini. Although the reasons for this association remain unclear, emerging evidence suggests that common factors prevalent in both conditions, like smoking, the metabolic syndrome, and diabetes, may predispose individuals to heart disease and stroke. However, sympathetic activation and metabolic dysregulation may constitute the common pathogenetic pathway. Repeated nocturnal heart rate and blood pressure rises accompanying PLMS, especially those occurring with microarousals [63], may facilitate development of daytime hypertension paving the way to heart disease and stroke [64]. More research is needed to evaluate the role of RLS and PLMS in increasing cardiovascular risk.

Physician as patient: a personal story of stroke

The final chapter is the personal account of a stroke narrated by Harold Smith, a renowned sleep specialist (Chapter 13). Dr. Smith suffered a disabling stroke at the height of his career as neurologist and sleep specialist. His account is most edifying and provides insights rarely retrieved from patients who suffer a stroke.

Concluding remarks

Scientific evidence linking sleep alterations, in particular sleep apnea, with stroke risk factors, cardiovascular disease, and stroke has been uncovered sufficiently well to consider sleep apnea as a strong risk factor for stroke and cardiovascular disease. Sleep apnea is a modifiable risk factor and therefore efforts to control this condition in patients at risk of vascular disease is a clinical endeavor that should be pursued vigorously, even though clinical research needs to persist in its quest to answer pressing pathophysiological questions.

References

1. *The Aphorisms of Hippocrates*. The Classics of Medicine Library. Birmingham, AL: Leslie B Adams Jr, Gryphons Editions Ltd, 1982.
2. Culebras A. Sleep and stroke. *Neurology* 2009; **29**: 438–45.
3. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; **328**: 1230–5.
4. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008; **5**: 136–43.
5. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med* 2011; **364**: 656–65.
6. Iadecola C. *Cerebrovascular Dysfunction in Chronic Intermittent Hypoxia*. Los Angeles, CA: International Stroke Conference, 2011.
7. Champagne K, Schwartzman K, Opatrny L, et al. Obstructive sleep apnoea and its association with gestational hypertension. *Eur Respir J* 2009; **33**: 559–65.
8. Poyares D, Guilleminault C, Hachul H, et al. Pre-eclampsia and nasal CPAP: part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention. *Sleep Med* 2007; **9**: 15–21.
9. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. *Clin Chest Med* 2011; **32**: 175–89.
10. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; **96**: 1897–904.
11. Cortelli P, Parchi P, Sforza E, et al. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. *Clin Auton Res* 1994; **4**: 57–62.
12. Friedman O, Logan AG. The price of obstructive sleep apnea-hypopnea: hypertension and other ill effects. *Am J Hypertens* 2009; **22**: 474–83.
13. Noda A, Nakata S, Koike Y, et al. Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. *Hypertens Res* 2007; **30**: 669–76.
14. Coccagna G, Mantovani M, Brignani F, et al. Laboratory note. Arterial pressure changes during spontaneous sleep in man. *Electroencephalogr Clin Neurophysiol* 1971; **31**: 277–81.
15. Hla KM, Young T, Finn L, et al. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. *Sleep* 2008; **31**: 795–800.
16. Kario K, Pickering TG, Matsuo T, et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852–7.
17. Narkiewicz K, Montano N, Cogliati C, et al. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; **98**: 1071–7.

18. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; **283**: 1829–36.
19. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342**: 1378–84.
20. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001; **19**: 2271–7.
21. Dernaika TA, Kinasewitz GT, Tawk MM. Effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea. *J Clin Sleep Med* 2009; **5**: 103–7.
22. Horne RS, Yang JS, Walter LM, et al. Elevated blood pressure during sleep and wake in children with sleep-disordered breathing. *Pediatrics* 2011; **128**: e85–92.
23. Amin R, Somers VK, McConnell K, et al. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertension* 2008; **51**: 84–91.
24. Naccarelli GV, Varker H, Lin J, et al. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009; **104**: 1534–9.
25. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; **114**: 119–25.
26. Lynch JJ, Schuchard GH, Gross CM, et al. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984; **53**: 1478–80.
27. Beelke M, Angeli S, Del Sette M, et al. Prevalence of patent foramen ovale in subjects with obstructive sleep apnea: a transcranial Doppler ultrasound study. *Sleep Med* 2003; **4**: 219–23.
28. Sanner BM, Doberauer C, Konermann M, et al. Pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Arch Intern Med* 1997; **157**: 2483–7.
29. Ciccone A, Nobili L, Roccatagliata DV, et al. Causal role of sleep apneas and patent foramen ovale in wake-up stroke. *Neurology* 2011; **76**: A170.
30. Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005; **353**: 2034–41.
31. Muñoz R, Durán-Cantolla J, Martínez-Vila E, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 2006; **37**: 2317–21.
32. Arzt M, Young T, Finn L, et al. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005; **172**: 1447–51.
33. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2010; **182**: 269–77.
34. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; **306**: 613–19.
35. Matthews EE, Aloia MS. Cognitive recovery following positive airway pressure (PAP) in sleep apnea. *Prog Brain Res* 2011; **190**: 71–88.
36. Neau JP, Paquereau J, Meurice JC, et al. Auditory event-related potentials before and after treatment with nasal continuous positive airway pressure in sleep apnea syndrome. *Eur J Neurol* 1996; **3**: 29–35.
37. Hill CM, Hogan AM, Onugha N, et al. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. *Pediatrics* 2006; **118**: e1100–8.
38. Hogan AM, Hill CM, Harrison D, et al. Cerebral blood flow velocity and cognition in children before and after adenotonsillectomy. *Pediatrics* 2008; **122**: 75–82.
39. Netzer N, Werner P, Jochums I, et al. Blood flow of the middle cerebral artery with sleep-disordered breathing. Correlation with obstructive hypopneas. *Stroke* 1998; **29**: 87–93.

40. Netzer NC. Impaired nocturnal cerebral hemodynamics during long obstructive apneas: the key to understanding stroke in OSAS patients? *Sleep* 2010; **33**: 146–7.
41. Jiménez PE, Coloma R, Segura T. Brain haemodynamics in obstructive sleep apnea syndrome. *Rev Neurol* 2005; **41**: S21–4.
42. Pizza F, Biallas M, Wolf M, et al. Nocturnal cerebral hemodynamics in snorers and in patients with obstructive sleep apnea: a near-infrared spectroscopy study. *Sleep* 2010; **33**: 205–10.
43. Alexandrov AV, Nguyen HT, Rubiera M, et al. Prevalence and risk factors associated with reversed Robin Hood syndrome in acute ischemic stroke. *Stroke* 2009; **40**: 2738–42.
44. Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. *J Hypertens* 2010; **28**: 2161–8.
45. Patel D, Mohanty P, Di Biase L, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010; **3**: 445–51.
46. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003; **107**: 2589–94.
47. Parra O, Sánchez-Armengol A, Bonnin M, et al. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J* 2011; **37**: 1128–36.
48. Bravata DM, Concato J, Fried T, et al. Continuous positive airway pressure: evaluation of a novel therapy for patients with acute ischemic stroke. *Sleep* 2011; **34**: 1271–7.
49. Dyken ME, Im KB. Obstructive sleep apnea and stroke. *Chest* 2009; **136**: 1668–77.
50. Yaggi H, Mohsenin V. Obstructive sleep apnoea and stroke. *Lancet Neurol* 2004 ; **3**: 333–42.
51. Hudgel DW, Devadatta P, Quadri M, et al. Mechanism of sleep-induced periodic breathing in convalescing stroke patients and healthy elderly subjects. *Chest* 1993; **104**: 1503–10.
52. Mohsenin V, Valor R. Sleep apnea in patients with hemispheric stroke. *Arch Phys Med Rehabil* 1995; **76**: 71–6.
53. Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med* 2000; **161**: 375–80.
54. Good DC, Henkle JQ, Gelber D, et al. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke* 1996; **27**: 252–9.
55. Sandberg O, Franklin KA, Bucht G, et al. Sleep apnea, delirium, depressed mood, cognition, and ADL ability after stroke. *J Am Geriatr Soc* 2001; **49**: 391–7.
56. Kaneko Y, Hajek VE, Zivanovic V, et al. Relationship of sleep apnea to functional capacity and length of hospitalization following stroke. *Sleep* 2003; **26**: 293–7.
57. Cherkassky T, Oksenberg A, Froom P, et al. Sleep-related breathing disorders and rehabilitation outcome of stroke patients: a prospective study. *Am J Phys Med Rehabil* 2003; **82**: 452–5.
58. Ryan CM, Bayley M, Green R, et al. Influence of continuous positive airway pressure on outcomes of rehabilitation in stroke patients with obstructive sleep apnea. *Stroke* 2011; **42**: 1062–7.
59. Bravata DM, Concato J, Fried T, et al. Auto-titrating continuous positive airway pressure for patients with acute transient ischemic attack: a randomized feasibility trial. *Stroke* 2010; **41**: 1464–70.
60. Portaluppi F, Cortelli P, Buonaura GC, et al. Do restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) play a role in nocturnal hypertension and increased cardiovascular risk of renally impaired patients? *Chronobiol Int* 2009; **26**: 1206–21.
61. Lindner A, Fornadi K, Lazar AS, et al. Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure. *J Sleep Res* 2012; **21**: 297–307.
62. La Manna G, Pizza F, Persici E, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis

treatment. *Nephrol Dial Transplant* 2011; **26**: 1976–83.
63. Pennestri MH, Montplaisir J, Colombo R, et al. Nocturnal blood pressure changes in patients with restless legs syndrome. *Neurology* 2007; **68**: 1213–18.
64. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep* 2009; **32**: 589–97.