Cardiovascular Comorbidities and Obstructive Sleep Apnea

Fátima Dumas Cintra, Dalva Poyares, Christian Guilleminault, Antonio Carlos Carvalho, Sergio Tufik, Angelo A. V. de Paola

Universidade Federal de São Paulo e Stanford University - São Paulo, SP, Brazil - Stanford, CA , USA

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a prevalent condition in the general population. It is associated with increased cardiovascular risk and often goes unrecognized. Its diagnose requires a high degree of clinical suspicion, particularly on the part of cardiologists, and it may be confirmed by polysomnography. Continuous positive airway pressure (CPAP) therapy is highly effective, since it improves sleep breathing pattern, promotes restful sleep and thus enhances the quality of life of these patients, in addition to attenuating or reversing many cardiovascular complications related to OSAHS. This paper addresses the pathophysiology and clinical features of cardiovascular comorbidities associated with the syndrome.

Introduction

Cardiovascular disease is one of the primary causes of mortality worldwide[1]. In the city of São Paulo, cardiovascular diseases associated with atherosclerosis are the leading cause of death, similar to developed countries[2,3]. A number of studies[4-6] confirm the role of cigarette smoking, high LDL-cholesterol levels, low HDL-cholesterol levels, diabetes mellitus, systemic arterial hypertension, family history, obesity, physical inactivity, central obesity, metabolic syndrome, and alcohol consumption in the genesis of atherosclerosis and its clinical complications.

In addition to these factors, recent evidence shows increased cardiovascular mortality in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS)[7]. The role of this syndrome as a cardiovascular risk factor deserves the careful attention of the cardiologist, because this condition is often undiagnosed[8].

OSAHS is a disorder characterized by recurrent complete or partial upper airway obstruction during sleep, resulting in apneic episodes, oxyhemoglobin desaturation, frequent arousals (figures 1 and 2) and consequent daytime sleepiness. This syndrome is far more common in men. Its incidence in middle-aged men and women in the literature ranges from 1% and 5% and 1.2% and 2.5%, respectively[9-13], and may increase with age[14]. It is often associated with other cardiovascular diseases; moreover, it is estimated that 40% of the patients with systemic hypertension have OSAHS, undiagnosed and untreated[15,16].

Chart 1 shows some important definitions for interpreting and diagnosing this condition.

Pathophysiology

Increased upper airway collapse during sleep is associated with increased respiratory effort and change in nasal and oral airflow, which may trigger hypoxemia and hypercapnia[20]. This process results in arousal with resumption of breathing. Abnormal respiratory events and arousals may alternate many times during the night[21].

During each episode of obstructive apnea/hypopnea, the inspiratory effort against an occluded airway is accompanied by negative pressure in the pleural space. As apnea persists, hypoxemia and hypercapnia become more marked, leading to pulmonary vasoconstriction and the development of transient pulmonary hypertension. There is however, a stimulation of the sympathetic nervous system, causing systemic vasoconstriction and arterial hypertension; in some cases, systolic blood pressure may reach significantly high nocturnal levels, even in subjects with normal daytime blood pressure

Additionally, the hypoxia and subsequent reoxygenation phenomenon, repeated many times during the night, causes changes in reperfusion, with free radical production[23], and oxidative stress is now considered a major contributor to the cardiovascular consequences observed in this group of patients[24]. Association of OSAHS with obesity[25], predominance in male and postmenopausal women, as well as the systemic effects triggered with its onset, strongly suggest that OSAHS is a systemic disease, rather than a local abnormality[26,27]. Other important evidence favoring the systemic disease

Mailing Address: **Fátima Dumas Cintra** • Av. Marcos Penteado de Ulhoa Rodrigues, 1001 - 06543-330 – Santana de Parnaíba, SP - Brazil
E-mail: fatimacintra@interair.com.br
Received on 12/08/05 • Accepted on 12/28/05

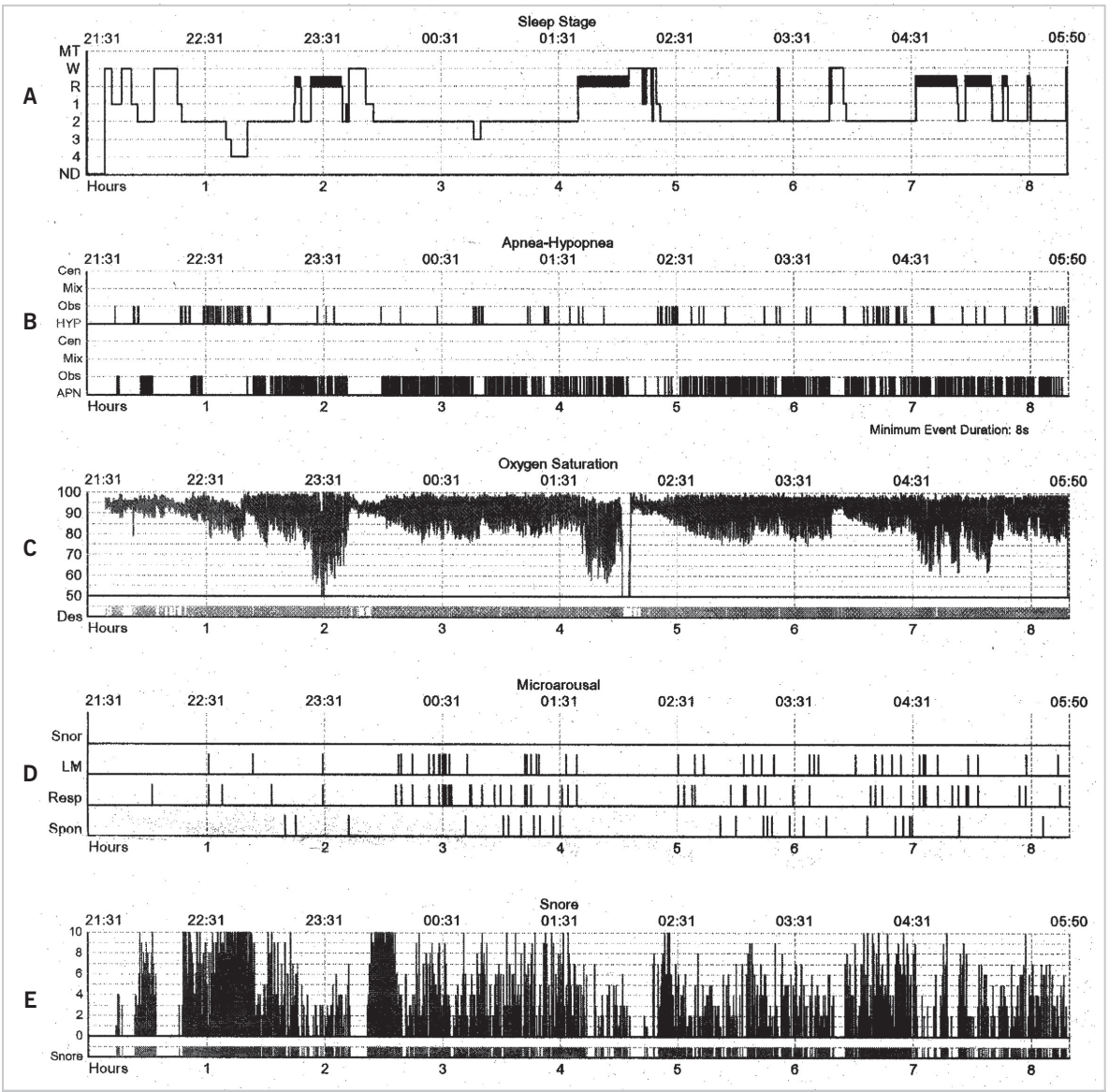

Fig. 1 *– Example of a compressed overnight polysomnographic graph in a patient with marked obstructive sleep apnea. A) hypnogram; B) apneic and hypopneic events; C) frequent events with marked drops in oxyhemoglobin saturation; D) microarousals (sleep fragmentation); E) loud and frequent snoring*

hypothesis for OSAHS is its correlation with higher inflammatory cytokine levels and insulin resistance. Inflammatory cytokines, tumor necrosis factor-α (TNF- α), and interleukin-6 (IL-6) are involved in the physiological regulation of sleep[28] and are abnormally elevated in apneic patients, when compared to normal and obese subjects[29,30]. However, the correlation between OSAHS and insulin resistance seems to be independent of obesity[31].

Cardiovascular Consequences

The main cardiovascular consequences are changes in autonomic nervous system activity, arterial hypertension, cardiac arrhythmias, coronary artery disease, stroke, and congestive heart failure.

Changes in autonomic nervous system activity

Heart rate and blood pressure changes observed in obstructive sleep apnea are likely to be secondary to autonomic nervous system activation during every apneic event[32]. This was demonstrated even in patients with mild OSAHS[33,34]. During these events, a progressive increase in sympathetic activity occurs, reaching its peak at apnea termination, followed by a marked decrease during recovery[35,36].

However, the mechanisms by which OSAHS causes persistent sympathetic activation, that is, even during wakefulness, are not entirely clear. Some evidence emphasizes the role of hypoxia in this phenomenon:

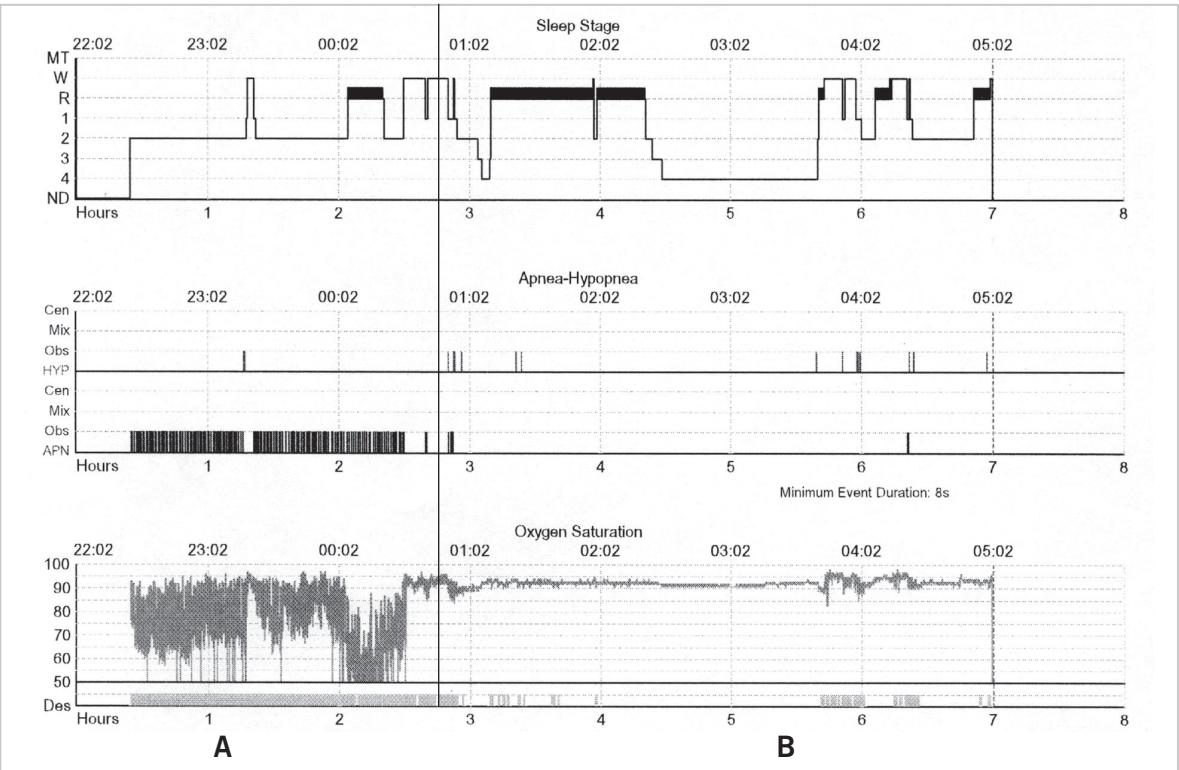

Fig. 2 – Example of a compressed overnight polysomnographic graph in a patient with marked obstructive sleep apnea followed by the introduction of nasal CPAP. A) observe the hypnogram, number of abnormal breathing events and intense oxyhemoglobin desaturation. B) after nasal CPAP introduction, observe the normalization of hypnogram with REM sleep rebound recording, abnormal breathing events, and oxyhemoglobin desaturation

Chart 1 – Term Definition[17-19]

Term	Definition
Polysomnography	Polygraphic sleep recording, including electroencephalogram (EEG), electroocculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), and respiratory parameters.
NREM sleep	Characterized by electroencephalographic slow waves associated with specific graphic elements.
REM sleep	Characterized by EEG desynchronization, rapid eye movements, muscle atonia, and dreams.
Arousals	Transient awakening lasting more than three seconds.
Apnea	Reduction of > 80% in oronasal airflow during more than ten seconds.
Hypopnea	Reduction of > 20% in oronasal airflow during more than ten seconds, usually accompanied by either a decrease in oxyhemoglobin saturation or an arousal
Apnea-hypopnea index (AHI)	Frequency of apneic or hypopneic episodes per hour of sleep; it is a measure of sleep apnea severity.
Oxygen desaturation	Decrease of > 3% in oxyhemoglobin saturation, often caused by apnea or hypopnea.
Obstructive sleep apnea-hypopnea syndrome	AHI > five per hour of sleep accompanied by symptoms such as snoring, restless sleep, nocturnal dyspnea, morning headaches, excessive daytime sleepiness, and arterial hypertension.

urinary norepinephrine concentrations are inversely proportional to nadir nocturnal oxyhemoglobin saturation. Furthermore, the ventilatory changes that determine hypoxia and hypercapnia cause an increase in muscle sympathetic nerve activity, which may persist for up to twenty minutes following stimulus withdrawal[37]. The carotid sinus seems to play a role in the process between exposure to intermittent nocturnal hypoxia and development of sustained elevation in autonomic activation levels, because baroreflex regulation and sensitivity are reduced in patients with OSAHS, compared to controls[38]. Current evidence suggests that the intermittent nocturnal hypoxic stimulus of peripheral chemoreceptors increases the sympathetic tone in these patients even during wakefulness and optimal oxygen supply[39,40].

Moreover, autonomic nervous system studies employing heart rate variability demonstrate that the high-frequency component (parasympathetic tone) of heart rate variability of OSAHS patients declines and the low-frequency component (sympathetic tone) increases. This abnormal pattern seems to reflect sympathetic predominance in the autonomic modulation of OSAHS[41].

Hypertension

OSAHS is an independent risk factor for systemic arterial hypertension (SAH)[42-47]. SAH prevalence in OSAHS patients ranges from 40% to 90%, and the opposite, OSAHS prevalence in SAH patients, ranges from 22% to 62%[43]. Recent studies corroborate this high prevalence between both conditions[48] and show that, in four years, subjects with apnea/hypopnea index (AHI) greater than fifteen per hour of sleep have a five-fold risk (45% likelihood) of developing SAH[43]. A study with 44 patients with drug-resistant hypertension showed that 83% had OSAHS[49].OSAHS patients show great blood pressure (BP) variability during the night, and they may not experience the nocturnal dip observed in normal patients, resulting in higher mean night-time BP values, even when daytime BP is normal. This BP behavior may be due to negative intrathoracic pressure with reduced cardiac output and differential activation of baroreceptors, hypoxia, hypercapnia, breathing-related arousal and increased sympathetic activity[50].

Continuous positive airway pressure (CPAP) has proved to be effective in the treatment of patients with OSAHS and SAH[51,52]. In a series of eleven patients with refractory SAH, CPAP reduced nocturnal blood pressure[53]. Furthermore, in twelve patients with severe OSAHS, the use of CPAP decreased plasma norepinephrine and urinary catecholamine metabolites[54].

Thus far, therefore, OSAHS should be considered in the differential diagnosis of refractory systemic arterial hypertension, and the use of CPAP may help in reducing both daytime and night-time blood pressure[55,56].

Cardiac arrhythmias

Some authors have already studied the relationship between OSAHS and cardiac arrhythmias[57,58]; however, there is no consensus in the medical literature concerning results[57,58] and prevalence of tachyarrhythmia and bradyarrhythmia. This may be partly explained by the unknown incidence of OSAHS in the general healthy population and by the high incidence of hypertension and cardiovascular diseases in OSAHS patients. However, it is known that the use of CPAP in OSAHS patients may reduce cardiac arrhythmias, just as artificial cardiac stimulation may attenuate breathing disorders[59,60]. Figure 3 shows an example of sinus pause associated with apneic event in an OSAHS patient.

Atrial fibrillation (AF) deserves underscoring, because it has been studied in the largest number of clinical trials related to sleep-disordered breathing[61-66]. Its prevalence seems to increase in patients with OSAHS and congestive heart failure (CHF) or recent myocardial revascularization[61,62]. As already stated, OSAHS causes intermittent hypoxemia, sympathetic activation, and abrupt changes in blood pressure, which may be related to the development and recurrence of AF. In a prospective study[62] of patients referred for electrical cardioversion of atrial fibrillation/atrial flutter, 82% of the untreated or inadequately treated OSAHS patients experienced recurrent AF, compared to 42% of the treated patients. Moreover, in the untreated group, recurrence was even higher among those who showed greater drop in oxygen saturation during the apneic event. These data suggest that appropriate treatment with CPAP may reduce AF recurrence in OSAHS patients.

Ventricular ectopies were reported in up to 66% of OSAHS patients. However, in a prospective study of 147 patients who underwent simultaneous polysomnography and Holter monitoring, no increase in ventricular arrhythmias was found[67]. In view of discrepant reports in the medical literature, it is difficult to establish a direct relationship between the syndrome and ventricular arrhythmias. Yet, analyzing the relationship between ventricular ectopies and oxyhemoglobin desaturation in patients with OSAHS[68], a marked increase is found in ventricular ectopy frequency when oxygen saturation drops below 60%, and the relationship between apneic events and ventricular arrhythmias seems to exist solely in patients with important desaturation during the night.

Patients with this syndrome experience ventricular arrhythmias mainly during sleep, unlike patients with normal sleep[68], and ventricular tachycardia is more common in OSAHS patients (0-15%) than in the general population (0-4%)[69]. Bradyarrhythmias are strongly associated with OSAHS. Guilleminault *et al*.[70] have found sinus pause (> 2.5 seconds), second-degree atrioventricular block, and sinus bradycardia in 11%, 8%, and 7% of the patients, respectively. Koehler *et al.*[71] analyzed factors involved in heart blocks in patients with OSAHS and concluded that most cases occur during REM sleep and periods with oxygen desaturation of at least 4%.

Despite conflicting reports in the literature, oxygen saturation drop during apneic episodes seems to be an important factor triggering cardiac arrhythmias in patients with sleep apnea-hypopnea syndrome, and its frequency is associated with hypoxia severity.

Coronary artery disease

Despite the growing incidence of OSAHS and the concomitant increase in cardiovascular mortality[9], most studies face important limitations, because many risk factors, such as obesity, masculine gender and age, among others, are the same as those for hypertension and coronary artery disease (CAD). Therefore, it seems difficult to pinpoint the risk for CAD attributed to OSAHS; however, convergent observations suggest that OSAHS is an important factor associated with CAD.

In OSAHS, the increase in peripheral sympathetic nerve activity during sleep to twice the normal values persists during wakefulness[72] and may contribute to acute coronary events in the early morning hours. In

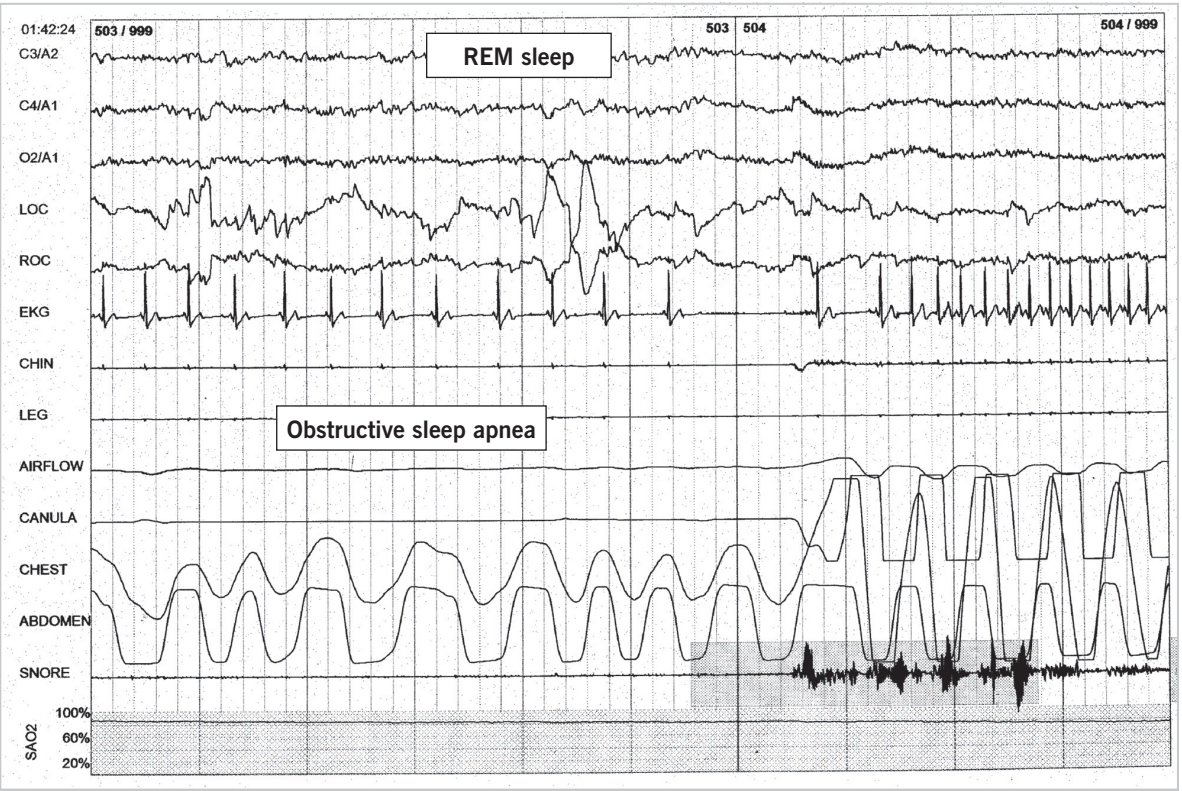

Fig. 3 *– Example of a thirty-second epoch graphic containing an obstructive sleep apnea event with sinus pause followed by increment in heart rate*

addition to autonomic nervous system involvement, both the inflammation and endothelial injury observed in OSAHS are likely to participate in the mechanisms involved in CAD[73].

In a well-conducted study evaluating the impact of OSAHS therapy on long-term cardiovascular outcomes (86.5 ± 39 months) in CAD patients, those appropriately treated experienced a significant reduction in cardiovascular event risk, defined as cardiovascular death, acute coronary syndrome, admission for heart failure, or need of myocardial revascularization[74].

Nocturnal ST-segment changes consistent with myocardial ischemia are common in patients with OSAHS and CAD. Mooe et al[75] evaluated the occurrence of nocturnal myocardial ischemia and its relationship to sleep-related breathing disorders. ST-segment depressions occurred in 31% of the patients studied. Temporal association between electrocardiographic findings and apneic events was found in 19% of the cases, more frequently in men ($p < 0.01$) and in more severely disordered breathing.

Stroke

Among stroke patients, sleep-disordered breathing incidence, the obstructive form predominantly, may exceed 50%[76]. It remains quite unclear, however, whether these events detected after stroke are a consequence of the cerebrovascular event or a preexistent condition. As with coronary artery disease, OSAHS and stroke also share many risk factors, and it is equally difficult to prove a cause-effect relationship.

Dziewas et al[77] analyzed the frequency of sleep-disordered breathing in groups of patients with first and recurrent ischemic stroke. Patients with recurrent stroke showed higher mean apnea-hypopnea index (AHI) when compared to patients with first-ever stroke (26.6/h *vs.* 15.1/h, $p < 0.05$) and most commonly had OSAHS. In the multivariate analysis adjusted for clinical variables and risk factors, sleep apnea was considered an independent risk factor for stroke recurrence, and the authors advocate the use of polysomnography in this group of patients for risk stratification.

OSAHS most probably contributes to recurrent stroke through several mechanisms, such as systemic arterial hypertension, increased platelet aggregation, blood hypercoagulability, and endothelial dysfunction, among others. Moreover, blood flow to the brain declines during apnea, due to reduction in cardiac output, which may predispose risk subjects to stroke, such as those with atheromatous lesions in carotid and vertebral circulations. This may be significantly more important during REM sleep, when brain oxygen demand is higher.

In addition, apnea may impair cognitive function in patients with previous history of stroke, since it causes excessive daytime sleepiness and poor concentration

and memory[78]. Finally, randomized clinical trials examining apnea therapy and neurological outcomes are still lacking.

Congestive heart failure

Several studies also showed an important association between congestive heart failure (CHF) and OSAHS. In the Javaheri et al[79] study, 81 men with CHF underwent polysomnography, and 11% were found to have obstructive sleep apnea syndrome. In the Sleep Heart Health study[80], apneic patients with an AHI > 11 per hour showed a 2.38 risk of developing CHF, regardless of other established risk factors, exceeding those found for other cardiovascular complications associated with OSAHS, such as hypertension, CAD, and stroke.

It is also believed that CHF contributes to the development of OSAHS for two reasons, namely, decreased upper airway muscle tone during the resting phase of the periodic breathing typical of CHF and fluid accumulation in the soft tissues of the cervical region, contributing to the tendency of upper airway collapse.

Echocardiographic studies showed both systolic[81] and diastolic[82] dysfunction with increasing AHI. Possible mechanisms include hypoxia effects (determining ischemia and impaired contractility), myocyte injury (due to higher levels of circulating catecholamines), and intrathoracic pressure swings that accompany apneic episodes (changing relaxation and left ventricular end-systolic and end-diastolic volumes).

Finally, the diagnosis of sleep-disordered breathing in CHF patients may provide valuable prognostic information and a potential therapeutic option for this group of patients[83].

Inflammatory, endothelial, and thrombotic changes in osahs

Decline or absence of physiological mechanisms involved in vascular relaxation was demonstrated in response to endothelium-dependent substances (increased vasoconstrictor, endothelin, and reduced nitric acid and prostacyclin availability)[84,85]. Another evidence of endothelial damage was documented by enhanced expression of adhesion molecules, leading to increased adherence of monocytes to endothelial cells[86]. OSAHS may also trigger recurrent oxidative stress[87], probably owing to greater production of oxygen-reactive species by monocytes and granulocytes. These findings reinforce previous results regarding increased production of superoxide radicals from polymorphonuclear neutrophils in patients with OSAHS[88] and low levels of nitric oxide[89]. Plasma homocystein levels were also reported to be elevated in this syndrome[90], as a result of endothelial dysfunction combined with excessive production of free radicals. Serium haptoglobin and amyloid A protein were also reported to be higher[91,92].

The relationship between inflammatory process and cardiovascular diseases has been repeatedly postulated[93]. OSAHS patients are chronically exposed to recurrent hypoxia and sleep fragmentation, showing increased C-reactive protein and interleukin-6 levels, when compared to controls[94]. It is also likely that C-reactive protein levels in these patients are higher because of associated obesity[95]. All these endothelial, blood clotting, and inflammatory changes may contribute somewhat to higher cardiovascular risk and atherogenesis in OSAHS patients. Finally, CPAP therapy may improve these changes; however, discontinuation of therapy leads to the reappearance of abnormalities[96-103].

References

1. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries and risk factors in 1990 and projected to 2020. USA. Harvard School of Health; 1996.
2. Lolio CA, Laurenti R. Evolução da mortalidade por doença isquêmica do coração no município de São Pauo, 1970 a 1981. Arq Bras Cardiol. 1986; 46: 153.
3. Uemura K, Pisa Z. Recent trends in cardiovascular disease mortality in 27 industrialized countries. Wld Hlth Stat Quart. 1971; 38: 1617-25.
4. Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. Am Heart J. 1990; 120(3): 672-6.
5. Kannel WB. Lessons from curbing the coronary artery disease epidemic for confronting the impending epidemic of heart failure. Med Clin North Am. 2004; 88: 1129-33.
6. Avezum A, Piegas LS, Pereira JC. Fatores de risco associados com infarto agudo do miocárdio na região metropolitana de São Paulo. Uma região desenvolvida em um país em desenvolvimento. Arq Bras Cardiol. 2005; 84: 206-13.
7. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005; 365: 1046-53.
8. Kramer NR, Cook TE, Carlisle CC, Corwin RW, Millman RP. The role of the primary care physician in recognizing obstructive sleep apnea. Arch Intern Med. 1999; 159: 965-8.
9. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-age adults. N Engl Med. 1993; 328: 1230-35.
10. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing: Prevalence. Am J Respir Crit Care Med. 1995; 152: 711-6.
11. Lavie P. Sleep apnea in industrial workers. In Guilleminault C, Lugaresi E, editors. Sleep-wake disorders: natural history, epidemiology and long-term evolution. Philadelphia: Lippincott Raven Press; 1983: 127-35.
12. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. Thorax. 1991; 46: 85-90.
13. Gislason T, Benediktsdottir B, Bjornsson JK, Kjartansson G, Kjeld M, Kristbjarnarson H. Snoring, hypertension, and sleep apnea syndrome:

an epidemiologic survey of middle-aged women. Chest. 1993; 103: 1147-51.

14. Bixler EO, Kales A, Soldatos CR, Vela-Bueno A, Jacoby JA, Scarone S. Sleep apneic activity in a normal population. Res Commun Chem Pathol Pharmacol. 1982; 36: 141-52.

15. Strohl KP, Redline S. Recognition of obstructive sleep apnea. Am J Respir Crit Care Med. 1996; 154: 279-89.

16. Silverberg DS, Oksenberg A. Are sleep-related breathing disorders important contributing factors to the production of essential hypertension? Curr Hypertens Rep. 2001; 3: 209-15.

17. EEG arousals: scoring rules and examples. A preliminary report from Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep. 1992; 15: 173-84.

18. Rechtschaffen A, Kales A. A manual of standardized terminology, technique and scoring system for sleep stages of human sleep, Los Angeles Brain Information Service, Brain Information Institute, Los Angeles, CA; 1968.

19. Sleep-Related Breathing Disorders in Adults: Recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep. 1999; 22: 667-89.

20. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol. 1978; 44(6): 931-8.

21. Wiegand L, Zwillich CW. Obstructive sleep apnea. Dis Mon. 1994; 40(4): 197-252.

22. Strohl KP, Novak RD, Singer W, Cahan C, Boehm KD, Denko CW, Hoffstem VS. Insulin levels, blood pressure and sleep apnea. Sleep. 1994; 17(7): 614-8.

23. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med. 1985; 312(3): 159-63.

24. Findley LJ, Boykin M, Fallon T, Belardinelli L. Plasma adenosine and hypoxemia in patients with sleep apnea. J Appl Physiol. 1988; 64(2): 556-61.

25. Guilleminault C. State of the art. Sleep and control of breathing. Chest. 1978; 73(2): 293, 297-9.

26. Vgontzas AN, Bixler EO, Chrousos GP. Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev. 2005;9(3):211-24.

27. Yun AJ, Lee PY, Bazar KA. Autonomic dysregulation as a basis of cardiovascular, endocrine, and inflammatory disturbances associated with obstructive sleep apnea and other conditions of chronic hypoxia, hypercapnia, and acidosis. Med Hypotheses. 2004; 62(6): 852-6.

28. Opp MR, Kapas L, Toth LA. Cytokine involvement in the regulation of sleep. Proc Soc Exp Biol Med. 1992; 201(1): 16-27.

29. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab. 1997; 82(5): 1313-6.

30. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab. 1998; 83(3): 847-50.

31. Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. J Intern Med. 2003; 254(1): 32-44.

32. Coy TV, Dimsdale JE, Ancoli-Israel S, Clausen J. Sleep apnoea and sympathetic nervous system activity. J Sleep Res. 1996; 5: 42-50.

33. Guilleminault C, Poyares D, Rosa A, Huang YS. Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes. Sleep Med. 2005; 6(5): 451-7.

34. Poyares D, Guilleminault C, Rosa A, Ohayon M, Koester U. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. Clin Neurophysiol. 2002; 113(10): 1598-606.

35. Smith ML, Neidermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea-induced sympathoexcitation. J Auton Nerv Syst. 1996; 56: 184-90.

36. Morgan BJ, Carbtree DC, Palta M, Skatrud J. Combine hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. J Appl Physiol. 1995; 79(1): 205-13.

37. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analyss during sleep. J Hypertension. 1997; 15: 1621-6.

38. Jo JA, Blasi A, Valladares E, Juarez R, Baydur A, Khoo MC. Model-based assessment of autonomic control in obstructive sleep apnea syndrome during sleep. Am J Respir Crit Care Med. 2003; 167(2):128-36.

39. Arabi Y, Morgan BJ, Goodman B, Puleo DS, Xie A, Skatrud JB. Daytime blood pressure elevation after nocturnal hypoxia. J Appl Physiol. 1999; 87(2): 689-98.

40. Xie A, Skatrud JB, Puleo DS, Morgan BJ. Exposure to hypoxia produces long-lasting sympathetic activation in humans. J Appl Physiol. 2001; 91(4): 1555-62.

41. Belozeroff V, Berry RB, Khoo MC. Model-based assessment of autonomic control in obstructive sleep apnea syndrome. Sleep. 2003; 26(1): 65-73.

42. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000; 283(14): 1829-36.

43. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000; 342(19): 1378-84.

44. Hedner J. Regulation of systemic vasculature in obstructive sleep apnea syndrome. Sleep. 2000; 23(Suppl 4): S132-5.

45. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000; 320(7233): 479-82.

46. Sin DD, Fitzgerald F, Parker JD, Newton GE, Logan AG, Floras JS, et al. Relationship of systolic BP to obstructive sleep apnea in patients with heart failure. Chest. 2003; 123(5): 1536-43.

47. Silverberg DS, Oksenberg A, Iaina A. Sleep related breathing disorders are common contributing factors to the production of essential hypertension but are neglected, underdiagnosed, and undertreated. Am J Hypertens. 1997; 10(12 Pt 1): 1319-25.

48. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease – Cross-sectional results of the Sleep Heart Study. Am J Respir Crit Care Med. 2001; 163: 19-25.

49. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertension. 2001; 19(12): 2271-7.

50. Fletcher EC. The relationship between systemic hypertension and obstructive sleep apnea: facts and theory. Am J Med. 1995; 98(2): 118-28.

51. Hla KM, Skatrtud JB, Finn L, Palta M, Young T. The effect of correction of sleep-disordered breathing on BP in untreated hypertension. Chest. 2002; 122(4): 1111-2.

52. Sanner BM, Tepel M, Markmann A, Zidek W. Effect of continuous positive airway pressure theraphy on 24-hour blood pressure in

patientes with obstructive sleep apnea syndrome. Am J Hypertens. 2002; 15(3): 251-7.

53. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, et al. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J. 2003; 21(2): 241-7.

54. Hedner J, Darpo B, Ejnell H, Carlson J, Caidahl K. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea cardiovascular implications. Eur Respir J 1995; 8: 222-9.

55. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995; 96(4): 1897-904.

56. Pepperell JC, Davies RJ, Stradling JR. Systemic hypertension and obstructive sleep apnoea. Sleep Med Rev. 2002; 6(3): 157-73.

57. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Prevalence and significance. Am J Med. 1982; 73: 317-21.

58. Guilleminault C, Connoly SJ, Winkle RA. Cardiac arrhythmias and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983; 52: 490-4.

59. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000; 101: 392-7.

60. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med. 2002; 346: 404-12.

61. Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. Coron Artery Dis. 1996; 7: 475-8.

62. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, et al. Obstructive Sleep Apnea and recurrence of atrial fibrillation. Circulation. 2003; 107: 2589-94

63. Schulz R, Eisele HJ, Seeger W. Nocturnal atrial fibrillation in a patient with obstructive sleep apnoea. Thorax. 2005; 60(2): 174.

64. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004; 110(4): 364-7.

65. Porthan KM, Melin JH, Kupila JT, Venho KK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study. Chest. 2004; 125(3): 879-85.

66. Flemons WW, Remmers JE, Gillis AM. Sleep apnea and cardiac arrhythmias. Is there a relationship? Am Rev Respir Dis. 1993; 148: 618-21.

67. Roche F, Xuong ANT, Court-Fortune I, Costes F, Pichot V, Duverney D, et al. Relationship among severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance. PACE. 2003; 26: 669-77.

68. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest. 1985; 88: 335-440.

69. Cutler MJ, Hamdan AL, Hamdan MH, Ramaswamy K, Smith ML. Sleep apnea: from nose to the heart. J Am Board Farm Pract. 2002; 15: 128-41.

70. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983; 52: 490-4.

71. Koehler U, Fus E, Grimm W, Pankow W, Schafer H, Stammnitz A, et al. Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment. Eur Respr J. 1998; 11: 434-9.

72. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest. 1993; 103: 1763-8.

73. Libby P, Ridker PM, Maresi A. Inflammation and atherosclerosis. Circulation. 2002; 105: 1135-43.

74. Milleron O, Pilliere R, Foucher A, de Roquefeuil F, Aegerter P, Jondeau G, et al. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. Eur Heart J. 2004; 25(9): 728-34.

75. Mooe T, Franklin KA, Wiklund U, Rabben T, Holmstrom K. Sleep-disordered breathing and myocardial ischemia in patients with coronary artery disease. Chest. 2000; 117(6): 1597-602.

76. Bassetti CL. Sleep and stroke. Semin Neurol. 2005; 52(1): 19-32.

77. Dziewas R, Humpert M, Hopmann B, Kloska S, Ludemann P, Ritter M, et al. Increased prevalence of sleep apnea in patients with recurring ischemic stroke compared with first stroke victims. J Neurol. 2005; 252 (11): 1394-8; Epub 2005 Jul 20.

78. Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnoea. Sleep Med Rev. 1999; 3(1): 59-78.

79. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations. Circulation. 1998; 97: 2154-9.

80. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, 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(1): 19-25.

81. Laaban JP, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. Chest. 2002; 122: 1133-8.

82. Fung JW, Li TS, Choy DK, Yip GW, Ko FW, Sanderson JE, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. Chest. 2002; 121: 422-9.

83. Wilcox I, McNamara SG, Wessendorf T, Willson GN, Piper AJ, Sullivan CE. Prognosis and sleep disordered breathing in heart failure. Thorax. 1998; 53(3): S33-6.

84. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstruvtive sleep apnea. Sleep. 2003; 26(1): 15-9.

85. Pepin JI, Levy P. Pathophysiology of cardiovascular risk in sleep apnea syndrom (SAS). Rev Neurol. 2002; 158: 785-97.

86. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med. 2002; 165(7): 934-9.

87. Lavie L. Obstructive sleep apnoea syndrome - an oxidative stress disorder. Sleep Med Rev. 2003; 7(1): 35-51.

88. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous airway pressure therapy. Am J Respir Crit Care Med. 2000; 162: 566-8.

89. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, et al. Circulation nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med. 2000; 162: 2166-71.

90. Lavie L, Perelman A, Lavie P. Plasma homicysteine levels in obstructive sleep apnea patients. Chest. 2001; 120: 900-8.

91. Lavie L, Lotan R, Hochberg I, Herer P, Lavie P, Levy AP. Haptoglobin polymorphism is a risk factor for cardiovascular disease in patients with obstructive sleep apnea syndrome. Sleep. 2003; 26(5): 592-5.

92. Svatikova A, Wolk R, Shamsuzzaman AS, Kara T, Olson EJ, Somers VK. Serum amyloid a in obstructive sleep apnea. Circulation. 2003; 108(12): 1451-4.

93. Ross R. Atherosclerosis – an inflamatory disease. N Engl J Med. 1999; 340: 115-26.

94. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation. 2003; 107(8):1129-34.

95. Guilleminault C, Kirisoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. Sleep. 2004; 15; 27(8): 1507-11.

96. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation. 2000; 21; 102(21): 2607-10.

97. Kraiczi H, Caidahl K, Samuelsson A, Peker Y, Hedner J. Impairment of vascular endothelial function and left ventricular filling: association with the severity of apnea-induced hypoxemia during sleep. Chest. 2001; 119(4): 1085-91

98. Teramoto S, Kume H, Yamamoto H, Ishii T, Miyashita A, Matsuse T, et al. Effects of oxygen administration on the circulating vascular endothelial growth factor (VEGF) levels in patients with obstructive sleep apnea syndrome. Intern Med. 2003; 42(8): 681-5.

99. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease.JAMA. 2003; 290(14): 1906-14.

100. Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. Am J Respir Crit Care Med. 2004; 169(3): 354-60.

101. Dyugovskaya L, Lavie P, Lavie L. Phenotypic and functional characterization of blood gammadelta T cells in sleep apnea. Am J Respir Crit Care Med. 2003; 168(2): 242-9.

102. Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. Am J Respir Crit Care Med. 2002; 165(1): 67-70.

103. Von Kanel R, Le DT, Nelesen RA, Mills PJ, Ancoli-Israel S, Dimsdale JE. The hypercoagulable state in sleep apnea is related to comorbid hypertension. J Hypertens. 2001; 19(8): 1445-51.