Archives of the Balkan Medical Union
vol. 51, no. 2, pp. 205-208
June 2016

REVIEW

SLEEP APNEA SYNDROME AND CARDIOVASCULAR RISK

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Summary

Obstructive sleep apnea (OSA) is a chronic disease that affects mainly the adults. The obstructive sleep apnea syndrome (OSAS) is characterized by episodes of obstructive apneas of hypopneas during sleep, disrupted sleep with respiratory effort-related arousals, with daytime symptoms such as sleepiness, fatigue, poor concentration. Studies have shown that OSA is a risk factor for cardiovascular diseases, such as arterial hypertension, stroke, coronary heart disease, chronic heart failure, arrhythmias. The mechanisms behind this increased association are the activation of the sympathetic nervous system, oxidative stress with endothelial dysfunction and chronic inflammation. Given the complex relationships between OSAS and cardiovascular diseases, patients with OSAS should be screened for cardiovascular diseases and viceversa, patients with diagnosed cardiovascular diseases should be screened for OSAS, preferably by polysomnography.OSAS is an important cause of resistant arterial hypertension, a common comorbidity in sleep apnea. Ischemic heart disease is also common in OSAS patients, and it is associated with higher risk of cardiovascular events. Atrial fibrillation and other tachyarrhythmias occur frequently in patients with OSAS, especially during the night. Treatment of OSAS in patients with heart failure may increase the left ventricle ejection fraction and improve the quality of life, by improving the symptoms of heart failure.
Key words: obstructive sleep apnea, hypertension, heart failure, arrhythmias, coronary artery disease.

Résumé

Le syndrome d'apnée du sommeil et le risque cardiovasculaire

L'apnée obstructive du sommeil (AOS) est une maladie chronique qui affecte principalement les adultes. Le syndrome d'apnée obstructive du sommeil (SAOS) est caractérisé par des épisodes d'apnées obstructives ou de hypopnées pendant le sommeil, qui est perturbé, avec éveils liés à l'effort des voies respiratoires, des symptômes diurnes tels que la somnolence, la fatigue, le manque de concentration. Des études ont montré que l'AOS est un facteur de risque pour les maladies cardiovasculaires, comme l'hypertension artérielle, l'accident vasculaire cérébral, la maladie coronarienne, l'insuffisance cardiaque chronique, les arythmies. Les mécanismes derrière cette association sont l'activation du système nerveux sympathique, le stress oxydatif avec la dysfonction endothéliale et l'inflammation chronique. Compte tenu des relations complexes entre le SAOS et les maladies cardiovasculaires, les patients atteints de SAOS devraient être examinés pour les maladies cardiovasculaires et viceversa, les patients atteints de maladies cardio-vasculaires devraient être examinés pour SAOS, de préférence par polysomnographie. SAOS est une cause importante de l'hypertension artérielle résistante, une comorbidité fréquente chez les patients avec apnée du sommeil. La cardiopathie ischémique est également fréquente chez les patients avec SAOS, et elle est associée à un risque plus élevé d'événements cardiovasculaires. La fibrillation auriculaire et d'autres tachyarythmies se produisent fréquemment chez les patients souffrant de SAOS, surtout pendant la nuit. Le traitement du SAOS chez les patients atteints d'insuffisance cardiaque peut augmenter la fraction d'éjection du ventricule gauche et améliorer la qualité de vie, en améliorant les symptômes de l'insuffisance cardiaque.
Mots-clé: apnée obstructive du sommeil, l'hypertension, l'insuffisance cardiaque, les arythmies, la maladie coronarienne

Introduction

Obstructive sleep apnea (OSA) is a chronic disease that affects mainly the adults, but it may appear also in children. The obstructive sleep apnea syndrome (OSAS) is characterized by episodes of obstructive apneas or of hypopneas during sleep, disrupted sleep with respiratory effort-related arousals, with daytime symptoms such as sleepiness, fatigue, poor concentration. The prevalence of obstructive sleep apnea

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is increasing, mainly due to increasing prevalence of risk factors such as obesity. 9% of adult women and 24% of adult men are affected by the obstructive sleep apnea syndrome (1). Moreover, 4% of women and 9% of men have moderate to severe forms of obstructive sleep apnea (1). Studies have shown that OSA is a risk factor for cardiovascular diseases, such as arterial hypertension, stroke, coronary heart disease, chronic heart failure, arrhythmias (2-5). The mechanisms behind this increased association are the activation of the sympathetic nervous system, oxidative stress with endothelial dysfunction and chronic inflammation (6). The increased activity of the sympathetic nervous system during sleep leads to increases in heart rate and blood pressure. The increased sympathetic nerve activity and catecholamines subsequently lead to acceleration of atherosclerosis, vascular dysfunction, hypoxic vasoconstriction and vascular remodelling, with releasing of pro-inflammatory mediators.

The risk factors for OSAS are obesity, advanced age, male gender, craniofacial or upper respiratory system soft tissue anomalies. Other risk factors are a family history of OSAS, smoking, nasal congestion, menopause, use of benzodiazepines, alcohol consumption, diseases such as Down syndrome, thyroid diseases (hypothyroidism, acromegaly), end-stage renal disease, congestive heart failure, chronic obstructive pulmonary disease, stroke. OSAS is characterized by repetitive episodes of upper respiratory tract collapse during sleep, with complete cessation of reduced airflow, despite the presence of respiratory efforts. These pathophysiologic disturbances lead to changes of gas exchange, with hypoxemia, hypercapnia and fragmented sleep. The abnormal breathing results in hemodynamic, inflammatory and metabolic effects that may contribute to the pathogenesis of the cardiovascular diseases associated with OSAS (7).

Cardiovascular consequences of OSAS

The main cardiovascular consequences of OSAS are arterial hypertension, coronary heart disease, arrhythmias, heart failure and pulmonary hypertension.

The link between OSAS and hypertension is well known. Many studies have demonstrated that sleep apnea is associated with increased risk of arterial hypertension, independently of other factors (8,9). The Sleep Heart Health Study showed a linear relationship between mean systolic and diastolic blood pressure values and OSA severity (8). A Canadian study, population-based, has found that each apneic event per hour increased the odds of hypertension by 1% (9). Some studies have found that OSAS is more related to isolated diastolic or combined systolic/diastolic hypertension (10). The association of OSAS with hypertension is particularly important in patients with resistant hypertension, defined as the lack of control of blood pressure values despite the use of at least three antihypertensives, one of them being a diuretic. One study has found that 71% of patients with resistant hypertension have OSAS, as compared to 38% of patients with controlled systemic hypertension (11). The major pathophysiologic mechanisms linking OSAS and resistant hypertension are hyperaldosteronism, increased sympathetic tone, and obesity.

Coronary heart disease

Coronary heart disease has increased prevalence in patients with OSAS, although the true association between the two diseases is difficult to be demonstrated, due to the common risk factors. Several studies have suggested that the prevalence of coronary heart disease is 3 to 5 times higher in patients with OSAS compared to control populations (12,13). Observational studies revealed that severe OSA is associated with a significantly increased risk of cardiovascular events, both non-fatal and fatal (14,15). OSAS is a risk factor for atherosclerosis, with increased carotid arteries wall thickness, which is a marker of cardiovascular disease and a predictor of morbidity and mortality (13). The effective treatment of OSAS with continuous positive airway pressure (CPAP) has been shown to decrease the risk of cardiovascular events and to prevent the coronary heart disease (16). The association between OSAS and coronary heart disease is stronger in severe forms of OSAS, independently of obesity and other common risk factors. A large prospective study on 1651 men followed for a period of 10 years after polysomonography has demonstrated the cardiovascular morbidity associated with OSAS (14). Patients with severe OSAS (mean apnea-hypopnea index 43 events per hour of sleep) had a higher rate of cardiovascular events (both fatal and non-fatal) than untreated patients with mild to moderate forms (14). The cardiovascular events were myocardial infarction, acute coronary syndrome or stroke. Another studies demonstrated that OSAS may further worsen the pre-existing coronary artery disease (17,18). In one study, polysomnography was performed in 89 consecutive patients with acute coronary syndrome treated by percutaneous coronary intervention (17). OSAS (defined as an apnea-hyponea index $\geq$ 10 per hour of sleep) was diagnosed in 51 patients (57%). During the period of follow-up (227 days), the incidence of major cardiovascular events was higher in patients with OSA than in patients without OSA.

The results of short-term studies and observational data have suggested that the CPAP therapy may have a beneficial effect on the cardiovascular outcomes in patients with OSAS and ischemic heart disease (14,16,19), but the potential benefits of CPAP therapy on reducing cardiovascular events have not yet been confirmed in randomized clinical trials.

Arrhythmias

Arrhythmias are also frequently encountered in patients with OSAS, especially during the night (20-22). The most common ones are ventricular extrasystoles, atrial fibrillation and tachy-brady syndrome (20-22). Patients with OSAS have a 4 times higher risk of atrial fibrillation, 3 times higher risk of nonsustained ventricular tachycardia and 2 times higher risk of ventricular ectopy (21). This association is indepen-

dent of obesity and other confounding factors. One study on 400 patients with moderate to severe OSAS has found a 3% prevalence of atrial fibrillation on 24-hour Holter monitoring, approximately 3 times higher than the prevalence of atrial fibrillation in general population (23). Also, the prevalence of OSAS in patients with atrial fibrillation is increased, with a range of 30-80% (21). This association is independent of other common risk factors, such as obesity, advanced age, arterial hypertension or heart failure. Observational data also suggest that OSAS is a risk factor for recurrent atrial fibrillation after ablation. In six studies, patients with OSAS and radiofrequency ablated atrial fibrillation had a 25% higher risk of recurrent atrial fibrillation (24). There is some data, although limited, about the efficacy of CPAP therapy on reducing the risk of recurrent atrial fibrillation, but this hypothesis needs to be studied further in prospective studies.

The bradycardia-tachycardia arrhythmia may be encountered during episodes of apnea and hypopnea. During apnea, due to vagal stimuli, the patients develop bradycardia. After the respiratory event, the sympathetic activation results in tachycardia. Intermittent hypoxia in OSAS is the main stimulus for arrhythmogenesis, with delayed depolarization which triggers automaticity. Bradyarrhythmias occur in up to 18 percent of patients with severe OSAS (apnea hypopnea index > 30 events per hour) (25).

Tachyarrhythmias and ventricular ectopy (bigeminy, trigeminy, quadrigeminy, nonsustained ventricular tachycardia) have been also associated with OSAS (26). In one observational study, 228 patients with OSAS were compared to 338 control subjects (21). In the group of 228 patients, the prevalence of nocturnal atrial fibrillation, nonsustained ventricular tachycardia and ventricular ectopy were higher than in the control group, even after adjusting for confounding factors. As in the other cardiovascular comorbidities, therapy with CPAP may have a beneficial role in improving the arrhythmias of patients with OSAS. One prospective study on 36 patients diagnosed with OSAS and cardiac arrhythmias demonstrated that in patients with OSAS, adding CPAP to the pharmacological therapy has favorable effects on preventing recurrences, heart rate control in patients with atrial fibrillation and decrease in frequency and/or severity of ventricular extrasystoles (27).

Heart failure

Heart failure is another important comorbidity of patients with OSAS. Several studies have reported a higher prevalence of OSAS in patients with heart failure as compared to general population (28,29). OSAS is more common in men than in women with heart failure (28). Risk factors for OSAS in patients with heart failure are obesity, older age and male gender (28). Patients with ischemic heart failure have increased risk of hypoxia-related events, such as cardiac arrhythmias and worsening myocardial ischemia, as compared to non-ischemic heart failure. The effective treatment of OSAS with CPAP may reduce the nocturnal blood pressure and heart rate, with reduced left ventricle after load and improved clinical symptoms (30). One clinical trial of heart failure patients with severe OSAS has revealed that fixed-pressure CPAP increased the left ventricle ejection fraction by 9% and decreased the systolic blood pressure and heart rate (31). However, another randomized study has found no improvement in left ventricle ejection fraction in heart failure patients with OSAS after CPAP (32). The explanation of these differences may consist in different trial design or patients characteristics.

Sudden cardiac death

Some data suggested that cardiac arrhythmias encountered in OSAS may lead to a higher risk of sudden cardiac death. A study on 107 patients with OSAS that were followed for seven years revealed that the rate sudden cardiac death was increased in those that did not use the CPAP therapy, as compared to those who used it (7% versus 0%) (16). Patients with OSAS have a three times higher risk of sudden cardiac death during the night, as compared to general population or to patients without OSAS (33).

There are also studies that revealed a link between OSAS and an increased risk of venous thromboembolism or pulmonary hypertension (34,35).

Conclusion

In conclusion, OSAS may be considered an important risk factor for cardiovascular diseases, which represent a main cause of morbidity and mortality in these patients. Given the complex relationships between OSAS and cardiovascular diseases, patients with OSAS should be screened for cardiovascular diseases and viceversa, patients with diagnosed cardiovascular diseases should be screened for OSAS, preferably by polysomnography. OSAS is an important cause of resistant arterial hypertension, a common comorbidity in sleep apnea. Ischemic heart disease is also common in OSAS patients, and it is associated with higher risk of cardiovascular events. Atrial fibrillation and other tachyarrhythmias occur frequently in patients with OSAS, especially during the night. Treatment of OSAS in patients with heart failure may increase the left ventricle ejection fraction and improve the quality of life, by improving the symptoms of heart failure.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-1235.
2. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. Circulation 2010;122:352-360.
3. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034-2041.
4. 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;182:269-277.
5. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased

incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002;166:159-165.
6. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing: in collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118:1080-1111.
7. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009; 373:82.
8. 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;283:1829-1836.
9. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000;320:479-482.
10. Haas DC, Foster GL, Nieto FJ, et al. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. Circulation 2005; 111:614.
11. Gonçalves SC, Martinez D, Gus M, et al. Obstructive sleep apnea and resistant hypertension: a case-control study. Chest 2007; 132:1858.
12. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med. 2000;162:81-86.
13. Unruh ML, Enright PL, Polak JF, et al. The relationship of sleep apnea to carotid wall thickness among a large cohort of older adults. Sleep. 2005;20:A112.
14. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365: 1046-1053.
15. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. Am J Respir Crit Care Med. 2001;164:1910-1913.
16. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest. 2005;127:2076-2084.
17. Yumino D, Tsurumi Y, Takagi A, et al. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. Am J Cardiol 2007; 99:26.
18. Milleron O, Pillière R, Foucher A, et al. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. Eur Heart J 2004; 25:728.
19. Buchner NJ, Sanner BM, Borgel J, Rump LC. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. Am J Respir Crit Care Med 2007; 176:1274.
20. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in patients with sleep apnea syndrome. Am J Cardiol. 1983;52:490-494.
21. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2006; 173:910-916.
22. HarbisonJ, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome, effects of nasal continuous positive air way pressure therapy. Chest. 2000;118: 591-595.
23. 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.
24. Ng CY, Liu T, Shehata M, et al. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol 2011; 108:47.
25. Rossi VA, Stradling JR, Kohler M. Effects of obstructive sleep apnea on heart rhythm. Eur Respir J 2013; 41:1439.
26. Raghuram A, Clay R, Kumbam A, et al. A systematic review of the association between obstructive sleep apnea and ventricular arrhythmias. J Clin Sleep Med 2014; 10:1155.
27. Giorgiana Dediu, Stefan-Dumitrache Rujinski, Răzvan Lungu, Sabina Frunză, Camelia Diaconu, Daniela Bartoş, Miron Alexandru Bogdan. Positive pressure therapy in patients with cardiac arrhythmias and obstructive sleep apnea. Pneumologia (The Journal of the Romanian Society of Pneumology) 2015, vol. 64, no 1:18-22.
28. Yumino D, Wang H, Floras JS, et al. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. J Card Fail 2009;15:279 – 85.
29. Ferrier K, Campbell A, Yee B, et al. Sleep-disordered breathing occurs frequently in stable out patients with congestive heart failure. Chest 2005;128:2116 –22.
30. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular after load in patients with heart failure. Circulation 1998; 98:2269 –75.
31. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348: 1233–41.
32. Smith LA, Vennelle M, Gardner RS, et al. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. Eur Heart J 2007;28:1221–7.
33. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352:1206.
34. Lippi G, Mattiuzzi C, Franchini M. Sleep apnea and venous thromboembolism. A systematic review. Thromb Haemost 2015; 114:958.
35. Yamakawa H, Shiomi T, Sasanabe R, et al. Pulmonary hypertension in patients with severe obstructive sleep apnea. Psychiatry Clin Neurosci 2002; 56:311.