Editorial

Obstructive Sleep Apnoea and Hypertension: A Growing Clinical Challenge

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Obstructive sleep apnoea (OSA) has a foremost place among the causes of secondary hypertension[1] and has been implicated in several cases of resistant hypertension.[2] Given the high prevalence of OSA among hypertensives, the significance of sleep history evaluation is often underestimated in the everyday clinical practice of hypertension management. OSA diagnosis in hypertensives not only steers us towards the appropriate therapeutic choices for controlling blood pressure (BP) levels effectively, but in addition identifies a group of subjects at high risk beyond the traditional risk factors.[3,4] Indeed, observational and experimental evidence suggests that OSA may extend the cardio-metabolic risk burden by its independent association with hypertension, coronary artery disease, stroke, arrhythmia, and heart failure, while obesity and abnormalities in glucose metabolism represent an adverse pairing that is frequently clustered with OSA.[5]

Hypertension and sleep apnoea risk factors: a unified adverse substrate?

The obesity epidemic has prompted the recognition of an interaction between OSA and increased BP. Hypertension is a complex disease with a mosaic of potential interactive aetiologies, such as age, gender, nutrition, environment, stress, obesity and genetics. Along the same lines, the prevalence of OSA increases with age and excess of adiposity, while male gender, familial aggregation and genetic predisposition are common in the OSA phenotype. Further risk factors associated with OSA and hypertension are smoking, alcohol consumption, hypothyroidism and polycystic ovary syndrome, while pregnancy may be accompanied by either OSA or hypertension.[6]

Hypertension is present in well over a third of middle-aged subjects, while OSA is found in 25% of middle-aged men and 10% of middle-aged women. Other common characteristics of OSA and hypertension, beyond their potent association with obesity and male gender, is that both conditions are often clinically under-diagnosed and may be accompanied by an increased risk of cardiac and vascular damage.

Although hypertension and OSA are common in the general population, epidemiological studies suggest that their co-morbid prevalence exceeds that which would be anticipated to occur by chance alone. These observations, based on cross-sectional data, have been further strengthened by prospective studies demonstrating that increasing severity of OSA is a risk factor for the development of incident hypertension over 4 years.[7] Other small randomized, controlled trials have demonstrated that effective treatment of OSA in

hypertensives was accompanied by significant decreases not only in night-time but also in daytime BP.

Interaction between sleep and blood pressure: the adverse effects of restless sleep

BP is rather lower during sleep in comparison with wakefulness, while the dipping BP sleep-linked phenomenon (i.e. the reduction of the systolic and diastolic BP component by at least 10%) is mainly guided by the appropriate physiological autonomic neural drive.[8] The increased parasympathetic activity in tandem with the incremental sympathetic withdrawal, together with the depth of non rapid-eye-movement (REM) sleep, results in a reduction of BP levels, heart rate, cardiac output and peripheral vascular resistance. In contrast, during REM sleep a transient increased sympathetic overdrive could be registered; thus, the haemodynamic parameters mentioned above fluctuate at a higher level.[9] REM sleep is rather limited in OSA; nevertheless, because of muscle atonia, apnoeas are more pronounced and consequently the upper airway is more prone to collapse in that sleep mode compared with the non-REM sleep period. Apart from the low sleeping depth, sleep architecture is fragmented because of repeated arousals. Thus, OSA imitates a peculiar condition of "semi-wakefulness" attested by both daytime sleepiness and a poor quality of life. Consequently, the occurrence of a non-dipping BP profile in OSA is at least a not surprising epiphenomenon,[10] while sleep deprivation could be advocated as a further condition in the same setting.

Although the adverse effect of a non-dipping hypertensive profile[11] is well documented by the heightened risk of stroke, progression of renal disease, and incidence of heart failure—conditions observed frequently among OSA patients—data concerning sleep deprivation sequelae are still limited. Nevertheless, the National Health And Nutrition Examination Survey I (NHANES I)[12] showed that, over 10 years of follow-up in a middle-aged population, self-reported sleep duration of less than seven hours was associated with a higher body mass index and an increased likelihood of obesity, as compared to those reporting more than seven hours of sleep. While it is well known that the development of hypertension may be mediated in large part through co-morbid obesity, there are experimental and observational data implicating sleep debt as an independent risk factor for hypertension, a hypothesis that has solid biological plausibility. The cumulative BP load and exposure to an activated sympathetic nervous system is increased as the time awake is prolonged, while the protective effects of reduced BP and sympathetic withdrawal are truncated.[13] Using the same NHANES I data,[14] it was shown that the incident hypertension was increased over a ten-year period in those with self-reported sleep duration less than five hours per night, a finding further confirmed by the Sleep Heart Health Study (SHHS), where the highest prevalence of hypertension was seen in those reporting less than six hours of sleep per night.[15]

Cardiovascular effects of the vulnerable airway

Repetitive upper-airway collapses during sleep and the resulting paroxysmal nocturnal hypoxia and hypercapnia induce a variety of neural, humoral and cellular effects. Furthermore, apnoeas are accompanied by significant increases in the negative intrathoracic pressure and arousals from sleep.

Hypoxia-related sympathetic overdrive may contribute to the chronic OSA-related pathophysiological consequences, since increased muscle sympathetic nerve activity and circulating catecholamine levels are well documented not only during sleep, but even in the waking state. In addition, the aetiological treatment of OSA with continuous positive airway pressure has been found to attenuate sympathetic overdrive.[16] Peripheral chemoreflex sensitivity is selectively increased in OSA subjects compared with normal controls, while reduced baroreflex sensitivity extends beyond the sleeping period.[17] The arousal-independent sympathetic overdrive, as has been shown in experimental animal models, is incriminated as a possible accelerator of hypertensive responses in OSA. Thus, whether arousals might contribute to sustained hypertension in OSA is still an unresolved issue.[18]

Systemic subclinical inflammation is enhanced in OSA subjects, a condition that may result from both the apnoea-related hypoxia and the local repeated mechanical injury of the upper airway. Diverse inflammatory vasoactive mediators, including C-reactive protein, cytokines and adhesion molecules, were found to be increased in OSA subjects in comparison with normal controls, and recently a similar relation was demonstrated in hypertensives with OSA compared to hypertensives without OSA.[19] Since inflammation plays a pivotal role in all stages of atherosclerosis, and the level of subclinical inflammation is correlated in a "dose-related" manner with OSA severity, OSA may contribute at least partially to a degree

of vascular impairment beyond that which could be attributed to hypertension *per se*. Additionally, activated T-cells and monocytes have been reported in cultures from OSA subjects. Thus, inflammation-mediated vascular damage is further facilitated, since the aforementioned cells are potential producers of proinflammatory cytokines and may promptly adhere to the vessel wall. While there is evidence of an increased release of oxygen species in patients with OSA, as a likely consequence of intermittent re-oxygenation associated with recurring apnoea, the interaction with other molecular mechanisms, such as inflammatory pathways, has not been fully evaluated. However, they may be at least partially responsible for the reduced nitric oxide bioavailability observed among OSA patients.[20]

Endothelial dysfunction is often seen in patients with hypertension, and it has been further demonstrated that levels of asymmetric dimethyl-arginine, an intrinsic inhibitor of nitric oxide synthase, are increased in OSA independently of the ambulatory pulsatile load.[19] However, so far the measurement of endothelin levels has yielded inconclusive results that are still under debate. Mounting evidence indicates that the small-vessel dilatory response to vasoactive substances such as acetylcholine is blunted in OSA,[21] but it remains unclear whether conduit vessel endothelial function is also attenuated.

Impaired glucose tolerance and increased insulin resistance have been noted in several reports that evaluated OSA patients independently of body size, while intermittent hypoxia inducing insulin resistance seems to be dependent on the disruption of leptin pathways. Leptin probably exerts pleiotropic functions in OSA, not only by its effects on metabolism and obesity but also by affecting ventilatory function, since the expression of the human leptin gene is regulated by hypoxia.[22,23]

Finally, an adverse haemodynamic long-term consequence of OSA may be its effect on left ventricular transmural pressure, given that the heart in these patients is subjected to repeated acute increases in such pressure several hundred times each night, over many years. These increases in the negative intrathoracic pressure induced by obstructive apnoeas have the potential acutely to trigger myocardial ischaemia or arrhythmias, and over time may impair tonic and reflex vagal heart rate modulation, stimulating left ventricle hypertrophy, ventricular remodelling and impairment of the elastic properties of the aorta.[24]

Subclinical cardiovascular phenotype in hypertensives with OSA

From a clinical point of view, the combination of OSA and hypertension underlines the accelerated derangement of cardiovascular properties, given that these two entities exert a synergistic damaging effect over time, and accordingly hypertensives suffering from OSA might be at higher cardiovascular risk. Indeed, it was shown recently that OSA has an incremental adverse effect on vascular properties by means of increased aortic stiffness, as assessed by aortic to femoral pulse wave velocity.[25] In a purely hypertensive population, the presence of OSA predicted increased levels of albumin-to-creatinine ratio within the normal range, independently of ambulatory pulsatile load.[26] The increased aortic stiffness and the greater intima-media thickness observed in OSA, in light of the established correlation between microalbuminuric phenotype and widespread atherosclerosis, suggest that albuminuria-related atherosclerosis may be a result of both OSA-driven and hypertension-induced arterial functional and structural adaptations. Furthermore, as discussed previously, progressive cardiac adaptations, such as systolic and diastolic dysfunction, are likely to occur in the natural history of both OSA and hypertension, predisposing to the development of heart failure, which in turn may aggravate OSA severity. In summary, in the setting of OSA and hypertension a vicious circle is established that has adverse effects on cardiovascular properties and sleep architecture. Thus, an early and possibly aggressive multifaceted approach aiming to control both OSA and hypertension should be instituted.

Conclusions

To date there is growing evidence to suggest that OSA is an independent predictor for the development of hypertension and that it is associated with an adverse cardiovascular outcome. Furthermore, OSA and hypertension share a common pattern of risk factors, with obesity having a pivotal role in this setting. The pathophysiological mechanisms activated during obstructive apnoeas promote a variety of detrimental effects on both the vasculature and the heart, yielding early atherosclerosis and cardiac remodelling processes, respectively, beyond the effects that could be attributed to hypertension alone. Consequently, the coexistence of OSA and hypertension resembles a “deadly duo”. Early diagnosis and aetiological treatment of

OSA in hypertensives, in combination with the identification and elimination of underlying risk factors, may be beneficial for both BP control and the improvement of cardiovascular outcome.

References

1. Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens. 2007; 25: 1751-1762.
2. Calhoun DA, Jones D, Textor S, et al; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008; 117: e510-526.
3. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J. 2006; 28: 596-602.
4. 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.
5. Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol. 2005; 99: 1998-2007.
6. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008; 5: 136-143.
7. 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: 1378-1384.
8. Staessen J, Bulpitt CJ, O'Brien E, et al. The diurnal blood pressure profile. A population study. Am J Hypertens. 1992; 5: 386-392.
9. Somers VK, Dyken ME, Mark AL, et al. Sympathetic nerve activity during sleep in normal subjects. N Engl J Med. 1993; 328: 303-307.
10. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnea in drug resistant hypertension. J Hypertens. 2001; 19: 2271-2277.
11. Konstantopoulou AS, Papargyriou IK, Antoniadou ES, Konstantopoulou PS, Papadogiannis DE. Masked hypertension: a new entity under investigation. Hellenic J Cardiol. 2006; 47: 232-235.
12. Gangwisch JE, Malaspina D, Boden-Albala B, et al. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep. 2005; 28: 1289-1296.
13. Egan BM. Sleep and hypertension: burning the candle at both ends really is hazardous to your health. Hypertension. 2006; 47: 816-817.
14. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short-sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension. 2006; 29: 833-839.
15. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: The Sleep Heart Health Study. Sleep. 2006; 29: 1009-1014.
16. Chrysostomakis SI, Simantirakis EN, Schiza SE, et al. Continuous positive airway pressure therapy lowers vagal tone in patients with obstructive sleep apnoea-hypopnoea syndrome. Hellenic J Cardiol. 2006; 47: 13-20.
17. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. Circulation. 1999; 99: 1183-1189.
18. Norman D, Loredo JS, Nelesen RA, et al. Effects of continuous positive airway pressure versus supplemental oxygen on 24-h ambulatory blood pressure. Hypertension. 2006; 47: 840-845.
19. Thomopoulos C, Tsioufis C, Dimitriadis K, et al. Obstructive sleep apnoea syndrome is associated with enhanced sub-clinical inflammation and asymmetric dimethyl-arginine levels in hypertensives. J Hum Hypertens 2008; doi:10.1038/jhh.2008.101.
20. Tsioufis C, Dimitriadis K, Stefanadis C, Kallikazaros I. The emerging role of subclinical inflammation in hypertension-associated early renal dysfunction: focus on microalbuminuria. Hellenic J Cardiol. 2006; 47: 361-365.
21. Kato M, Roberts-Thompson P, Phillips B. Impairment of endothelium dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation. 2000; 102: 2607-2610.
22. Strohl KP, Novak RD, Singer W, et al. Insulin levels, blood pressure and sleep apnea. Sleep. 1994; 17: 614-618.
23. Ambrosini G, Nath AK, Sierra-Honigmann MR, Flores-Riveros J. Transcriptional activation of the human leptin gene in response to hypoxia. J Biol Chem. 2002; 277: 34601-34609.
24. Floras JS, Bradley TD. Treating obstructive sleep apnea: is there more to the story than 2 millimeters of mercury? Hypertension. 2007; 50: 289-291.
25. Tsioufis C, Thomopoulos K, Dimitriadis K, et al. The incremental effect of obstructive sleep apnoea syndrome on arterial stiffness in newly diagnosed essential hypertensive subjects. J Hypertens. 2007; 25: 141-144.
26. Tsioufis C, Thomopoulos K, Dimitriadis K, et al. Association of obstructive sleep apnea with urinary albumin excretion in essential hypertension: a cross-sectional study. Am J Kidney Dis. 2008; 52: 285-293.