

Sleep apnea as a risk factor for hypertension

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Purpose of review

High blood pressure and obstructive sleep apnea are closely related, and the latter is considered to induce hypertension. The primary underlying mechanism is sympathetic activation triggered by apneic episodes. This type of hypertension is difficult to treat. The purpose of this review is (1) to evaluate the epidemiological data in view of the current focus on preclinical sleep apnea and prehypertension, (2) to examine additional factors that might contribute to high blood pressure, and (3) to indicate the best therapeutic strategy for treatment of hypertension in these patients.

Recent findings

Cardiovascular effects of sleep apnea can be detected early in the course of the disease, and young subjects are particularly susceptible to its deleterious effect. Blood pressure profiles in these patients show higher diastolic blood pressure and no nocturnal dipping. The renin-angiotensin axis in conjunction with other vasoactive hormones add to the sympathetic activation in elevating blood pressure in sleep apnea. Pro-inflammatory cytokines further contribute to the atherosclerotic consequences that primarily affect the heart and brain, and spare the kidneys. Mounting evidence indicates that treatment of sleep apnea using positive airway pressure, palato-nasal surgery and weight reduction correct the associated hypertension. Conversely, antihypertensive therapy is less effective.

Summary

Even the early stages of sleep apnea are associated with high blood pressure and cardiovascular consequences. Despite our knowledge of the role of the sympathetic activation and vasoactive hormones, no specific antihypertensive therapy is superior, and the optimal way of controlling hypertension is to treat sleep apnea and associated obesity.

Keywords

antihypertensive medication, continuous positive airway pressure, hypertension mechanism, obstructive sleep apnea epidemiology, weight reduction

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Abbreviations

CPAP continuous positive airway pressure
OSA obstructive sleep apnea

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Introduction

Obstructive sleep apnea (OSA) syndrome and hypertension are conditions that coexist in many patients. Large epidemiological studies estimated the prevalence of hypertension as 25% and the prevalence of OSA as 2–4% [1]. Over the last few years, attention has focused on mild and preclinical conditions which mainly progress to overt clinical conditions. The Joint National Committee 7 Report [2] defined prehypertension as blood pressure levels as low as 120–139/80–89. Similarly, studies have focused on the clinical significance of only snoring and upper airway resistance syndrome that does not achieve the diagnostic criteria for OSA [3]. Subjects with snoring only already showed a higher prevalence of hypertension and other cardiovascular complications [4]. These new definitions and classifications of OSA and hypertension call for a review of the data regarding the association between early OSA and hypertension, as well as the prevalence of OSA among subjects with prehypertension. It is important to follow the progression of OSA to determine whether intervention could prevent the development of OSA-induced hypertension. If prevention is viable, this would justify the rationale behind the novel concept of preclinical OSA and prehypertension, as it promotes evaluation of these subjects and identification of causes that, with intervention, could alter the progression and development of hypertension.

An interesting resemblance exists between the prevalence of OSA and the prevalence of hypertension, with respect to gender and age. Hypertension occurs more frequently among males than in premenopausal females, but this gap diminishes at postmenopausal age. Similarly, the predominance of OSA in males has been indicated frequently, with male/female ratios of 2:1 or 3:1 [1,5,6]. Nevertheless, some studies demonstrated that the association between gender and susceptibility to OSA could be moderated by age. Thus, according to Resta *et al.* [7], the prevalence of OSA in obese, postmenopausal women (aged 55 and older) and men of the same age is similar, but higher compared with that for premenopausal women [5]. Young *et al.* [8] further supported the view that menopausal transition is an important factor associated with increased likelihood of OSA, in which

the odds ratio for OSA in perimenopausal women was 1.2, and 2.6 in postmenopausal women. In another study [5], the prevalence of OSA in postmenopausal women on hormone replacement therapy was found to be fairly low (0.5%), but higher in postmenopausal women not receiving hormone replacement therapy (2.7%). These combined findings indicated that the association between OSA prevalence and gender is not as straightforward as previously considered.

The association between obstructive sleep apnea and hypertension

The association between OSA and hypertension is well established. Even early OSA of short duration is associated with high blood pressure. In a relatively large population study it was found that snoring only is independently associated with hypertension; this relationship was strongest in young subjects [4]. Sjöström *et al.* [9] also demonstrated that the influence of OSA on hypertension is more pronounced in younger and middle-aged men than in those over 60 years of age. In their case-controlled study, an overnight sleep study was performed in a population-based, age-stratified sample of 102 hypertensive men, aged 43–82 years, and 102 non-hypertensive controls. Hypertensive subjects had a significantly higher prevalence of OSA than non-hypertensive subjects. When the subjects were divided into two groups according to age (less than 60 and at least 60 years), the association between OSA and hypertension was most prevalent in younger men [adjusted odds ratio, 4.3 (95% confidence interval), 1.0–19.3 versus 2.1 (95% confidence interval, 0.7–6.5)]. Our group evaluated young adults who were screened for, and eventually diagnosed with, OSA. These subjects had higher diastolic blood pressure and no metabolic differences (in lipid profiles and fasting glucose levels) relative to controls [10^{*}]. Until recently, despite the well-established association between OSA and hypertension, it was unclear whether there was a causal relationship between the two conditions. Of late, longitudinal studies have demonstrated the causal relationship between the two phenomena. In a key study, Peppard *et al.* [11] found an association between severity of sleep-disordered breathing at baseline and the presence of hypertension 4 years later, independent of known confounding factors.

Mechanisms of obstructive sleep apnea-induced hypertension

Despite extensive research, the underlying mechanisms of OSA-induced hypertension are not entirely understood. A large body of evidence indicates that sympathetic activation plays a central role in OSA-induced hypertension. Meticulous studies using animal models and clinical observations established the hypothesis that apnea activates hypoxic and hypercapnic

reflexes, via chemoreceptors, which, in turn, generate a profound elevation in sympathetic nerve activity and cyclical changes in parasympathetic nerve activity. These autonomic effects contribute to the associated cardiovascular consequences. A population-based study in males with hypertension showed that OSA was independently associated with increased urinary concentrations of extraneuronal metabolites of catecholamines, suggesting increased sympatho-adrenal activity [12]. The autonomic function could be an important determinant of the development of hypertension in OSA. A recent model-based assessment was used to detect abnormal autonomic function in patients with OSA [13]. In the future, this model may be used to further elucidate the role of the autonomic nervous system in the pathogenesis of OSA-induced hypertension.

Volume overload may also be involved in the pathogenesis of OSA-induced hypertension. This hypothesis was not supported initially by laboratory findings of normal plasma renin activity and aldosterone and elevated atrial natriuretic peptide. Recently, Møller *et al.* [14^{••}] measured 24 h blood pressure and plasma levels of vasoactive hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin, and endothelin-1) in 24 patients with OSA and in 18 controls. As expected, the patients with OSA had higher blood pressure levels without nocturnal dipping and had higher blood levels of angiotensin II and aldosterone. Moreover, a positive correlation was found between angiotensin II levels and daytime blood pressure ($r = \sim 0.5$) [14^{••}].

Insulin resistance may also contribute to the pathogenesis of hypertension in patients with OSA. The typical patient with this condition is overweight, with insulin resistance that may induce hypertension. In a study of 185 subjects with documented OSA, Ip *et al.* [15] showed that OSA is an independent determinant of insulin resistance in obese and non-obese subjects. Furthermore, analysis of the relationship between insulin resistance and hypertension revealed that, in their cohort, insulin resistance was a significant factor in the hypertension [15].

Vasculopathy associated with obstructive sleep apnea-induced hypertension

Hypertension in OSA is associated with accelerated atherosclerosis. Inflammatory cytokines and adhesion molecules play a role in the pathogenesis of atherosclerosis. Several studies have provided evidence that these processes are also important in OSA-induced hypertension. C-reactive protein, an inflammatory protein, is an important marker of cardiovascular morbidity. Shamsuzzaman *et al.* [16] found higher plasma C-reactive

protein levels in 22 patients with newly diagnosed OSA than in that of the controls. Furthermore, C-reactive protein levels were independently associated with severity of OSA [16]. Likewise, in a prospective study, subjects with angiographically proven coronary artery disease and OSA had higher intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin levels relative to subjects in a control group [17]. Ohga *et al.* [18] found that circulating levels of intercellular adhesion molecule-1, interleukin-8 and monocyte chemoattractant protein-1 in patients with untreated OSA were significantly higher than those in controls, but decreased with continuous positive airway pressure (CPAP) treatment [18]. In their study of OSA, Dyugovskaya *et al.* [19] found an abnormality in the expression of CD 15 and CD 11c that led to increased intracellular production of reactive oxygen species, all connected with increased vascular injury in OSA.

All of the aforementioned mechanisms accelerate vasculopathy associated with OSA-induced hypertension. Indeed, increased arterial stiffness has been found recently in OSA by beat-to-beat tonometry during apneic episodes recorded by nocturnal polysomnography [20].

Characteristics of obstructive sleep apnea-induced hypertension

Blood pressure and hemodynamic profiles of OSA-induced hypertension are distinctive. A clinically important marker of OSA-induced hypertension is the lack of diurnal variation of blood pressure. In patients with OSA, blood pressure does not 'dip' at night, regardless of whether or not they have hypertension. This feature of diurnal blood pressure variation is a marker for future development of hypertension [21]. Lack of nocturnal blood pressure dipping was confirmed by Loredó *et al.* [22], who showed a high prevalence of non-dipping (84%) in a population of untreated patients with mild-to-severe OSA. The pattern of blood pressure variation during the day was unaffected by sleep quality [22]. Another feature of OSA-induced hypertension is the high diastolic component [23]. We have recently shown that diastolic blood pressure is already elevated early in the course of OSA [10*].

End-organ damage of obstructive sleep apnea-induced hypertension

The heart, brain and kidneys are the organs typically damaged by long-standing hypertension. However, OSA-induced hypertension has a predilection for the heart and brain, and spares the kidneys. Two relatively recent studies showed no clear evidence that OSA leads to clinically significant proteinuria. One case-control study showed that the prevalence and severity of proteinuria were similar in OSA patients and controls

[24]. Casserly *et al.* [25] studied 148 patients with OSA and found that clinically significant proteinuria was rare in sleep apnea. These results led the authors to suggest that a finding of nephrotic range proteinuria in subjects with OSA-induced hypertension deserves a thorough renal evaluation and should not be attributed to sleep apnea [25]. Unlike the kidneys, the heart and brain are severely affected in OSA-induced hypertension. In a cross-sectional analysis of sleep-disordered breathing and self-reported cardiovascular disease, Shahar *et al.* [26] studied 6424 individuals who underwent ambulatory polysomnography: 16% of the subjects reported at least one manifestation of cardiovascular disease (myocardial infarction, angina, coronary revascularization procedure, heart failure, or stroke). Sleep-disordered breathing was more significantly associated with self-reported heart failure and stroke than with self-reported coronary heart disease. Blankfield *et al.* [27] reported that congestive heart failure was more prevalent among patients with OSA. A prospective study with echocardiographic follow-up showed diastolic dysfunction in OSA-induced hypertension even before the patients developed heart failure [23].

Patients with untreated OSA also experienced a higher recurrence rate of atrial fibrillation after cardioversion than patients without a polysomnographic diagnosis of sleep apnea. Appropriate treatment with CPAP in these patients with OSA is associated with a lower recurrence rate of atrial fibrillation [28]. Cardiovascular disease occurs more frequently in severe OSA. It is noteworthy that OSA is fivefold more frequent in patients with a history of cerebrovascular accident [29].

Genetics of obstructive sleep apnea-induced hypertension

In view of the distinctive clinical profile of OSA, there are reasons to believe that OSA *per se* has a specific genetic background. In addition, it is possible that obesity, a major feature of OSA, may be partly based on pleiotropic effects. This may occur if the same gene, or set of genes, influences ponderosity and ventilatory control and/or craniofacial morphology. The co-occurrence of OSA, central obesity, hypertension and type 2 diabetes suggests that OSA may be part of the 'metabolic' syndrome, which may be largely influenced by genes that influence insulin resistance, hypertension and body-fat distribution [30]. Nevertheless, evidence of the genetic basis of OSA-induced hypertension is still in its infancy. Population studies [31] found that frequent snoring was more common among black and Hispanic women and Hispanic men than among their white, non-Hispanic counterparts, even after adjusting for body mass index and other factors. This study implied that a genetic background may determine the likelihood of developing OSA. A specific genotype was

studied in OSA-induced hypertension: a case-control analysis was performed to investigate the role of the angiotensin-converting enzyme gene insertion (I)/deletion (D) polymorphism in hypertensive patients with OSA [32]. Zhang *et al.* [33] found that the frequency of allele *I* and *II* genotypes was significantly higher in OSA, and that the higher frequency of angiotensin-converting enzyme gene *I* allele and *II* genotype were closely associated with hypertensive patients with OSA. Another association between genotyping and OSA found only that *D/II* allele of angiotensin-converting enzyme and black males may be at increased risk of severe OSA [33].

Management and treatment

Reducing the blood pressure by treating OSA is further proof of the causal relationship between the two phenomena. In a prospective study of 40 patients with OSA, Fisher *et al.* [34] found that, in untreated patients, OSA severity did not necessarily increase over time, but the subjects did develop associated hypertension or ischemic heart disease. Therefore, it is important to treat patients with OSA, as this not only improves the OSA-related symptoms, but could prevent and treat associated cardiovascular morbidity and mortality. Indeed, over the last few years, extensive data have accumulated regarding this issue. The main therapeutic strategies include CPAP, naso-palate surgery and weight control. All these options also improve blood pressure control. The literature, almost in its entirety, concurs that these interventions lower blood pressure.

A short period (1 week) of CPAP treatment was somewhat disappointing, as a similar reduction in blood pressure was observed in both CPAP-treated and placebo-treated patients [35]. Several studies that administered CPAP for longer periods showed clear and durable benefits [36–39]. It appears that CPAP lowers blood pressure only in hypertensive patients, whereas in normotensive patients the blood pressure changes are marginal and clinically negligible [40]. The effect of CPAP extends beyond blood pressure reduction and improves the hormonal profile in these patients, i.e. plasma renin and angiotensin II [14••]. The beneficial effect of surgery also has been clearly shown. Shibata *et al.* [41] demonstrated a decrease in blood pressure of at least 40 mmHg after surgery in 19 of 31 patients with OSA. The reduction in blood pressure was observed mainly in those who showed improvement in OSA symptoms [41].

Weight loss improves obstructive sleep apnea-induced hypertension

Symptoms of OSA improve markedly with weight loss. Therefore, continual weight loss should be a primary

aim in the management of severely obese patients with OSA. Efforts to reduce weight should include the consideration of weight-reduction surgery if a low-calorie diet and pharmacotherapy have failed. Low-risk laparoscopic obesity surgery should be considered for selected patients with obesity and OSA [42]. Gastric bypass surgery should be offered early to patients with morbid obesity and OSA to prevent the development of diabetes and hypertension, and their complications [43].

Drug treatment for obstructive sleep apnea-induced hypertension

OSA is one of the common, unrecognized, drug-resistant forms of hypertension [44]. Lowering the blood pressure is a great challenge in patients with OSA, as they do not respond as well to antihypertensive medications. Treating the OSA may improve blood pressure control. Therefore, OSA should be considered in patients with refractory hypertension.

As a general rule, patients with obesity and hypertension are salt-sensitive and have increased plasma volume. Therefore, a non-pharmacological approach including a low-calorie diet and sodium restriction should be the initial treatment for every obese hypertensive patient with OSA. If a non-pharmacological approach has failed to achieve the desired blood pressure, antihypertensive medications should be initiated. Despite the close link between sympathetic activation and OSA-induced hypertension, studies have failed to show a consistent benefit from beta-blockers relative to other treatments in these patients. Kraiczi *et al.* [45] compared treatment of OSA-induced hypertension with the following compounds: atenolol, amlodipine, enalapril, losartan or hydrochlorothiazide. They found that atenolol lowered only office diastolic, but not office systolic, blood pressure. Atenolol reduced mean night-time ambulatory diastolic and systolic blood pressure more effectively than did amlodipine, enalapril, or losartan, but not hydrochlorothiazide. Severity of sleep-disordered breathing and well-being during the day were not significantly influenced by any of the study compounds [45]. It is possible that when patients with OSA suffer from sustained hypertension, structural changes already exist in the vascular tree, and so the therapeutic approach should be based on standard treatment similar to that for essential hypertension.

Conclusion

In summary, OSA is a reversible and treatable cause of hypertension. Physicians should be aware that OSA, in the early stages and of short duration, signifies cardiovascular consequences. Similarly, when subjects are diagnosed with prehypertension, efforts should be made to identify treatable causes to prevent progression to

hypertension; OSA is one of these causes. The fundamental mechanisms of OSA-induced hypertension are now better understood, and are more complex than mere sympathetic activation. In addition, pro-inflammatory cytokines further contribute to the atherosclerotic consequences which primarily affect the heart and brain, and spare the kidneys. Despite this knowledge, any type of antihypertensive therapy is less effective, and the foremost therapeutic strategy is to treat OSA and associated obesity.

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