Contribuição Internacional

Sleep-disordered breathing as a risk factor for hypertension and cardiovascular morbidity

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Abstract

Obstructive sleep apnea (OSA) has been linked to hypertension and cardiovascular morbidity in several epidemiological and clinical studies. A recent prospective study has shown a dose-response association between sleep-disordered breathing at baseline and the presence of *de novo* hypertension 4 years later that was independent of confounding factors. These findings strongly indicate that OSA may play a causal role in development of hypertension. The mechanisms underlying the link between OSA and cardiovascular disease are not completely established. However, there is increasing evidence that autonomic mechanisms are implicated. A number of studies have shown consistently that patients with obstructive sleep apnea have high levels of sympathetic nerve traffic. Remarkably, the high sympathetic drive is present even during daytime wakefulness when subjects are breathing normally and no evidence of hypoxia or chemoreflex activation is apparent. The vast majority of OSA patients remain undiagnosed. Thus, acting through sympathetic neural mechanisms, OSA may contribute to or augment elevated levels of blood pressure in a large proportion of the hypertensive patient population. It is important to consider OSA in the differential diagnosis of hypertensive patients who are obese. Obstructive sleep apnea should be especially considered in those hypertensive patients who respond poorly to combination therapy with antihypertensive medications.

Keywords: Obstructive sleep apnea; Hypertension; Cardiovascular morbidity.

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Introduction

There is growing recognition of the widespread incidence and health consequences of obstructive sleep apnea (OSA)[1-5]. OSA appears of particular importance in the obese subjects. Up to 40% of morbidly obese subjects have significant OSA and the vast majority of these patients remains undiagnosed[2,3]. For many years, obstructive sleep apnea was

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linked primarily to impaired cognitive function and daytime somnolence[6]. However, there is increasing evidence that obstructive sleep apnea may also be linked to hypertension, stroke and myocardial infarction[7-12]. Chronic sympathetic activation appears to be a key mechanism underlying the relationship between OSA, hypertension and cardiovascular morbidity. This review examines the evidence linking sleep apnea with hypertension and the role of excessive sympathetic drive and abnormalities in reflex circulatory control as mechanisms of elevated blood pressure in sleep apnea.

Evidence linking OSA to hypertension and cardiovascular disease

Obstructive sleep apnea (OSA) has been linked to cardiovascular morbidity and mortality in several epidemiological and clinical studies[7-12].

Animal models of sleep apnea have provided strong evidence for a causal relationship with hypertension[13]. While several studies in humans have demonstrated that patients with sleep apnea have an increased blood pressure and a higher incidence of hypertension[14-16], the causal nature of this relationship has not been definitively established. Studies of sleep apnea have been limited frequently by the presence of co-existing disease, medication use, and the absence of control subjects matched for obesity and age. Thus it is often unclear whether cardiovascular abnormalities evident in these patients are in fact secondary to medications, hypertension, obesity, or sleep apnea *per se*. While a number of confounding factors may influence our interpretation of the data linking obstructive sleep apnea to hypertension and other cardiovascular diseases, the weight of evidence provides increasing support for a causal relationship between obstructive sleep apnea and hypertension.

The most compelling evidence linking OSA and hypertension was provided by data from the Wisconsin Sleep Cohort Study[17,18]. It has been shown that there is a gradual increase in both ambulatory daytime and sleeping blood pressures depending on the apnea-hypopnea index. The apnea-hypopnea index is an assessment of the severity of obstructive sleep apnea. It is traditionally considered that an apnea-hypopnea index of less than 5 events per hour is normal. However, data from Young et al.[17] indicate that in a gradation of the apnea-hypopnea index from 0 to greater than 15, there is a stepwise increase in blood pressure as the severity of obstructive sleep apnea worsens. These findings suggest two important concepts. First, that severity of obstructive sleep apnea is linked to blood pressure level even within the normotensive range of blood pressures. Second, that even sleep apnea which is considered to be mild, may also contribute significantly to overall blood pressure levels. Follow-up studies have recently a dose-response association between sleep-disordered breathing at baseline and the presence of *de novo* hypertension 4 years later[18]. The odds ratios for the presence of hypertension at the four-year follow-up study according to the apnea-hypopnea index at base line were estimated after adjustment for base-line hypertension status, body-mass index, neck and waist circumference, age, sex, and weekly use of alcohol and cigarettes. Relative to the reference category of an apnea-hypopnea index of 0 events per hour at base line, the odds ratios for the presence of hypertension at follow-up were 1.42 (95 percent confidence interval, 1.13 to 1.78) with an apnea-hypopnea index of 0.1 to 4.9 events per hour at base line as compared with none, 2.03 (95 percent confidence interval, 1.29 to 3.17) with an apnea-hypopnea index of 5.0 to 14.9 events per hour, and 2.89 (95 percent confidence interval, 1.46 to 5.64) with an apnea-hypopnea index of 15.0 or more events per hour[18]. Thus, the findings of this prospective study strongly suggest that sleep-disordered breathing is a risk factor for hypertension in the general population.

Sympathetic activity in OSA patients during sleep

Responses to sleep in normal individuals should to be taken into account when evaluating the responses to sleep in OSA. Normal sleep is associated with distinct alterations in blood pressure and heart rate[19]. During non-REM sleep there is a reduction in heart rate, blood pressure, and sympathetic nerve traffic. During Stage IV sleep, heart rate, blood pressure and sympathetic activity are lowest. During REM sleep there is a marked increase in sympathetic activity (about two-fold the levels seen during wakefulness). Thus, the changes in autonomic circulatory control are dependent upon sleep stage[19]. By contrast, the sympathetic and hemodynamic profile during sleep in patients with OSA is dictated primarily by the duration and severity of apnea rather than by sleep stage itself.

Patients with obstructive sleep apnea undergo repetitive obstructions to normal breathing during sleep. As a consequence of obstructed breathing, these patients undergo recurrent and often prolonged (up to one minute) periods of cessation of air flow, with consequent decreases in arterial oxygen content and increased arterial

carbon dioxide levels. Blood pressure increases gradually during apnea because of the vasoconstrictor effect of the sympathetic response to hypoxia and hypercapnia[20]. On resumption of breathing, there is a consequent increase in venous return, and cardiac output increases. This increased cardiac output enters a vasoconstricted peripheral vasculature which results in abrupt and sometimes marked increases in arterial pressure[20]. In a subject who is normotensive during wakefulness, the blood pressure surge at the end of the apneic event can reach levels as high as 250/110 mmHg.

The stress imposed on the cardiovascular system by simultaneous hypoxia, hypercapnia, sympathetic activation, circulating catecholamines and surges in blood pressure may have deleterious effects on the cardiovascular system. This is especially true in patients who have underlying heart failure. It has been shown that treatment of patients with heart failure who have obstructive sleep apnea, with continuous positive airway pressure, results in increases in ejection fraction[21]. In some patients with unexplained episodic pulmonary edema, the marked increases in afterload as a consequence of obstructive sleep apnea may be implicated[22].

Sympathetic activity in OSA patients during wakefulness

The increases in sympathetic activity during sleep may be explained by repetitive apneas. Remarkably, the high sympathetic drive is present even during daytime wakefulness when subjects are breathing normally and both arterial oxygen saturation and carbon dioxide levels are also normal (Figure 1). This is true whether these patients are newly diagnosed, never treated sleep apneic patients on no medications, or whether they are on antihypertensive therapy[23-25].

Cardiovascular variability in OSA

In addition to high levels of sympathetic activity, OSA patients have clear-cut abnormalities in cardiovascular variability during wakefulness. Blood pressure variability is markedly increased (Figure 2) and RR variability is decreased in patients with OSA[26]. This alteration occurs even in the absence of hypertension, heart failure or other disease states. The degree of derangement in cardiovascular variability is linked to the severity of obstructive sleep apnea[26].

Mechanisms underlying the derangement in neural control in OSA

Possible mechanisms underlying the derangement in neural control in sleep apnea include abnormalities in chemoreflex function. The arterial chemoreceptors may exert important influences on neural circulatory control even during normoxia. Elimination of the influences of arterial chemoreceptors using 100% oxygen in a double-blind study showed that patients with OSA, suppression of the chemoreflexes slowed heart rate and decreased MSNA[27]. Furthermore, we have shown that autonomic, hemodynamic, and ventilatory responses to peripheral chemoreceptor activation by hypoxia are selectively potentiated in patients with OSA[28]. Thus, potentiated chemoreflex function may contribute to the abnormalities in cardiovascular variability.

Other mechanisms include baroreflex dysfunction[29,30], vasoconstrictor effects of nocturnal endothelin release[31], endothelial dysfunction[32] and inflammation[33].

Effects of treatment of OSA

Therapeutic strategies for OSA include sleep postural changes, avoidance of sleeping on the back, weight loss, avoidance of alcohol and

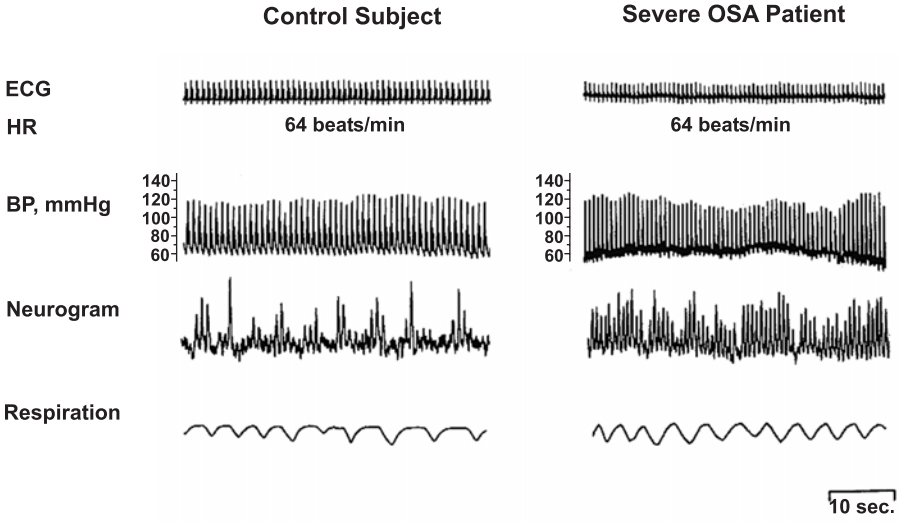

Figure 1 – Electrocardiogram (ECG), blood pressure, sympathetic neurograms, and respiration in a control subject (left) and in a patient with severe obstructive sleep apnea (OSA; right) showing faster heart rate, increased blood pressure variability and markedly elevated muscle sympathetic nerve activity in the patient with OSA. From reference 25 with permission of the American Heart Association.

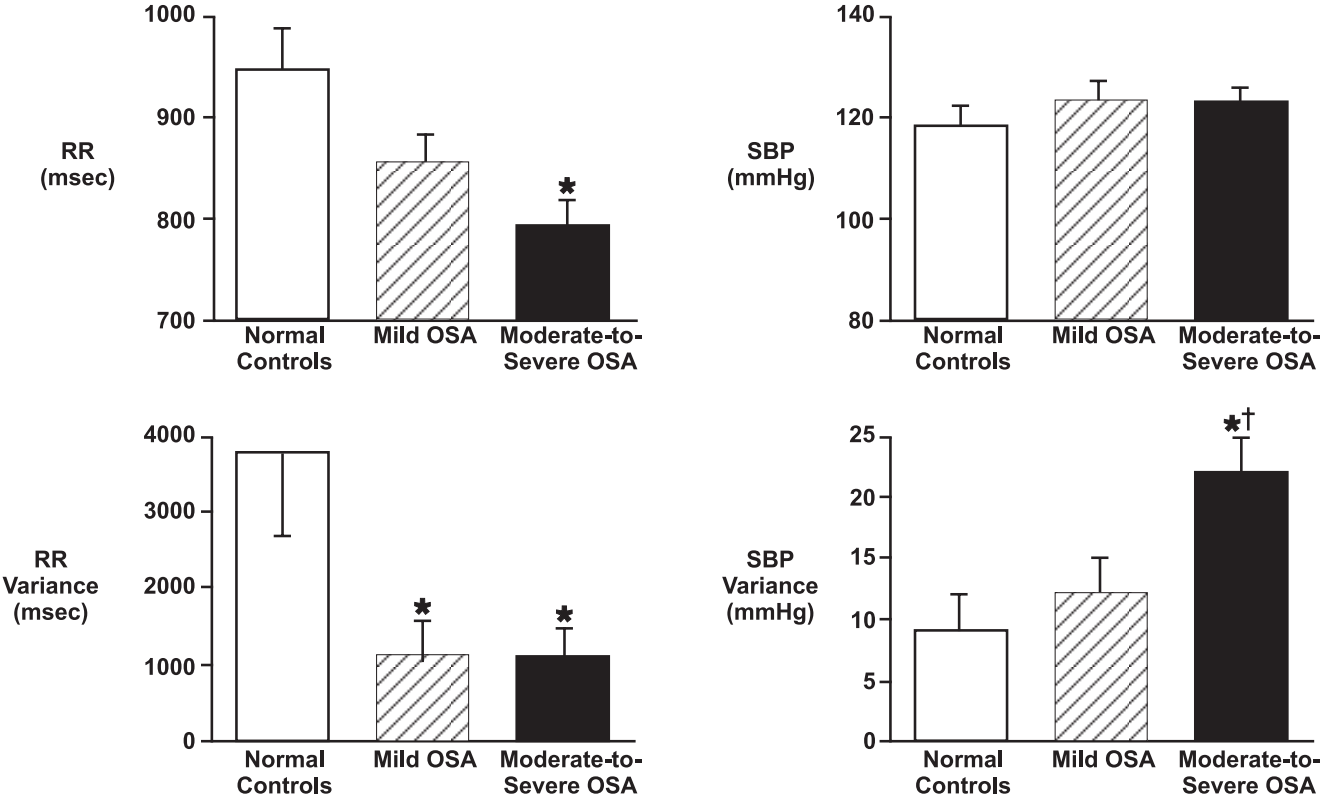

Figure 2 – RR interval, SBP and their variances in control subjects (n = 16), patients with mild OSA (n = 18) and patients with moderate-to-severe OSA (n = 15). RR interval was reduced in the patients with moderate-to-severe OSA compared with the control subjects. Patients with mild OSA and patients with moderate-to-severe OSA had an attenuated RR variance in comparison to that in the control subjects. SBP variance was markedly increased in patients with moderate-to-severe OSA, compared to either control subjects or patients with mild OSA. *P < 0.05 *vs* controls; † P < .05 *vs* mild OSA. Data are means ± SEM. From reference 26 with permission of the American Heart Association.

sedative hypnotics and upper airway surgical procedures. The most widely used treatment consists of continuous positive airway pressure (CPAP) administered during the night. CPAP treatment prevents airway collapse during inspiratory efforts. Treatment with continuous positive airway pressure (CPAP) results in acute and marked reduction in nocturnal sympathetic nerve traffic and blunts blood pressure surges during sleep[20].

Effective long-term treatment of OSA by CPAP treatment of OSA has been shown to improve blood pressure control in hypertensive patients, particularly when blood pressure is measured over 24 hours[34-36]. This benefit is seen in both systolic and diastolic blood pressure, and during both sleep and wake. The benefit is larger in patients with more severe sleep apnea, but is independent of the baseline blood pressure[35]. The benefit is especially large in patients taking drug treatment for blood pressure[35].

We have recently tested the hypothesis that long-term CPAP treatment will decrease MSNA in otherwise healthy OSA patients[37]. We studied 11 OSA patients treated with CPAP and 9 OSA patients who remained untreated. Measurements of MSNA were obtained at baseline, and after 1 month, 6 months and one year, in order to provide insight into the timing and stability of response to CPAP treatment. MSNA was similar during repeated measurements in the untreated group. We were not able to demonstrate a decrease in MSNA after one month of CPAP treatment (Figures 3 and 4). However, we found a significant decrease in sympathetic traffic after 6 months and one year of treatment (Figures 3 and 4). Thus, long-term CPAP therapy is required in order to attenuate the sympathetic activation observed in patients with OSA.

Implications for treatment of hypertension

It is important to consider OSA in the differential diagnosis of hypertensive patients who are obese. Furthermore, undiagnosed OSA is extremely prevalent (up to 83%) in patients with hypertension resistant to conventional drug therapy[38]. Thus, obstructive sleep apnea should also be considered in those hypertensive

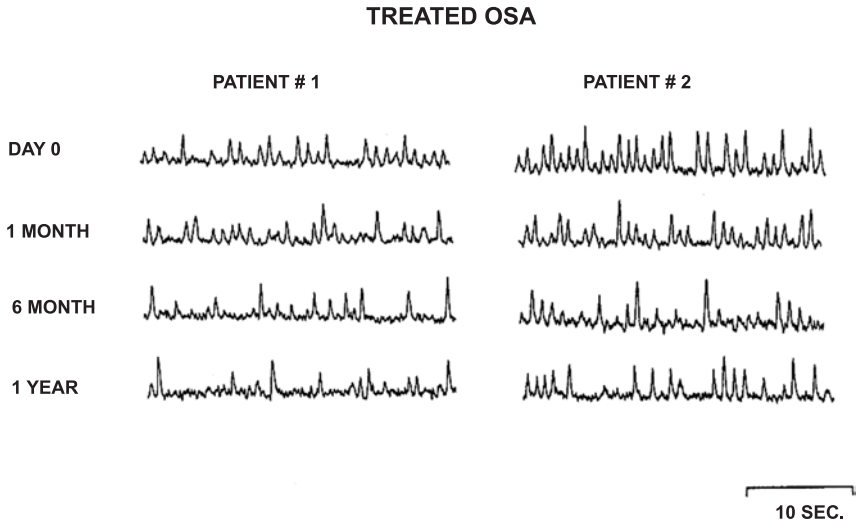

Figure 3 – Sympathetic neurograms during repeated measurements in two treated patients with OSA. Measurements were obtained at baseline (day 0), and after 1 month, 6 months and 1 year of CPAP treatment. Long-term CPAP treatment decreased MSNA, as evident from the measurements obtained at 6 months and one year. From reference 37 with permission of the American Heart Association.

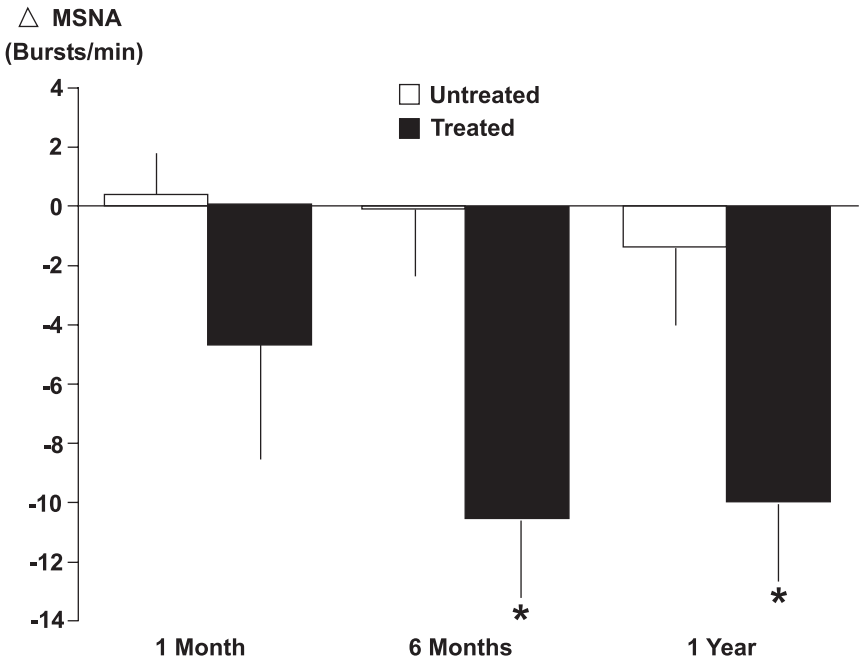

Figure 4 – Changes of muscle sympathetic nerve activity (MSNA) during repeated measurements in the untreated OSA patients (n = 9) and in the OSA patients treated with CPAP (n = 11). MSNA did not change in untreated patients. In treated patients, MSNA was decreased after 6 months and 1 year of CPAP treatment (* $P < .05$ *vs* baseline). From reference 37 with permission of the American Heart Association.

patients who respond poorly to combination therapy with antihypertensive medications. In particular, there is growing evidence that hypertensive patients, who are classified as "non-dippers" on ambulatory pressure measurements, should be investigated for obstructive sleep apnea[39].

Conclusions

Patients with obstructive sleep apnea are at increased risk for hypertension and cardiovascular disease. Mechanistic studies of sympathetic traffic and chemoreflex responses in patients with sleep apnea and patients with hypertension have provided very suggestive evidence for an interaction between these disease states. During sleep, repetitive apneic episodes result in hypoxemia and carbon dioxide retention, which cause increases in sympathetic nerve activity and elicit humoral vasoconstrictor responses. Of particular interest in understanding neurogenic hypertension in sleep apnea is the persistence of high levels of sympathetic traffic in sleep apnea patients even during daytime normoxic wakefulness. Sleep apnea may contribute to elevated levels of blood pressure in a large proportion of the hypertensive patient population. Unrecognized obstructive sleep apnea may be implicated in the cardiovascular derangements that are thought to be linked to obesity, and to the association between obesity and cardiovascular morbidity. Long-term continuous positive airway pressure treatment decreases muscle sympathetic nerve activity and improves hypertension control in patients with obstructive sleep apnea.

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