

REVIEW SERIES

Non-dipping pattern of hypertension and obstructive sleep apnea syndrome

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There is growing recognition of cardiovascular consequences of obstructive sleep apnea (OSA). Recurrent episodes of airway obstructions result in hypoxia and hypercapnia increasing sympathetic neural tone, which in turn causes vasoconstriction and marked increases in blood pressure (BP). BP response to OSA may be important in understanding the absence of nocturnal BP fall in the subgroup of hypertensive patients termed 'non-dippers'. Even mild sleep apnea can increase nocturnal BP through different mechanisms including hypoxemia, sympathetic activation, mechanical changes and disruption of normal sleep. Sleep apnea may be an important factor in determining the increased cardiovascular risk in hypertensive non-dippers. Effective treatment of sleep apnea may attenuate neurohumoral and metabolic abnormalities, improve diurnal BP control and conceivably reduce cardiovascular risk. This review examines the evidence linking OSA to non-dipping pattern of hypertension, and discusses potential mechanisms underlying this link. We will review first, prognostic value of nighttime BP; second, the cardiovascular consequences of sleep apnea; third, the evidence for altered diurnal BP profile in sleep apnea; fourth, the mechanisms contributing to both nocturnal and daytime hypertension in sleep apnea; fifth, the benefits of sleep apnea treatment and finally implications for hypertension management.

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INTRODUCTION

Ambulatory monitoring has shown that the 24-h blood pressure (BP) profile is characterized by considerable variability and a marked diurnal rhythm.^{1–5} A substantial component of BP variability during ambulatory monitoring can be accounted for by changes in activity. However, the physiological mechanisms responsible for the variability and the diurnal rhythm of BP are not completely understood.⁶ Nevertheless, there is growing evidence that sympathetic nerve activity contributes importantly to BP variability and the diurnal BP profile.^{7,8}

Normally, BP decreases during sleep by at least 10% of the awake value, and occurrence of 'dipping' correlates directly with the amount of deep sleep and inversely with indices of sleep fragmentation.⁹ There has been great interest in the mechanisms and clinical significance of the 'dipper' or 'non-dipper' pattern of ambulatory BP profiles.

Obstructive sleep apnea (OSA) and the consequent nighttime BP surges may be involved in the increased cardiovascular morbidity that characterizes those hypertensive patients without nocturnal BP decline.

This review examines the evidence linking OSA to non-dipping pattern of hypertension, and discusses potential mechanisms underlying this link. We will review first, prognostic value of nighttime BP; second, the cardiovascular consequences of OSA; third, the evidence for altered diurnal BP profile in OSA; fourth, the mechanisms contributing to both nocturnal and daytime hypertension in OSA;

fifth, the benefits of OSA treatment and finally implications for hypertension management. Because of the space limitations, only few references relevant to specific areas can be included.

PROGNOSTIC VALUE OF NIGHTTIME BP

Ambulatory BP is a better predictor of cardiovascular risk than office BP. The risk of cardiovascular morbidity and mortality increases more steeply from office to home, day, 24 h and night BP^{10,11} (Figure 1).

A blunted nocturnal BP dip phenomenon is common in hypertensive patients.¹² It has been suggested that both non-dipping^{13–15} and extreme dipping^{16–18} are associated with more pronounced target organ damage. Furthermore, a lack of nocturnal dipping has been related to an increased risk of cardiovascular events.^{19–23} The night-to-day blood pressure ratio predicts cardiovascular and non-cardiovascular mortality.²⁴ Finally, a recent study by Muxfeldt *et al.*²⁵ in resistant hypertension indicates that the nocturnal BP variability patterns provide valuable prognostic information for stratification of cardiovascular morbidity and mortality risk, above and beyond other traditional cardiovascular risk factors and mean ambulatory BP levels.

Interestingly, a recent study by Eguchi *et al.*²⁶ indicates that also nocturnal non-dipping of heart rate predicts cardiovascular events in hypertensive patients. The risk of future cardiovascular events was shown to be markedly higher in those whose heart rate does not

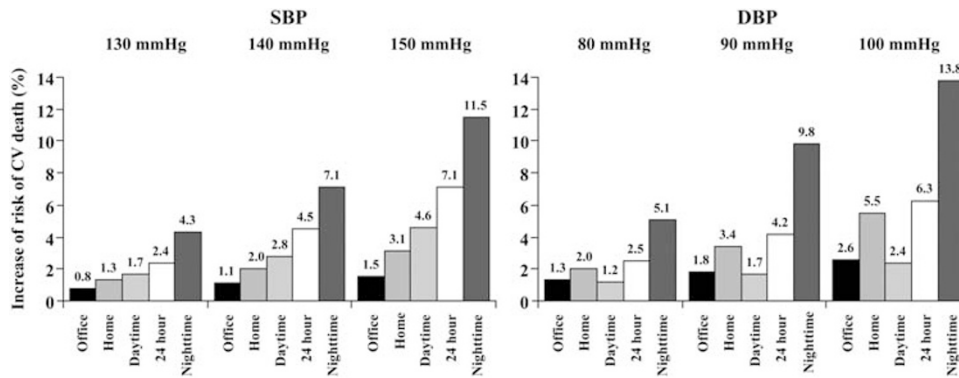


Figure 1 Increase in 11-year risk of cardiovascular (CV) mortality for 10 mmHg increase in office, home and ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) at various initial values in the Pressioni Arteriose Monitorate E Loro Associazioni study (from Sega *et al.*,¹¹ with permission).

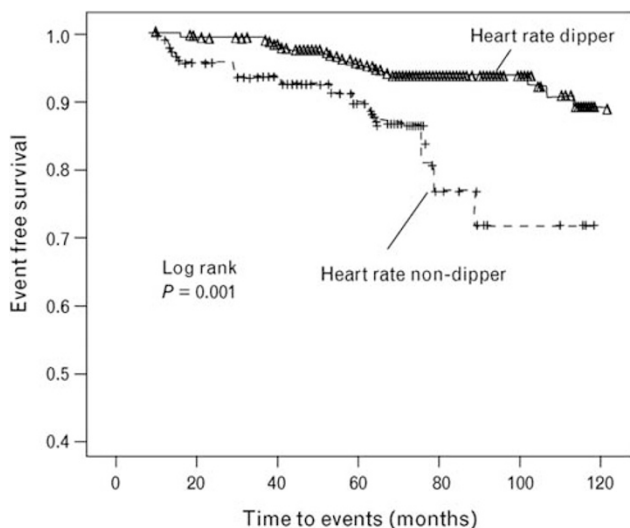


Figure 2 Event-free survival in hypertensive patients according to heart rate dipping pattern in 497 hypertensive patients (from Eguchi *et al.*,²⁶ with permission).

exhibit the typical nocturnal decline (Figure 2). This relationship was independent of non-dipping of BP.

CARDIOVASCULAR CONSEQUENCES OF OSA

There is growing recognition of cardiovascular consequences of OSA.^{27–29} Several studies provided evidence that OSA patients have increased BP and a higher incidence of hypertension.^{30–32} Conversely, patients with essential hypertension are more likely to have sleep-disordered breathing. This association is particularly evident within a group of patients with hypertension refractory to conventional therapy. Up to 84% of these hypertensive subjects may have previously undiagnosed OSA.^{33,34}

The Wisconsin Sleep Cohort Study has shown a dose–response relationship of sleep-disordered breathing at baseline and the incidence of hypertension in a 4 year observation.³⁵ The association between OSA and arterial hypertension is affected by aging. The analysis of the Sleep Heart Health Study³⁶ has shown an independent association of OSA and hypertension in the group of middle-aged, but not in the elderly subjects. Noda *et al.*³⁷ have shown that the survival rate in middle-aged patients with OSA was significantly lower than that in the age and sex-adjusted control Japanese population, but this

pattern was not seen among the elderly patients. Distinct effects of OSA in populations of different ages have been attributed to differences in concomitant disease, underlying risk factors for sleep disordered breathing (similar to relative contributions of obesity vs. ventilatory control abnormalities) and to differences in physiological responses to intermittent upper airway occlusion.³⁶

OSA has also been shown to be an independent risk factor for the development of left ventricular hypertrophy.^{38,39} Several longitudinal studies have documented increased cardiovascular morbidity in OSA patients.^{40–42} OSA has been shown to be a significant risk factor for the composite outcome of death and stroke, independent of other risk factors including hypertension and atrial fibrillation.⁴³ Finally, patients with OSA have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the findings in the general population.⁴⁴

OSA AND NON-DIPPERS

Prevalence of hypertension is underdiagnosed in OSA patients if BP is assessed by office readings only. In the Wisconsin Sleep Cohort Study, Young *et al.*³¹ found a linear relationship between 24-h BP and AHI that was independent of confounding factors such as body mass index. Baguet *et al.*⁴⁵ have shown that ambulatory BP monitoring might be of particular significance in the hypertension diagnosis of OSA patients (Figure 3). Although 42% of their OSA patients showed office hypertension, 58% had daytime hypertension and 76% had nighttime hypertension. Hypertensive patients, in whom there is an absence of a nocturnal BP decline (non-dippers), are at increased risk for cardiac and vascular events.^{46,47} The nocturnal BP profile in non-dipper hypertensive patients is strikingly similar to that described in studies of 24 h BP measurements in patients with OSA. Pankow *et al.*⁴⁸ have shown that non-dipping of nocturnal BP in patients with OSA is related to apnea severity. Lavie *et al.*⁴⁹ have also reported that BP during sleep correlated significantly with the apnea hypopnea index. In a study, directed specifically at male non-dippers with essential hypertension, Portaluppi *et al.*⁵⁰ concluded that hypertensive non-dippers had a high probability of coexisting sleep-disordered breathing. Interestingly, a significant relationship between evening-to-morning BP difference and AHI was confirmed in men but not in women.⁵¹ A 'non-dipping' pattern was found in 48–84% of patients with OSA, and its frequency increases with OSA severity.^{52,53}

Detection of intermittent BP surges during sleep and non-dipping pattern in OSA syndrome patients can be further improved by the newly developed non-invasive hypoxia-triggered monitoring system.^{54,55}

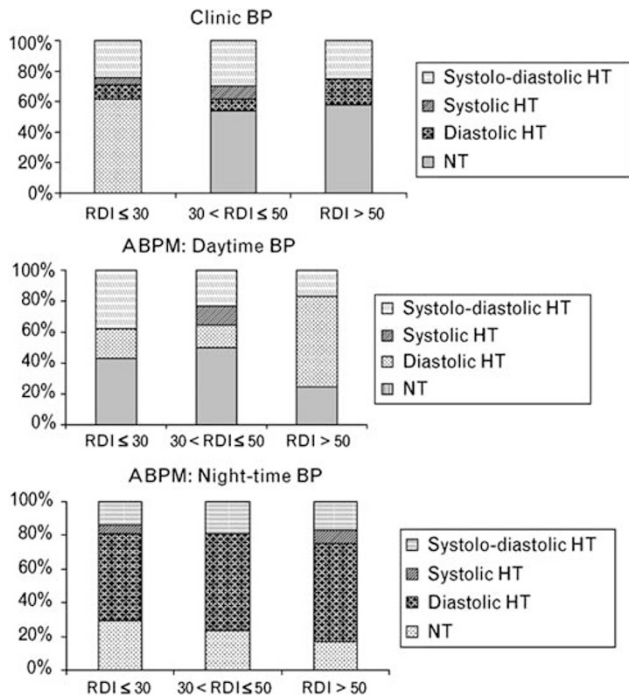


Figure 3 Relative proportions of different pattern of hypertension (HT) using clinical and ambulatory blood pressure measurements (ABPM) in newly diagnosed obstructive sleep apnea patients. BP, blood pressure; NT, normotension (from Baguet *et al.*,⁴⁵ with permission).

MECHANISMS CONTRIBUTING TO NON-DIPPING PATTERN OF HYPERTENSION IN OSA

Recurrent episodes of airway obstructions result in hypoxia and hypercapnia increasing sympathetic neural tone, which in turn causes vasoconstriction.⁵⁶ Sympathetic nerve activity rises progressively during the time of apnea and is enhanced further by the arousal. On resumption of breathing, cardiac output increases which coincides with the constricted peripheral vasculature. This results in marked increases in arterial pressure. BP and sympathetic activity in sleep-apneic patients are highest during rapid eye movement sleep, as it is during this sleep stage that apneas are most prolonged. Because of repetitive vasoconstriction and BP surges, BP overall does not decrease during sleep in patients with OSA.

OSA-related repetitive hypoxemia with consequent chemoreflex activation, sympathetic excitation and nighttime BP surges may be involved in the above described cardiovascular events in sleep-apneic patients (Figure 4). This hemodynamic instability, related to respiratory efforts, hypoxemia and arousal, may lead to increased risk of cardiac arrhythmias and sudden cardiac death. It may also favor ischemic or hemorrhagic stroke, decompensation of a chronic heart failure condition, as well as the development of chronic arterial hypertension in these patients.

High levels of sympathetic activity in OSA patients are associated with profound abnormalities in cardiovascular variability during wakefulness. This alteration occurs even in the absence of hypertension or heart failure. OSA patients' BP variability exhibit marked increase, heart rate is faster and the RR variability is decreased.⁵⁷ The degree of derangement in cardiovascular variability is closely linked to the severity of syndrome. Possible mechanisms underlying autonomic control abnormalities include chemoreflex dysfunction⁵⁸ and impaired baroreceptor function.^{59,60}

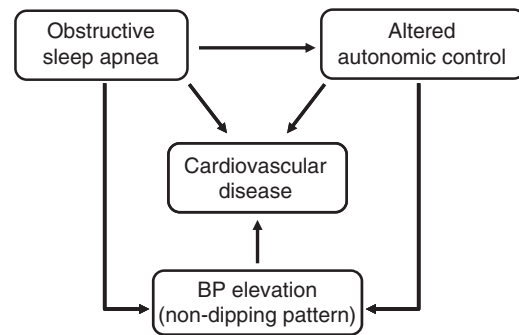


Figure 4 Mechanisms linking obstructive sleep apnea with cardiovascular disease.

Other factors implicated in the non-dipping pattern of hypertension in OSA patients include impaired endothelium-dependent vasodilation,^{61,62} suppressed nitric oxide production,^{63,64} higher levels of plasma asymmetric dimethylarginine (ADMA),⁶⁵ oxidative stress,^{66,67} increased concentrations of endothelin-1,⁶⁸ low-grade inflammation,^{69–71} and increased levels of circulating intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and L-selectin.⁷²

BENEFITS OF OSA TREATMENT

The most common and highly efficient therapeutic procedure of eliminating airway obstruction at night consists of use of a continuous positive airway pressure (CPAP). In addition to the use of airway assistance device, OSA therapeutic strategy comprises weight loss (inclusive of bariatric surgery), upper airway surgical procedures, use of mandibular protruding devices, avoidance of alcohol and sedative hypnotics and sleep postural changes. In case of patients with concomitant heart failure, treatment options include bilevel and adaptive pressure support servoventilation.

Treatment with CPAP results in acute and marked reduction in nocturnal sympathetic nerve traffic and blunts BP surges during sleep. Long-term effective CPAP treatment has been shown to improve nocturnal and daytime BP control.^{73–75} The beneficial effects of the use of a CPAP appliance is especially evident in patients with more severe OSA.⁷⁶

CPAP therapy leads to beneficial neurohormonal changes that may facilitate hypertension management. Long-term CPAP treatment decreases neural sympathetic activity measured by microneurography in otherwise healthy OSA patients.⁷⁷ There is evidence that CPAP therapy may reduce risk of incidence of fatal and non-fatal cardiovascular events in male OSA patients as compared with untreated OSA patients.⁷⁸

IMPLICATIONS FOR HYPERTENSION MANAGEMENT

Close link between OSA and hypertension has important implications for cardiovascular prevention and treatment. OSA may contribute to elevated levels of BP in a large proportion of hypertensives, and should be strongly suspected in obese individuals with resistant hypertension, especially in those with non-dipping pattern of BP. Already in 1997, the 6th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure had recommended OSA to be considered in patients with resistant hypertension.⁷⁹ The more recent seventh report from this Committee has broadened their recommendations. According to the Seventh Joint National Committee Report, all of the hypertensive patients with body mass index above 27 kg m⁻² should be thoroughly screened for the

presence of sleep-disordered breathing.⁸⁰ The 2007 European Society of Hypertension and of the European Society of Cardiology guidelines have also listed OSA as one of the most important causes of resistant hypertension.⁸¹

CONCLUSIONS

BP response to sleep in OSA patients may be important in understanding the absence of nocturnal BP decrease in the subgroup of hypertensive patients termed 'non-dippers'. Even mild OSA can increase nocturnal BP through different mechanisms including hypoxemia, sympathetic activation, mechanical changes and disruption of normal sleep. OSA can prevent the physiological decrease in BP and, when severe, it can increase nocturnal BP compared with awake values. Moreover, OSA increases BP variability during sleep, with further potentiation of chronic stress on the vessel wall. OSA may be an important factor in determining the increased cardiovascular risk in hypertensive non-dippers. Effective treatment of OSA may attenuate neurohumoral and metabolic abnormalities, improve BP control and conceivably reduce cardiovascular risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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