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REVIEW

Obstructive sleep apnea syndrome and hypertension: ambulatory blood pressure

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Obstructive sleep apnea syndrome (OSAS) is an independent risk factor for hypertension and cardiovascular disease. OSAS is the frequent underlying disease of secondary hypertension and resistant hypertension. OSAS increases both daytime and night-time ambulatory blood pressures through the activation of various neurohumoral factors including the sympathetic nervous system and the renin–angiotensin–aldosterone system. In particular, OSAS predominantly increases ambulatory BP during sleep compared with the awake period, with the result that OSAS is likely to be associated with the non-dipping pattern (diminished nocturnal BP fall) or riser pattern (higher sleep BP than awake BP) of nocturnal BP. An additional characteristic of ABP in OSAS is increased BP variability. The newly developed non-invasive hypoxia-trigger BP-monitoring system detected marked midnight BP surges (ranging from around 10 to 100 mm Hg) during sleep in OSAS patients. The exaggerated BP surge may trigger OSAS-related cardiovascular events occurring during sleep. Clinically, as nocturnal hypoxia is the determinant of morning minus evening BP difference (ME difference), OSAS should be strongly suspected when morning BP cannot be controlled $<$135/85 mm Hg with increased ME difference even by the specific antihypertensive medications targeting morning hypertension such as bedtime dosing of antihypertensive drugs. Understanding the characteristics of OSAS-related hypertension is essentially important to achieve perfect BP control over a 24-h period, including the sleep period, for more effective prevention of cardiovascular disease.
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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), one of the leading causes of hypertension, is a risk for advancing atherosclerosis and for triggering cardiovascular events, particularly those occurring during the sleep period. In the recently published guidelines for the management of hypertension, more strict blood pressure (BP) control during a 24-h period is particularly stressed for high-risk hypertensive patients.[1,2] Hypertensive patients with OSAS constitute one of the high-risk groups that receive more benefit from strict BP control. Thus, understanding the characteristics of OSAS-related hypertension is essentially important to achieve perfect BP control over a 24-h period, including the sleep period, for more effective prevention of cardiovascular disease.

CAUSE OF HYPERTENSION

OSAS is the most common identifiable cause of secondary hypertension that could be recognized as a high-risk metabolic syndrome. Being male and obese are the two major risk factors for OSAS; however, the prevalence of OSAS has not been shown in Japan.

OSAS and hypertension are likely to accompany each other; the prevalence of OSAS has been underscored in hypertensive patients.[3] Fifty percent or more of all OSAS patients have hypertension and around 30% of all obese hypertensive patients in Western countries may have OSAS. The higher rates of coexistence of hypertension and OSAS are due to the increased prevalence of obesity, a background factor in both conditions.

However, the precise prevalence of OSAS in hypertensive patients has not been identified in Japan. We have previously studied the prevalence of SAS diagnosed using the same polysomnography device and the same criteria (15 $>$apnea hypopnea index (AHI)) as that of the Sleep Heart Health Study (SHHS) in 452 Japanese hypertensive patients.[4] The prevalence of OSAS in Japanese hypertensives was around 10%, and this value was one-third that of the Western hypertensive participants of the New York SHHS (Figure 1). OSAS increases with obesity in Japan, but is also frequently observed in non-obese individuals with particular skeletal characteristics of the face such as micrognathia.[5]

The association between OSAS and hypertension is found before both conditions become clinically overt. In the population-based Wisconsin Sleep Cohort Study, an increase in AHI was a predictor of future hypertension independently of age and body mass index.[6] In addition, there is an independent linear association between AHI and 24-h BP levels.[7]

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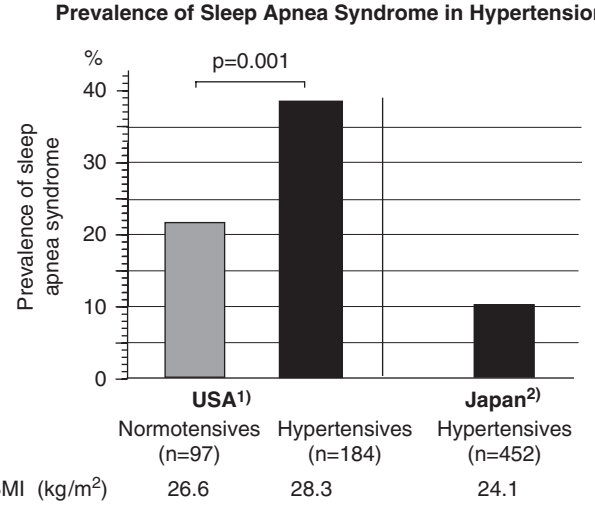

Figure 1 Prevalence of sleep apnea syndrome in hypertension. [1)]New York Sleep Heart Health Study; [2)]Jichi Medical University Ambulatory BP Monitoring Study Wave 2 Core; BMI, body mass index.

The impact of OSAS on hypertension is higher for diastolic hypertension in younger individuals than for systolic hypertension in the elderly.[8] Sleep is important for increased BP in younger individuals. A recent study evaluated the quantity and quality of sleep using actigraphy in adolescence individuals; short sleep duration (<6.5 h) and decreased sleep efficacy ($<85\%$) were independent risk factors for prehypertension.[9]

In the population-based Jichi Medical School Cohort,[10] as well as the Suita Study,[11] prehypertension is a risk factor for cardiovascular disease, particularly stroke, in Japan. The strong and independent determinant of prehypertension was obesity, particularly in younger subjects aged <50 years.[12] In the community-dwelling subjects (aged 45 years), a 10% increase in body mass index over 4 years increased the risk of moderate to severe OSAS sixfold, and the risk was suppressed by body weight reduction.[13] Thus, adequate control of body weight is essential for the prevention of OSAS-related hypertension from a young age.

RESISTANT HYPERTENSION

OSAS is known to be a frequent cause of resistant hypertension (Table 1).[14] Resistant hypertension is defined when BP levels cannot be controlled $<140/90$ mm Hg by the use of three drugs, including diuretics.[1] Some reports have shown that the prevalence of OSAS (defined as AHI >10) is 80% or more,[15] and that OSAS is the independent determinant of uncontrolled hypertension in younger hypertensive patients aged <50 years.[16] An increased level of plasma aldosterone is reported to be associated with resistant hypertension in OSAS patients.[17]

MASKED HYPERTENSION

The most important characteristic of OSAS-related hypertension is the higher frequency of masked hypertension such as nocturnal hypertension and morning hypertension (Table 1).

Masked hypertension is defined as an average clinic BP of $<140/90$ mm Hg and home BP of $\geqslant 135/85$ mm Hg or an average 24-h BP on ambulatory BP monitoring of $\geqslant 130/80$ mm Hg.[1,2,18,19] Masked hypertension includes morning hypertension, stress-induced hypertension, such as workplace hypertension,[1] and nocturnal hypertension. Nocturnal hypertension is defined as a sleeping BP of $>120/70$ mm Hg, and morning hypertension is defined as a morning BP of $>135/85$ mm Hg.[1] OSAS increases the awake BP during the daytime, but more extensively it increases nocturnal BP during the sleep period. Thus, OSAS patients are likely to have a non-dipper/riser pattern of nocturnal BP. This nocturnal hypertension (non-dipper/riser pattern) could be detected as morning hypertension by self-measured home BP monitoring (Figure 2).[20]

Table 1 Characteristics of hypertension with obstructive sleep apnea syndrome

Resistant hypertension
Masked hypertension
Nocturnal hypertension (non-dipper·riser pattern, midnight BP surge)
Morning hypertension (exaggerated morning BP surge)
Hypertension with increased heart rate
Diastolic (predominant) hypertension in younger

Abbreviation: BP=blood pressure.

It is important to suspect OSAS when morning hypertension (assessed using self-measured BP monitoring) cannot be controlled $<135/85$ mm Hg even by the specific antihypertensive treatment targeting morning hypertension using bedtime administration of antihypertensive drugs. In addition, the increased difference between morning and evening BP (ME-BP difference) detected by self-measured home BP monitoring may suggest the presence of OSAS in uncontrolled hypertension. Nocturnal hypoxia is one of the determinants of increased ME-BP difference in BP, and an increase in ME-BP difference is associated with hypertensive heart disease, particularly concentric left ventricular hypertrophy and future stroke events in hypertensive patients independently of the average of morning and evening BPs.[21,22]

NON-DIPPER/RISER IN NOCTURNAL BLOOD PRESSURE

Non-dippers (reduced nocturnal BP fall) and risers (higher nocturnal BP than daytime BP) are at risk of hypertensive target organ damage and subsequent cardiovascular events.[23–29] The related conditions of non-dippers and risers are as follows: (1) reduced circulating volume (congestive heart failure, chronic kidney disease, etc), (2) autonomic nervous dysfunction (orthostatic hypotension, diabetes, etc) and (3) poor sleep quality (SAS, depression, etc) (Figure 2).[30] The prevalence of OSAS is higher in these conditions, such as congestive heart failure, chronic kidney disease, diabetes, and so on, and may partly contribute to increased nocturnal hypertension.

MIDNIGHT SURGE IN SLEEP BLOOD PRESSURE

Another important characteristic of OSAS-related nocturnal hypertension accompanies the increased BP variability during sleep. In OSAS patients, an invasive BP monitoring showed transient BP surges because of sympathetic activation at the time of the sleep apnea episode. A continuous non-invasive BP monitoring, such as Finapress, could also detect the transient BP surge; however, the absolute BP value is inaccurate. We have recently developed a new home BP-monitoring system in which reduction of O_2 desaturation owing to each apnea episode triggers a cuff-inflation system to accurately measure the sleep apnea-associated BP variation during sleep.[31] Using this new system, we have monitored BP during sleep in OSAS patients and found that there are marked individual differences (from 10 to 100 mm Hg) in the degree of midnight BP surges triggered by a similar degree of desaturation at the time of the sleep apnea episode. Figure 3 shows a case that exhibited marked midnight BP

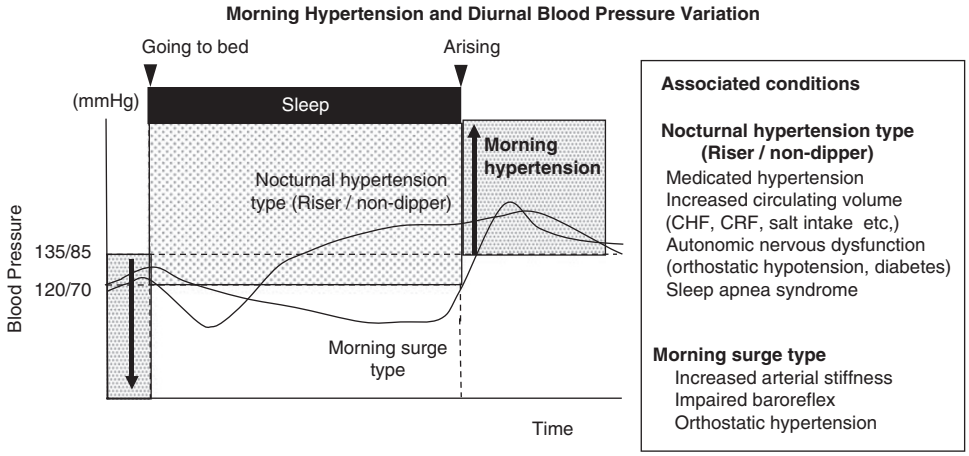

Figure 2 Morning hypertension and diurnal blood pressure variation. CHF, congestive heart failure; CRF, chronic renal failure.

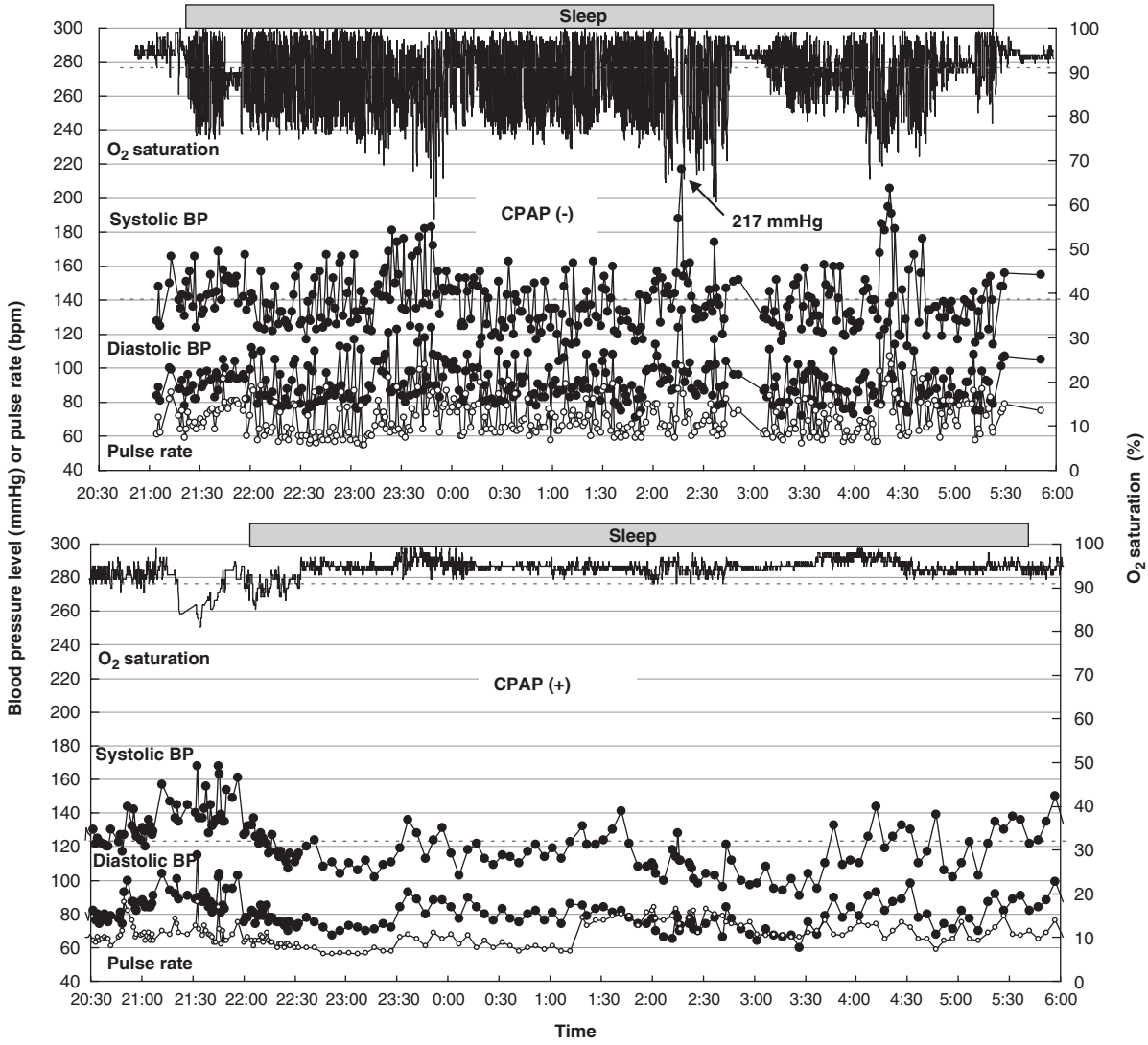

Figure 3 Sleep apnea-related midnight BP surges detected by newly developed hypoxia-trigger BP-monitoring system. (Upper figure) Using this system, we monitored the sleeping BP in a 54-year-old male patient (body mass index: 33.1 kg m^{-2}) with severe obstructive sleep apnea. BP variation during sleep as actually augmented (s.d. of sleeping BPs = 16.6 mm Hg), with several high BP peaks (3.4% of the total systolic BPs measured during sleep were above 180 mm Hg). (Lower figure) During continuous positive airway pressure (CPAP), in addition to the reduction of average BPs (−18.6 mm Hg systolic and −11.4 mm Hg diastolic), BP variation also decreased with reduced peak BPs.

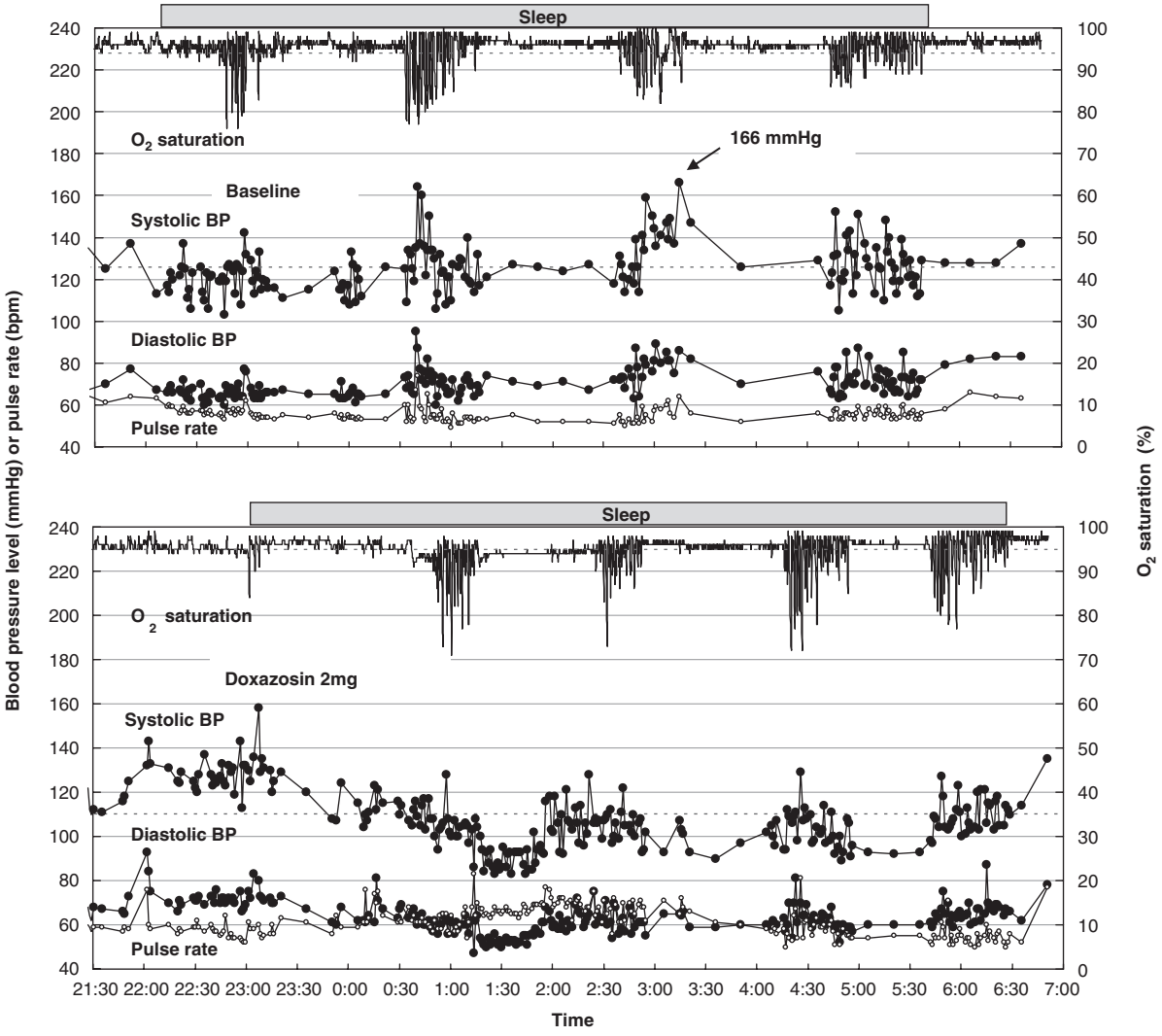

Figure 4 Reduction of sleep apnea-related midnight BP surges by α-adrenergic blockade. (Upper figure) Periodic clusters of sleep apnea episodes triggered midnight BP surges >160 mm Hg. (Lower figure) Bedtime dosing of doxazosin (2 mg) did not reduce the periodic hypoxic episodes, but diminished nocturnal BP levels and midnight BP surges <140 mm Hg.

surges triggered by sleep apnea episodes. These BP surges were significantly diminished by continuous positive airway pressure therapy. The increased midnight BP surge may be a missing direct link between OSAS and cardiovascular events occurring particularly during sleep.

The individual difference and pathogenesis of midnight BP surges remain unclear. A bedtime dosing of α-adrenergic blockade diminished this BP surge (Figure 4), indicating that midnight BP surge is predominantly triggered by sympathetic nervous activation and subsequent vasoconstriction. In OSAS patients, BP reactivity to sympathetic activation may be increased. Even in children without any atherosclerosis, morning BP surge is exaggerated in severe OSAS patients compared with non-OSAS subjects.[32]

CONCLUSION

Hypertensive patients with OSAS constitute a high-risk group, and the characteristic of ambulatory BP in OSAS patients is uncontrolled nocturnal/morning hypertension with midnight BP surge. Strict BP control to lower the target level with particular attention to nocturnal BP is required to prevent target organ damage and cardiovascular events occurring particularly during sleep.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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