Original Article

Diurnal Blood Pressure Variation in Patients with Sleep Apnea Syndrome

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Sleep apnea syndrome (SAS) is an important risk factor for hypertension and cardiovascular diseases. Diurnal blood pressure (BP) changes are evaluated by 24 h ambulatory blood pressure monitoring (ABPM). The purpose of this study was to clarify the relationship between diurnal BP variation and SAS severity, as well as the impact of antihypertensive therapy on diurnal BP variation. Patients seen at our clinic between April and September 2006 with excessive daytime sleepiness or apnea were enrolled. All patients had polysomnography and ABPM. Mean 24 h BP and nighttime BPs were significantly higher in the SAS group than in the non-SAS group. No significant differences were observed in daytime BPs between the two groups. SAS patients had a high mean 24-h BP and an elevated nighttime BP, both of which increased as SAS severity increased. Nighttime BPs were significantly higher in the moderate SAS group than in the non-SAS group. Nighttime BP and morning BP were significantly higher in the severe SAS group than in the non-SAS group. With respect to antihypertensive agents' effects on diurnal BP changes, there were no significant differences between the SAS and non-SAS groups. In conclusion, compared with non-SAS patients, patients with SAS had a higher 24-h BP, especially nighttime BP. Patients with moderate SAS tended to have elevated nighttime BP. In patients with severe SAS, elevated BP was sustained during the night despite the use of antihypertensive agents. (*Hypertens Res* 2008; 31: 185–191)

***Key Words*: sleep apnea syndrome, diurnal blood pressure variation, antihypertensive agents**

Introduction

Sleep apnea syndrome (SAS) is a treatable form of disordered breathing in which the upper airway closes repeatedly during sleep. SAS is defined as the presence of a pathological number of apnea or hypopnea episodes that disturb respiratory flow during sleep. This syndrome is normally associated with nighttime arousals and/or excessive daytime sleepiness. Several cross-sectional analyses have shown an increased risk of stroke in patients with sleep-disordered breathing; the increased risk is of a magnitude similar to those of other cardiovascular risk factors (*1*).

SAS is also known as an important risk factor for hypertension (*2*), and blood pressure (BP) elevation is related to the severity of SAS (*3*).

Recently, 24-h ambulatory blood pressure monitoring (ABPM) has demonstrated the importance of diurnal BP variation. Previous studies have shown that SAS patients had high mean 24-h BP (*3*) and elevated nighttime BP that increased as the SAS severity increased (*4*, *5*). Unfortunately, most ABPM studies of SAS patients have evaluated only daytime and nighttime BPs; few studies have investigated diurnal BP variation for 24-h periods.

It has been reported that acute ischemic stroke and acute myocardial ischemia frequently occur 1 to 2 h after awakening, and that the presence of a high nighttime BP might trigger their occurrence (*6*, *7*). Kario *et al*. (*8*) reported that high

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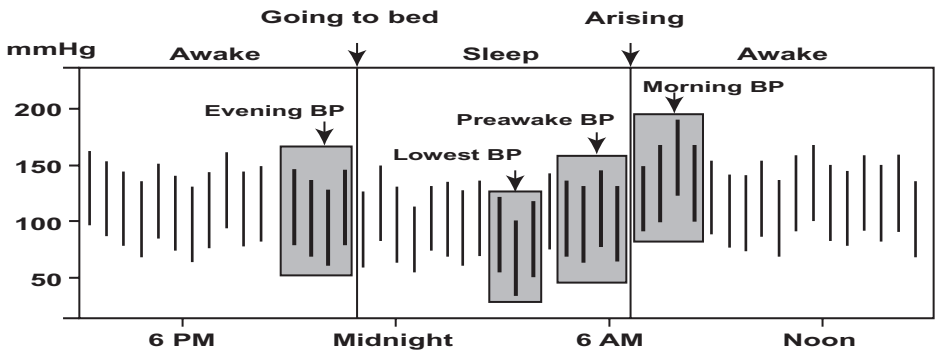

Fig. 1. *The category of diurnal BP variation. BP values: the average of 4 BP recording; awake BP: the avarege of BP measurements recorded during the rest of the day; sleep BP: the average of BP measurements from the time when the patient went to bed until the time he/she got out of bed; evening BP: the 2 h before going to bed; morning BP: the 2 h after waking up; preawake BP: the 2 h before waking up; lowest BP: the average of the 3 lowest BP reading at nighttime; nocturnal BP fall (%): 100×[1 − sleep BP/awake BP ratio] (10).*

early morning BP is probably a risk factor for asymptomatic cerebral infarction in hypertensive patients.

These findings suggest a possible relationship between diurnal BP variation in SAS patients and cardiovascular disease. Therefore, the present study was conducted to clarify the relationship between diurnal BP variation and SAS severity, as well as the impact of antihypertensive therapy on diurnal BP variation.

Methods

Patients who were seen in our clinic between April and September 2006 due to excessive daytime sleepiness or apnea that had been observed by others were enrolled. All patients had polysomnography (PSG) and ABPM. Blood samples were collected at the first examination to measure blood glucose level, hemoglobin A1c (HbA1c), total cholesterol, and triglyceride. The following exclusion criteria were used: a history of heart disease, respiratory disease, or renal disease; less than 15 years of age; withholding of consent to undergo ABPM. The present study was approved by the Institutional Committee on Human Research of St. Marianna University School of Medicine (No. 1080). Written informed consent was obtained from all patients prior to enrollment.

Polysomnography

SAS was diagnosed based on the results of full PSG (SleepwatcherLEEP WATHCER®, Compumedics, Australia; or Polymate®, Miyuki Giken, Tokyo, Japan). The PSG included an electroencephalogram (EEG), an electro-oculogram, a chin electromyogram, and an electrocardiogram. Four-channel electroencephalography electrodes were attached to the right and left sides at the top and back of the head. A thermistor and a nasal cannula were placed at the nostril and mouth to measure the respiratory airflow; a strain gauge sensor monitored respiratory movements of the chest and abdominal walls. The arterial oxygen saturation (SpO_2) was continuously measured using a pulse oxymeter. Sleeping states were analyzed manually according to the method described by Rechtschaffen and Kales in 1968 (*9*). Apnea was defined as continuous cessation of breathing airflow for 10 s or more per hour of sleep; hypopnea was defined as a reduction in breathing airflow of 50% or more of a normal breath with an SpO_2 desaturation of 3% or an EEG arousal response. The number of SpO_2 drops of at least 3% during sleep was defined as 3% oxygen desaturation index (ODI). The apnea-hypopnea index (AHI) was calculated as the total number of apnea and hypopnea episodes per hour of sleep based on the PSG results. Patients with an AHI≥5/h were diagnosed as having SAS. The severity of SAS was classified according to the AHI: non-SAS (AHI<5), mild (5≤AHI<15), moderate (15≤AHI<30), and severe (30≤AHI).

Arousal response referred to a sudden change from sleeping to waking states induced by outer stimuli, which was defined as 10 s or more in the sleeping state before arousal response and 3 s or more of a frequency change on electroencephalography due to waking.

Twenty-Four-Hour ABPM

Noninvasive 24-h ABPM was performed using an FM-800® (Fukuda Denshi, Tokyo, Japan) or a TM-2431® (A&D, Tokyo, Japan) monitor at consulting rooms in out hospital within 2 months before or after PSG. During ABPM, patients were allowed to continue taking their antihypertensive agents. Long-acting agents were administered to patients who took only one kind of antihypertensive. The BP cuff was attached to the left arm, while the main monitor was attached to the waist. BP was recorded every 30 min for 24 h. The ABPM data obtained by the oscilloscopic method were analyzed according to the method described by Kario *et al*. (*10*)

(Fig. 1). The following BP indices were defined: mean 24-h BP, the average BP of the 24-h ABPM; sleep BP, the average BP during sleep at night; awake BP, the average BP during the rest of the day; BP 1 h before sleep, the average BP of 3 readings 1 h before sleep; lowest BP, the average BP of 3 readings centered on the lowest reading during sleep; preawake BP, the average of 4 readings during the 2 h just before awakening; and morning BP, the average of 4 readings during the 2 h immediately after awakening. The percentage of nocturnal BP reduction was calculated as follows: $100 \times (1 - \text{sleep BP/awake BP})$. We also subclassified the patients according to the percentage of nocturnal BP reduction, as follows: extreme dipper, the nocturnal BP reduction was ≥20%; dipper, the reduction was 10% to <20%; non-dipper, the reduction was 0% to <10%; and risers, the reduction was <0%.

Statistical Analysis

The data are expressed as mean±SD. The unpaired Student's *t*-test and the χ^2 test were used to compare the mean values of parameters between the two groups. Differences among the four groups were analyzed using analysis of variance (ANOVA), and the Bonferroni correction was used for multiple testing. Statistical significance was set at $p<0.05$. Simple regression analysis was used to assess the relationship between the two groups.

Results

Patient Characteristics

A total of 54 eligible patients, including 49 who were diagnosed with obstructive SAS and 5 with non-SAS, were enrolled. Table 1 shows the clinical characteristics of the 54 patients (47 males and 7 females), with a mean age of 55.2±12.6 years and a mean AHI of 31.2±21.8/h. Five patients were in the non-SAS group, 10 in the mild group, 12 in the moderate group, and 27 in the severe group; the mean AHIs in each group were 2.5±1.9/h, 9.6±2.5/h, 23.1±4.3/h and 48.1±17.3/h, respectively. The numbers of patients taking antihypertensive agents were 3 in the mild group, 5 in the moderate group, 16 in the severe group, and none in the non-SAS group.

Table 1. Clinical Characteristics

Number	54
Male/female	47/7
Age (years)	55.2±12.6
Height (cm)	167.8±8.1
Body weight (kg)	75.3±15.1
Body mass index	25.7±5.1
AHI (/h)	31.2±21.8
3% ODI (/h)	31.6±20.9
Mean SpO_2 (%)	93.2±6.7
Arousal (/h)	17.6±23.4
REM (%)	14.7±11.3
Stage 3 (%)	10.3±11.3
Stage 4 (%)	3.6±4.1
Antihypertensive agents	
None	30
Calcium channel blocker	15
Angiotensin receptor blockade	14
Angiotensin converting enzyme inhibitor	13
β-Blocker	5
α-Blocker	2
Diuretics	2
Blood sample data	
Total cholesterol (m/dL)	184.3±23.2
Triglyceride (mg/dL)	152.3±98.5
Plasma glucose (mg/dL)	111.5±22.9
HbA1c (%)	5.4±0.5

Values are mean±SD. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2, arterial oxygen saturation; REM, rapid eye movement.

Diurnal BP Variation and Coronary Risk Factors between SAS Patients and Non-SAS Patients

Table 2 shows the relationship between the presence of SAS and diurnal BP variation. The mean 24-h BP and the mean sleep BP were significantly higher in the SAS group than in the non-SAS group ($p=0.038$ and $p=0.008$, respectively). As well, the lowest BP and preawake BP were significantly higher in the SAS group than in the non-SAS group ($p=0.003$ and $p=0.013$, respectively). The percentages of nocturnal BP reduction in the non-SAS and SAS groups were 15.0±5.6% and 7.4±7.9%, respectively ($p=0.042$). No significant differences were observed between the two groups in mean awake BP, evening BP, and morning BP. Moreover, there were no significant differences between the two groups in cardiovascular risks, such as BMI, total cholesterol, triglyceride, blood glucose level, or HbA1c.

The Relationship between SAS Severity and Diurnal BP Variation

The relationships between SAS severity and the ABPM data are shown in Fig. 2. The mean 24-h BP, mean sleep BP, and lowest BP were significantly higher in the moderate and severe SAS groups than in the non-SAS group ($p=0.045$ and $p=0.003$ [Fig. 2A], $p=0.014$ and $p=0.0008$ [Fig. 2B], and $p=0.0056$ and $p=0.0003$ [Fig. 2C], respectively). The awake BP and preawake BP were similar in each SAS group. Morning BPs (Fig. 2D) were significantly higher in the severe SAS groups than in the mild and non-SAS groups ($p=0.00167$, $p=0.0029$ respectively). Evening BP did not show any significant differences among the SAS groups. The percentage of

Table 2. The Relationship between the Presense of SAS and Diurnal BP Variation

	SAS group (n=49)	Non-SAS group (n=5)	p value
Average BP (mmHg)	129.8±11.6	118.0±13.5	<0.05
Awake BP (mmHg)	133.6±11.8	126.0±16.6	0.195
Evening BP (mmHg)	127.9±16.7	128.2±27.1	0.973
Sleep BP (mmHg)	123.5±13.6	106.4±7.8	<0.01
Lowest BP (mmHg)	114.9±12.7	96.6±6.8	<0.01
Preawake BP (mmHg)	125.9±15.3	107.6±13.0	<0.05
Morning BP (mmHg)	135.2±14.4	123.4±15.4	0.88
Nocturnal BP fall (%)	7.4±7.9	15.0±5.6	<0.05
BMI (kg/m^2)	27.0±5.1	24.4±5.5	0.72
Total cholesterol (mg/dL)	183.7±23.6	190.6±19.4	0.64
Triglyceride (mg/dL)	155.5±100.4	121.4±80.2	0.78
Plasma glucose (mg/dL)	111.9±23.7	108.6±14.3	0.31
HbA1c (%)	5.4±0.5	5.1±0.5	0.68

p<0.05 *vs*. non-SAS group. SAS, sleep apnea syndrome; BP, blood pressure; BMI, body mass index. Underlined part: significant difference.

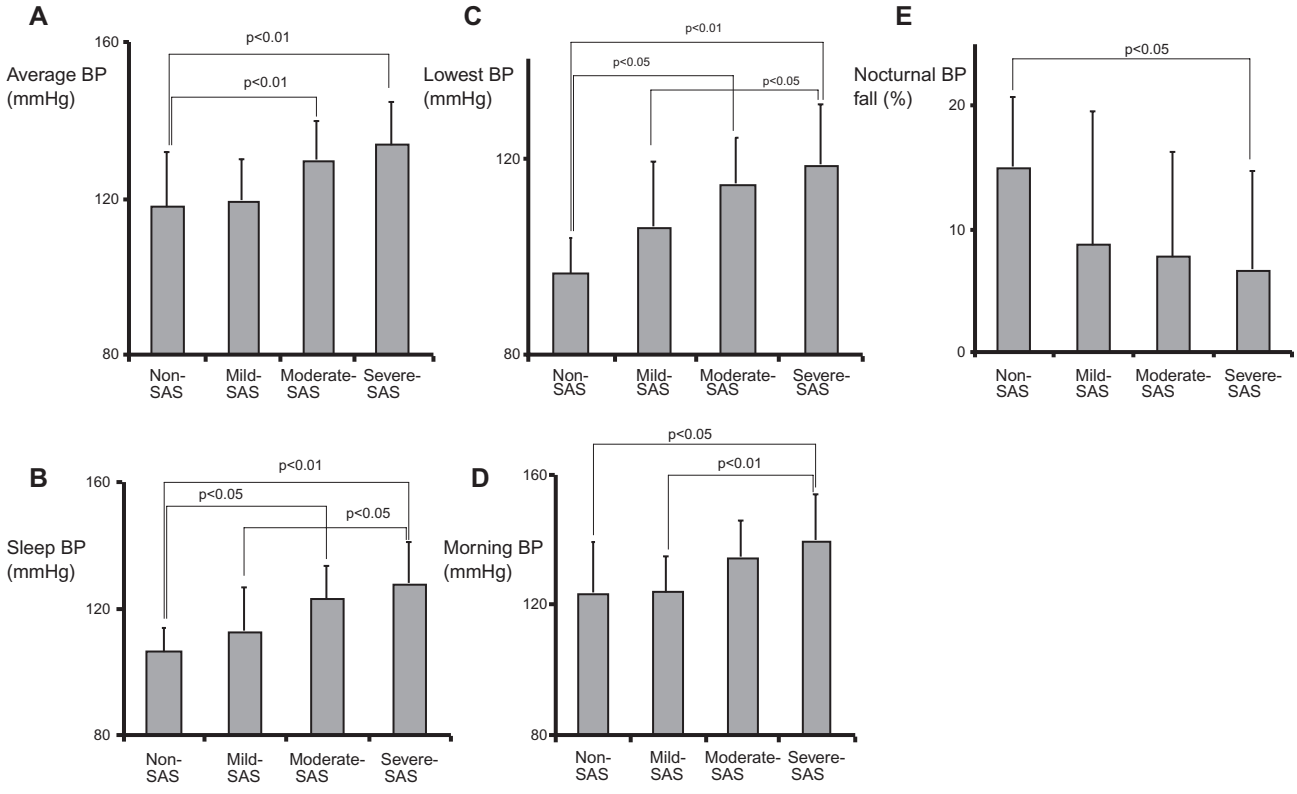

Fig. 2. *The relationship between SAS severity and 24 h average BP (A), Sleep BP (B), Lowest BP (C), Morning BP (D) and Nocturnal BP fall (E). Values are mean±SD.*

nocturnal BP reduction (Fig. 2E) decreased as AHI increased. No significant differences were observed in any of the ABPM parameters between the mild and non-SAS groups.

The percentages of dippers and non-dippers in the AHI<15 and AHI≥15 groups were 57.1% and 14.3% (AHI<15) and 42.5% and 47.5 (AHI≥15), respectively. On the other hand, the percentages of risers were 14.3% (AHI<15) and 10.0% (AHI≥15), respectively, and no significant difference was observed. The AHI<15 group showed dipper-type BP variations, whereas the AHI≥15 group had a significantly high

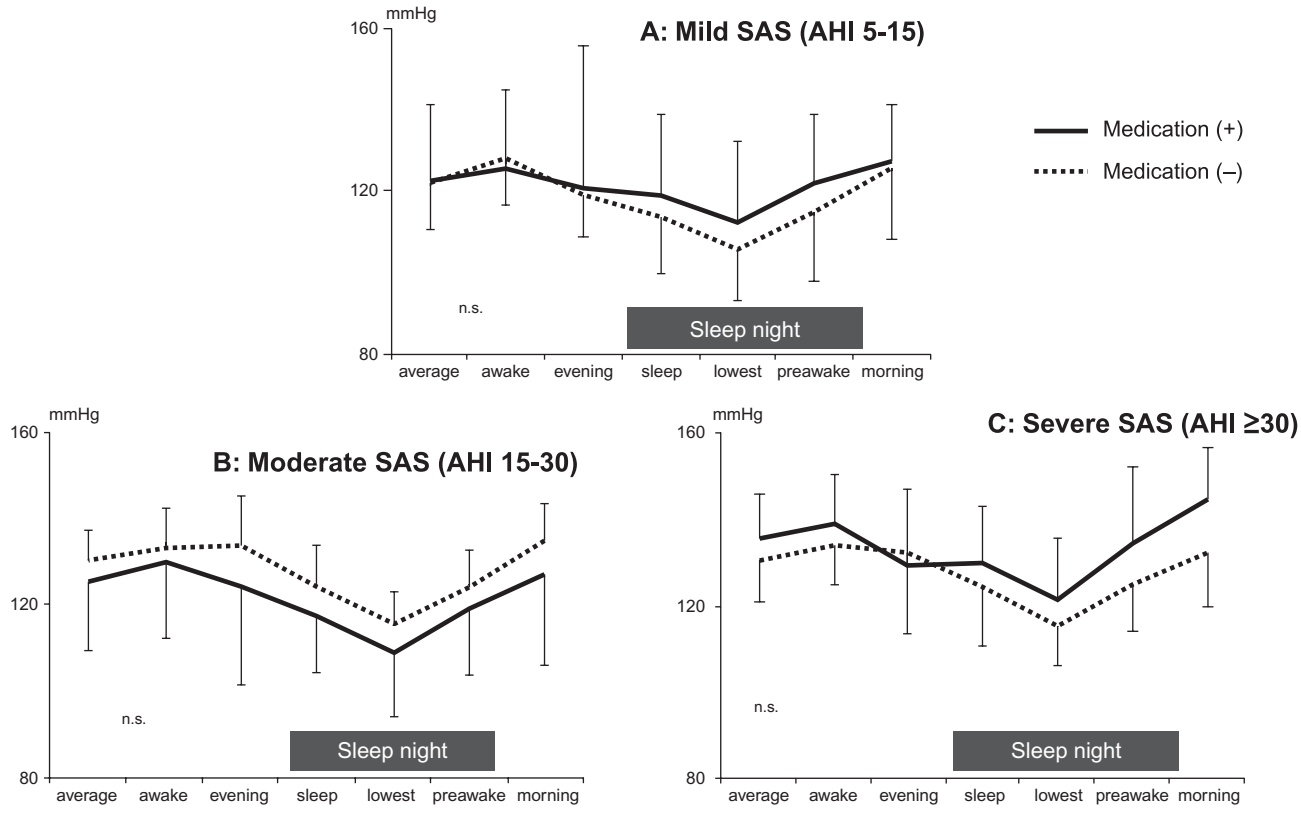

Fig. 3. *The effect of antihypertensive agents on diurnal BP variation in each SAS severity group. Values are mean±SD.*

nondippers percentage ($p=0.05$). Riser-type BP variation was observed in both groups at similar rates.

The relationships between the mean 24-h BP and AHI or 3% ODI were $r=0.412$ ($p=0.002$) and $r=0.36$ ($p=0.008$), respectively, which indicated significantly positive relationships between them. However, no relationship was observed between the mean 24-h BP and the lowest SpO_2 or arousal index.

The Effects of Antihypertensive Agents on Diurnal BP Variation in Each SAS Severity Group

To evaluate the effects of antihypertensive agents on diurnal BP variation in SAS patients, the ABPM parameters were compared between SAS patients who were either treated or not treated with antihypertensive agents. The non-SAS group was not included in this evaluation, as none of the patients in that group was taking antihypertensive medication. There were no significant differences in any of the ABPM parameters between the 16 patients treated with antihypertensive agents and the 11 patients not treated with antihypertensive agents in the severe SAS group (Fig. 3A); the mild and moderate SAS groups had similar results (Fig. 3B, C).

Discussion

Several studies have reported a relationship between SAS and hypertension (*4*, *5*). In the United Sates, the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) suggested that SAS was a major cause of secondary hypertension. SAS has also been recognized as an important risk factor for cardiovascular diseases, including ischemic heart disease, cerebrovascular disease, and chronic heart failure. It is presumed that, in addition to autonomic dysfunction or hypoxic stress accompanying SAS, nocturnal BP elevation in SAS patients may cause cardiovascular disease. However, the exact mechanism remains to be elucidated.

In the ABPM Wave 1 study, Kario *et al*. (*10*) identified the following risk factors for cerebrovascular diseases: less than 10% nocturnal BP reduction (non-dipper pattern), nocturnal BP elevation (riser pattern), and high morning BP. In the present study, we aimed to clarify the relationship between SAS severity and the ABPM parameters that Kario *et al*. (*8*) identified as cardiovascular risk factors.

Diurnal BP Variation and Coronary Risk Factors between SAS Patients and Non-SAS Patients

All nighttime BP parameters, such as mean sleep BP, lowest BP, and preawake BP, were significantly higher in SAS patients than in non-SAS patients. SAS patients had a lower rate of nocturnal BP reduction than non-SAS patients, similar to the findings of Kario *et al*. (*8*). However, in the present study, all of the nighttime BP parameters were higher in SAS patients than in non-SAS patients. This suggests that nocturnal BP elevation due to SAS is an important risk factor for cardiovascular events.

Narkiewicz *et al*. (*11*) studied the mechanism responsible for hypertension in SAS patients and found that intermittent hypoxia during sleep apnea and hypopnea led to a sustained elevation of muscle sympathetic nerve activity. Parati *et al*. (*12*) investigated baroreflex sensitivity and reported that parasympathetic nerve activity was depressed in SAS patients. In addition, other factors, such as capillary endothelial damage (*13*), augmented renin-angiotensin system (RAS) activity (*14*), inflammation (*15*, *16*), and oxidative stress (*17*), have also been reported as factors related to hypertension in SAS patients. However, the mechanism of midnight hypertension in SAS patients was not investigated in this study.

In the present study, the SAS group had a higher morning BP than the non-SAS group; this result is similar to that reported by Kario (*18*). Those authors also reported that sustained high BP at night might be a major cause of early morning hypertension. Therefore, it is vital to use ABPM to investigate and evaluate diurnal BP variation in SAS patients to manage cardiovascular disease risk factors.

The Influence of SAS Severity on Diurnal BP Variation

It is well known that SAS severity is assessed on the basis of various indices, such as AHI, 3% ODI, and the lowest SpO_2. Since AHI correlated well with the mean 24-h BP in the present study, SAS severity was classified according to AHI. Pancow *et al*. (*19*) noted that the percentage of nocturnal BP reduction decreased as SAS severity increased; the results of the present study are in agreement with this observation. In the present study, nighttime BP parameters, such as mean sleep BP, lowest BP, and preawake BP, were significantly higher in the moderate and severe SAS patients than in the non-SAS group; however, there was no significant difference in the nighttime BP between the mild SAS and non-SAS patients. Therefore, it could be assumed that nighttime BP starts to increase as SAS severity increases. Meanwhile, daytime BPs, such as mean daytime, morning, and evening BP, were significantly elevated only in the severe SAS group. No significant difference in daytime BPs was observed in the mild and moderate SAS patients compared to the non-SAS patients.

Kario *et al*. (*8*) reported that morning hypertension is the most important independent predictor of a future clinical stroke in elderly hypertensive patients. Although morning BP was not elevated in patients with mild to moderate SAS patients in the present study, morning BP should be monitored, especially in patients with severe SAS. On the other hand, diurnal BP variation in patients with mild SAS is similar to that in non-SAS patients.

The Effect of Antihypertensive Agents on ABPM in SAS Patients

Several studies have investigated the relationship between antihypertensive agents and SAS treatment (*e.g.*, continuous positive air pressure and oral appliance) (*20*, *21*). To date, no study has evaluated antihypertensive agents' effects on diurnal BP variation. We hypothesized that β-blockers and RAS inhibitors, such as angiotensin-converting enzyme (ACE)-inhibitors and angiotensin II blockers, might have favorable effects in SAS patients, because sympathetic nervous activity, as well as RAS activity, is augmented during sleep. In the present study, antihypertensive therapy had no effect on diurnal BP variation and sustained nighttime BP in the moderate and severe SAS groups.

The patients took antihypertensive agents that had been prescribed by their doctors; none of the patients were prescribed short-acting antihypertensive medications. No significant differences were observed in diurnal BP variation between patients treated with antihypertensive agents and those not treated with antihypertensive agents. Thus, antihypertensive agents had sufficient effect on the augmented sympathetic nerve activity related to SAS that lasted until early morning. Along with continuous positive airway pressure (CPAP) therapy, SAS patients required appropriate antihypertensive agents to treat morning and nighttime hypertension.

Study Limitations

Since there were only 5 non-SAS patients in the present study, a comparative study with a larger number of control subjects is needed. The results of the present study may have been affected by the antihypertensive agents prescribed by the patients' doctors; the details of prescription were not studied. However, this study was not designed to directly assess the effects of drugs. It is vital to conduct a further study with accumulated data and to assess the effects of each antihypertensive agent and its dose method.

The parameters assessed in the present study were based on a study by Kario *et al*. (*10*). There is no consensus about common ABPM evaluation methods; nevertheless, ABPM has identified morning BP as a risk factor of cardiovascular events. ABPM criteria should be established in the future.

We did not investigate or evaluate the mechanism by which hypertension occurs in SAS a patient. This will be the focus of our future studies.

SAS patients have higher 24-h BP than non-SAS patients; in particular, nocturnal BP elevation was marked in SAS patients. Severe SAS patients tended to have elevated BP not only at night but also in the morning. Sustained high nighttime BP was observed in patients with moderate or severe SAS, even if they took antihypertensive agents.

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