Relationship between Sympathetic Nerve Activity Evaluated by Pulse Rate Variability and Blood Pressure Early in the Morning in Sleep Disordered Breathing

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Objective/Background : This study was performed to clarify whether sleep disordered breathing (SDB) contributes to increases in sympathetic nerve (SN) activity during sleep and the development of hypertension.

Patients/Methods : Polysomnography and pulse rate variability (PRV) analysis using a photoplethysmograph were performed simultaneously in 153 male subjects and evaluated by instantaneous time-frequency analysis using the complex demodulation method. Parasympathetic nerve (PN) activity and SN activity were assessed by the amplitude of high-frequency (HF) and the ratio of low-frequency (LF) to HF amplitude (LF/HF ratio), respectively. Blood pressure (BP) before going to bed and early in the morning were measured in all subjects.

Results : The subjects were classified according to the severity of SDB as normal (apnea hypopnea index (AHI) <5 events/h, $n=99$), mild SDB ($5\leq$AHI<15 events/h, $n=28$), and moderate-to-severe SDB groups (AHI≥ 15 events/h, $n=26$). The mean LF/HF ratio was higher according to sleep stage in the order REM sleep>light sleep>slow wave sleep in all groups. The mean LF/HF ratio in each sleep stage and BP both before going to bed and early in the morning were significantly higher in the moderate-to-severe SDB group compared with normal subjects and the mild SDB group and showed a significant correlation with arousal index. The multiple regression model showed that independent associations for the systolic BP early in the morning were age, BMI, cumulative % time with $SpO_2<90$ % (CT90) as an index of hypoxemia during sleep, and decreased sleep efficiency.

Conclusion : The findings of this study suggested that the frequent arousal due to SDB may contribute to the increased SN activity, and that hypoxemia during sleep and sleep disturbance in addition to age and obesity may be associated with increased SBP early in the morning in moderate-to-severe SDB. *Shinshu Med J 67 : 241—251, 2019*

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Key words : obstructive sleep apnea, heart rate variability, electric photoplethysmograph, arousal index, hypoxemia

I Introduction

In patients with obstructive sleep apnea (OSA), the repeated episodes of apnea and hypopnea during sleep result in sleep disturbance, hypoxemia, hypercapnia, and large swings of intrathoracic pressure, which may result in increased sympathetic nerve (SN) activity[1)-3)]. Increased SN activity may contribute to the development of comorbidities, including hypertension[4)], myocardial infarction[5)], and cerebrovascular disease[6)], and adversely affect prognosis[7)8)]. OSA has been listed as an important risk factor for the development of hypertension early in the morning and poorly controlled hypertension[9)]. It has been suggested that the increased SN activity may con-

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tribute to the development of hypertension, especially early in the morning.

Analysis of heart rate variability (HRV) is a simple and non-invasive method to assess autonomic nerve function, generally evaluated by power spectrum analysis of HRV[10]. The ratio of the power of low-frequency bundle (LF) and high-frequency bundle (HF), the LF/HF ratio, represents SN activity and the power of HF represents parasympathetic nerve (PN) activity. It has been demonstrated that the LF/HF ratio is increased in central sleep apnea and OSA[10)11)]. However, sleep architecture has been shown to affect autonomic nerve (AN) activity[12)], and HRV parameters have also been shown to vary among sleep stages[13)]. In rapid eye movement (REM) sleep, SN activity is the highest among the sleep stages and SN activity is suppressed and PN activity is elevated during slow wave sleep (SWS) in normal subjects. It has been demonstrated that there is a close correlation between SWS and HF power[14)15)]. One reason for the higher SN activity during sleep in OSA may involve a lack of SWS. However, there is little evidence regarding whether SN activity is also increased at each sleep stage in OSA.

The present study was performed to clarify whether the status of sleep disordered breathing (SDB) may contribute to increases in SN activity during each sleep stage and the development of hypertension early in the morning. Attended polysomnography (PSG) and recording of pulse rate variability (PRV) using an electric photoplethysmograph instead of electrocardiography (ECG) were simultaneously performed in 165 male company employees, and AN activity in each 30-s epoch on PSG was evaluated by instantaneous time-frequency analysis of PRV using the complex demodulation method.

Ⅱ Materials and Methods

A Subjects

All male workers of a transport company were eligible for inclusion in this study. Most were employed to drive trucks over long distances. All male workers provided written informed consent to participate in this study. Consequently, we performed a complete survey of all male workers ($n=165$) from this company. All subjects were of Japanese ethnicity and were not undergoing continuous positive airway pressure (CPAP) treatment. Subjects who showed arrhythmia＞10 % of total pulse rate, atrial fibrillation, and who were receiving treatment with agents affecting AN function or antihypertensive agents were excluded from the analysis.

B Protocol

The protocol of this study was approved by the institutional research ethics committee of Shinshu University School of Medicine (No. 657 September 6 2005, No. 658 January 4 2006). Subjects underwent PSG between February 2006 and August 2007. Before PSG, all subjects were asked whether they had arrhythmia and were being treated with agents affecting AN function or antihypertensive agents, and were surveyed for daytime sleepiness using the Japanese version of the Epworth Sleepiness Scale (JESS) and physical received an examination. Blood pressure (BP) was measured three times at around 20：30 before the PSG examination and around 06：30 early in the morning just after PSG. The blood pressure was measured in the supine position, and the second and third measurements were adopted and averaged. All subjects underwent simultaneous PSG and recording of PRV using an electric photoplethysmograph (Denso Co., Ltd., Kariya, Japan), which was installed on the mid-posterior part of the forearm, 5 cm from the left wrist, between 21：00 and 06：00 in an accommodation facility at the Asahi campus of Shinshu University. To obtain interpretable data and responses from both the PSG and pulse-wave measurement, the timing of both devices was synchronized. Based on the results of PSG, the subjects were classified according to the severity of SDB. Subjects with apnea hypopnea index (AHI)＜5 events/h were classified as the normal group, subjects with 5≤AHI＜15 events/h were classified as the mild SDB group, and subjects with AHI≥15 events/h were classified as the moderate-to-severe group. The autonomic nerve function, PSG data, and BP were compared among the three groups. Further, the mean HF amplitude and LF/HF ratio in

each sleep stage were analyzed in all three groups and the differences among sleep stages were compared. In addition, the independent determinants of increased SN activity or increased BP early in the morning were analyzed in the mild and mild-to-moderate SDB groups.

C Polysomnography

Standard overnight attended polysomnography (PSG) was performed starting at 20 : 00, and the data were collected from 21 : 00 to 06 : 00 the next morning. The bed was covered with a sheet-form respiratory movement sensor[16]. The PSG was recorded with a digital polygraph (Alice III ; Chest Co. Ltd., Tokyo, Japan). We used standard polysomnographic montages consisting of C4-A2, C3-A1, O2-A1, and O1-A2 electroencephalograms, left and right electrooculograms, submental electromyogram, nasal pressure cannula, oronasal airflow, left and right tibial electromyograms, thoracoabdominal inductance plethysmograms, percutaneous oxygen saturation (SpO_2), a neck microphone, body position sensors, and a modified lead II ECG. The sleep stages and respiratory events were scored according to the AASM Manual for the Scoring of Sleep and Associated Events[17]. The average hourly frequency of apneic and hypopneic episodes was defined as AHI. Total sleep time (TST) was used as the denominator in the calculation of AHI. Arousal index is the mean number of sleep disruption events per hour of total sleep time. Arousals were defined as rapid EEG frequency shift continued for ≥ 3 s in duration and scored according to the criteria of the American Sleep Disorders Association[18]. Sleep efficiency was defined as the ratio of total sleep time (TST) to the total time in bed (TIB). TIB was taken as the time between lights out and lights on[17].

D Analysis of autonomic nerve function

In this study, we evaluated PRV in the frequency domain using a photoelectric plethysmograph instead of HRV analyzed by ECG. The nocturnal autonomic nerve functions were evaluated by instantaneous time-frequency analysis of PRV using a complex demodulation (CD) method[19)20]. This method, a time local version of harmonic analysis, provides the time-dependent changes in amplitude of a particular frequency component as a function of time. The PRV technique using the same device has already been validated against the traditional HRV[21]. The sampling frequency of the electric plethysmograph was 20 Hz. When the pulse-wave peak-to-peak interval (PPI) was shortened by > 20 % of the mean of the preceding 10-beat intervals of PPI, the PPI was automatically excluded from analysis as an isolated/sporadic premature supraventricular/ventricular contraction or body movement. The frequency spectra of the PPI data were estimated for the range between 0 and 0.40 Hz and divided into two components depending on their central frequencies ; one domain between 0.04 and 0.15 Hz was labeled as the band with LF and the other between 0.15 and 0.40 Hz as the band with HF. The LF/HF ratio was used as a marker of SN discharge to the cardiac sinus node[9]. The mean values of HF amplitude were used as markers of PN discharge[22]. The amplitudes of LF and HF bundles and the LF/HF ratio were calculated as the mean values of one epoch (30 s) of PSG consistent with the analysis of sleep staging. Finally, the total mean amplitude of HF and LF/HF ratio in each sleep stage (non-REM stage 1-4 and REM sleep) were calculated.

E Statistical analysis

Values in the text, tables, and figures are shown as the means ± SEM. The Mann-Whitney U test was used for comparison of variables among the normal, mild SDB, and moderate-to-severe SDB groups and sleep stages in each group. Spearman's rank correlation coefficient was used for bivariate correlation analysis. Multiple linear regression analysis was performed to identify variables that were significantly associated with systolic BP (SBP) early in the morning. Explanatory variables were age, BMI, sleep efficiency, arousal index, cumulative % time with $SpO_2 < 90$ % (CT90), and mean LF/HF ratio. A value of $P \leq 0.15$ was used to identify candidate variables, and then variables were removed from the regression model if $P > 0.1$. All statistical analyses were performed using StatFlex version 6 for Windows (Artech Co., Ltd., Osaka, Japan). In all analyses, $P <$

Table 1 Characteristics among normal subjects (AHI＜5 events/h) and subjects with mild (5≤AHI ＜15 events/h) and moderate-to-severe (AHI≥15 events/h) SDB

	Normal	Mild	Moderate-to-severe
n	99	28	26
Age, years	40.4±1.2	44.5±1.6	52.3±1.7**††
BMI, kg/m^2	22.7±0.3	24.2±0.5**	26.5±0.7**†
Neck circumference, cm	36.9±0.2	37.6±0.4	39.5±0.5**††
Waist circumference, cm	79.6±0.8	85.0±1.5**	91.8±2.0**†
SBP before going to bed, mmHg	128.0±1.7	129.9±2.9	138.9±3.0**†
DBP before going to bed, mmHg	79.8±1.2	83.1±2.0	87.8±2.0**
SBP early in the morning, mmHg	121.8±1.7	124.5±3.1	140.6±3.1**††
DBP early in the morning, mmHg	78.4±1.2	80.5±2.0	90.0±2.3**††
ΔSBP, mmHg	−6.2±1.3	−5.5±2.4	1.7±2.1**†
ΔDBP, mmHg	−1.4±1.0	−2.6±1.4	2.2±1.5†
JESS	4.1±0.4	4.6±0.6	6.0±0.8*

Values are means±SEM. $^{*}P<0.05$ and $^{**}P<0.01$ vs. normal. $^{\dagger}P<0.05$ and $^{\dagger\dagger}P<0.01$ vs. mild SDB.
AHI, apnea hypopnea index; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; ΔSBP or ΔDBP, difference of SBP or DBP before going to bed and early in the morning; JESS, Japanese version of the Epworth sleepiness scale; SDB, sleep disordered breathing.

0.05 was taken to indicate statistical significance.

Ⅲ Results

The data for 12 of the total of 165 subjects were excluded because of arrhythmia＞10 % and lack of data＞10 % due to poor device attachment. Subjects treated with antihypertensive agents were also excluded. Finally, the data of 153 subjects were included in the analyses. Ninety-nine subjects were without SDB (normal group), 28 subjects had mild SDB, and 26 subjects had moderate-to-severe SDB. The subjects in the moderate-to-severe SDB group had significantly higher age, BMI, and both neck and waist circumferences in comparison with the normal and mild SDB groups **(Table 1)**. In addition, the JESS score was significantly higher in the moderate-to-severe group than the normal group. Furthermore, the SBP before going to bed and both SBP and DBP early in the morning, and the difference in SBP between before going to bed and early in the morning were significantly higher in the moderate-to-severe SDB group than in the normal and mild SDB groups **(Fig. 1)**. **Table 2** shows the data of PSG for the three groups. There were no significant differences in TST, sleep efficiency, or percentage of stage 2 sleep between the groups. The subjects in the moderate-to-severe group showed the highest percentage of stage 1 sleep and lowest percentages of stage 3 and 4 sleep and REM sleep compared with the normal group. Almost all of the subjects with SDB showed obstructive sleep apnea. All of the subjects in the moderate-to-severe group showed frequent arousal on EEG and desaturation represented by 3 % ODI (cumulative desaturation events with SpO_2≥3 %/h) and severe hypoxemia represented by CT90 (cumulative % time with SpO_2＜90 %) consistent with episodes of apnea and hypopnea during sleep. **Table 3** shows the results of AN function of TST, light sleep (stage 1＋stage 2 sleep), SWS (stage 3＋stage 4 sleep), and REM sleep. The mean LF/HF ratios showed the order REM sleep＞light sleep＞SWS sleep in all groups. The LF/HF ratio in each sleep stage and the BP both before going to bed and early in the morning were higher in the moderate-to-severe group than in the normal and mild SDB groups. In the mild SDB and moderate-to-severe groups, the mean LF/HF ratio in TST was significantly correlated with age and arousal index **(Fig. 2**, left side) with correlation coefficients＞0.4 **(Table 4)**. Similarly, the SBP early in the morning was significantly correlated with age, DBP early in the morning, and mean HF amplitude **(Fig. 2**, right side). In

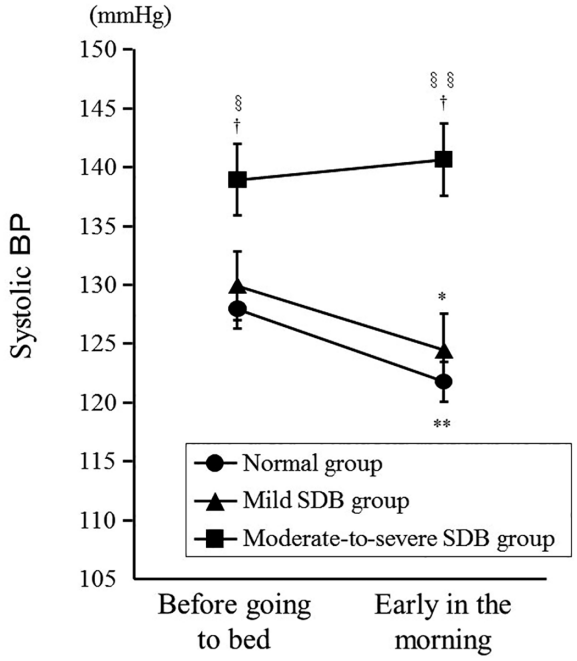

Fig. 1 Changes in systolic BP from the mean values before going to bed to those early in the morning in the normal group (AHI<5 events/h), mild SDB group (5≤AHI<15 events/h), and moderate-to-severe SDB group (AHI≥15 events/h)

Values are mean±SEM. $^{*}P<0.05$, $^{**}P<0.01$ vs. values before going to bed, $^{\dagger}P<0.01$ vs. normal group, $^{\S}P<0.05$, $^{\S\S}P<0.01$ vs. mild SDB group.

Abbreviations : AHI, apnea hypopnea index ; BP, blood pressure ; SDB, sleep disordered breathing.

Table 2 Results of PSG among normal subjects (AHI<5 events/h) and subjects with mild (5≤AHI<15 events/h) and moderate-to-severe (AHI≥15 events/h) SDB

	Normal	Mild	Moderate-to-severe
n	99	28	26
TST, min	478±10	493±20	483±23
Sleep efficiency, %	76.6±1.2	79.3±2.2	78.1±3.2
Stage 1, %	18.5±0.9	21.9±1.8*	26.3±2.9*
Stage 2, %	62.4±0.9	60.9±1.7	59.9±3.0
Stage 3, %	2.1±0.3	0.6±0.3**	0.4±0.2**
Stage 4, %	0.2±0.1	0.0±0.0	0.0±0.0*
REM sleep, min	17.2±0.5	16.1±1.1	13.3±1.0**
AHI, events/h	1.7±0.1	8.5±0.5**	37.2±3.2**†
AI, events/h	0.5±0.1	3.2±0.6	21.7±3.1**†
OAI, events/h	0.3±0.1	2.5±0.5**	20.1±3.0**†
Arousal index, events/h	25.5±1.3	25.1±2.1	41.5±2.9**†
CT90, %	0.5±0.2	1.2±0.4**	12.3±3.0**†
3 % ODI, events/h	2.7±0.2	9.0±0.6**	35.5±3.0**†

Values are means ± SEM. $^{*}P<0.05$ and $^{**}P<0.01$ vs. normal. $^{\dagger}P<0.01$ vs. mild SDB.

AHI, apnea hypopnea index ; TST, total sleep time ; REM, rapid eye movement ; AI, apnea index ; OAI, obstructive apnea index ; CT90, cumulative % time with $SpO_2<90$ % ; 3 %ODI, cumulative number of desaturation events with $SpO_2\geq3$ %/h ; SDB, sleep disordered breathing.

Table 3 Comparison of mean LF/HF ratio and HF amplitude in each sleep stage among normal subjects (AHI＜5 events/h) and subjects with mild (5≤AHI＜15 events/h) and moderate-to-severe (AHI≥15 events/h) SDB.

	Normal	Mild	Moderate-to-severe
n	99	28	26
LF/HF ratio			
All sleep stages	0.77 ± 0.02	0.83 ± 0.05	1.02 ± 0.05**†
Stage 1 and 2	0.78 ± 0.02	0.83 ± 0.05	1.03 ± 0.05**†
Stage 3 and 4	0.66 ± 0.02§	0.69 ± 0.05	0.94 ± 0.07**††
Stage REM	0.99 ± 0.03§§§	1.07 ± 0.08§§§	1.24 ± 0.08**§§
HF amplitude, ms			
All sleep stages	30.9 ± 1.4	31.6 ± 3.0	24.3 ± 1.6*†
Stage 1 and 2	31.4 ± 1.4	32.0 ± 2.9	24.8 ± 1.7*
Stage 3 and 4	30.8 ± 1.5	30.4 ± 4.3	25.7 ± 2.4
Stage REM	28.8 ± 1.4§	30.2 ± 3.5	21.7 ± 1.3*§§

Values are means ± SEM. $^{*}P<0.05$ and $^{**}P<0.01$ vs. normal. $^{\dagger}P<0.05$ and $^{\dagger\dagger}P<0.01$ vs. mild SDB, $^{\S}P<0.01$ vs. stage 1 and 2, $^{\S}P<0.05$ and $^{\S\S}P<0.01$ vs. stage 3 and 4.
LF, low frequency ; HF, high frequency ; AHI, apnea hypopnea index ; REM, rapid eye movement ; SDB, sleep disordered breathing.

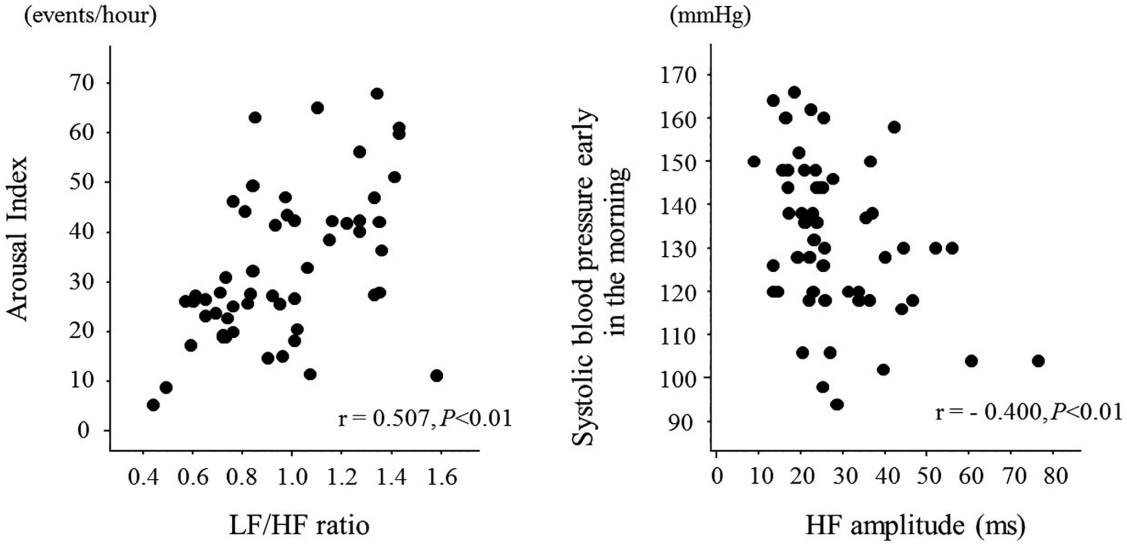

Fig. 2 Relationships between the mean LF/HF ratio and arousal index (left side) and between the mean HF amplitude and systolic blood pressure early in the morning (right side).
Abbreviations : LF, low frequency ; HF, high frequency.

multiple linear regression analysis in the total study population, we selected age, BMI, sleep efficiency, arousal index, CT90, and mean LF/HF ratio as explanatory variables for SBP early in the morning based on single linear regression analysis and medical evidence regarding the association with SBP. Arousal index was selected instead of AHI or 3 % ODI because these variables were closely associated with each other, and the arousal index directly reflected sleep disturbance due to SDB. A regression model with the variables age, BMI, sleep efficiency, arousal index, CT90, and mean LF/HF ratio were proposed (**Table 5** upper panel). Furthermore, the mean LF/HF ratio was significantly correlated with age (r = 0.42), and the arousal index was significantly correlated with CT90 (r = 0.45). Both the mean LF/

Table 4 Correlation coefficients calculated by single linear regression analysis between the LF/HF ratio or BP early in the morning and age, anthropometry, JESS, or polysomnography data in subjects with mild and moderate-to-severe SDB ($n=54$)

	LF/HF ratio	SBP (EM)
Age, years old	0.53**	0.43**
BMI, kg/m^2	0.06	0.17
Neck circumference, cm	0.06	0.20
Waist circumference, cm	0.16	0.20
SBP (EM), mmHg	0.34*	–
DBP (EM), mmHg	0.33*	0.85**
JESS	0.08	−0.03
Sleep efficiency, %	0.09	0.00
AHI, events/h	0.36**	0.28*
SWS, %	−0.07	−0.02
REM, %	−0.22	0.03
Arousal index, events/h	0.51**	0.32*
CT90, %	0.32*	0.34*
3 %ODI, events/h	0.30*	0.36**
LF/HF ratio	–	0.34*
HF amplitude, ms	−0.53**	−0.40**

*$P<0.05$ and **$P<0.01$.

Abbreviations: JESS, Japanese version of the Epworth sleepiness scale; EM, early in the morning; LF, low frequency; HF, high frequency; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; AHI, apnea hypopnea index; SWS, slow wave sleep; REM, rapid eye movement; CT90, cumulative % time with $SpO_2<90$ %; 3 %ODI, cumulative number of desaturation events with $SpO_2\geq 3$ %/h; SDB, sleep disordered breathing.

Table 5 Results of multiple linear regression analysis in all subjects ($n=153$)

Criterion Variables	Explanatory Variables	stdβ	P values
SBP early in the morning (Model 1: r = 0.555, $P<0.0001$)			
	Age	0.37	<0.0001
	BMI	0.21	0.0034
	Sleep efficiency	−0.11	0.1118
	Arousal index	0.10	0.2301
	CT90	0.13	0.1081
	LF/HF ratio	0.04	0.6379
SBP early in the morning (Model 2: r = 0.547, $P<0.0001$)			
	Age	0.40	<0.0001
	BMI	0.21	0.0033
	CT90	0.18	0.0136
	Sleep efficiency	−0.11	0.1094

Abbreviations: SBP, systolic blood pressure; BMI, body mass index; CT90, cumulative % time with $SpO_2<90$ %; LF, low frequency; HF, high frequency.

HF and arousal index showed poor associations, and were therefore excluded. Finally, a significant regression model was proposed consisting of age, BMI, CT90, and sleep efficiency (**Table 5** lower panel). These findings indicated that age, BMI, CT90, and sleep efficiency were significantly and independently associated with increased SBP early in the morning.

Ⅳ Discussion

PSG and PRV were examined simultaneously and

analyzed in 153 male employees. The SN activity showed the order REM sleep＞light sleep＞SWS in all groups. The SN activity in each sleep stage and the BP both before going to bed and early in the morning were higher in subjects with moderate-to-severe obstructive SDB than in the normal and mild SDB groups. The increased SN activity was closely correlated with age ($r=0.53$) and arousal index ($r=0.51$). Multiple linear regression analysis indicated that age, BMI, hypoxemia during sleep represented by CT90, and decreased sleep efficiency were significantly and independently associated with SBP early in the morning. These findings suggested that the frequent cortical arousal due to SDB may contribute to the increased SN activity, and that hypoxemia during sleep in addition to age and obesity may be associated with the increased SBP early in the morning in moderate-to-severe SDB.

In this study, an electric photoplethysmograph was used to evaluate HRV instead of ECG. This has been proposed as a surrogate for ECG in analysis of HRV due to its ease of application. The pulse frequency demodulation technique using the same electric photoplethysmograph used in this study has been validated previously against traditional HRV[22] and provided a reliable assessment of PRV.

The method for direct measurement of SN activity involves measurement of muscle SN activity by microneurography[23]. However, this method is invasive and requires specialized skill to perform. HRV analysis is a simple and non-invasive method, but it is subject to a number of problems, including poor time resolution and the effects of differences in sleep architecture on AN function. Generally, HRV has been evaluated by classical power spectrum analysis, including the fast Fourier transform algorithm or the autoregressive approach. However, the time resolution is low and requires at least 100 heart beats, so it requires approximately 2 minutes to obtain the data necessary for definitive analysis of the frequency domains contained in the R-R intervals of the heartbeat[24)25]. On the other hand, the sleep stage is judged by each 30-s epoch. Therefore, HRV cannot be analyzed using the classical method. The complex demodulation (CD) method used in the present study enabled measurement of transitional changes in instantaneous amplitude of the target frequency domain from short-time recordings lasting for 6.7 s, corresponding to approximately seven beats[19)20]. Therefore, instantaneous time-frequency analysis using the CD method could allow analysis of PRV for each 30-s epoch.

It has been reported that SN activity changes according to sleep stage in the order REM sleep＞light sleep＞SWS in normal subjects[11)14]. In subjects with moderate-to-severe SDB, the SN activity was elevated at all sleep stages compared to normal subjects, and also showed the order REM sleep＞light sleep＞SWS. The SN activity during REM was significantly higher than those in light sleep and SWS. The SN activity evaluated by microneurography has also been shown to be increased during sleep, especially during stage 2 of non-REM sleep and REM sleep, when apnea severity and oxygen desaturation are greatest[26]. Liang et al.[27] recently reported AN function in each sleep stage evaluated by HRV in patients with sleep apnea-hypopnea syndrome with AHI≥10 events/h. The LF/HF ratio was increased in all stages, consistent with the observations of the present study, and subjects with coexisting respiratory events and cortical arousals showed the highest values at all stages. They concluded that respiratory events break the parasympathetic/sympathetic balance, and subsequent arousal enhances this imbalance. In the present study, a significant correlation was observed between SN activity and arousal index. SN activity has been shown to be highest at the end of an episode of apnea, and a large increase in blood pressure is observed together with cortical arousal after reopening of the upper airway[28]. In the present study, the BP in the moderate-to-severe SDB group was significantly higher and weakly correlated with hypoxemia during sleep, intermittent desaturation, arousal index, SN activity, and suppressed PN activity in addition to age. The age, BMI, hypoxemia during sleep due to SDB, and decreased sleep efficiency were independently associated with the increased SBP early in the morning in all sub-

jects. It has been suggested that hypoxemia, hypercapnia, changes in cardiohemodynamics by marked negative intrathoracic pressure, and frequent arousal due to apnea and hypopnea may cause increases in SN activity, and thus contribute to the risk of developing hypertension, especially masked hypertension, such as midnight surge and morning surge types[29)30)]. In the present study, a strong correlation between increased SBP early in the morning and SN activity was not observed. Both the SN activity and SBP were strongly correlated with age, and may mask the relationship. However, the hypoxemia and sleep disturbance due to SDB were independently associated with increased SBP. These findings suggest that the cortical arousals due to apnea and hypopnea cause the burst of SN, and that hypoxemia and sleep disturbance may contribute to the increase in SBP early in the morning. However, a close relationship between SN activity and SBP was not observed as these variables may be strongly affected by age and BMI.

This study had several limitations. First, the moderate-to-severe SDB group showed higher age and BMI because the SDB is usually affected by age and BMI. Age is an important factor affecting AN function, which also affects BP together with obesity. These factors may have affected the results of the present study. Therefore, further age- and BMI-matched studies or a longitudinal approach would be required to clarify the relationship between increased SN activity and hypertension early in the morning. Second, all subjects were male because most of the company employees were male, so differences related to sex could not be evaluated. Third, the distribution of SDB severity was skewed toward mild SDB, with only 16 subjects showing severe SDB≥30 events/h. However, it may be meaningful to determine the significance of differences according to severity and relationships with BP even in a population relatively skewed toward mild-to-moderate SDB. Finally, BP was only evaluated before and after PSG examination. The diagnosis of early morning hypertension should be performed based on the mean of at least 5 days[31)], but this could not be accomplished in the present study.

V Conclusion

Frequent arousal due to SDB may contribute to increased SN activity, and hypoxemia during sleep and sleep disturbance in addition to age and obesity may be associated with the increased SBP early in the morning in moderate-to-severe SDB.

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Conflict of Interest

The authors declare no conflicts of interest associated with this report.

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