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ORIGINAL ARTICLE

Relationship between chronic kidney disease and sleep blood pressure in patients with sleep apnea syndrome

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Chronic kidney disease (CKD) is common disease in patients with sleep apnea syndrome (SAS), which is considered to be responsible for secondary and nocturnal hypertension. In this study, we assessed blood pressure (BP) changes in SAS patients with CKD. Of 460 Japanese outpatients with suspected SAS who underwent ambulatory BP monitoring within 3 months of overnight polysomnography, 198 patients (172 males and 26 females) who were not receiving treatment with antihypertensives or nitroglycerin were enrolled. The estimated glomerular filtration rate (eGFR) was calculated, and the patients were stratified into the high (H; eGFR $\geqslant$ 60 ml min^{-1} per 1.73 m^2) or the low (L; eGFR $<$ 60 ml min^{-1} per 1.73 m^2) group. The patients in the L group were significantly older than those in the H group ($P<0.001$), and body mass index was significantly smaller in the L group than in the H group ($P=0.025$). The rate of patients treated with statin ($P=0.030$) and the levels of both triglyceride ($P=0.006$) and creatinine ($P<0.001$) differed significantly between the two groups. The sleep data, 24-h BP, awake BP and morning BP showed no significant differences between the two groups. However, sleep systolic and diastolic BPs were significantly higher in the L group (122.5 ± 16.7 mm Hg and 81.1 ± 12.2 mm Hg, respectively) than in the H group (117.1 ± 11.8 mm Hg, $P=0.033$; and 76.1 ± 9.5 mm Hg, $P=0.012$, respectively). SAS patients with CKD had elevated sleep BP. This result suggests that appropriate treatments for both SAS and CKD prevent sleep BP elevation, which is considered a risk factor for the onset risk of a cardiovascular event.
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Keywords: ambulatory blood pressure monitoring; circadian blood pressure; estimated glomerular filtration rate; nocturnal hypertension; polysomnography

INTRODUCTION

It is important to consider blood pressure (BP) outside of a clinic setting when treating patients with hypertension, because BP measurements obtained in a clinic setting are not representative of BP outside of the clinic setting. Abnormal changes in circadian BP are considered to increase the risk of cardiovascular event. Patients with nocturnal hypertension or a morning BP surge tend to have a higher incidence of silent cerebrovascular disease[1] and greater intima-media and relative wall thickness compared with normotensive patients.[2] Nocturnal hypertension and morning BP surge are induced by sleep disordered breathing, which can be observed in 22% of Japanese adult males.[3] Typical clinical features of BP changes in patients with sleep disordered breathing and those with sleep apnea syndrome (SAS) are nocturnal hypertension and non-dipper patterns of circadian BP. As the severity of SAS increases, sleep BP is elevated even in a patient whose BP is within the normal range in the clinic. Moreover, the incidence of nocturnal cardiovascular events while sleeping increases in these patients.[4–6]

Chronic kidney disease (CKD) seems to be tightly linked with nocturnal hypertension and morning BP surge.[7] CKD poses a high risk for the onset of cardiovascular disease. Early detection and appropriate treatment delays the progression of kidney disease and prevents the incidence of cardiovascular disease.[8] It is possible that nocturnal BP elevation and morning BP surges, which can be observed in many CKD patients, may contribute to the occurrence of cardiovascular disease.

In this study, we focused on SAS patients who were not treated with antihypertensives and hypothesized that increases in severity of renal dysfunction were positively correlated with nocturnal BP elevation. We used 24-h ambulatory BP monitoring (ABPM) to determine whether there was a link between the severity of CKD and circadian BP changes in SAS patients.

METHODS

Subjects

This study included 460 Japanese outpatients with SAS who presented to the St Marianna University School of Medicine Hospital between April 2006 and December 2009 who underwent overnight polysomnography (PSG) and ABPM within 3 months of PSG. Of these, 198 patients (172 males and 26 females) who were not treated with antihypertensives or nitroglycerin were enrolled. We investigated prescribed drugs and dosing regimens, including insulin injection, p.o. antihyperglycemics and antihyperlipidemics. Patients with heart disease,

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respiratory disease, those receiving dialysis, renal transplant recipients and those aged <18 years were excluded from this study. All study patients were diagnosed as having obstructive SAS.

Blood parameters

High-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides (TG), hemoglobin A1c, brain natriuretic peptide and creatinine were measured in the fasting state. According to the recommendation of the Japanese Society of Nephrology, the estimated glomerular filtration rate (eGFR) was calculated based on the following equations: eGFR for males (ml min^{-1} per 1.73 m^2)=194×Cr$^{-1.094}$×age$^{-0.287}$; eGFR for females (ml min^{-1} per 1.73 m^2)=194×Cr$^{-1.094}$×age$^{-0.287}$×0.739.[9] All patients were stratified into either the high (H; eGFR ⩾60 ml min^{-1} per 1.73 m^2) or the low (L; eGFR <60 ml min^{-1} per 1.73 m^2) group based on eGFR.

Polysomnography

SAS was determined from the results of full PSG using SLEEP WATCHER (Compedics, Australia) or Polymate (Miyuki Giken, Tokyo, Japan). A nasal cannula was placed at the nares to measure the respiratory airflow using a disposable airflow sensor, and a strain gauge sensor monitored respiratory movements of the chest and abdominal walls. Arterial oxygen saturation (SpO_2) was continuously monitored using a pulse oxymeter. The trained technicians analyzed sleep states according to the manufacturer's manual.[10] Apnea was defined as a continuous cessation of breathing airflow for 10 s or more per hour of sleep; hypopnea was defined as a 50% or greater reduction in breathing airflow with a SpO_2 desaturation ⩾3%. The apnea–hypopnea index (AHI) was calculated from the PSG results as the total number of episodes of apnea and hypopnea per hour of sleep. A cumulative percentage of time at saturation below 90% (CT 90%), ⩾3% oxygen desaturation index, the number of desaturation episodes per hour of sleep and 4% oxygen desaturation index were also calculated.

24-h ABPM

Non-invasive ABPM was performed for 24 h using a FM-800 (Fukuda Denshi, Tokyo, Japan) at 30-min intervals.[11] ABPM and PSG were performed on two different days. BP was measured by the oscilloscopic method with an automated BP cuff or by the Korotkoff method. The ABPM data were analyzed based on the method described by Kario *et al.*,[1] and the following systolic BP and diastolic BP were measured: sleep BP, the average BP during sleep at night; awake BP, the average BP during the rest of the day; morning BP, the average BP 1.5 h immediately after awakening.

Statistical analysis

The data are expressed as means ± standard deviation. Differences between the two groups were determined by the analysis of variance; Student's *t*-test was used for multigroup comparisons. Before multivariate analysis was performed, the relationship between two variables was indicated by the correlation coefficient. The analysis of covariance was also used for evaluation of the variables. All analysis was performed using JMP software for Windows (version 7.0; SAS Institute, Carey, NC, USA). Statistical significance was established at $P<0.05$.

Ethics

This study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki. The study protocol was approved by the St Marianna University School of Medicine Institutional Committee on Human Research (No. 1142). Written informed consent was obtained from all of the patients before their enrollment in the study.

RESULTS

Backgrounds

The patients' backgrounds are summarized in Table 1. The patients in the L group were significantly older than those in the H group ($P<0.001$). The body mass index (BMI) was significantly higher in the H group than in the L group ($P=0.025$). The number of patients treated with statin was significantly greater in the L group than in the H group ($P=0.030$). There were no significant differences in High-density lipoprotein and low-density lipoprotein cholesterol levels, hemoglobin A1c or brain natriuretic peptide between the two groups; however, TG and creatinine were significantly higher in the L group than in the H group ($P<0.006$ and $P<0.001$, respectively). The L group had a significantly lower eGFR than the H group ($P<0.001$). When we stratified the study patients into each CKD stage based on eGFR,[9] 44 patients (22%) were stage 1 (eGFR ⩾90 ml min^{-1} per 1.73 m^2), 125 patients were stage 2 (eGFR: 60–89 ml min^{-1} per 1.73 m^2), 29 patients were stage 3 (eGFR: 30–59 ml min^{-1} per 1.73 m^2), and none were stage 4 or stage 5.

Table 2 shows the obtained sleep data. All study patients had obstructive SAS. We found no significant differences in the AHI, apnea index, central apnea, obstructive apnea, mixed apnea, arousal index, 3% oxygen desaturation index, 4% oxygen desaturation index, CT 90% or lowest oxygen saturation between the two groups.

Table 1 Patients' backgrounds

	All patients	*H group*	*L group*	P-*value*
Number of patients	198	169	29	
Sex (M/F)	172/26	160/9	12/17	
Age (years)	47.6 ± 13.4	45.4 ± 12.5	60.7 ± 10.9	<0.001
BMI (kg m^{-2})	26.7 ± 4.9	27.1 ± 5.0	24.9 ± 3.9	0.025
Antihypertensives no.	0	0	0	
Insulin no. (%)	7 (4)	6 (4)	1 (3)	NS
Statin no. (%)	103 (52)	82 (49)	21 (72)	0.030
HDL cholesterol (mg dl^{-1})	51.8 ± 17.1	52.7 ± 17.6	46.7 ± 12.6	NS
LDL cholesterol (mg dl^{-1})	125.0 ± 33.7	125.6 ± 32.9	121.4 ± 38.6	NS
TG (mg dl^{-1})	200.0 ± 133.3	179.6 ± 131.5	254.0 ± 142.1	0.006
Hb A1c (%)	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.4	NS
BNP (pg ml^{-1})	33.7 ± 33.5	35.3 ± 36.5	26.5 ± 11.5	NS
Creatinine (mg dl^{-1})	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.1	<0.001
eGFR (ml min^{-1} per 1.73 m^2)	79.1 ± 21.6	84.0 ± 19.3	50.6 ± 6.3	<0.001

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; F, female; H, high; Hb A1c, glycosylated hemoglobin; HDL, high-density lipoprotein; L, low; LDL, low-density lipoprotein; M, male; NS, non-significant; TG, triglyceride.
The values are presented as the mean ± s.d.

Table 2 Sleep data

	All patients	*H group*	*L group*	P-*value*
AHI (per h)	32.9 ± 25.7	32.1 ± 25.2	38.0 ± 28.2	NS
AI (per h)	16.4 ± 20.8	15.9 ± 21.2	19.2 ± 18.2	NS
CA (per h)	0.9 ± 2.1	1.0 ± 2.4	0.9 ± 2.2	NS
OA (per h)	15.0 ± 20.2	14.6 ± 21.0	16.7 ± 16.8	NS
MA (per h)	0.8 ± 3.0	0.5 ± 2.0	1.6 ± 5.6	NS
Arousal index (per h)	35.0 ± 22.4	34.6 ± 22.6	37.0 ± 21.7	NS
3% ODI (per h)	31.9 ± 26.1	31.0 ± 25.3	37.4 ± 30.4	NS
4% ODI (per h)	25.5 ± 25.8	24.5 ± 24.8	31.6 ± 30.5	NS
CT 90% (%)	7.0 ± 14.6	6.5 ± 12.8	10.2 ± 18.6	NS
Lowest oxygen saturation (%)	79.7 ± 14.9	79.8 ± 15.5	79.1 ± 10.7	NS

Abbreviations: AHI, apnea–hypopnea index; AI, apnea index; CA, central apnea; CT 90%, cumulative percentages of time at saturation below 90%; eGFR, estimated glomerular filtration rate; H, high; L, low; MA, mixed apnea; OA, obstructive apnea; ODI, oxygen desaturation index. The values are presented as the mean ± s.d.

Table 3 Blood pressure

Period	*Blood pressure (mm Hg)*	*All patients*	*H group*	*L group*	P-*value*
24 h	Systole	127.3 ± 11.0	126.9 ± 10.4	129.7 ± 13.7	NS
	Diastole	83.7 ± 8.9	83.2 ± 8.3	86.6 ± 11.9	NS
Awake	Systole	132.3 ± 11.4	132.1 ± 11.2	134.0 ± 12.9	NS
	Diastole	86.9 ± 9.3	86.6 ± 8.6	88.9 ± 12.5	NS
Sleep	Systole	117.9 ± 12.7	117.1 ± 11.8	122.5 ± 16.7	0.033
	Diastole	76.8 ± 10.1	76.1 ± 9.5	81.1 ± 12.2	0.012
Morning	Systole	131.7 ± 13.4	131.4 ± 13.3	133.2 ± 14.3	NS
	Diastole	87.8 ± 11.1	87.7 ± 10.5	88.4 ± 13.9	NS

Abbreviations: H, high; L, low; NS, non-significant.
The values are presented as the mean ± s.d.

Table 4 Correlations between sleep blood pressure and each variable

	Systolic sleep blood pressure		*Diastolic sleep blood pressure*	
Relative correlation	*R*	P-*value*	*R*	P-*value*
All patients				
Age	0.045	0.531	0.103	0.150
AHI	0.383	<0.001	0.309	<0.001
eGFR	−0.068	0.343	−0.161	0.023
H group				
Age	−0.072	0.352	−0.025	0.749
AHI	0.347	<0.001	0.240	0.002
eGFR	0.021	0.783	−0.082	0.291
L group				
Age	0.242	0.207	0.350	0.063
AHI	0.496	0.006	0.551	0.002
eGFR	0.006	0.974	−0.065	0.740

Abbreviations: AHI, apnea–hypopnea index; eGFR, estimated glomerular filtration rate; H, high; L, low; R, correlation index.

eGFR and BP

No significant differences in 24-h systolic and diastolic BPs, awake systolic and diastolic BPs, or morning systolic and diastolic BPs were found between the two groups (Table 3). In contrast, sleep systolic and diastolic BPs were significantly higher in the L group (122.5 ± 16.7 mm Hg and 81.1 ± 12.2 mm Hg) than in the H group (117.1 ± 11.8 mm Hg, P=0.033; and 76.1 ± 9.5 mm Hg, P=0.012).

Table 5 Determinant factors of sleep systolic blood pressure by multivariate analysis

Variable	P-*value*	*Variable*	P-*value*
All patients			
Age	0.283	Age*AHI	0.682
AHI	0.790	Age*eGFR	0.349
eGFR	0.353	AHI*eGFR	0.707
		Age*AHI*eGFR	0.521
H group			
Age	0.199	Age*AHI	0.117
AHI	0.148	Age*eGFR	0.159
eGFR	0.179	AHI*eGFR	0.114
		Age*AHI*eGFR	0.097
L group			
Age	0.199	Age*AHI	0.117
AHI	0.148	Age*eGFR	0.159
eGFR	0.179	AHI*eGFR	0.114
		Age*AHI*eGFR	0.097

Abbreviations: age*AHI; interaction between age and AHI; age*AHI*eGFR, interaction among age, AHI and eGFR; age*eGFR, interaction between age and eGFR; AHI, apnea–hypopnea index; eGFR, estimated glomerular filtration rate; H, high; L, low.

Table 6 Determinant factors of sleep diastolic blood pressure by multivariate analysis

Variable	P-*value*	*Variable*	P-*value*
All patients			
Age	0.446	Age*AHI	0.507
AHI	0.696	Age*eGFR	0.829
eGFR	0.701	AHI*eGFR	0.582
		Age*AHI*eGFR	0.183
H group			
Age	0.900	Age*AHI	0.750
AHI	0.915	Age*eGFR	0.964
eGFR	0.974	AHI*eGFR	0.788
		Age*AHI*eGFR	0.655
L group			
Age	0.900	Age*AHI	0.750
AHI	0.915	Age*eGFR	0.964
eGFR	0.974	AHI*eGFR	0.788
		Age*AHI*eGFR	0.655

Abbreviations: age*AHI; interaction between age and AHI; age*AHI*eGFR, interaction among age, AHI and eGFR; age*eGFR, interaction between age and eGFR; AHI, apnea–hypopnea index; eGFR, estimated glomerular filtration rate; H, high; L, low.

We also analyzed correlations between sleep BP *vs.* age, AHI and eGFR individually, because these variables are considered to induce sleep BP elevation (Table 4). This analysis was performed in the all patient group, in the H group and in the L group, respectively. The result of the analysis demonstrates correlations between sleep systolic or diastolic BPs and AHI in all three groups. Among them, the L group revealed a remarkable correlation between two data sets: sleep systolic BP (r=0.496, P=0.006) and sleep diastolic BP (r=0.551, P=0.002).

Analysis of covariance was used to confirm which variables affected sleep BP. We evaluated the mean age, AHI and eGFR in the study patient group, in the H group, and in the L group, respectively (Tables 5 and 6). No independent determinant of sleep systolic or diastolic BP was found.

DISCUSSION

The prevalence and incidence of SAS and CKD are increasing in clinical practice; both are currently regarded as common diseases.[3,9] The result of this study demonstrated higher sleep BP in SAS patients with CKD compared with those without CKD, even though the severity of SAS was similar. This result suggested that SAS and CKD might synergistically induce nocturnal hypertension, which probably increases the risk of onset of cardiovascular disease.

Factors affecting renal function

In the patients' backgrounds, we found significant differences in the mean age, BMI and TG between the H and the L groups. One study has reported that most of the individuals with elevated creatinine levels tend to be older.[9] Therefore, the significant difference in the mean age between the two groups might be the reason for the difference in renal function.

Obesity is likely related to the prevalence of CKD.[12] In this study, the H group, which had better renal function than the L group, had higher BMI. Thus, BMI seemed to have a negative influence on renal function.

Hypertriglyceridemia is a risk factor for CKD progression.[13] The number of our patients with diabetes mellitus was relatively small; therefore, the result of this study was not sufficient to clarify the influence of TG on renal function.

Influential factors in circadian BP changes

Systolic BP elevation and diastolic BP reduction are common in the elderly and result in increased pulse pressure.[14] Moreover, the number of individuals with non-dipper pattern BP increases with age.[15] In this study, we found a significant difference in age between the H and the L group; however, multivariate analysis demonstrated that age was not a significant determinant of sleep BP.

Obesity is regarded as a risk factor for the incidence of hypertension because of its relation to sympathetic nerve activity, sodium retention and insulin resistance.[16] In this study, no significant difference in the severity of SAS was found between the L and the H group; however, BMI was significantly smaller in the L group which had higher sleep BP. Accordingly, we presumed that obesity had no influence on sleep BP elevation.

Hypertriglyceridemia poses a high risk for cardiovascular disease;[17] statin prevents the onset of cardiovascular disease.[18] Earlier studies have not elucidated a direct influence of hypertriglyceridemia or statins on BP changes. The result of this study indicated no direct influence of these factors on sleep BP elevation. As no significant difference in sleep data was found between the H and L groups, we concluded that the influence of SAS on sleep BP was similar in the two groups.

eGFR and BP

Among SAS patients who had similar disease severity, those with advanced CKD had elevated sleep BP; that is, sleep BP might be elevated as the severity of SAS increases (Table 4). The result of this study is similar to that of our previous study.[4] It has been reported that nocturnal hypertension contributes to the occurrence of cardiovascular disease and target organ damage.[1,2] Many investigators have reported that the risk of sudden death, heart failure or acute myocardial infarction increases during sleep in obstructive SAS patients.[5,6,19] These findings suggest that sleep BP control in these patients be desirable.

As to why SAS patients with CKD have higher sleep BP, in this study we found no independent factor that affected sleep BP elevation in SAS patients with CKD. A diminished nocturnal BP dip may protect against end-organ damage caused by decreased blood flow during sleep,[20] which supports our study result that SAS patients with severe CKD tended to have BP elevation.

BP dose not decrease during sleep in patients with renal dysfunction. The release of natriuretic peptides is not sufficient to regulate body fluid circulation during sleep in these patients, resulting in an increased body fluid volume and BP elevation.[21] When a CKD patient has SAS as an underlying disease, apnea during sleep augments sympathetic nerve activity and also increases BP. We thus suggest that abnormal BP changes caused by CKD induce sleep BP elevation.

SAS is associated with reduced renal function.[22] We assessed the relationship between SAS and CKD using a correlation analysis, resulting in no correlations between eGFR *vs.* AHI (-0.07, $P=0.36$) or CT 90% (-0.06, $P=0.41$). We postulate that this result is due to the high proportion of SAS patients in our study who did not have long-standing disease duration and had similar SAS severity. Accordingly, we concluded that SAS had no influence on CKD.

The result of this study suggested that the severity of CKD has a role in the induction of sleep BP elevation in SAS patients with CKD when the severity of SAS was similar. As most of our study patients had relatively mild renal dysfunction, eGFR might not be an independent predictor of sleep BP. Treatment of SAS prevents sleep BP elevation.[4] Along with this treatment, improvement of lifestyle and eating habits is required to lower BP and improve abnormal lipid metabolism and glucose tolerance. Both of these factors probably prevent nocturnal hypertension, a risk factor for the onset of cardiovascular events.[1]

Study limitations

It is difficult to find SAS patients who were not treated with antihypertensives. The number of patients with mild renal dysfunction in the L group was small. In this study, urinary protein was not obtained. Additional studies with a larger population are necessary to accumulate sufficient data to address the association between SAS and renal function. One study suggested that ABPM has limited reproducibility;[23] however, our study demonstrated a significant difference in sleep BP between the H and L groups, which could support the reliability of our study.

CONCLUSION

Patients with SAS complicated by CKD had sleep BP elevation. The results of our study suggest that appropriate treatments of both SAS and CKD would be effective in treating nocturnal hypertension, which is considered a risk factor for the onset of cardiovascular events.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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