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Increased low-grade inflammation and plasminogen-activator inhibitor-1 level in non-dippers with sleep apnea syndrome

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Abstract

Objective—Patients with sleep apnea syndrome (SAS) have an increased risk of cardiovascular events and frequently show a non-dipper pattern (blunted nocturnal decline <10%) of systolic blood pressure (BP). We investigated neurohumoral activation and risk factors in relation to nocturnal BP dipping pattern and SAS.

Methods—We conducted sleep polysomnography and ambulatory BP monitoring, and measured high-sensitivity C-reactive protein (hsCRP), tissue-type plasminogen activator inhibitor-1 (PAI-1), and neurohumoral factors in 121 outpatients with suspected SAS, who were classified in 4 groups depending on the presence or absence of dipping/non-dipping and SAS.

Results—Non-dippers with SAS had higher hsCRP (overall $P < 0.001$), PAI-1 (overall $P = 0.004$), and aldosterone levels (overall $P = 0.010$) than any of the other 3 groups. After adjustment for significant covariates such as age, sex, body mass index, waist circumference, smoking, alcohol drinking, aspirin use, presence of DM, and insulin, non-dippers with SAS still had a higher hsCRP level than non-dippers without SAS (geometric mean: 1.47 vs. 0.37 mg/L, $P = 0.001$). In multiple linear regression analysis controlling for confounding factors that related with SAS, hsCRP was significantly correlated with 3% oxygen desaturation index ($P = 0.047$). PAI-1 was also highest in the non-dippers with SAS, but this was not independent of obesity. PAI-1 was correlated with insulin ($r = 0.32$, $P = 0.002$) and hsCRP levels ($r = 0.26$, $P = 0.005$).

Conclusion—Non-dipper status was associated with an increased hsCRP in patients who also had SAS, but not in those who did not, and hsCRP was closely affected by the desaturation level. PAI-1 is also increased in non-dippers with SAS, and is related to insulin and hsCRP.

Keywords

sleep apnea syndrome; non-dipper; high-sensitivity C-reactive protein; plasminogen activator inhibitor-1

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Introduction

Sleep apnea syndrome (SAS) is reported to be associated with an increased risk for atherosclerosis [1], prevalence [2] and incidence of hypertension [3], cardiovascular events [4,5], and sudden death during sleep [6]. Patients with SAS often have a blunted nocturnal blood pressure dip (non-dipper status) during 24-hour ambulatory blood pressure monitoring (ABPM) [7], and continuous positive airway pressure (CPAP) converts non-dippers to dippers [8].

Non-dippers are reported to have increased risk for left ventricular hypertrophy [9], silent cerebral infarcts [10], and cardiovascular mortality [11]. The non-dipper status may contribute to an increased risk for cardiovascular events in patients with SAS. However, there are no data about the differences in risk factors of cardiovascular events in patients classified according to dipper status and SAS.

High-sensitivity C-reactive protein (hsCRP), a marker of low-grade inflammation, is reported to be a marker of atherosclerosis [12], hypertensive target organ damage [13], and cardiovascular events [14]. The hsCRP level is also reported to be increased in patients with SAS [15,16], but there are no data that show differences of hsCRP between non-dippers with SAS and non-dippers without SAS.

Additionally, plasminogen-activator inhibitor-1 (PAI-1), a marker of fibrinolysis, is thought to be a risk factor for cardiovascular events [17]. PAI-1 gene transcription was reported to be stimulated by hypoxia in an experimental model [18]. However, the differences in PAI-1 level among dippers and non-dippers with or without SAS have remained unclear, and the relationships of PAI-1 level with apnea-hypopnea index (AHI), hypoxia, obesity, and other humoral factors are also unknown.

The purpose of this study was to evaluate the relationship of hsCRP and PAI-1 in patients classified according to dipper status and SAS, and evaluate the factors in SAS that are associated with hsCRP and PAI-1 level.

Methods

Patients

We evaluated 121 patients who underwent polysomnography (PSG) because of suspected sleep apnea syndrome (such as symptoms of daytime sleepiness or snoring), and who were conducted ABPM and blood examinations in this study. The patients enrolled in this study were selected from 134 consecutive patients who underwent PSG for diagnosis of SAS in our hospital between September 2001 and October 2004, after excluding 13 patients because of incomplete data.

Clinic BP was measured as the average of 2 consecutive measurements made after patients had rested for at least 5 minutes in a seated position on the day of ABPM measurement. Diabetes was diagnosed as fasting glucose ≥ 7.0 mmol/L (126 mg/dl), a random serum glucose ≥ 11.1 mmol/L (200 mg/dl) and/or anti-diabetic drugs use. Hyperlipidemia was defined as a total cholesterol level ≥ 5.7 mmol/L (220 mg/dL), triglyceride level ≥ 1.7 mmol/L (150 mg/dl) and/or oral lipid-lowering agent use. Smokers were defined as current smokers. Patients who were drinking alcohol every day were defined as alcohol drinkers. Body mass index (BMI) was calculated as weight (in kilograms)/[height (in meters)]².

The institutional review board of Jichi Medical University approved this study.

Polysomnography

Overnight fully diagnostic sleep polysomnography was performed using a P series model 4 Plus (Compumedics Ltd, Australia) or E series/PSG (Compumedics Ltd, Australia), that recorded the following parameters: ECG, central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, nasal airflow, using a nasal cannula and pressure transducer, naso-oral airflow, using a thermistor (P series) or thermo couple (E series), and respiratory effort using chest and abdominal piezoelectric belts. Oxyhemoglobin saturation (SpO₂) was monitored using a pulse oximeter (Probe Nonin Oximeter 8000J). Sleep staging was scored according to the criteria of Kales and Rechtschaffen [19]. Apneas were defined as decrements in airflow >90% from baseline for a period >10 seconds, and hypopneas were defined as decrements in airflow >50% but <90% from baseline for a period >10 seconds [20]. The number of apneas and hypopneas per hour of sleep were calculated to obtain the AHI. SAS was defined as AHI>15 according to a previous report [21]. Respiratory events were judged primarily from the nasal cannula-pressure transducer.

ABPM

ABPM was measured using a validated machine: TM-2425 (A&D Co., Japan). Measurements were performed at 30-min intervals for 24 hours on a weekday just before or after the PSG. Nighttime parameters (BP and pulse rate) were defined by the averages from the time after going to bed to the time before waking up, and daytime parameters were defined by the averages from the time after awakening to the time before going to bed. The patients reported the time of awakening and going to bed. The night/day ratios of systolic blood pressure were calculated. Nocturnal BP fall was calculated as 1 minus the night/day ratio of systolic blood pressure and expressed as a percentage. Patients were classified into the following 2 dipping groups on the basis of the nocturnal BP fall: dippers, with a fall larger than 10%; and non-dippers, with a fall less than 10 %. SpO₂ was also measured during ABPM. The oxygen desaturation index (ODI) was defined as the total number of episodes of oxyhemoglobin desaturation >3%, divided by the total sleep time.

Blood examination

Blood samples were drawn from the antecubital vein in the fasting state in the morning after the diagnostic PSG. All blood samples were measured in the same laboratory (SRL, Inc., Tokyo, Japan). Serum hsCRP level was measured by nephelometry (NA Latex CRP kit, Dade Behring, Tokyo, Japan). The plasma levels of PAI-1 were determined using commercially available latex photometric immunoassay kits for PAI-1 (Mitsubishi Kagaku Iatron, Tokyo, Japan). Blood for measurement of plasma renin activity (PRA) and aldosterone was drawn into tubes containing EDTA. PRA was measured by radioimmunoassay (SRL Inc., Tokyo, Japan). Angiotensin II measurements were made by radioimmunoassay (SRL Inc., Tokyo, Japan). Aldosterone concentrations were measured with the use of a commercially available radioimmunoassay (SRL Inc., Tokyo, Japan). Catecholamine concentrations were measured by high performance liquid chromatography (Tosoh Corporation, Tokyo, Japan).

Statistical analysis

Data are shown as the mean $\pm$ S.D. The values of hsCRP had a skewed distribution and the analyses of these values were performed for the log-transformed values. One-way analysis of variance (ANOVA) was performed to detect differences among the patients in the 4 groups, and Tukey's honestly significant differences test was used for multiple pairwise comparisons of means among the groups. Analysis of covariance (ANCOVA) was performed to detect differences among the groups after adjustment for confounding factors, and the Bonferroni test was used for multiple pairwise comparisons. Correlations between

AHI and BMI, hsCRP level, aldosterone level and PAI-1 level were analyzed using Pearson's test. HsCRP, aldosterone, and PAI-1 levels were correlated with some other variables; therefore, analysis of covariance and partial correlation coefficients were examined to rule out their effects on these parameters in multiple linear regression analysis. The computer software SPSS version 11.0 (SPSS Inc., Chicago, USA) was used for the analyses and probability <0.05 was considered statistically significant.

Results

Patients

The mean age of the patients was 58.1 ± 15.1 years old; there were 90 men and 31 women, and the mean BMI was 26.3 ± 4.4 kg/m². There were 25 non-dippers with SAS, 44 dippers with SAS, 24 non-dippers without SAS, and 28 dippers without SAS.

Characteristics of patients classified according to the presence or absence of SAS and dipping status

The characteristics of patients classified according to the presence or absence of SAS and dipping status are shown in Table 1. The age was younger and the percentage of men was higher in the patients with SAS than in those without SAS. The percentage of patients who were taking antihypertensive medications was 47.1 % (calcium channel blockers 30%, angiotensin II receptor blockers 15 %, angiotensin-converting enzyme inhibitors 6.7 %, diuretics 2.5 %, alpha-blockers 8.3 %, and beta-blockers 7.5 %). The percentages of patients who were taking aspirin, statins, and oral antidiabetic drugs were 17.4 %, 5.0 %, and 2.5 %, respectively. As shown in Table 1, there were no significant differences in the use of medications among the 4 groups.

Polysomnogram parameters, BPs, and neurohumoral factors

Differences in polysomnographic parameters in the 4 groups of patients are shown in Table 2. Non-dippers with SAS had the most severe AHI and 3% ODI; however, non-dipping status did not closely follow the severity of SAS. There were no BP differences among the groups. The neurohumoral factors in the 4 groups of patients are shown in Table 3. Non-dippers with SAS had significantly higher hsCRP levels than the other 3 groups. Even after adjustment for significant confounding factors including age, sex, BMI, waist circumference, smoking, drinking, aspirin use, presence of DM, and insulin level, the non-dippers with SAS still had significantly higher hsCRP than the non-dippers without SAS, and than the dippers with SAS (Figure 1). Although non-dippers with SAS also had the highest PAI-1 level, differences from the other groups were not significant after adjustment for BMI ($P=0.22$).

Patients who were taking antihypertensive medication had lower aldosterone levels (99.8 ± 38.4 vs. 84.2 ± 36.4 pg/ml, $P=0.023$), higher adrenaline (14.0 ± 11.0 vs. 18.3 ± 12.3 pg/ml, $P=0.043$) and higher noradrenaline (285 ± 153 vs. 367 ± 197 pg/ml, $P=0.013$) than those without antihypertensive medication. There were no statistical differences in hsCRP, aldosterone, and PAI-1 levels between users of different antihypertensive drug classes (such as calcium channel blockers, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, alpha-blockers, beta-blockers) and non-users. Patients who were taking diuretics ($N=3$) had higher hsCRP level than those who were not ($P=0.019$). There were 6 patients with resistant hypertension (number of antihypertensive drug ≥ 3 and $\text{CBP} \geq 140/90$ mmHg), and had a significantly higher AHI than those without resistant hypertension (42.1 ± 20.9 vs. 23.2 ± 20.1 event/hr, $P=0.027$). But, there were no significant differences in hsCRP ($P=0.91$) and PAI-1 ($P=0.20$) between the patients with and without resistance hypertension.

Correlations of neurohumoral factors and factors related to SAS

Log₁₀hsCRP level was correlated with BMI ($r=0.34$, $P<0.001$), AHI ($r=0.38$, $P<0.001$), 3% ODI ($r=0.42$, $P<0.001$), insulin ($r=0.20$, $P=0.031$), and aldosterone ($r=0.18$, $P=0.048$). After controlling for these confounding factors in multiple regression analysis, log₁₀hsCRP level was correlated with 3% ODI ($\beta=0.25$, $P=0.047$) (Table 4). Even after we added significant confounding factors including age, sex, smoking, alcohol drinking, aspirin use, and diabetes to the model, log₁₀hsCRP level had a tendency to be correlated with 3% ODI ($\beta=0.21$, $P=0.089$).

PAI-1 level was correlated with BMI ($r=0.38$, $P<0.001$), AHI ($r=0.31$, $P=0.001$), 3% ODI ($r=0.31$, $P<0.001$), arousal index ($r=0.18$, $P=0.043$), insulin ($r=0.44$, $P<0.001$), aldosterone ($r=0.17$, $P=0.065$), and log₁₀hsCRP levels ($r=0.38$, $P<0.001$). After controlling for these confounding factors in multiple regression analysis, PAI-1 was correlated with insulin ($\beta=0.32$, $P=0.002$) and log₁₀hsCRP ($\beta=0.26$, $P=0.005$) (Table 4). Even after we added significant confounding factors including age, sex, smoking, alcohol drinking, aspirin use, and diabetes to the model, PAI-1 was still correlated with insulin ($r=0.37$, $P<0.001$) and log₁₀hsCRP level ($r=0.28$, $P=0.002$).

Aldosterone level was correlated with BMI ($r=0.19$, $P=0.034$), AHI ($r=0.26$, $P=0.004$), arousal index ($r=0.18$, $P=0.045$), Insulin ($r=0.29$, $P=0.001$), and log₁₀hsCRP levels ($r=0.18$, $P=0.048$), and was weakly correlated with 3% ODI ($r=0.16$, $P=0.078$). After controlling for these confounding factors related to SAS in multiple regression analysis, aldosterone was correlated with insulin ($\beta=0.23$, $P=0.039$) (Table 4), and this correlation remained significant ($\beta=0.26$, $P=0.022$) even after we added other significant confounding factors including age, sex, smoking, alcohol drinking, aspirin use, and diabetes to the model.

Discussion

Non-dippers with SAS had increased hsCRP independently of significant confounding factors including BMI, while non-dippers without SAS did not. This indicates that non-dipper status itself was not associated with increased hsCRP. In contrast, the presence of SAS (AHI>15) was associated with increased hsCRP (in relation to the desaturation level) independently of dipping status. PAI-1 was also increased in non-dippers with SAS, but this was not independent of obesity, although it was related to both insulin and hsCRP.

Increased risks of non-dippers for cardiovascular events may be partly explained by background diseases that lead to the non-dipper state. Thus in a population-based study, Bjorklund et al. [22] reported that the majority of non-dipping men did not have an increased cardiovascular risk, although non-dippers who had diabetes did. There may be 2 types of non-dippers (with and without other risk factors such as SAS and/or diabetes), and the risks of non-dipper status may be partly explained by the subjects' backgrounds that lead to non-dipper status. Verdecchia, et al. [23] reported that non-dippers with sleep deprivation induced by cuff inflations during nighttime ABPM did not have increased cardiovascular mortality.

Some of the mechanisms by which SAS may increase blood pressure include the renin-angiotensin-aldosterone system [24,25], sympathetic nerve activation [26], endothelial dysfunction [27], endothelin [28], and oxidative stress [29]. These parameters also have been reported to be correlated with hsCRP levels [30–33]. It has been reported that hsCRP is increased with the severity of SAS independently of BMI [16], and that treatment with nasal continuous positive airway pressure lowers hsCRP in association with reduction of AHI [34]. In our present study, hsCRP level was more significantly correlated with 3% ODI than with AHI. On the other hand, Norman et al.[35] reported that supplementing nocturnal

oxygen supply did not reduce the nighttime blood pressures in patients with obstructed SAS, but that continuous positive airway pressure therapy did reduce it. Mechanisms that increase hsCRP (e.g. desaturation) and cause non-dipping status (e.g. impaired respiration) may be more important in non-dippers with SAS.

The pathophysiological mechanisms that increase PAI-1 are likely to be complicated in patients with SAS. PAI-1 is reported to be increased by various factors (i.e., obesity and/or metabolic syndrome [36], and hypoxia [37]). Experimental studies have demonstrated that production of PAI-1 is increased with hypoxia [38]. In the present study, the PAI-1 level was increased in non-dippers with SAS, and this relationship was partly accounted for by the insulin level and hsCRP. von Kanel et al. [39] reported that measures reflecting apnea severity (higher AHI and more of the nighttime spent with $\text{SpO}_2 < 90\%$), and sleep efficiency (percentage of sleep duration divided by duration of time in bed) were related to PAI-1, but insulin and hsCRP were not measured in their analysis. In the present study, PAI-1 levels were more significantly correlated with insulin and hsCRP than hypoxia or AHI, and the increased level of PAI-1 in non-dippers with SAS might be induced by inflammation associated with desaturation.

Study limitations

There were some subjects in the present study who were taking antihypertensive medications, which might have affected some of the neurohumoral factors that we measured, although there were no statistical differences in medication use among the 4 groups of patients. The patients who were taking antihypertensive medication had lower aldosterone levels than those who were not. However, even in an analysis of only patients who were taking no antihypertensive medication, aldosterone in non-dippers with SAS tended to be higher than in non-dippers without SAS (data not shown). Additionally, 6 patients were taking statins and which is reported to decrease hsCRP. In the present study, patients who were taking statins had lower hsCRP; however, even when we analyzed our data excluding for patients who were taking statins, the results were almost similar (data not shown).

Conclusion

Non-dipper status on its own was not associated with an increased level of hsCRP, whereas SAS was. There was also an additive effect such that the highest levels were seen in patients with SAS who were also non-dippers. HsCRP was closely affected by the nocturnal desaturation level. PAI-1 is also increased in non-dippers with SAS, and is related to increases of insulin and hsCRP.

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Figure 1. High-sensitivity C-reactive protein level in patients according to dipper status and sleep apnea syndrome

AHI indicates apnea-hypopnea index; hsCRP, high-sensitivity C-reactive protein. Data are shown as geometric mean. Overall P values were calculated by ANCOVA after adjustment for significant covariates such as age, sex, body mass index, waist circumference, smoking, drinking, aspirin use, presence of diabetes, and insulin level. Intergroup differences were calculated by the Bonferroni test. Probability 0.05 was considered statistically significant.

Table 1

Characteristics of the patients with/without non-dipper and sleep apnea syndrome

	AHI<15			AHI≥15		
	Dipper (n=28)	Non-dipper (n=24)	Dipper (n=44)	Non-dipper (n=25)	P	
Age, years	61.9±12.0	66.6±14.2	51.7±13.6 ^{***}	56.7±17.0	<0.001	
Male, %	57.1	54.2	88.6	88.0	0.001	
Body mass index, kg/m ²	25.0±3.4	24.3±3.2	26.8±3.5	28.8±6.1 ^{***}	0.001	
Waist, cm	86.7±9.8	82.7±8.1	91.1±10.4 [†]	93.5±13.5 ^{††}	0.002	
Regular alcohol drinkers, %	3.6	0.0	15.9	4.0	0.056	
Current smokers, %	32.1	29.2	54.5	60.0	0.043	
Pack-years	38.7±10.0	17.4±16.4	23.8±12.9	28.5±16.6	0.12	
Diabetes, %	10.7	4.2	0.0	10.7	0.065	
Hyperlipidemia, %	10.7	4.2	18.2	8.0	0.32	
Number of antihypertensive drugs	0.48±0.80	0.74±0.92	0.85±1.3	0.95±0.97	0.42	
Antihypertensive drug use, %	39.3	66.7	40.9	48.0	0.17	
Calcium channel blockers use, %	25.0	37.5	30.2	28.0	0.80	
ARBs, %	3.6	16.7	18.6	20.0	0.28	
ACE inhibitors use, %	10.7	0.0	7.0	8.0	0.47	
Diuretics use, %	0.0	0.0	2.3	8.0	0.22	
alpha-blockers use, %	3.6	8.3	11.6	8.0	0.70	
beta-blockers use, %	3.6	12.5	9.3	4.0	0.55	
Nitrates use, %	3.6	0.0	2.3	4.0	0.80	
Aspirin use, %	32.1	16.7	6.8	20.0	0.050	
Other antiplatelet drugs use, %	0.0	12.5	4.5	4.0	0.25	
Statins use, %	7.1	12.5	0.0	4.0	0.14	

ARB indicates angiotensin II receptor blockers use; ACE inhibitors, angiotensin converting enzyme inhibitors. Over all P values were calculated by ANOVA. Intergroup differences were calculated by Tukey's honestly significant test:

* P<0.05,

** P<0.01, and

*** P<0.001 vs. the patients with AHI<15 and dipper,

[†] $P < 0.05$,^{††} $P < 0.01$, and^{†††} $P < 0.001$ vs. the patients with AHI < 15 and non-dipper, and[§] $P < 0.05$ vs. the patients with AHI ≥ 15 and dipper.

Polysomnogram parameters in the patients with/without non-dipper and sleep apnea syndrome

Table 2

	AHI<15			AHI≥15			P
	Dipper (n=28)	Non-dipper (n=24)	Dipper (n=44)	Non-dipper (n=25)			
Daytime sleepiness, %	14.3	16.7	11.4	24.0			0.58
Median AHI, /hr	4.2	3.5	34.2	36.9			
Arousal index, /hr	29.0±13.0	27.4±9.5	39.2±18.5**†	43.7±19.9***†††§§§			<0.001
Obstructive apnea, /hr	2.1±2.3	1.7±2.6	16.7±12.1	22.1±18.9			<0.001
Central apnea, /hr	0.7±1.3	0.8±1.9	2.2±3.7	2.4±3.5			0.041
Sleep efficiency, %	64±17	63±13	68±18	64±18			0.69
SpO ₂ 3% Dip, /hr	9.6±5.7	13.4±9.9	24.2±15.9***†	34.6±24.1***†††§			<0.001
SpO ₂ <90%, /hr	1.2±1.5	2.5±3.6	12.3±12.2*†	26.4±22.7***††			<0.001
Clinic SBP, mmHg	148.4±19.6	142.4±16.7	145.6±21.1	145.8±21.5			0.76
Clinic DBP, mmHg	83.3±8.6	79.5±10.9	85.1±12.7	82.0±11.2			0.27
Clinic HR, mmHg	68.4±15.4	69.7±11.0	76.0±14.2	70.4±13.7			0.10
24-hr SBP, mmHg	135.1±5.6	133.1±16.7	133.0±14.3	137.0±17.8			0.75
24-hr DBP, mmHg	79.6±8.8	76.6±11.4	81.4±9.4	81.8±11.0			0.22
24-hr HR, /min	70.4±8.2	66.8±7.9	73.2±9.3†	68.6±10.5			0.036

Data were shown as mean±SD or percentage. Sleep efficiency was calculated as percentage of sleep duration (min) divided by duration in bed (min). Over all P values were calculated by ANOVA. Intergroup differences were calculated by Tukey's honestly significant test:

* P<0.05,

** P<0.01, and

*** P<0.001 vs. the patients with AHI<15 and dipper,

† P<0.05,

†† P<0.01, and

††† P<0.001 vs. the patients with AHI<15 and non-dipper, and

§ P<0.05 vs. the patients with AHI≥15 and dipper.

Table 3

Neurohumoral factors according to dipper status and sleep apnea syndrome

	AHI<15				AHI≥15	
	Dipper (n=28)	Non-dipper (n=24)	Dipper (n=44)	Non-dipper (n=25)	P	
Plasma renin activity, ng/ml/hr	1.3±1.5	0.7±0.5	2.1±5.8	1.5±1.5	0.44	
Aldosterone, pg/ml	86.1±28.8	74.7±31.1	97.0±34.6	108.5±51.0 ^{††}	0.010	
Angiotensin II, pg/ml	7.2±10.0	4.8±4.6	10.6±19.2	9.7±4.2	0.31	
Adrenalin, pg/ml	16.2±10.1	20.6±17.9	14.0±9.8	15.1±8.5	0.16	
Noradrenalin, pg/ml	308±193	317±189	318±161	358±191	0.76	
Dopamine, pg/ml	7.8±7.7	10.8±11.1	7.1±4.0	8.0±5.4	0.23	
Fasting blood sugar, mg/dl	108.9±49.0	99.2±16.9	98.3±4.7	101.6±101.6	0.43	
Triglyceride, mg/dl	125.7±64.0	108.2±55.8	155.2±142.9	161.9±130.5	0.29	
HDL cholesterol, mg/dl	53.8±17.8	46.0±8.3	47.8±15.4	45.8±10.9	0.13	
PAI-1, ng/ml	29.8±13.1	26.7±12.2	36.4±17.4	41.5±18.1 ^{*††}	0.004	
Insulin, μU/ml	10.5±5.9	9.1±4.9	11.8±7.0	14.2±10.0	0.078	
HOMA index	2.82±1.81	2.23±1.28	2.92±1.76	3.40±2.47	0.21	
Median HsCRP, mg/L	0.49	0.35	0.86	1.7		
Geometric mean hsCRP, mg/L	0.56 (0.27–1.16)	0.36 (0.13–0.98)	0.80 (0.25–2.58) [†]	1.64 (0.51–5.35) ^{**†††§}	<0.001	

PAI-1 indicates plasminogen activator inhibitor -1, and hsCRP, high-sensitivity C-reactive protein. Data were shown as mean±SD or percentage. Values of hsCRP were shown as median or geometric mean (SD range). Over all P values were calculated by ANOVA. Intergroup differences were calculated by Tukey's honestly significant test:

* P<0.05,

** P<0.01, and

*** P<0.001 vs. the patients with AHI<15 and dipper,

[†] P<0.05,

^{††} P<0.01, and

^{†††} P<0.001 vs. the patients with AHI<15 and non-dipper, and

[§] P<0.05 vs. the patients with AHI≥15 and dipper.

Table 4

Multiple linear regression analysis of hsCRP, aldosterone, and PAI-1

	Aldosterone		Log hsCRP		PAI-1	
	beta	P	beta	P	beta	P
Body mass index, kg/m ²	-0.02	0.89	0.19	0.12	0.06	0.60
AHI, /hr	0.18	0.18	0.12	0.35	0.01	0.95
3% ODI, /hr	-0.08	0.58	0.25	0.047	0.06	0.63
Arousal index, /hr	0.06	0.54	-0.02	0.81	0.71	0.43
Insulin, μ U/ml	0.23	0.039	-0.05	0.66	0.32	0.002
Aldosterone, pg/ml	-	-	0.07	0.42	-0.01	0.94
Log hsCRP, mg/L	0.08	0.42	-	-	0.26	0.005

AHI indicates apnea-hypopnea index; hsCRP, high-sensitivity C-reactive protein; PAI-1, plasminogen activator inhibitor-1; ODI, oxygen desaturation index. Values of beta and P were calculated using multiple linear regression analysis. Probability 0.05 was considered statistically significant.