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ARTICLE

Impact of obstructive sleep apnea on long-term blood pressure variability in Japanese men: a cross-sectional study of a work-site population

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Abstract

Blood pressure variability (BPV) has been shown to be associated with cardiovascular diseases. The effects on long-term BPV of obstructive sleep apnea (OSA) are not yet known. We evaluated a total of 1653 Japanese male workers (18–69 years) at a work site to diagnose OSA, and we divided them into three groups: non-OSA (apnea–hypopnea index (AHI): < 5, $n = 1414$), mild-to-moderate OSA ($5 \le$ AHI < 30: $n = 131$) and severe OSA (AHI ≥ 30: $n = 108$). The standard deviation and coefficient of variation of the subjects' BPV were calculated by using their annual blood pressure measurements at routine physical examinations from 2012 to 2015 (four measurements). The multivariable-adjusted BPV of systolic blood pressure (SBP) was significantly higher in the severe-OSA group compared to the non-OSA group. A multiple regression analysis also revealed that OSA was positively associated with BPV of SBP. We focused on the mild-to-moderate OSA group to evaluate the association of OSA treatment with BPV, because most of the severe-OSA subjects were being treated with continuous positive airway pressure or an oral appliance. The BPV of both systolic and diastolic blood pressure was significantly decreased in the treated subjects. These findings suggest that OSA is associated with increases in long-term BPV which was improved by the treatment of OSA in Japanese men of a work-site population.

Introduction

It is important to control blood pressure levels to prevent cardiovascular disease. It was shown that the increases in blood pressure fluctuations, which are classified into short- and long-term blood pressure variability (BPV), may lead to the increased incidence of cardiovascular disease independently of average blood pressure [1]. Many investigations have indicated that short-term BPV within a 24-h period (beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night changes) is independently associated with hypertensive target organ damage and cardiovascular diseases [2]. Long-term BPV, i.e., changes in blood pressure values occurring over more prolonged periods (days, weeks, months, seasons, years, and visit-to-visit), has been shown to have prognostic value for cardiovascular diseases [1, 2], and long-term BPV may be a strong predictor of vascular events compared to short-term BPV [1]. In addition, visit-to-visit BPV has been shown to be reproducible and not a random phenomenon [3].

Obstructive sleep apnea (OSA) is an important problem, and it was estimated that OSA is present in 24 and 9% of middle-aged men and women, respectively in the United States [4]. In our previous study, the prevalence of OSA in a male Japanese work-site population was estimated to be 13% [5]. OSA is characterized by repeated episodes of apnea and hypopnea due to upper airway inspiratory collapse during sleep. Consequently, the temporary

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decreases of blood oxygen saturation cause not only a temporary activation of the sympathetic nervous system and an increase in blood pressure during the nighttime, but also a sustained elevation of blood pressure during the daytime [6, 7].

OSA increases the events of cardiovascular disease [8, 9]; the treatment of OSA with continuous positive airway pressure (CPAP) might reduce blood pressure levels [10] and prevent cardiovascular disease [11]. Therefore, the diagnosis and treatment of OSA are important issues in the prevention of cardiovascular diseases.

Several studies have demonstrated that short-term BPV in individuals with OSA is increased during the nighttime, and that treatment with CPAP reduced the BPV in patients with good adherence to this therapy [12, 13]. However, little is known about whether OSA is associated with long-term BPV independently of blood pressure levels. Accordingly, we hypothesized that the presence of OSA increases long-term BPV, and that this increase in BPV may be associated with cardiovascular diseases. We conducted the present study to clarify the impact of OSA on long-term BPV. We evaluated the association of OSA with the variability of annually measured blood pressure values obtained as part of routine annual physical examinations in a working population.

Methods

Study population

The study group was consisted of 1653 male employees of a bus and railway company in Japan who ranged in age from 18 to 69 years (mean age 44.9 ± 0.2). Females were excluded from the present study, because they constituted only a small portion of the population. A screening test for OSA was performed from 2003 to 2011. All participants in the present study completed the routine annual physical examination during the years 2012–2015. Blood pressure values (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) measured annually in 2012–2015 were used to calculate each subject's BPV. The study protocol was approved by the Ethics Committee of Kyushu University.

Assessment of OSA

The screening test for OSA by using overnight pulse oximeter was conducted from 2003 to 2011 for all of the study participants except those who had been previously diagnosed with and treated for OSA. The 4% oxygen desaturation index (ODI), which represents the average number of oxygen desaturations ≥4% below the baseline level per hour, was calculated using the subject's pulse oximeter data. When a subject's 4% ODI was ≥10, he was defined as screening positive for OSA, and was referred to an appropriate clinic or hospital for the further evaluation of OSA by polysomnography.

Data collection

Annual blood pressure values in the subject's right arm after at least 5 min of rest in the sitting position were measured by a mercury sphygmomanometer in 2012 and 2013, and by an electronic oscillometric sphygmomanometer (ES-H55, Terumo Inc., Tokyo Japan) in 2014 and 2015. The measurements were repeated and the steady values of blood pressure were used for the present analysis. Serum aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (γ-GTP), low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, serum creatinine, serum uric acid, glucose and hemoglobin A1c (HbA1c) were measured in 2012. The value for HbA1c (%) was estimated as an NGSP (National Glycohemoglobin Standardization Program) equivalent value (%) calculated by the formula of HbA1c (%) = HbA1c (%, Japan Diabetes Society (JDS)) + 0.4%, considering the relational expression of HbA1c (%, JDS) measured by the previous Japanese standard substance and measurement method and HbA1c (%, NGSP) [14].

The estimated glomerular filtration rate (eGFR) was calculated using the following formula, which is an equation modified for Japanese men: eGFR (ml/min/1.73 m^2) = $194 \times age^{-0.287} \times serum\ creatinine^{-1.094}$ [15]. Body mass index (BMI) was defined as weight (in kg) divided by height (in m^2). Information on medical history, habitual alcohol intake, and current smoking were obtained by interview or questionnaires.

Data analysis

We used the subjects' blood pressure values measured annually from 2012 to 2015 (four times during this period) to calculate the standard deviation (SD) and the coefficient of variation (CV) as indexes of BPV. We divided the subjects into three groups according to the severity of OSA. The subjects who were found to be OSA screening negative ($n = 1402$) and those with an apnea–hypopnea index (AHI) of <5 as assessed by polysomnography ($n = 12$) comprised the non-OSA group ($n = 1414$; or approximately (approx.) 85.6% of the population). The subjects with AHI values of 5–29 were the mild-to-moderate OSA group ($n = 131$; approx. 7.9%), and those with AHI values of ≥30 were the severe-OSA group ($n = 108$; approx. 6.5%).

To analyze the association of OSA with BPV, we performed an analysis of variance followed by Dunnett's test

Table 1 Clinical characteristics of the subjects according to the severity of OSA

	Non-OSA	Mild-to-moderate OSA	Severe OSA
Number of subjects (*n*, %)	1414 (85.6)	131 (7.9)	108 (6.5)
Age (years)	44.6 ± 0.2	47.2 ± 0.7*	47.4 ± 0.7*
BMI (kg/m^2)	23.5 ± 0.1	26.1 ± 0.3*	28.0 ± 0.5*
SBP (mm Hg)	120.9 ± 0.3	125.2 ± 1.1*	128.0 ± 1.1*
DBP (mm Hg)	78.2 ± 0.3	80.8 ± 0.8*	83.5 ± 1.0*
SD of SBP (mm Hg)	7.5 ± 0.1	6.8 ± 0.1	7.8 ± 0.4
CV of SBP (%)	6.2 ± 0.1	5.5 ± 0.3*	6.1 ± 0.3
SD of DBP (mm Hg)	5.7 ± 0.1	5.3 ± 0.2	6.0 ± 0.3
CV of DBP (%)	7.4 ± 0.1	6.6 ± 0.3*	7.3 ± 0.3
LDL-cholesterol (mg/dl)	127.4 ± 0.8	131.6 ± 2.5	128.4 ± 2.8
HDL-cholesterol (mg/dl)	55.5 ± 0.4	52.7 ± 1.2	50.0 ± 1.1*
Triglyceride (mg/dl)	151.0 ± 3.2	180.0 ± 18.9*	179.4 ± 9.9
AST (IU/l)	23.1 ± 0.2	24.7 ± 0.9	26.6 ± 1.4*
ALT (IU/l)	27.4 ± 0.5	30.4 ± 1.7	35.7 ± 2.5*
γ-GTP (IU/l)	44.1 ± 1.1	55.6 ± 5.2*	52.6 ± 3.7
eGFR (ml/min/1.73 m^2)	82.8 ± 0.4	80.2 ± 1.2	79.8 ± 1.0*
Uric acid (mg/dl)	5.9 ± 0.03	6.1 ± 0.1	6.2 ± 0.1
Glucose (mg/dl)	96.7 ± 0.6	101.5 ± 2.1*	103.3 ± 2.2*
HbA1c (%)	5.6 ± 0.02	5.8 ± 0.1*	6.0 ± 0.1*
Habitual alcohol intake (*n*, %)	834 (59)	85 (65)	64 (59)
Current smoking (*n*, %)	665 (47)	58 (44)	55 (51)
Hypertension (*n*, %)	254 (18.0)	41 (31.3)*	48 (44.4)*
Antihypertensive use (*n*, %)	140 (9.9)	27 (20.6)*	31 (28.7)*

Values are given as the means ± SE or as a number (*n*, %)

OSA obstructive sleep apnea, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate transaminase, *ALT* alanine transaminase, *γ-GTP* gamma-glutamyl transpeptidase, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

*$P < 0.05$ vs non-OSA by Dunnett's multiple comparison test or by Bonferroni-corrected chi-square test

for multiple comparisons or chi-square test where appropriate. Comparisons between non-treated and treated subjects in the same OSA group were made using Student's *t*-test or Welch's *t*-test. We also performed a multiple regression analysis to determine the factors associated with BPV. Multicollinearity was assessed by using the variance inflation factor. A variance inflation factor of >3.0 was used as an indicator of multicollinearity. All of the statistical analyses were carried out using SAS software for Windows, ver. 9.4 (SAS, Cary, NC). *P* values < 0.05 were considered significant.

Results

Table 1 summarizes the clinical characteristics of the subjects according to the severity of OSA. Age, BMI, blood pressure values, HbA1c, and the prevalence of the subjects with hypertension or those with antihypertensive drugs were significantly higher in the subjects with OSA compared to those without OSA (non-OSA). In the subjects with severe OSA, the serum AST and ALT were significantly higher and HDL-C and eGFR were significantly lower compared to the non-OSA subjects. The SDs of blood pressures were not different between the subjects with OSA and without OSA. The CVs of blood pressures were lower in the mild-to-moderate OSA group.

Figure 1 shows the SD and CV data of the subjects' blood pressure values adjusted for age, BMI, HbA1c, eGFR, treatment for OSA, treatment for hypertension, alcohol intake, and current smoking habits. The SD and CV values for SBP and the SD for DBP were significantly higher in the subjects with severe OSA. This association of blood pressure variabilities with OSA in the SD and CV values for SBP was clearer when the subjects in the non-OSA group were restricted to those with AHI of <5 as assessed by polysomnography ($n = 12$) (Supplementary Figure 1). There are no obvious differences to the findings by excluding the subjects who had been prescribed antihypertensive drugs between 2012 and 2015 (Supplementary

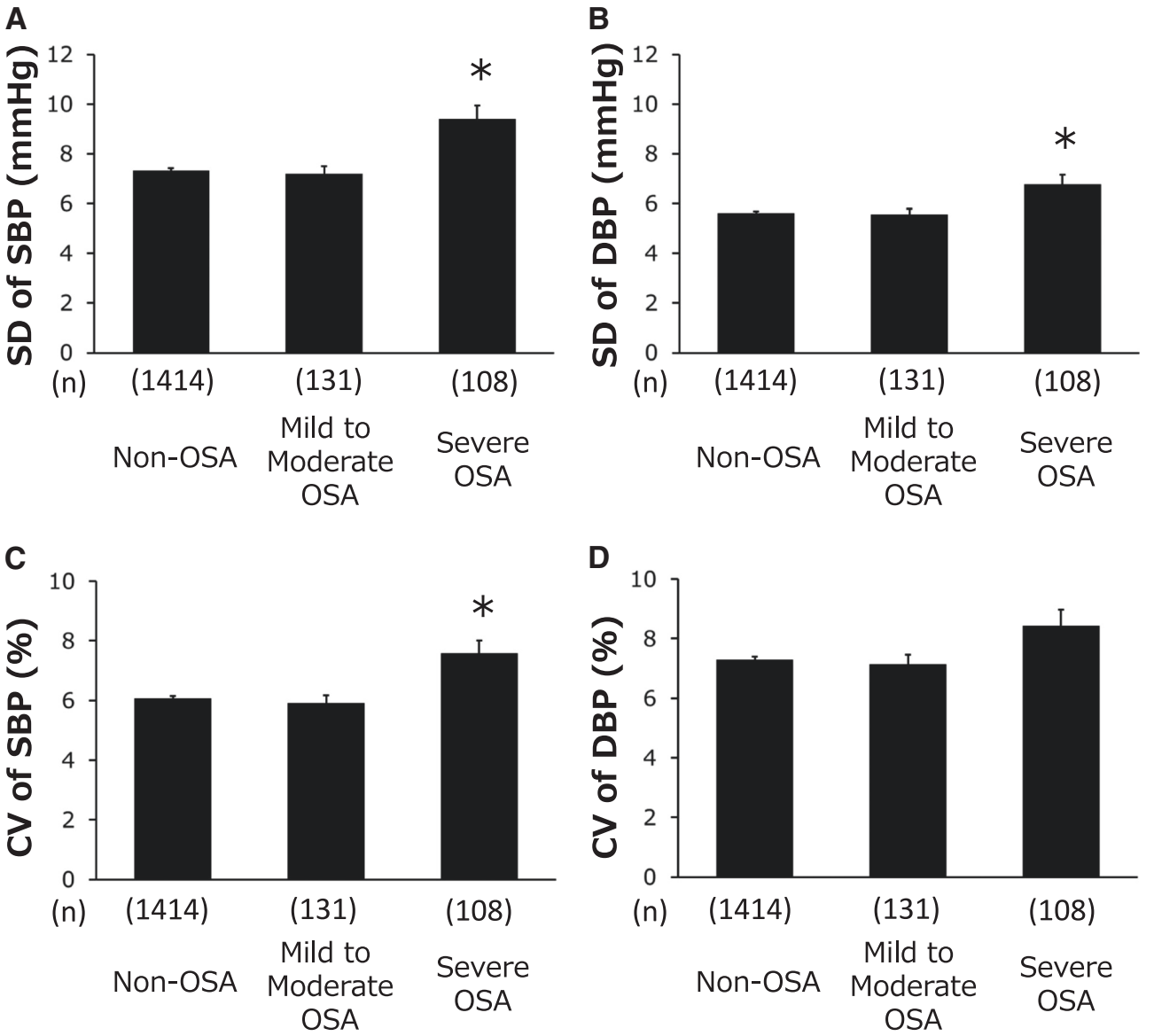

Fig. 1 Multivariable-adjusted means of the SD and the CV of SBP and DBP according to the severity of obstructive sleep apnea (OSA). (A) SD of SBP. (B) SD of DBP. (C) CV of SBP. (D) CV of DBP. Adjusted for age, BMI, HbA1c, eGFR, treatment for OSA, treatment for hypertension, alcohol consumption, and current smoking habits. Values are mean ± SE. CV coefficient of variation, SBP systolic blood pressure, DBP diastolic blood pressure. *P< 0.05 vs. non-OSA by Dunnett's multiple comparison test

Figure 2). Since most of the subjects with severe OSA (85.2%) were treated with CPAP or an oral appliance, we focused on the subjects with mild-to-moderate OSA to determine the association of OSA with its treatment. Figure 2 shows the association of OSA treatment with the BPV of the subjects with mild-to-moderate OSA: both the SD and CV of both SBP and DBP were significantly decreased in the subjects who were being treated for OSA, and were smaller than those in non-OSA (Fig. 1), but were almost equivalent levels of those in the non-OSA group diagnosed precisely by polysomnography (Supplementary Figure 1). The levels of blood pressures were not different between the treated and non-treated groups with mild-to-moderate OSA: 125.2 ± 1.3/81.0 ± 1.0 mm Hg and 125.0 ± 80.4 ± 1.5 mm Hg, respectively.

To identify the factors affecting long-term BPV, we performed a multiple regression analysis of the SD and CV of the annually measured blood pressures. The data presented in Tables 2 and 3 show that the SD and CV of SBP were positively associated with the severity of OSA independently of other confounding factors, including BMI, HbA1c, eGFR, the severity of OSA (no-OSA = 0, mild-to-moderate OSA = 1, and severe OSA = 2), OSA therapy, antihypertensive treatment, current smoking, and habitual alcohol intake. Treatment for OSA with CPAP or an oral appliance was negatively and significantly associated with

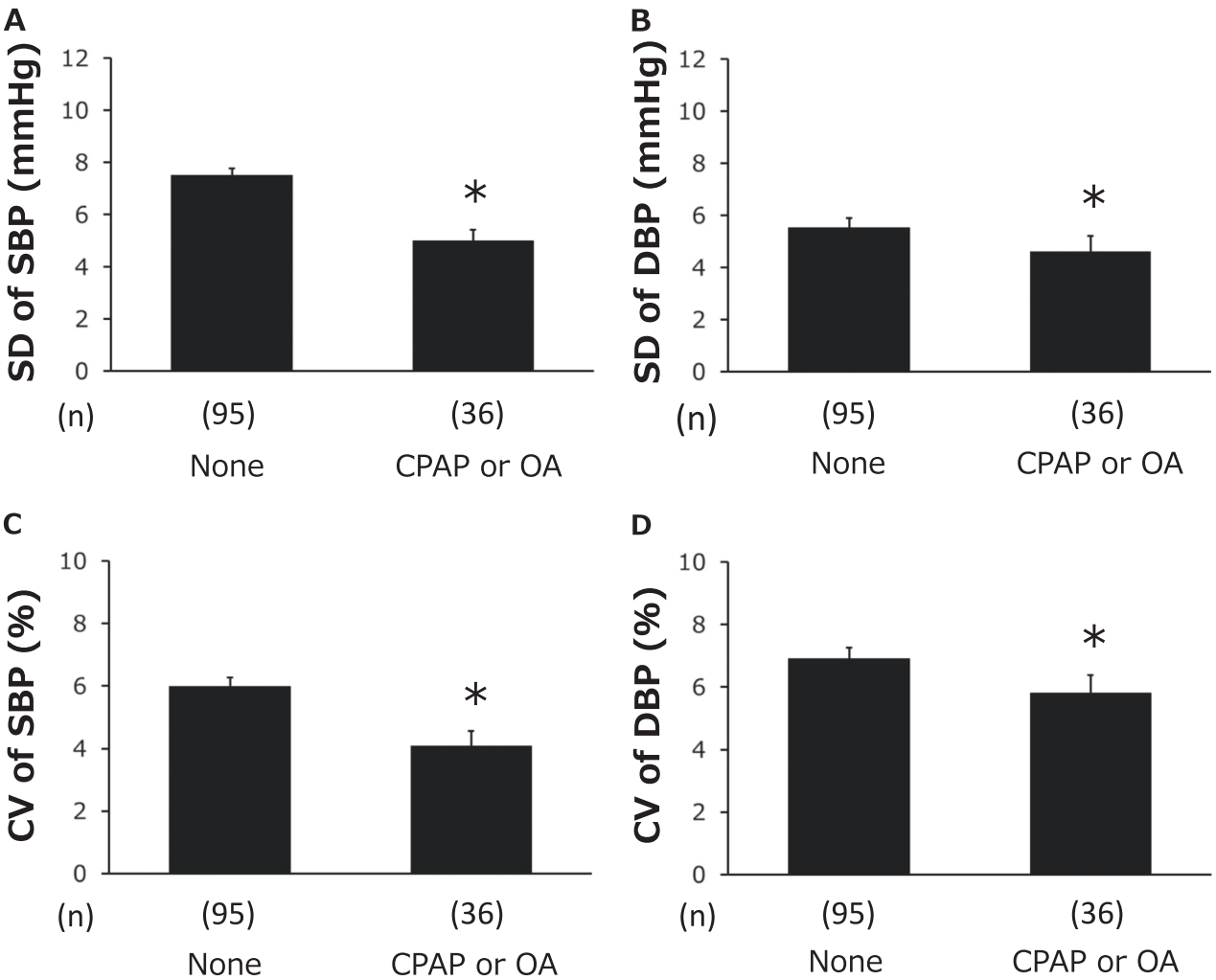

Fig. 2 Multivariable-adjusted means of the SD and CV of SBP and DBP in the subjects with mild-to-moderate obstructive sleep apnea (OSA). (A) SD of SBP. (B) SD of DBP. (C) CV of SBP. (D) CV of DBP. Adjusted for age, BMI, HbA1c, eGFR, treatment for hypertension, alcohol consumption, and current smoking habits. Values are mean ± SE. CV coefficient of variation, SBP systolic blood pressure, DBP diastolic blood pressure, None no treatment group, CPAP or OA the group treated with continuous positive airway pressure or oral appliance. $^*P < 0.05$ vs. none

Table 2 Multiple regression analysis for SD of blood pressures

Independent variables	SD of SBP		SD of DBP	
	β	*P* value	β	*P* value
Age	0.016	0.169	−0.041	<0.0001
BMI (kg/m^2)	−0.004	0.892	−0.005	0.782
OSA severity	0.635	0.015	0.359	0.071
OSA therapy	−1.638	0.002	−0.649	0.101
HbA1c (%)	−0.017	0.907	−0.013	0.910
eGFR (ml/min/1.73 m^2)	0.011	0.122	−0.001	0.822
Antihypertensive treatment	0.041	0.880	0.090	0.662
Current smoking	0.052	0.756	−0.021	0.867
Habitual alcohol intake	0.268	0.120	−0.094	0.471

Data given as mean ± SEM

SBP systolic blood pressure, *DBP* diastolic blood pressure, *OSA* obstructive sleep apnea, *BMI* body mass index, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate

Table 3 Multiple regression analysis for CV of blood pressures

Independent variables	CV of SBP		CV of DBP	
	β	*P* value	β	*P* value
Age	−0.005	0.631	−0.073	<0.0001
BMI (kg/m^2)	−0.048	0.024	−0.077	0.782
OSA severity	0.446	0.039	0.310	0.253
OSA therapy	−1.239	0.004	−0.631	0.242
HbA1c (%)	−0.060	0.618	0.011	0.940
eGFR (ml/min/1.73 m^2)	0.008	0.191	0.002	0.785
Antihypertensive treatment	−0.141	0.529	0.011	0.968
Current smoking	−0.002	0.987	−0.028	0.872
Habitual alcohol intake	0.041	0.774	−0.362	0.043

Data given as mean ± SEM

SBP systolic blood pressure, *DBP* diastolic blood pressure, *OSA* obstructive sleep apnea, *BMI* body mass index, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate

the SD and with the CV of SBP. The SD and the CV for DBP were also negatively and significantly associated with age; however, a relationship between the severity of OSA and DBP variability was not revealed (Tables 2 and 3). The association of the SD and CV of SBP with the OSA severity or the treatment for OSA was likely to be obvious, when the non-OSA subjects were restricted to those with AHI <5 that was precisely evaluated by polysomnography (Supplementary Tables 1 and 2).

Discussion

In the present study, variabilities of annually measured blood pressure were associated with OSA even after adjustment for age, BMI, HbA1c, eGFR, treatment for OSA, antihypertensive treatment, alcohol intake, and current smoking habits. Our multiple regression analysis also revealed that OSA severity was an independent variable affecting long-term systolic BPV, suggesting a close relationship between OSA and long-term BPV. Treatment for OSA improved BPV in the subjects with mild-to-moderate OSA. To the best of our knowledge, the present study is the first to demonstrate that the presence of OSA increases an individual's annually measured long-term BPV, which may be one aspect of the possible pathophysiological impact of OSA on cardiovascular and sympathetic regulation.

The short-term variability of blood pressure values during sleep has been shown to be increased in individuals with OSA [13, 16]. It was also demonstrated that short-term BPV was increased during the daytime [12]. Only a few studies are available regarding the effect of OSA on the long-term variability of visit-to-visit blood pressure values. Lettau et al. [17] recently evaluated the effects of CPAP therapy withdrawal on blood pressure variability. CPAP withdrawal showed only a minor increase (+1.14 mm Hg) in within-visit variability in SBP expressed as the SD of the triplicate measurements at baseline and at follow-up (day 14), and had no effect on day-to-day variability in home blood pressure measurement [17]. In a recent study reported by Shiina et al. [18], the visit-to-visit variability of monthly SBP values measured at a physician's office was increased in the patients with OSA, and the variability was decreased by treatment with CPAP. Our present findings are the first to demonstrate that the BPV determined by routine annual physical examinations, which are generally at a longer interval for blood pressure measurement compared to clinics or office visits, was also increased in individuals with OSA. Our results also revealed that BPV was decreased by OSA treatment in a subgroup of subjects with mild-to-moderate OSA.

These findings indicate that OSA is one of the factors that influence the long-term fluctuations of blood pressure values, although the mechanistic aspect was not determined in the present study. Visit-to-visit BPV has been shown to be involved in potential outcomes of cardiovascular disease such as stroke and coronary heart disease [1, 2], and the prevalence of cardiovascular disease is increased among individuals with OSA [8, 9]. The monitoring of an OSA patient's BPV over a period of years might be needed to prevent the development of cardiovascular disease.

Our present study was characterized by the fact that most of the subjects consist of young and middle-aged men (mean age 44.9 years) at a work site. Many studies of individuals with OSA recruited patients from clinic or hospital settings. In addition, the ages of our subjects were quite different from those of subjects in population-based epidemiological studies, most of whom were of older people. Several investigations have shown that younger individuals should be carefully managed for the treatment of OSA, because all-cause mortality was increased particularly in OSA patients <50 years old compared to the general population [19, 20]. Moreover, when OSA patients were treated with CPAP, all-cause mortality was similar to that in the general population [20]. These findings suggest that appropriate treatment for OSA would be particularly important in the younger subjects to prevent future cardiovascular diseases.

The effects of long-term BPV on the progression of cardiovascular disease have not yet been determined. However, visit-to-visit BPV was shown to have prognostic value and the variability of systolic rather than DBP was shown to be associated with subsequent all-cause mortality, coronary heart disease and stroke [1, 21, 22]. For example, the NHANES III study showed that higher visit-to-visit variability of SBP was associated with increased all-cause mortality over a 14-year follow-up [21]. In the UK-TIA trial, Rothwell et al. [1] demonstrated that visit-to-visit variability in SBP was significantly associated with subsequent stroke. In the present study, the SD and the CV of SBP and the SD of DBP differed between the subjects with severe OSA and those without OSA, although the CV of DBP was not different between these two groups. In addition, the treatment of OSA with CPAP or oral appliance significantly decreased SD and CV of SBP and DBP. These findings suggest that the association of OSA and its treatment with short- and long-term blood pressure variabilities may affect the future incidence of cardiovascular disease. It may be important to maintain an appropriate level of long-term BPV to prevent adverse prognostic consequences.

Cooper et al. [23] reported that the sensitivity of pulse oximetry for identifying OSA was 60%, 75%, and 100% for the patients with an AHI ≥5, ≥15, and ≥25, respectively. Although the sensitivity depends on the populations studied, and diagnostic criteria for OSA and instrument used for the test, pulse oximetry may be effective for screening

subjects with moderate-to-severe OSA, but not for those with mild OSA [23, 24]. In the present study, 4% ODI of ≥10 by pulse oximeter was used for the screening test for OSA to find a candidate for the treatment of OSA. Since only the subjects who were defined as screening positive for OSA were evaluated by polysomnography, the screening-negative subjects with the milder OSA may be classified as the non-OSA group. In fact, blood pressure variabilities in the mild-to-moderate OSA group treated with CPAP or oral appliance were even smaller compared to those in the non-OSA group, while there were almost same levels of blood pressure variabilities between the non-OSA and mild-to-moderate OSA groups (Figs. 1 and 2). However, when we analyzed our study by restricting non-OSA subjects to those with AHI <5 that was precisely evaluated by polysomnography, the levels of blood pressure variabilities in the non-OSA group tended to be smaller, and the levels of blood pressure variabilities in the treated subjects with mild-to-moderate OSA were almost same as non-OSA subjects (Supplementary Figure 1).

Our present study is limited by the fact that the underlying mechanisms of increased long-term BPV in OSA have not been determined. It has been proposed that BPV was influenced by behavior patterns (e.g., working days and weekends), emotional and environmental factors such as changes in temperature over the seasons, and large-artery stiffening [25]. OSA is characterized by repeated episodes of apnea and hypopnea due to upper airway inspiratory collapse during sleep, and the consequent intermittent decreases in blood oxygen saturation activate the sympathetic nervous system in response to chemoreceptor stimulation [12]. Chronic intermittent hypoxia also attenuates the sensitivity of baroreceptors, resulting in an increase in sympathetic activity [26]. This sympathetic hyperactivity has been shown to be prolonged and sustained in individuals with OSA during the daytime [6, 27]. In addition, various vasoconstrictive hormones including norepinephrine, endothelin-1, and angiotensin II are released by hypoxia [28–30]. These pathophysiological factors induced by OSA might be combined and could be attributable to the increases in blood pressure levels and BPV. In fact, plasma norepinephrine concentrations were significantly associated with visit-to-visit BPV in patients with OSA [18]. Further studies focusing on changes in the sympathetic nervous system, baroreceptor reflex, and vascular stiffness are necessary to determine the underlined mechanisms of the effects of OSA on long-term BPV.

Our study has several limitations. First, not all of the subjects in this study were evaluated by polysomnography for the diagnosis of OSA. There might be more subjects who were screening negative who actually had OSA, and thus a smaller number of subjects might be classified as having mild-to-moderate OSA. Second, we did not evaluate the adherence to CPAP treatment. It has been shown that good adherence to CPAP is important to improve the blood pressure variability in patients with OSA [18]. Third, most of our subjects with severe OSA were treated with CPAP, and it would thus be difficult to evaluate the association of treatment of OSA with the BPV in the subjects with severe OSA.

In conclusion, our analyses revealed that OSA was closely associated with the long-term variability of annually measured blood pressure values in a work-site population of young and middle-aged Japanese males. The treatment of OSA with CPAP or an oral appliance was related to the decreased BPV. Further studies are needed to determine the role of long-term BPV on cardiovascular diseases, especially in individuals with OSA.

Compliance with ethical standards

Conflict of interest KM received research funding from Daiichi Sankyo. TO received honoraria from Sanwa Kagaku Kenkyusho. TK received honoraria from Daiichi Sankyo, and research funding from Daiichi Sankyo, Takeda Pharmaceutical, Astellas Pharma, Chugai Pharmaceutical, MSD, Boehringer Ingelheim, EA Pharma, Sanofi Aventis, Pfizer, Kissei Pharmaceutical, Kyowa Hakko Kirin, Asahi Kasei Medical, Otsuka Pharmaceutical, Torii Pharmaceutical, and Bayer.

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