cluding age, hypertension, atrial fibrillation, and diabetes,[10] and it can be used as a surrogate endpoint for subclinical cerebrovascular damage.

It remains controversial whether SDB is a cause or a consequence of cardiovascular disease (CVD). Previous articles have reported a prognostic value of SDB in terms of functional recovery or survival or both, either for nocturnal desaturation (ND) or directly demonstrating respiratory events during the night in patients with stroke.[11–13] Data from the Sleep Heart Health Study[14] showed a relationship between the presence of apnea and stroke in a cross-sectional population-based study. However, longitudinal data are still lacking. Both SDB and SCI share several common cardiovascular risk factors such as aging, hypertension, and obesity. In addition, relationships between SDB and silent cerebrovascular damage have not been clarified yet in a community screening. Therefore we performed this study to investigate whether SDB is related to silent cerebrovascular damage in a high-risk but apparently healthy Japanese general population.

Methods

Because this study was originally designed to reduce the prevalence of stroke, we enrolled a study population with a high risk of stroke.

Study Population

We studied 146 asymptomatic subjects (108 women and 38 men, mean age 67.4 ± 9.0 years, range 42 to 89 years). We enrolled the subjects into our study from the annual health screening in Nishiarita town, Saga prefecture, Japan. The number of town residents >40 years of age was 5323. Those who underwent their companies' health check or who were unwilling to have this health check were excluded in advance as potential subjects. Of the 2784 residents invited, 1511 subjects participated in the conventional health check in 2001. A total of 283 high-risk subjects (187 female and 96 male) were identified. In addition, 170 subjects who visited the hospital to undergo further examination (65.2% for women and 50.0% for men) were recruited; of those, 146 subjects who successfully underwent overnight pulse oximetry were finally recruited for this study (Fig. 1). High-risk subjects were defined as meeting more than three of the following nine criteria; 1) blood pressure (BP) >140/90 mm Hg; 2) total cholesterol >250 mg/dL; 3) left ventricular (LV) hypertrophy by electrocardiography and meeting either the Cornell voltage criteria (RaVL + SV_3 >28 mm in men and 20 mm in women) or Sokolow-Lyon criteria (SV_1 + RV_5 or RV_6 >35 mm, R aVL >11 mm, RaVF >20 mm); 4) hemoglobin A_1c >6.5%; 5) proteinuria, 6) high waist-to-hip ratio (men >0.95, women >0.80); 7) current heavy smoker (>30 cigarettes/day); 8) heavy drinker (ethanol >84 g/day); or 9) family history of stroke. We excluded patients with respiratory illness (such as chronic obstructive pulmonary disease), renal failure, hepatic damage, secondary or malignant hypertension, ischemic or other cardiac disease, congestive heart failure, arrhythmia (including atrial fibrillation or other arrhythmia), stroke (including transient ischemic attacks), or other severe concomitant disease. Data on duration of hypertension, smoking status, alcohol intake, and family history of stroke were based mainly on self-reported information.

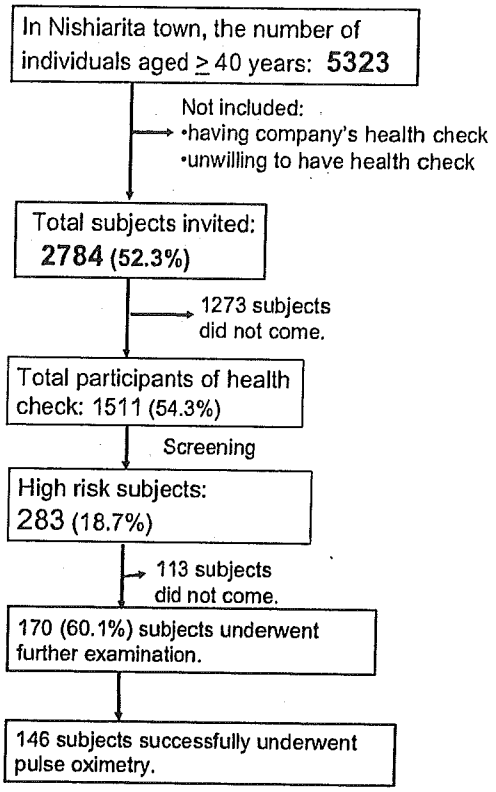

FIG. 1. Selection of subjects for the study.

This study was approved by the Research Ethics Committee, Jichi Medical School, Tochigi, Japan. All subjects studied were ambulatory and all gave informed consent for the study.

Pulse Oximetry

A pulse oximetry PULSOX-3Si (Minolta Co., Osaka, Japan) was used to evaluate nocturnal oxygen saturation change. We performed nocturnal pulse oximetry only for outpatients. The device was attached to the left arm when the subjects went to bed and was removed after they awakened. The sensor probe was fitted to the second or third finger and secured with tape or a finger glove to prevent detaching. The internal memory of this device stores the values of blood oxygen saturation by performing a moving average for the last 5 sec, updated every 1 sec; this sampling time was short enough to avoid underestimation of oxygen desaturation.[15] Data were downloaded to a personal computer via an interface (PULSOX IF-3; Minolta) and analyzed using proprietary software supplied with the equipment (DS-3 version 2.0a; Minolta) as previously described.[16] We used the value of oxygen desaturation per hour (oxygen desaturation index [ODI]) as an indicator of

Table 1. Baseline characteristics of the patients studied

Characteristic	Hypoxia (n = 36)	Nonhypoxia (n = 110)	P value
Age (y)	70.8 ± 7.0	66.3 ± 9.3	.008
Male sex (%)	11 (31%)	27 (25%)	.514
Body mass index (kg/m^2)	24.1 ± 3.5	23.3 ± 2.9	.174
Hypertension (%)	15 (42%)	48 (44%)	1.000
Diabetes (%)	4 (11%)	10 (9%)	.747
Smoking (%)	5 (14%)	13 (12%)	.773
Systolic BP (mm Hg)	154 ± 14	159 ± 19	.23
Diastolic BP (mm Hg)	89 ± 8.9	86 ± 11	.24
LV mass index (g/m^2)	133 ± 32	124 ± 40	.23
Total cholesterol (mg/dL)	219 ± 33	228 ± 41	.24
Triglyceride (mg/dL)	126 ± 53	122 ± 86	.82
Hematocrit (%)	40.3 ± 3.8	40.7 ± 3.5	.65
Serum creatinine (mg/dL)	1.00 ± 0.2	0.96 ± 0.2	.049
HemoglobinA_1c (%)	5.5 ± 0.9	5.3 ± 0.6	.25
Urinary microalbumin (mg/g · Cr)	51 ± 126	43 ± 141	.76
3% ODI (dips/h)	10.1 ± 4.0	2.2 ± 1.4	<.001
4% ODI (dips/h)	6.2 ± 3.4	1.2 ± 1.2	<.001
Time spent SpO_2<90% (min)	11.8 ± 35	2.9 ± 9	.017
Time spent SpO_2<90% (%)	2.2 ± 6.6	0.6 ± 1.8	.022
Sleep time (h)	7.9 ± 1.0	7.5 ± 1.4	.064

BP = blood pressure; HbA_1c = hemoglobinA_1c; LV = left ventricular; ODI = oxygen desaturation index; SpO_2 = pulse oximetry oxygen saturation.

Data are shown as number (%) or as mean ± SD.

SDB. A 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which blood oxygen fell by >3%. The 3% ODI, 4% ODI, and time spent pulse oximetry oxygen saturation (SpO_2) <90% (%) during the estimated sleep time >4 h computed for each subject was used for the analysis. We defined the hypoxia group by the highest quartile of 3% ODI level as >5.5 times per hour in this study, and others were defined as nonhypoxia group.

Brain MRI

Brain MRI was carried out in all 146 subjects using a superconducting magnet with a main strength of 0.5 T (Toshiba MRT50GP, Tokyo, Japan). The brain was imaged in the axial plane at a 7-mm slice thickness. T_1-weighted images were obtained using a short spin-echo pulse sequence with a repetition time of 470 msec and an echo time of 15 msec. T_2-weighted images were obtained using a long spin-echo pulse sequence with a repetition time of 4000 msec and echo times of 120 msec. The matrix size was 256 × 256 pixels. An SCI was defined exclusively as a low signal intensity area (>3 mm, but all were <15 mm), depicted on T_1-weighted images, that was also visible as a hyperintense lesion on T_2-weighted images, as previously described.[17] The MRI images of the subjects were randomly stored and interpreted by reviewers who were blind to the subjects' names and characteristics.

Other Measurements

The LV mass index detected by echocardiography (SSD 2200, Aloka, Tokyo, Japan) was calculated by a method previously described.[18] Carotid plaque was assessed by carotid ultrasonography (LOGIQ500, GE Yokogawa Medical Systems, Tokyo, Japan), and carotid plaque score was calculated by a method previously reported.[19] Mean and maximal intima-media thicknesses (IMT) were measured as described.[20] Urinary microalbumin was measured by a latex agglutination photometric immunoassay with an automated immunochemistry analyzer (LX-6000; Eiken Chemical Co., Tokyo, Japan).

Sleep time was estimated from self-reports.

Statistical Analysis

All statistical analyses were carried out with SPSS/Windows, version 11.0J (SPSS Inc., Chicago, Illinois). Data are expressed as the mean (± standard deviation) or as percentages. The χ^2 test was used to calculate proportions. Unpaired t tests were used for comparison of variables between the hypoxia and nonhypoxia groups (Tables 1 and 2). Factors correlated with the number of SCI, carotid plaque score, LV mass index, and urinary microalbumin were calculated with simple regression analysis (Table 3). Multiple logistic regression analysis was performed to analyze factors associated with the prevalence of SCI (Table 4). Because we considered that nocturnal desaturation involves various confounding factors, we examined nine essential variables to confirm the independence of nocturnal hypoxia as the determinant of SCI. Spearman's correlation was used for bivariate analysis. A two-sided P value < .05 was considered to be statistically significant.

Table 2. Comparison of hypertensive target organ damages

Characteristic	Hypoxia (n = 36)	Nonhypoxia (n = 110)	P value
Number of SCI (/person)	1.0 ± 1.5	0.7 ± 1.2	.21
Prevalence of SCI (%)	57	35	.029
Carotid plaque score	2.9 ± 3.9	1.6 ± 2.5	.019
Mean IMT (mm)	0.81 ± 0.12	0.71 ± 0.11	.352
Maximum IMT (mm)	0.90 ± 0.14	0.88 ± 0.13	.364
Prevalence of carotid plaque (%)	69	49	.036
LV mass index (g/m^2)	133 ± 32	124 ± 40	.23
Prevalence of LVH (%)	69	52	.082
Urinary microalbumin (mg/g · Cr)	51 ± 126	43 ± 141	.764
Presence of albuminuria (%)	26	22	.643

IMT = intima-media thickness; LV = left ventricular; LVH = left ventricular hypertrophy; SCI = silent cerebral infarct.
Data are shown as the number (%) or as mean ± SD.

Results

Baseline Characteristics of the Study Population

Table 1 shows the characteristics of the 146 study subjects separated into two groups: the hypoxia group (n = 36) and the nonhypoxia group (n = 110). Sex, body mass index (BMI), smoking, diabetes, total cholesterol, triglyceridea, hematocrit, and urinary microalbumin, systolic BP, and diastolic BP were similar between the two groups, but age and serum creatinine were higher in the hypoxia than in the nonhypoxia group.

Nocturnal Hypoxia

The mean 3% ODI value was 4.2 ± 4.1/h in the subjects overall. The histogram of 3% ODI (times/h) is shown in Fig. 2. The 3% ODI values of hypoxia group were widely distributed, ranging from mild to severe. Age was significantly correlated with 3% ODI (r = 0.293, P < .001). There were no hypoxic subjects <54 years of age, but the percentage of hypoxia > 55 years was not increased as the age increased. When the subjects were divided into groups according to each 1 (kg/m^2) BMI, the hypoxic subjects were not increased by higher BMI values. Both obese and nonobese subjects had similar ratios of nocturnal hypoxia, but the percentage of hypoxia was lowest in the groups with BMI of 21 and 22.

Subjectively assessed quality of sleep were similar between the hypoxia and nonhypoxia groups (75% v 78%, P = .456).

Silent Cerebral Infarcts

As shown in Table 2, the prevalence of SCI was significantly higher in the hypoxia than in the nonhypoxia group

Table 3. Factors correlated with hypertensive target organ damages

Characteristic	Number of SCI (number/person)	Carotid plaque score (number/person)	LV mass index (g/m^2)	Urinary microalbumin (mg/g · Cr)
Age (y)	0.230*	0.354†	0.289†	−0.001
Male sex	0.099	0.243*	0.322†	−0.206
Body mass index (kg/m^2)	0.033	−0.152	−0.031	0.107
Diabetes	0.084	−0.053	0.016	0.278*
Smoking	0.126	0.135	0.089	−0.138
Waist circumference (cm)	0.054	0.031	0.161	0.030
Serum creatinine (mg/dL)	0.100	0.184‡	0.043	−0.082
HbA_1c (%)	0.037	0.023	0.036	0.149
Systolic blood pressure (mm Hg)	0.196*	0.155	0.286†	0.109
Total cholesterol (mg/dL)	−0.081	−0.062	−0.456†	0.004
Hematocrit (%)	−0.064	0.062	−0.119	0.006
3% ODI (dips/h)	0.318†	0.172‡	0.126	0.099
4% ODI (dips/h)	0.327†	0.127	0.130	0.110
Time spent SpO_2<90% (%)	0.171‡	0.100	0.164‡	0.026

ODI = oxygen desaturation index; other abbreviations as in Tables 1 and 2.
Data are shown as correlation coefficient (r) calcurated with simple regression analysis (Speaman). Dummy code was defined as sex: male = 1, female = 0; diabetes: present = 1, absent = 0; smoking: present = 1, absent = 0.
* P < .01, † P < .001, ‡ P < .05.

Table 4. Determinants of silent cerebral infarct (SCI)

Variable	SCI	*P* value
Systolic blood pressure (10 mm Hg)	1.22 (1.00–1.48)	.048
Nocturnal hypoxia	2.42 (1.10–5.30)	.026

Adjusted odds ratios for silent cerebral infarcts were calculated by stepwise method (forward selection method). The following conventional risk factors were selected as independent variables: age, male gender, body mass index, total cholesterol, systolic blood pressure, hematocrit, hemoglobinA_1c, serum creatinine and presence of nocturnal hypoxia.

(57% *v* 35%, $P = .029$). Table 3 shows the factors correlated with hypertensive target organ damage, determined by simple regression analysis. Age ($r = 0.23$, $P < .01$), systolic BP ($r = 0.196$, $P < .05$), 3% ODI ($r = 0.318$, $P < .001$), 4% ODI ($r = 0.327$, $P < .001$), and time spent SpO_2 <90% ($r = 0.171$, $P < .05$) were significantly correlated with the number of SCI. As shown in Table 4, we calculated the adjusted odds ratios for the relational factors of silent cerebral infarcts by the stepwise method (ie, forward selection method). We selected the following conventional risk factors as independent variables: age, sex, BMI, total cholesterol, systolic BP, hematocrit, hemoglobinA_1c, serum creatinine, and presence of nocturnal hypoxia. Even after the adjustment for these confounding factors, nocturnal hypoxia found to be an independent relational factor of SCI in our population.

In the present study, the locations of SCI were predominantly deep white matter or basal ganglia. We compared the dominance of these locations between the hypoxia and nonhypoxia groups, and found that there were no significant differences in the SCI location between these two groups.

Nocturnal Hypoxia and Target Organ Damages

The prevalence of carotid plaque and the carotid plaque score were significantly higher in the hypoxia than in the nonhypoxia group, but there were no significant differences in mean IMT and maximal IMT (Table 2). As shown in Table 3, age ($r = 0.354$, $P < .001$), male sex ($r = 0.243$, $P < .01$), serum creatinine ($r = 0.184$, $P < .05$), and 3% ODI ($r = 0.172$, $P < .05$) were significantly and positively correlated with carotid plaque score. However, the relationships between carotid plaque score and age, sex, creatinine, and 3% ODI were diminished after the multivariate analysis.

As shown in Tables 2 and 3, LV mass index and urinary microalbumin were not significantly different between the hypoxia and nonhypoxia groups and were not significantly correlated with 3% ODI value.

Discussion

In the present study, nocturnal hypoxia assessed with overnight pulse oximetry was found to be independently associated with the prevalence of SCI among a high-risk community-dwelling Japanese population. To our knowledge, this is the first report to demonstrate the relationships between SDB and SCI. In a previous Japanese epidemiologic study (the Hisayama study), the determinants of SCI were high BP, diabetes, atrial fibrillation, and history of coronary heart disease.[21] Although these risk factors overlapped that of SDB, no data have been published that direct showing the relationship of SDB with SCI.

Cause-Effect Relationships Between SDB and SCI

In previous studies, no relationsips were found between SDB and white matter disease or silent cerebral infarcts.[22–24] However in the present study we found a relationship between SDB and prevalence of SCI. The location of SCI in the present study was mainly in basal ganglia or deep white matter lesions but not in the respiratory center. Therefore it does not seem that breathing patterns were directly influenced by SCI.

In previous reports, a higher percentage of SDB was observed in stroke patients, and SDB was associated with poor functional outcomes in survivors and higher mortality.[11] A higher prevalence of SDB was observed in stroke patients having similar frequencies of risk factors compared with age-matched control subjects.[25] The mechanism of abnormal breathing patterns (periodic breathing) in stroke patients regardless of lesion site are explained by prolonged blood circulation from the heart to brain. Because SCI can be recognized as a subclinical stroke,[7–9] the same pathogenic mechanisms as those in stroke patients can be suggested in SCI patients.

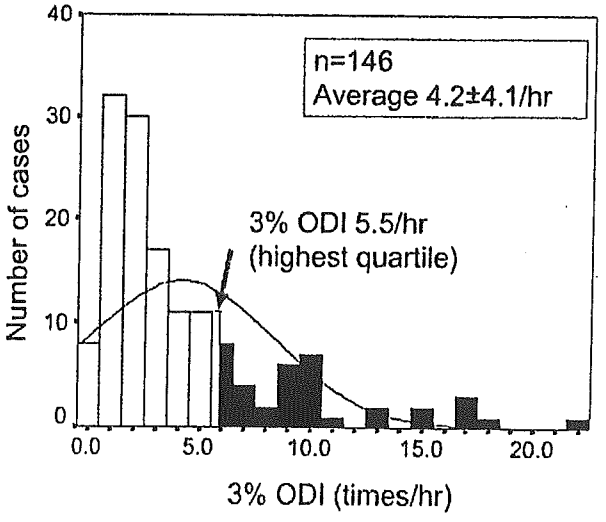

FIG. 2. Histogram of 3% O_2 desaturation index (3% oxygen desaturation index, times per hour).

On the other hand, there are several pathophysiologic mechanisms of stroke in SDB patients. Alteration of cerebral hemodynamics, hypoxemia, and dysfunction of cerebral autoregulation are suggested as the main mechanisms of cerebral ischemia in patients with SDB.[2] The decrease in arterial blood pressure and gradual rise in intracranial pressure during apnea result in decreased cerebral perfusion pressure.[26] Pronounced cerebral blood flow velocity changes during apneic episodes and the concomitant alterations of vessel wall tension might lead to chronic strain on the brain vessels and formation of atherosclerosis.[2,27] Augmented mechanical stress on the cardiovascular system and increased variability of blood flow by augumented BP variability increases sheer stress induced platelet activation at atherosclerotic stenotic sites.[28] In SDB subjects SCI may be formed by the same mechanism.

In the present study, although the BP level was not different between the hypoxia and nonhypoxia groups, age and serum creatinine were higher in the hypoxia than in the nonhypoxia group. Although more advanced age was significantly correlated with the extent of SDB,[29] when the ages were divided into 5-year groups, the percentages in the hypoxia group >55 years of age was not different in the present study. However, more advanced age itself could be a predictor of SDB, as older patients have a significant number of respiratory events without clear clinical indications. Systolic BP level was another significant determinant of SCI. Although we could not perform ambulatory BP monitoring for all subjects, not only BP levels but also both short and long term BP variation would have been enhanced in the hypoxia group.[28] Further studies are needed to clarify whether the BP variability would be augmented in SDB subjects.

Characteristics of Japanese Population

As is widely known, obesity is one of the strongest risk factors for SDB. However, in our population, the rate of hypoxia was similar among the different BMI groups. It has been reported that in Asian subjects with SDB the relative risk of obstructive sleep apnea attributable to obesity was less than in subjects of white ethnicity.[30]

We previously reported the associations between SCI and nondipper hypertension,[31] extreme dipping,[32] diabetic hypertension,[33] and insulin resistance.[34] There is a possibility that greater numbers of subjects with SDB were included in these high-risk population groups. The common pathologic pathway in the population may be higher sympathetic activity and resulting higher peripheral resistance. In previous reports, higher sympathetic tone was reported in nondipper,[35] insulin resistant,[36] and diabetic[36] populations. The strength of our study is that even in a nonobese population, SDB reflects not only target organ damages but also increased sympathetic tone resulting from hypoxic stress during sleep. We hypothesize that even among nonobese older women, those with greater risk factors for sleep apnea could have a greater presence of SCI.

Accuracy of Pulse Oximetry

The accuracy of overnight pulse oximetry was recently reported.[5,6,37] Magalang et al reported that oxygen desaturation indexes and the Δ index provided similar levels of diagnostic accuracy.[5] The combination of indexes improved the precision of the predicted apnea–hypopnea index (AHI) and may offer a potentially simpler alternative to polysomnography (sensitivity 90%, specificity 70%). Using case designation criteria of 15/h for AHI and respiratory disturbance index, the sensitivity and specificity were 98% and 88%, respectively.[5] In clinical practice, other SDB such as upper airway resistance syndrome, central sleep apnea syndrome, and mixed type exist. Nakamata et al reported that the validity of the pulse oximetry was fairly good for detecting an AHI of >5 by polysomnography using a cutoff threshold of 3% ODI = 5.[6] However specificity, sensitivity, and predictive value depend on the previous likelihood of developing the disease, and accuracy data obtained when evaluating patients with suspected sleep apnea would not be the same in a different group of patients with a previously low likelihood of having sleep apnea.

Our study has several limitations. The first is that we did not use a respiratory recording device. The diagnosis of SDB cannot be confirmed only by pulse oximetry. Second, the relatively small sample size presumably limited the ability to detect differences in IMT, LV mass, and other markers of risk. Third, we did not conduct a precise sleep respiratory survey (extent of snoring, apnea, or sleep quality), because this study originally did not target SDB patients.

In conclusion, SDB assessed by overnight pulse oximetry was associated with SCI in a high-risk, nonobese, Japanese, community-dwelling population at cardiovascular risk.

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Original Article

Altered Aortic Properties in Elderly Orthostatic Hypertension

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To investigate the impact of arterial properties on orthostatic blood pressure (BP) dysregulation in older hypertensives, orthostatic BP dysregulation, a common phenomenon in elderly hypertensives, is associated with target organ damage and falls. However, the mechanism of orthostatic BP dysregulation remains unclear. The pulse wave velocity (PWV), related arterial stiffness, and the augmentation index (AI), a measure of arterial wave reflection, were measured in 365 older hypertensives. We classified the study patients into an orthostatic hypertension (OHT) group with orthostatic increase of systolic BP (SBP) of ≥20 mmHg (n=27) and an orthostatic normotension (ONT) group with an orthostatic increase of SBP of <20 mmHg and orthostatic SBP decrease of <20 mmHg (n=338). Orthostatic AI was significantly greater in the OHT group than in the ONT group (OHT: 6.5±12% *vs.* ONT: −5.6±12%, p<0.001), while supine AI and supine and orthostatic pulse rate were comparable between the two groups. There was no significant difference in the PWV between the OHT and ONT groups. Orthostatic hypertension was affected by altered aortic properties and associated with augmented wave reflection of arterial pressure. (*Hypertens Res* 2005; 28: 15–19)

***Key Words*: aortic properties, augmentation index, orthostatic hypertension**

Introduction

Orthostatic hypotension, often found in elderly hypertensives with autonomic nervous dysfunction (a large subgroup of elderly hypertensives), is well recognized as a risk factor for falls, syncope and cardiovascular events (*1–4*). However, there have been few reports on orthostatic hypertension (OHT), in which the blood pressure (BP) increases with orthostatic postural change (*5–11*). Although some reports have suggested that an orthostatic BP increase predicts an increased risk of developing coronary artery disease (*5, 7*) and cerebrovascular disease (*8, 10*), the clinical significance and mechanism of OHT remain unclear.

One report showed that the patients with OHT had higher seated systolic BP (SBP) than those without OHT (*7*). Generally, the progressive appearance of the reflected wave in systole and eventual summation with the forward incident wave results in augmentation of the SBP (*12*).

We speculated that aortic properties play an important role in orthostatic BP increase. However, there have been no reports about the relationship between aortic properties and orthostatic BP change. In this study, we investigated the relationship between aortic properties and orthostatic BP increase.

Methods

Patients

We enrolled 382 hypertensive patients who satisfied the following criteria: 1) supine BP (measured by standard cuff methods after resting 5 min in a supine position) ≥140 mmHg for SBP and/or ≥90 mmHg for diastolic BP (DBP); or 2) treatment of hypertension ≥ 3 months without a change of anti-hypertensive drugs at either of two Japanese hospital

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Table 1. Clinical and BP Characteristics

	Normal group (n=338)	Orthostatic hypertension (n=27)
Age (years)	60±12	65±10
Male (%)	55	48
Body mass index (kg/m^2)	24±3.2	25±2.7
Smoking (%)	24	12
Hyperlipidemia (%)	32	19
Diabetes mellitus (%)	10	29*
Coronary artery disease (%)	14	29
Cerebrovascular disease (%)	8	0
Treated hypertension (%)	64	63
Ca antagonist (%)	40	28
ARB (%)	30	28
β-Blocker (%)	11	12
ACE inhibitor (%)	13	16
Diuretics (%)	11	8
α1-Blocker (%)	7	0
Supine brachial		
SBP (mmHg)	142±18	136±18
DBP (mmHg)	86±11	83±12
HR (bpm)	68±11	67±12
Standing brachial		
SBP (mmHg)	142±19	163±19**
DBP (mmHg)	91±13	97±13*
HR (bpm)	74±13	74±12

*p<0.05, **p<0.001 *vs.* normal group. BP, blood pressure; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; SBP, systolic BP; DBP, diastolic BP; HR, heart rate.

clinics. The entry period was January 2002 to December 2002. Informed consent was obtained from all study participants, and the study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School.

Pules Wave Velocity (PWV) and Augmentation Index (AI) Measurements

BP, PWV and AI were measured with the subject in a supine position after 5 min of rest using an automatic waveform analyzer (formPWV/AI; Colin Co., Komaki, Japan). The validity and reproducibility of brachial-ankle PWV using this autonomic waveform analyzer have been reported in type 2 diabetes patients (*13*), patients with coronary artery disease (*14*, *15*), and patients on chronic dialysis (*16*). AI was determined by arterial applanation tonometry incorporating an array of 15 micropiezoresistive transducers placed on the right carotid artery (formPWV/AI; Colin Co.) and was calculated from the aortic pressure waveform (*17*). Carotid BP was estimated by the pressure signal obtained using tonometry, by equating the carotid mean arterial pressure to the brachial artery measurement as previously described (*18*). PWV and supine AI were simultaneously recorded. Standing AI was measured with the subject in a standing position for at least 3 min. The orthostatic AI change was taken as the difference between the supine and standing AI.

Table 2. Profiles of Aortic Properties

	Normal group (n=338)	Orthostatic hypertension (n=27)
PWV (cm/s)	1,754±390	1,707±369
Supine AI (%)	23±17	21±18
Standing AI (%)	17±19	28±16*

*p<0.05 *vs.* normal group. PWV, pulse wave velocity; AI, augmentation index.

Definition of OHT

Brachial BP and heart rate (HR) were measured with the subject in a supine position after resting 5 min in the supine position, and then with the subject in a standing position for at least 3 min. No patients developed presyncope or syncope in the standing position. We classified the patients into an OHT group with an orthostatic SBP increase ≥ 20 mmHg (n=27) and an orthostatic normotension group (ONT) with an orthostatic SBP increase < 20 mmHg and orthostatic SBP decrease < 20 mmHg (n=338). We excluded 17 patients who had an orthostatic SBP decrease ≥ 20 mmHg, because the prevalence of α-adrenergic blockade use (40%) in this group was significantly higher than that in the OHT (0%, p<0.001) or ONT (7%, p<0.001) group.

Statistical Analysis

A two-tailed paired t-test was used to compare mean values between the two groups. An χ^2 test was applied to examine differences in prevalence between the two groups. A value of p<0.05 was considered to be statistically significant.

Results

There were no significant differences in the frequency of antihypertensive drug use between the two groups. The prevalence of diabetes mellitus and the standing SBP and DBP were higher in the OHT group than in the ONT group, while the supine SBP was lower in the OHT group than in the ONT group (Table 1).

There was no significant difference in the estimated carotid BP ofthe supine position between the OHT and ONT group (137±18 *vs.* 143±22 mmHg). However, the carotid BP of the standing position was higher in the OHT group than in the ONT group (167±19 *vs.* 141±22 mmHg, p< 0.001).

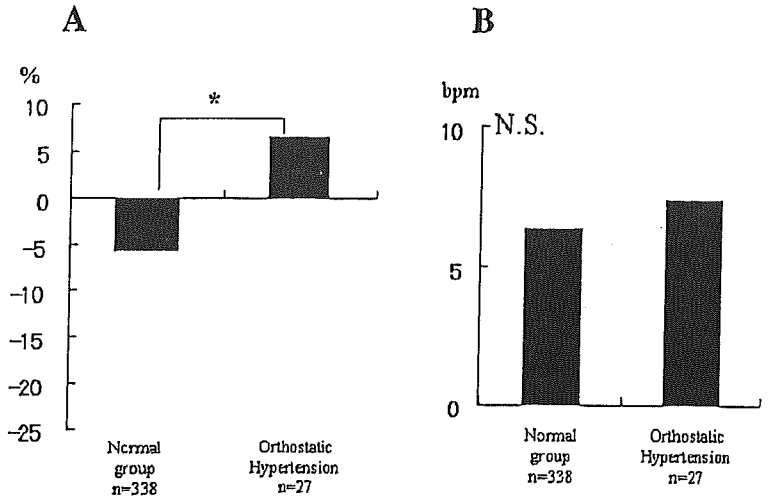

Fig. 1. *Orthostatic changes in augmentation index (A) and heart rate (B). *p < 0.001 between the indicated colums.*

There was no significant difference in the PWV or supine AI between the two groups. Standing AI was higher in the OHT group than in the ONT group (Table 2).

Figure 1 shows the orthostatic changes in AI and HR in the two groups. The orthostatic change in AI was higher in the OHT group than in the ONT group. There was no significant difference in the change of HR between the two groups.

Discussion

In this study, the orthostatic AI change of the OHT group was significantly higher than that of the ONT group, indicating that OHT might be determined by functional arterial properties related to the orthostatic change in the amount and site of wave reflection. We observed an excessive augmentation of the reflected pressure wave in the OHT patients.

In regard to PWV, there was no significant difference between the OHT and ONT group. PWV is related to aortic distensibility and compliance by the Bramwell-Hill equation (*19*). PWV is known to be an indicator of arterial stiffness (*20–23*), and has been regarded as a marker reflecting vascular damage (*24, 25*). Therefore, the mechanism of OHT might not be simply progressed in arterial stiffness.

There was no significant difference in PWV or AI in the supine position between the OHT group and ONT group. However, AI in the standing position and orthostatic AI change were significantly higher in the OHT group than in the ONT groups. AI is determined by the intensity and timing of reflected pressure waves (*26*). The intensity of aortic wave reflection is a determinant of the vascular tone of the peripheral artery (*27, 28*). The augmentation of a reflected pressure wave occurs earlier as a consequence of the new reflecting site provided by the increased peripheral resistance (*27, 28*). The mechanism of OHT remains unclear, although some pathogenic processes have been reported (*6*). In an earlier study, we reported that plasma norepinephrine and vasopressin levels during tilting were significantly higher and that the orthostatic norepinephrine increase tended to be higher in a group of subjects with OHT than in those with ONT (*10*). This finding suggests that orthostatically induced sympathetic activation might play some role in the pathogenesis of OHT. In OHT, sympathetic activation accompanied by orthostatic change might increase the vascular tonus, which is related to the augmentation of reflected pressure waves. In the present study, the prevalence of diabetes mellitus was 40% in the OHT group. Orthostatic hypotension is a well-known complication caused by autonomic denervation in patients with long-term poor control of blood glucose levels. One report demonstrated (*29*) that OHT was a novel complication in normotensive diabetic patients and that the hypersensitivity of the cardiopulmonary baroreflex and sympathetic nervous system might contribute to the pathogenesis of OHT. The incidence of diabetes mellitus in this study might have played a role in the orthostatic BP increase.

In addition, cardiac factors are among the important determinants of AI (*12*). One report demonstrated a linear relation between AI and HR in a pacing study, with AI decreasing by 4% for every 10 bpm increments in HR (*30*). Because of the proportionality between ejection time and cardiac cycle duration, the peak of the forward traveling wave occurs earlier at faster HR. In this study, there were no significant differences in orthostatic BP change between the OHT and ONT groups. Therefore, orthostatic AI change appears not to be explained by the orthostatic HR change.

In a recent study in which the study groups findings were adjusted for age and 24-h SBP, we reported that elderly hypertensive patients with OHT often have advanced silent cerebrovascular diseases, and they may be at elevated risk of overt clinical cerebrovascular events (*10*). In addition, other authors have reported that AI was an independent predictor of

mortality due to end-stage renal failure in hemodialysis patients with normal PWV (*31*). In the present study, there was no significant difference in AI or PWV between the OHT and ONT group. This result suggests that the OHT group may have consisted of hypertensives without abnormal arterial structure but with impaired functional arterial properties that were detected as an excess augmentation of arterial wave reflection.

Increased BP variability may contribute to an increase in the risk for hypertensive target organ damage (*32*). Morning BP increase is reported to be associated with cardiac hypertrophy in hypertensive patients (*33*), and this may trigger cardiovascular events (*34*). We previously reported that ambulatory BP variability was increased more markedly in a group of patients with OHT than in an ONT group (*10*). This BP variability may have been partly due to the augmentation of reflected waves.

In this study, the prevalence of administration of α-adrenergic blockers was higher in the OHT group than in the ONT group. Postural hypotension, one of the side effects of using α-adrenergic blockers, is often seen in the early phase, and is not rare in the chronic phase, of drug therapy (*35*). In this study, all patients had taken anti-hypertensive drugs for at least 3 months. In our previous study, we reported that the orthostatic BP increase was selectively abolished by α-adrenergic blockers (*10*). This might indicate that administration of α-adrenergic blockers diminished the orthostatic AI increase. In the present study, the ONT group showed a higher rate of calcium antagonist use that the OHT group. Slavachevsky *et al.* suggested that calcium antagonists might induce a greater decline in orthostatic BP than angiotensin converting enzymes (*36*). This may also indicate that administration of a calcium antagonist diminished the orthostatic BP increase in the present study.

In a previous study by Safer *et al.*, carotid BP was shown to be a more sensitive marker of mortality in end-stage renal disease than brachial BP (*18*). In the present study, there was no significant difference in supine carotid BP between the ONT and OHT group, but standing carotid BP was higher in the OHT group than the ONT group. In the OHT group, standing carotid BP was higher than standing brachial SBP. In addition, the present study that altered aortic properties in elderly patients with orthostatic hypertension could be successfully assessed by carotid BP. Carotid BP might be a better predictor of target organ damages than brachial BP.

Our findings indicated that excessive augmentation of arterial wave reflection was the predominant mechanism of OHT. The OHT group may have consisted of hypertensive patients without abnormal arterial structure but with abnormal functional properties resulting in elevated risk of hypertensive cerebrovascular disease.

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Morning Blood Pressure Hyper-reactivity Is an Independent Predictor for Hypertensive Cardiac Hypertrophy in a Community-Dwelling Population

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Background: Morning blood pressure (BP) surge seems to be a risk factor for cardiovascular events. Although physical activity after arising significantly affects morning BP surge, it has remained unclear whether morning BP surge after controlling for physical activity (morning BP reactivity) is associated with target organ damage.

Methods: We performed ambulatory BP monitoring with simultaneous actigraphy and echocardiography in 120 community-dwelling Japanese subjects. We determined the waking time by actigraphy, and defined morning BP surge (MBPS) as the average of systolic BP during the 2 h after awakening minus the average of systolic BPs during the 1 h that included the lowest sleep BP. The ratio of MBPS/(sum of the 2-h physical activity after the arising time)$^{0.5}$ was calculated as the morning BP reactivity (MBPR).

Results: In all the subjects studied (n = 120), MBPR was positively associated with left ventricular (LV) mass index (r = 0.30, P = .001). The MBPR had a positive association with both 24-h BP variability (SD) (r = 0.373, $P < .001$) and awake BP variability (r = 0.20, $P < .05$). The MBP hyper-reactive group (the highest quartile [Q4] of MBPR: n = 30) had significantly higher LV mass index than the nonreactive group (the other quartiles [Q1 to 3]: n = 90) (140 v 113 g/m^2, $P < .001$). Even after controlling for age, body mass index, gender, and 24-h systolic BP, the MBP hyper-reactive status still remained a strong predictor for LV hypertrophy.

Conclusions: Exaggerated MBPS, adjusted for physical activity, is associated with cardiac hypertrophy independent of ambulatory BP level in a community-dwelling population. Am J Hypertens 2005;18:1528–1533 © 2005 American Journal of Hypertension, Ltd.

Key Words: Morning blood pressure surge, morning blood pressure reactivity, left ventricular hypertrophy, physical activity, ambulatory blood pressure.

All types of cardiovascular complications, such as myocardial infarction, sudden cardiac death, ventricular fibrillation, ventricular tachyarrhythmia, and stroke, have higher incidences in the early morning.[1,2] In spite of the clinical importance of this phenomenon, the mechanism accounting for the higher incidence of cardiovascular events in the morning remains unclear. Ambulatory blood pressure (BP) exhibits significant diurnal variation subject to modification by various psychologic and physical stimuli during daily life.[3,4] Some studies have suggested that several factors, such as BP increase in the early morning (morning BP surge), augmented sympathetic nerve activity, increase of coronary artery tonus, increase in plasma catecholamines and cortisol concentration, aggregation of platelets, hypercoagulability, and decrease in fibrinolytic activity, could contribute to increase cardiovascular events in the morning.[5–7] Thus, morning hypertension and exaggerated BP variability in the morning may be more closely associated with cardiovascular risk than hypertension and BP variability during other periods.[8–10] We have recently found that morning BP surge is associated with the risk of stroke independent of 24-h BP level in hypertensive patients.[11] In older hypertensive patients, morning BP surge, particularly that due to

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α-adrenergic activity, is closely associated with silent cerebrovascular disease.[12] Previous reports also indicated that morning BP surge is associated with cardiac hypertrophy and increased QTc dispersion independent of the 24-h BP level in hypertensive patients.[13–15]

Because morning BP surge predominantly starts after awakening, physical activity after awakening is thought to be a main contributing factor for morning BP surge.[16] On the other hand, the degree of morning BP surge adjusted for physical activity, morning BP reactivity, may be associated with target organ damage. There have been no reports that investigated the correlation between morning BP surge adjusted for physical activity and hypertensive target organ damage. Therefore, we used ambulatory BP monitoring (ABPM) together with actigraphy, which could identify the precise waking time and could quantitatively assess physical activity after arising, to study the relationship between morning BP surge and hypertensive target organ damage in relation to physical activity.

Table 1. Characteristics of the study group

	Total
Number	120
Age (yr)	61 ± 11
Male, *n* (%)	56 (47)
Smoker, *n* (%)	15 (13)
Dyslipidemia, *n* (%)	43 (36)
Diabetes mellitus, *n* (%)	5 (4)
Clinic systolic BP (mm Hg)	135 ± 20
Clinic diastolic BP (mm Hg)	84 ± 11.1
24-h systolic BP (mm Hg)	124 ± 15.0
24-h diastolic BP (mm Hg)	75 ± 8.9
Sustained hypertension, *n* (%)	49 (40.8)
Morning systolic BP (mm Hg)	129 ± 18
Morning systolic BP surge (mm Hg)	27 ± 13
Morning BP reactivity (mm Hg/$G^{0.5}$)	18 ± 11
Morning physical activity (G)	2.9 ± 1.6
Left ventricular mass index (g/m^2)	120 ± 32
Intima–media thickness (mm)	0.69 ± 0.16

BP = blood pressure.
Data are shown as mean ± SD or number (percentage).

Methods

Subjects

The study subjects were participants in a specific cardiovascular annual health examination performed in the community-based residents aged 20 years or older in Miyori district in Kinugawa, Japan, in 1998. A total of 181 adults (33% of 541 residents aged 20 years or older) gave their informed consent and participated in this study.[17] This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan. We selected the study patients according to the following exclusion criteria: 1) those under antihypertensive therapy during the 2-week period before the examination, 2) those whose echocardiography findings could not be obtained clearly, 3) available number of BP measurements during ABPM <80% of total measurements, and 4) those who complained of severe sleep impairment due to ABPM. The final subjects consisted of 120 patients (56 men and 64 women, mean age 61 years) (Table 1). None of these study subjects overlapped with study subjects examined in our previous study on morning BP surge.[11] Clinic BP was measured after resting in a sitting position for 5 min by standard cuff methods.

24-h ABPM

Noninvasive ABPM was performed with an automatic device (TM2420, A & D Co. Inc., Tokyo, Japan), which recorded BP and heart rate every 30 min during both the awake period and sleep. The ambulatory data used in the present study were obtained by the oscillometric method. Each subject was asked to remain as motionless as possible each time the monitor took a reading during waking hours.

Normotension was determined when 24-h systolic BP was <130 mm Hg and diastolic BP was <80 mm Hg, and sustained hypertension was determined when 24-h systolic BP was ≥130 mm Hg or diastolic BP was ≥80 mm Hg. The subjects consisted of 71 normotensives and 49 untreated hypertensives diagnosed on the basis of ABPM.

We defined morning BP surge (MBPS) as the average of systolic BPs during the 2 h after awakening minus the average of systolic BPs during the 1 h that included the lowest sleep BP (Fig. 1). This definition was the same as that used in our previous study,[11] whose study population had no overlap with the present study population.

We classified the patients according to the percentage of nocturnal systolic BP reduction (100 × [1 − Sleep systolic BP/Awake systolic BP]) as follows: extreme dippers if the nocturnal systolic BP reduction was ≥20%; dippers if the decrease was ≥10% but <20%; nondippers if the decrease was ≥0% but <10%; and risers if it was <0%.[18,19]

Actigraphy

The ABPM device was equipped with an actigraph, which recorded the frequency of physical movement in two spatial axes. Physical activity was assessed continuously and recorded in 60-sec epochs throughout the 24-h period. The precise clock time of arising from bed was determined from the individual's diary and actigraph. In the case the arising time was disagreed between diary and actigraphy, we used the arising time written in each diary.

The morning physical activity of each subject was defined as the sum of the activity in the 2 h after the arising time. As the association between physical activity and BP shows the best fit when the square root transformation is applied to the activity measures,[20] we calculated the morning BP reactivity (MBPR) as the ratio of MBPS/(Sum of the 2-h activity after the arising time)$^{0.5}$ (Fig. 1). Of

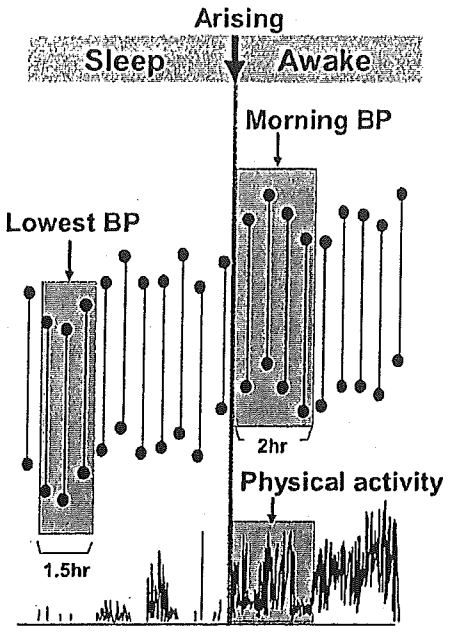

FIG. 1. Definition of morning blood pressure (BP) surge and reactivity.

subjects with equivalent magnitude of BP surge, those subjects with lesser degree of activity will have greater MBPR. We classified the patients according to the level of MBPR into four groups. The highest quartile (Q4) of MBPR was defined as the morning BP hyper-reactive group (n=30) and the other quartiles (Q1 to 3) as the morning BP nonreactive group (n = 90).

Echocardiography

The M-mode echocardiography was performed with two-dimensional monitoring just before attaching the ABPM device. Left ventricular mass index (LVMI) was calculated from Devereux formula[21] indexed to body surface area, as described previously.[17] Images of right and left common carotid arteries were obtained using a 7.5-MHz transducer. Measurement of intima–media thickness (IMT) of the far wall at the end-diastole was performed in B-mode, and the IMT value was defined as the mean of three measurements for both the left and right sides as described previously.[17]

Statistical Analysis

The unpaired Student t test and χ^2 test were used to test differences between the two groups in the mean values of continuous measures and prevalence rates. Pearson's correlation coefficients were used to examine the relationships among continuous measures. One-way analysis of variance (ANOVA) and of covariance (ANCOVA) (for controlling age and 24-h systolic BP) were performed to detect differences among groups. Tukey's honestly significant differences test was used for multiple pairwise comparisons of means among groups. Multiple logistic analysis was performed to estimate and test the independent effects on LVMI of various measures, including MBPR, 24-h systolic BP, age, and body mass index (BMI). The statistical calculations were performed with SPSS II (SPSS Inc., Tokyo, Japan). Differences/associations with $P < .05$ were considered to be statistically significant.

Results

Correlations Between Morning BP Reactivity, Clinic, or 24-h BP, Pulse Rate, and BP Variability

Table 2 shows the associations of MBPS and MBPR with clinic or 24-h systolic and diastolic BPs, and pulse rate. Age, clinic BPs, and 24-h BPs were significantly correlated with MBPR. On the other hand, there were no significant correlations between 24-h pulse rate and

Table 2. Correlations of morning blood pressure surge and reactivity with cardiovascular remodeling in total subjects

Parameter	Morning BP Surge		Morning BP Reactivity	
	r	*P*	*r*	*P*
Age	0.024	.792	0.244	.007
Clinic systolic BP	0.227	.013	0.405	<.001
Clinic diastolic BP	0.231	.011	0.279	.002
24-h systolic BP	0.399	<.001	0.439	<.001
24-h diastolic BP	0.308	.001	0.252	.005
24-h pulse rate	0.153	.094	0.016	.866
SD of 24-h systolic BP	0.506	<.001	0.373	<.001
SD of awake systolic BP	0.286	.001	0.198	.030
Left ventricular mass index	0.162	.077	0.296	.001
Intima–media thickness	0.001	.997	0.122	.183

Abbreviation as in Table 1.
Pearson's correlation coefficients are shown.

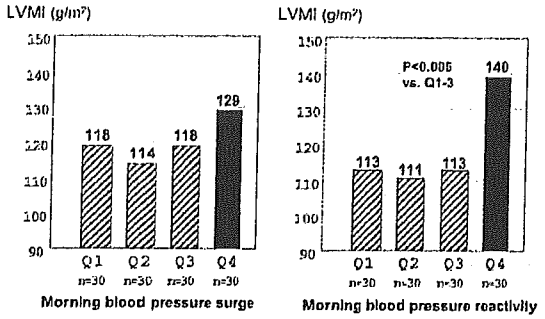

FIG. 2. Morning blood pressure surge or reactivity and hypertensive cardiac remodeling. Left ventricular mass index (LVMI) examined by echocardiography. We classified the patients into four groups according to the level of morning BP surge or reactivity, the lowest quartile (Q1) to highest quartile (Q4).

MBPR. The MBPR had positive relationships with 24-h BP variability (SD of BPs during 24-h period) and awake BP variability (SD of BPs during the awake period).

Relationships With Nocturnal BP Decreases

Because the definition of MBPS is related in part to the nocturnal BP decrease, we also studied the influence of nocturnal BP dipping status. The prevalence of extreme dippers, dippers, nondippers, and risers was not significantly different between the hyper-reactive group (10%, 63%, 27%, 0%, respectively) and the nonreactive group (3.3%, 63%, 32%, 1.1%, respectively). The nondippers (nondippers + risers: $n = 38$) tended to have higher LVMI than dippers (extreme dippers + dippers: $n = 82$) in the total sample (124 ± 34 *v* 117 ± 31 g/m^2), however, the difference was not statistically significant. There was no significant difference in the IMT between the dippers and nondippers (0.69 ± 0.13 *v* 0.68 ± 0.17mm, P = not significant).

Cardiac and Vascular Remodeling

Table 2 also shows the associations of MBPS and MBPR with cardiovascular parameters. In all the subjects studied ($n = 120$), MBPR was significantly positively associated with LVMI ($r = 0.30$, $P = .001$). The association between MBPS and LVMI was not statistically significant ($r = 0.16$, $P = .08$). There were no significant relationships between MBPS or MBPR and IMT. The arising-associated BP surge defined as the increase from the 2-h average BP value just before getting up to the 2-h average BP values after arising was not significantly associated with LVMI or IMT (data not shown).

The morning BP hyper-reactive group had significantly higher LVMI than the nonreactive group (140 *v* 113 g/m^2, $P < .001$) (Fig. 2). The cutoff value for identifying the group with the highest reactivity was 23.2 mm Hg/G$^{0.5}$. On the other hand, the difference in LVMI between the highest quartile of MBPS (Q4) and the lower quartiles (Q1 to 3) was not significant (129 *v* 117 g/m^2, $P = .07$). The morning BP hyper-reactive group was older (65 *v* 59 years, $P = .02$) and had higher 24-h BP (systolic: 133 *v* 121 mm Hg, $P < .001$; diastolic: 78 *v* 74 mm Hg, $P < .05$) than the nonreactive group (Table 3). Even after controlling for age and 24-h systolic BP, the morning BP hyper-reactive group still had significantly higher LVMI than the nonreactive group (132 *v* 115 g/m^2, $P = .01$). The prevalence of morning hyper-reactive group was significantly higher in the sustained hypertension group (diagnosed by ABPM) than in the normotensive group (38.8% *v* 15.5%, $P = .005$).

Furthermore, morning hyper-reactive status was a significant determinant for left ventricular hypertrophy (LVH) (LVMI >125 g/m^2) (Fig. 3). After adjusting for 24-h BP, age, sex, and BMI, the morning hyper-reactive status remained a significantly strong predictor for LVH.

There were significant associations between 24-h BP variability ($r = 0.228$, $P = .01$) and awake BP variability

Table 3. Characteristics of morning blood pressure reactivity subgroup

	Nonreactive Group Q1–3	Hyperreactive Group Q4
Number	90	30
Age (yr)	59 ± 10	65 ± 13*
Male, *n* (%)	41 (46)	15 (50)
Sustained hypertension, *n* (%)	30 (33)	19 (63)
24-h systolic BP (mm Hg)	121 ± 13	133 ± 17†
24-h diastolic BP (mm Hg)	74 ± 8	78 ± 10*
24-h pulse rate (/min)	68 ± 7	67 ± 8
SD of 24-h systolic BP (mm Hg)	17 ± 5	20 ± 4*
SD of awake systolic BP (mm Hg)	17 ± 6	19 ± 4*

Abbreviation as in Table 1.
Data are shown as mean ± SD.
* $P < .05$,
† $P < .001$ *v* non-reactive group.

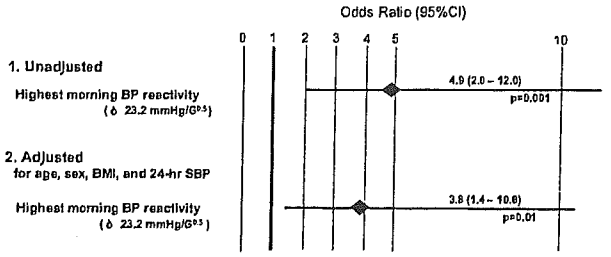

FIG. 3. The odds ratios and 95% confidence intervals for left ventricular hypertrophy by hyper-reactive status were calculated by multiple logistic regression analysis. We used the following conventional risk factors as covariates: age, sex, body mass index (BMI), and 24-h systolic BP (SBP).

($r = 0.204$, $P = .03$) and the LVH. Even after adjusting for 24-h BP variability ($P = .004$) or for awake BP variability ($P = .002$), the MBPR remained a significant predictor for LVH.

Discussion

In this study we found that the morning BP surge, adjusted for physical activity, was associated with cardiac hypertrophy in a community-dwelling population. In previous studies, which found that morning BP surge was an independent determinant of LVMI and of increased QTc dispersion, physical activity was not controlled for in the analysis.[13–15] In our previous study on a different population from that examined in the present study, LVH diagnosed by electrocardiography tended to be more common in individuals with exaggerated morning BP surge than in those with moderate morning BP surge,[11] although the difference between the two groups did not reach statistical significance. The advantages of the present study were that LVH was assessed using echocardiography and morning BP surge was defined more precisely using actigraphy.

One of the advantages of the present study is the precise determination of arising time, identified using actigraphy, to define morning BP surge. In our previous study, because we did not have actigraphy data, we used only diary documentation to identify the arising time.[11] In the present study, we determined the time of arising from bed by considering actigraphy data together with the individual's diary rather than defining it as a fixed time, and therefore the morning BP surge in the present study would be the most accurate to examine the association with target organ damage. Mansoor et al[22] previously examined the effects of actigraphy, diary, and fixed-time methods on the analysis of ambulatory BP. The actigraphic data of the ambulatory BP yielded results closer to those obtained with the diary than the fixed-time method. They concluded that researchers studying the early morning BP surge should consider using either actigraphy or a diary rather than fixed-time methods of analysis to identify times of awakening. Kuwajima et al[13] also used an active tracer equipped with an acceleration sensor to sense the start of physical activity related to awakening, but not awakening itself.

There is no consensus on the definition of the morning BP surge. Previously, Kuwajima et al[13] separated the increase in systolic BP into two parts. The first part was the increase in systolic BP from the lowest value for 3 h before arising to the value upon getting up, and the second part was the increase from the value upon getting up to the maximum BP 3 h after arising. The increase in systolic BP after getting up correlated more significantly with wall thickness, LVMI, and A/E ratio (the ratio of the peak of late diastolic filling and the peak of early diastolic filling) than those measurements before getting up. Gosse et al[15] reported that the morning BP surge defined as systolic BP elevation on arising minus the last supine systolic BP before arising was significantly associated with LVMI. However, in our present study the arising-associated BP surge defined as the increase from the 2-h average BP value just before getting up to the 2-h average BP values after arising was not significantly associated with LVMI or IMT (data not shown). In the present study, we used the same definition of morning BP surge that we used in our previous study,[11] whose study population had no overlap with that in the present study. The morning BP surge was defined as morning BP level (the 2-h average of BPs after waking) minus the night-time lowest BP (the 1-h average of BPs including the lowest BP during sleep).[11] This morning BP surge includes not only the magnitude of BP increase accompanied with arising but also the magnitude of BP increase from the night-time lowest BP to BP early in the morning before arising. The latter may be related to poor sleep quality in this period. Both surges may be attributable to different mechanisms leading to hypertensive target organ damage and subsequent cardiovascular events through different mechanisms. Further studies on hypertensive target organ damage and cardiovascular prognosis are necessary for the definition of morning BP surge.

No previous studies investigated the relationship between morning BP surge adjusted for physical activity (morning BP reactivity) and target organ damage. In the present study, even after controlling for age and 24-h systolic BP, both of which are significant determinants of LVMI, MBPR was independently associated with LVH. The MBPR is a measure of an individual's morning BP increase adjusted for an equal amount of morning physical activity. Our results indicated that a person whose BP increases more markedly with a given amount of activity in the morning had more advanced cardiac remodeling. Because there was no significant association between morning physical activity and LVMI, chronic exaggerated morning BP surge, as indicated by increased morning BP reactivity, seems to be the predominant determinant of cardiac remodeling.

The prevalence of morning hyper-reactive group was significantly higher in the sustained hypertension group than in the normotensive group, suggesting that BP might

more markedly increase with a given amount of activity in hypertensives than that in normotensives, partly because of impaired baroreceptor sensitivity and autonomic dysregulation. Because there was no significant association between the relative surge in morning BP (morning BP surge divided by 24-h BP level) and LVMI or with IMT, the absolute value of morning BP variability may be a more important determinant of cardiovascular overload.

In addition, there were significant associations between MBPR and ambulatory BP variability, and between ambulatory BP variability and the LVH. Even after adjusting for these ambulatory BP variabilities, MBPR remained a significant predictor for LVH. Therefore, the present data indicate that increased ambulatory BP variability may contribute to worsening of LVH, but MBPR is an independent predictor for hypertensive cardiac remodeling. However, there is the opposite possibility that the higher BP reactivity is favored for a higher increase in the cardiac output of a hypertrophied ventricle in the early stage of hypertensive heart disease. Because hypertrophied ventricles do not always show higher cardiac output, especially in eccentric hypertrophy, this possibility seems to be low. We need a prospective study to clarify this possibility before LVH develops.

Concerning the association between dipping status and MBPR, the prevalence of extreme-dippers, dippers, non-dippers, and risers were not significantlt different between the hyper-reactive group and in the nonreactive group. Therefore, we considered that morning BP surge adjusted for physical activity is one of independent predictors for LVH apart from nocturnal BP decreases.

We also investigated the relationship of MBPS or MBPR with carotid IMT, a measure of vascular remodeling. This relationship was not examined in any previous studies. In the present study, there was no significant relationship between morning BP surge and IMT. Thus, cardiac remodeling may be more susceptible to BP variability in the morning than vascular remodeling.

The reproducibility of morning BP surge parameters including MBPR is important. However, as this study subjects were community dwelling, we could not obtain the ABPM data twice or more. In future study, the reproducibility of parameters of morning BP surge should be evaluated.

In conclusion, morning BP surge contributes to ambulatory BP variability and might promote LVH. Furthermore, exaggerated morning BP reactivity, adjusted for physical activity, is associated with cardiac hypertrophy independent of ambulatory BP levels in a community-dwelling population.

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Case Report

A Case of Reversible Posterior Leukoencephalopathy Syndrome Caused by Transient Hypercoagulable State Induced by Infection

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We report a normotensive case of reversible posterior leukoencephalopathy syndrome caused by transient hypercoagulable state. Hypertension is the main risk factor for reversible posterior leukoencephalopathy syndrome, which is believed to occur as a result of high blood pressure-related dysfunction of cerebrovascular endothelial cells, because it commonly appears in hypertensive emergency. However, in this completely normotensive case, the typical clinical findings of reversible posterior leukoencephalopathy syndrome were triggered by transient hypercoagulable state without any blood pressure variation. The case was successfully treated with anticoagulation therapy using heparin. Thus, this case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction. (*Hypertens Res* 2005; 28: 619–623)

***Key Words*: reversible posterior leukoencephalopathy syndrome, endothelial dysfunction, normotensive, hypercoagulable state**

Introduction

Reversible posterior leukoencephalopathy syndrome was first described by Hinchkey *et al.* (*1*) in 1996, and occurs exclusively in patients with and frequently occurs in patients with hypertensive encephalopathy (*2*). The normal response of the cerebral arterioles to acute rising blood pressure is sympathetic nerve-mediated vascular constriction to prevent increasing blood flow (autoregulation). But in the case of reversible posterior leukoencephalopathy syndrome, the response does not work well when there is excess high pressure or recent onset of a modest increase in blood pressure, and excess dilatation of the arterioles following disruption of cerebral small vessel endothelial cells (*i.e.*, the blood-brain-barrier) can occur, resulting in vasogenic brain edema. Therefore, disruption of cerebral vascular endothelial cells plays a critical role in the pathogenesis of reversible posterior leukoencephalopathy syndrome. Recently, there have been several case reports indicating that not only high blood pressure, but also other factors, like cytotoxic drug using, connective tissue diseases (*1*, *3*, *4*) can contribute to the development of this syndrome *via* damage to cerebral vascular endothelial cells with no relation to blood pressure.

The endothelium are now considered as the largest "organ" in the body, and play a critical role not only in separating the

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Table 1. Variation of the Hematologic and Chemical Values during Hospitalization

Variable	On presentation	Four days after presentation (on attack)	On discharge
Hematocrit(%)	49.7	44.7	37.9
White blood cell (/mm^3)	5,500	11,500	4,400
Platelets (/mm^3)	161,000	106,000	183,000
Glucose (mg/dl)	99	116	87
Sodium (mmol/l)	143	140	144
Potassium (mmol/l)	4.37	4.14	3.94
Urea nitrogen (mg/dl)	12.4	15.7	9.6
Creatinine (mg/dl)	0.7	0.6	0.7
Total protein (g/dl)	8.1	6.8	6
C-reactive protein (mg/dl)*	0.26	1.5	0.26
PT-INR†	1.03	1.31	1.63
Fibrinogen (mg/dl)‡	390	129	252
TAT(ng/ml)§	2.5	16.5	2.2
PIC (μg/ml)‖	1.3	12.2	0.8
D-Dimer (μg/ml)¶	0.8	3.8	0.7
Anticardiolipin antibody: IgG (U/ml)**	<8	<8	<8
Anticardiolipin antibody: IgM (U/ml)††	0.8	1.7	0.8

It shows the variation of the hematologic and chemical values during hospitalization. *Normal range: <0.30 mg/dl. †PT-INR: prothrombin time-international normalized ratio. ‡Normal range: 111–333. §Thrombin-antithrombin III complex; normal range: ≤3.0. ‖Plasmin-$\alpha_2$plasmin inhibitor complex; normal range: ≤0.8. ¶Normal range: ≤1.0, **Normal range: ≤10.0. ††Normal range: ≤1.0.

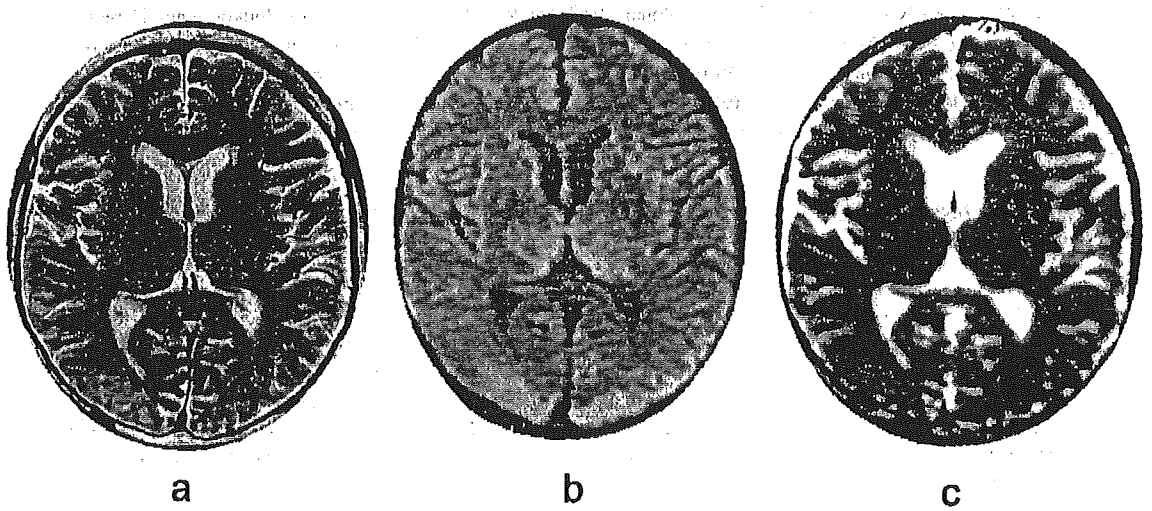

Fig. 1. *Neuroimagings of the brain. a:* T_2*-weighted magnetic resonance imaging. b: Diffusion-weighted magnetic resonance imaging. a and b, obtained on the day 8 after admission, show pale hyperintensity in both the frontal and posterior lobes involving both the subcortical white matter and gray matter. c: Apparent diffusion coefficiency maps demonstrating hyperintensity in the same lesion.*

vascular wall from circulation, but also in regulating blood pressure and inhibiting platelet aggregation, coagulation, inflammation, oxidative stress, and cell migration and proliferation (*5*). Hypertension, diabetes, dyslipidemia, smoking, obesity and aging are well known risk factors for impairment of endothelial cells (*6–9*), which in turn contributes to vascular constriction, thrombosis, vascular inflammation, pro-oxidation, atherosclerosis, and cardiovascular diseases (*10–14*). Hypertension is the most significant frequent problem resulting from cerebral endothelial cell dysfunction, and can introduce ischemic stroke (*15*), lacunar infarction, vascular dementia, and reversible posterior leukoencephalopathy syndrome. But there are many cases of such cerebrovascular disease of undetermined cause (*16, 17*). So, understanding more about these is very important for preventing and treating cerebrovascular disease.

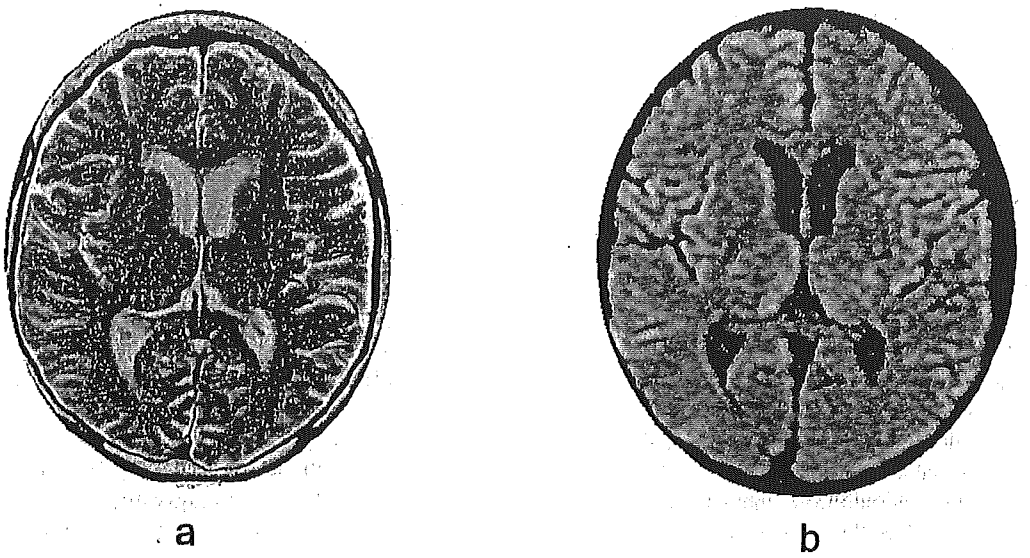

Fig. 2 *a: T_2-weighted magnetic resonance imaging. b: Diffusion-weighted magnetic resonance imaging. a and b, obtained on day 36 after admission, show complete resolution of the lesions.*

Here, we report a completely normotensive patient with reversible posterior leukoencephalopathy syndrome whose typical clinical and morphological abnormalities were triggered by transient hypercoagulable state induced by infection. Although there have been previous reports of normotensive individuals with this syndrome, this is the first report characterized by a hypercoagulable state. This case indicates that the hypercoagulable state and related cerebrovascular endothelial dysfunction played a role in the pathogenesis of reversible posterior leukoencephalopathy syndrome independent of blood pressure level.

Case Report

A 65-year-old woman was admitted to the hospital because of dyspnea on exertion. From 55 years old, she had noticed that her digits appeared to be cyanotic when exposed to cold. At age 59, she felt shortness of breath on light exertion, and this symptom gradually worsened. Two weeks before admission, she was diagnosed with limited systemic sclerosis with pulmonary hypertension at another hospital based on clinical symptoms and the results of blood analysis (positive for antinuclear antibodies and anticentromere antibodies), and transferred to our hospital.

On admission, her blood pressure was 102/68 mmHg, her pulse was 98 beats/min, and her respiration was 24 breaths/min. Her oxygen saturation was 88% while breathing ambient air, and reached 95% after supplementation of 2 l/min oxygen. On physical examination, the jugular vein was prominent. The breath sounds were normal, but a blowing holosystolic murmur was heard along the lower left sternal margin which was intensified during inspiration. The abdomen was normal, and there was peripheral edema (2+) at both lower extremities. Sclerodactyly and cyanosis were seen at her digits. The urine was normal and the results of hematologic and other laboratory tests are shown in Table 1. An electrocardiogram showed sinus tachycardia at a rate of 102 beats/min with right axis deviation and inverted T-wave from V1 to V4. Chest radiograph showed cardiomegaly and enlarged central pulmonary arteries. The echocardiogram demonstrated right ventricular enlargement pushing into the left ventricular cavity. Doppler studies revealed severe tricuspid regurgitation (pressure gradient: 75 mmHg). CT examination of the chest with contrast material and a perfusion lung scan were normal. An inserted Swan-Ganz catheter showed that the pulmonary arterial pressure was 83/40 mmHg, the pulmonary-capillary wedge pressure was 6 mmHg, and the cardiac output was 3.4 l/min.

After hospitalization her symptoms gradually improved by rest. On the fourth day, she complained of a sudden loss of vision without any vital changes, and just a few minutes later, she became uncommunicative. Because her respiration had weakened with severe hypoxia, intubation was required. During this attack, her blood pressure was 119/73 mmHg without abnormal elevation (<130/80 mmHg) and her pulmonary arterial pressure was 95/43 mmHg. Blood tests revealed a white blood cell count of 11,500/mm^3, platelets of 106.0×10^3/mm^3, C-reactive protein of 1.5 mg/dl, thrombin-antithrombin III complex of 16.5 ng/ml, plasmin-$\alpha_2$plasmin inhibitor complex of 12.2 μg/ml, D-dimer of 3.8 μg/ml, and an anticardiolipin antibody (IgM) titer of 1.7 U/ml (Table 1). Brain CT showed no abnormality. T_2-weighted and diffusion-weighted MRI showed a relatively hyperintensive region in both the frontal and posterior lobes involving both subcortical