Original Article

Altered Aortic Properties in Elderly Orthostatic Hypertension

Satoshi HOSHIDE, Kazuomi KARIO, Kazuo EGUCHI, Joji ISHIKAWA, Masato MORINARI, and Kazuyuki SHIMADA

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 automomic 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).

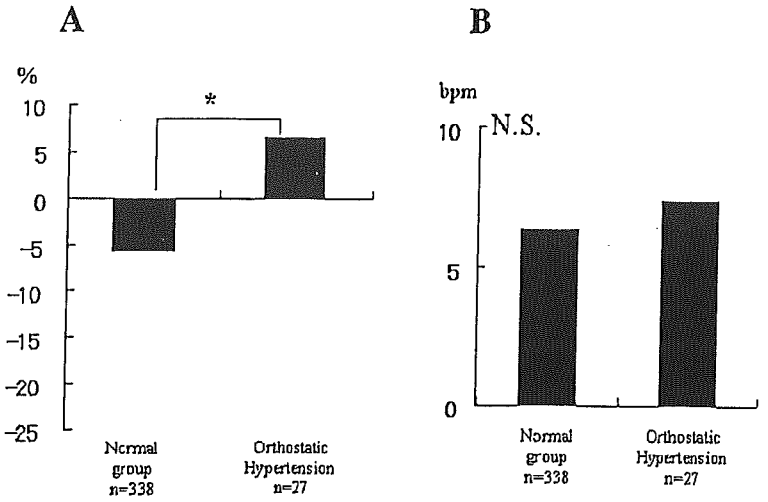

Fig. 1. *Orthostatic changes in augmentation index (A) and heart rate (B).* *$p < 0.001$ *between the indicated colums.*

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

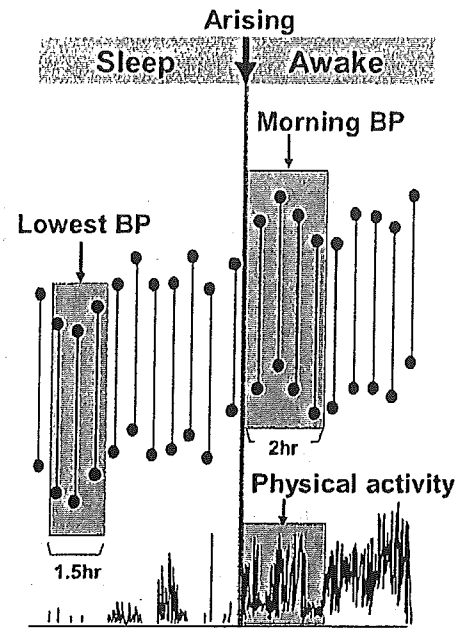

FIG. 1. Definition of morning blood pressure (BP) surge and reactivity.

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.

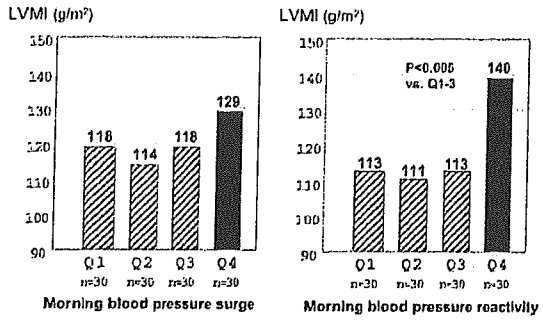

FIG. 2. Morning blood pressure surge or reactivity and hypertensive cardiac remodeling. Left ventricular mass index (LVMI) examined by echocardiography. We classified the patients into four groups according to the level of morning BP surge or reactivity, the lowest quartile (Q1) to highest quartile (Q4).

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.

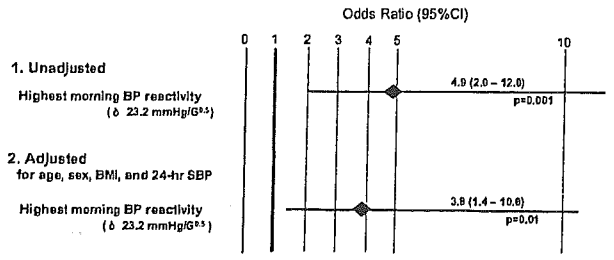

FIG. 3. The odds ratios and 95% confidence intervals for left ventricular hypertrophy by hyper-reactive status were calculated by multiple logistic regression analysis. We used the following conventional risk factors as covariates: age, sex, body mass index (BMI), and 24-h systolic BP (SBP).

(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.

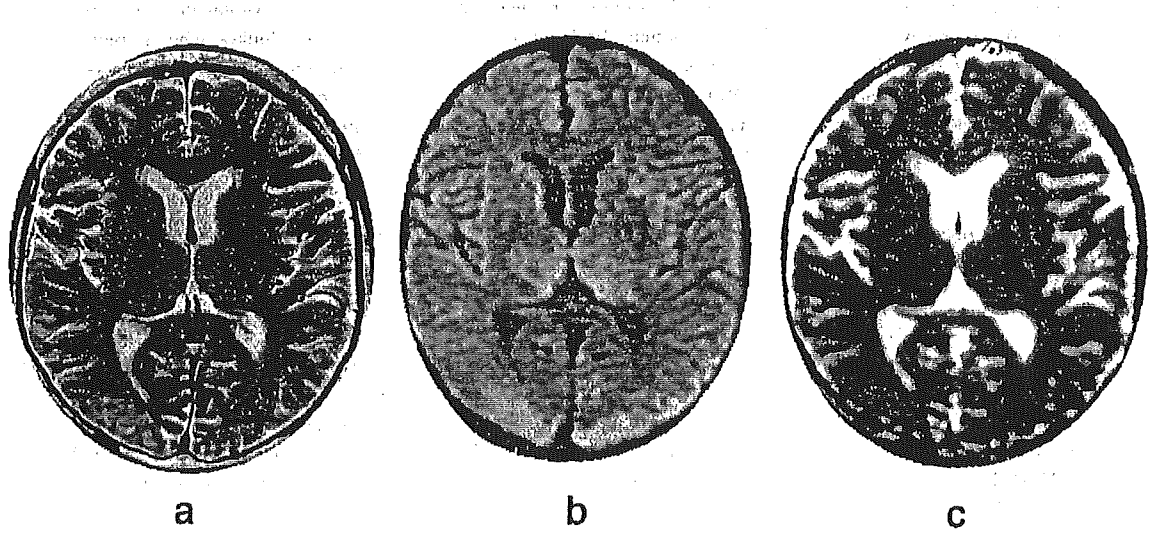

Fig. 1. *Neuroimagings of the brain. a: T_2-weighted magnetic resonance imaging. b: Diffusion-weighted magnetic resonance imaging. a and b, obtained on the day 8 after admission, show pale hyperintensity in both the frontal and posterior lobes involving both the subcortical white matter and gray matter.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

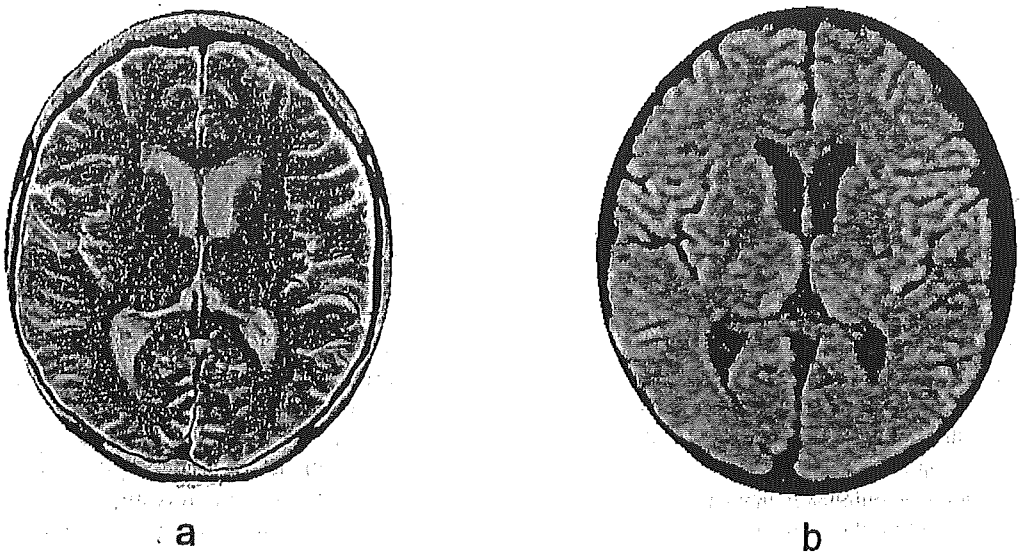

Fig. 2 *a: T_2-weighted magnetic resonance imaging. b: Diffusion-weighted magnetic resonance imaging. a and b, obtained on day 36 after admission, show complete resolution of the lesions.*

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

white matter and gray matter. Apparent diffusion coefficiency (ADC) maps demonstrated hyperintensity in these lesions (Fig. 1). The findings of magnetic resonance (MR) angiography were normal. Initially, central nervous system involvement through small vessel vasculitis was suspected, but because of its characteristic clinical features and radiological findings, a provisional diagnosis of reversible posterior leukoencephalopathy syndrome was considered. Antibiotics, continuous intravenous heparin and epoprostenol were started to treat her inflammation, hypercoagulable state and pulmonary hypertension. Her consciousness and vision recovered gradually and completely normal. Extubation was done 7 days later. A follow-up MRI performed on day 36 after admission showed complete resolution of the affected lesions (Fig. 2), and the elevated C-reactive protein, thrombin-antithrombin III complex, plasmin-$\alpha_2$plasmin inhibitor complex, and D-dimer level had subsided to normal levels (Table 1). On 71 days after administration, she was discharged under warfarin treatment.

Discussion

We here report a case of reversible posterior leukoencephalopathy syndrome caused by hypercoagulable state without hypertension. 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.

Reversible posterior leukoencephalopathy syndrome is characterized clinically by altered mental status, headache, seizures, and visual disturbances, and T_2-weighted and diffusion-weighted MRI findings of a hyperintense region in the parietal-occipital lobe involving lesions of the white matter, basal ganglia, brain stem, cerebellum, and gray matter (*1*, *18*). Analysis of ADC maps suggests that such abnormalities are caused by vasogenic edema rather than by ischemia (*18*). In the past, reversible posterior leukoencephalopathy syndrome has been considered to occur mainly in the posterior lobe and to be reversible disease as per its name. More recently, however, the syndrome has been considered irreversible in the manner of cerebral infarction or hemorrhages if the underlying causes are not treated, and the involved lesions are no longer considered specific to the posterior region (*19*). Our case also demonstrated that the abnormality is not restricted to the white matter or posterior lobe, but also occurs in the gray matter and anterior lobe. For this reason, we should reconsider the definition of reversible posterior leukoencephalopathy syndrome and decide on more appropriate terms described precisely.

Reversible posterior leukoencephalopathy syndrome is mostly associated with abrupt and severe hypertension occurring at eclampsia or acute renal failure, *etc.* However, it is also seen in patients treated with immunosuppressive or cytotoxic agents such as cyclosporine or tacrolimus (*1*), and in patients with connective tissue diseases such as systemic lupus erythematosus (*3*), and thrombotic microangiopathic states such as thrombotic thrombocytopenic purpura (*4*). Because some cases of the latter (*1*, *3*, *4*) occur even in the absence of hypertension, the pathogenesis of reversible posterior leukoencephalopathy syndrome is multifactorial, although the most fundamental mechanism is disruption of cerebral vascular endothelial cells.

The endothelium are now considered as the largest "organ" in the body, and play a critical role not only in separating the vascular wall from circulation, but also in regulating blood pressure and inhibiting platelet aggregation, coagulation, inflammation, oxidative stress, and cell migration and proliferation (*5*). Because endothelium are distributed systemically, such abnormalities are participating diffuse vascular beds damages (*12*, *13*) even though specific site is prone to be more or less (*20*). Because the cerebral endothelial cells form a blood-brain-barrier for preventing excess flux of ions, amino acids, and peptides into the brain through adherens and tight junctions (*21*), the interaction between endothelial cells and other factors could be more complex than at other sites. There are several well known risk factors for cerebral endothelial cell damage, including hypertension, diabetes, hyperlipidemia, smoking, aging, and obesity (*6*, *7*, *22*). Recently, several other possible factors have been suggested to play a role—*i.e.*, hyperhomocysteinemia, inflammation, infection, and hypercoagulability (*23*, *24*)—although further evidence will be needed to confirm these relations. Nevertheless there are still many deteriorating factors to be remained undetermined (*16*, *17*), so we have to break such enigmas and promote the strategies for preventing and treating cerebrovascular disease (*25*).

In our case, there were no well known cardiovascular risk factors and used no cytotoxic agents, but there was only a transient hypercoagulable state corresponding with the event. Because the patient was complicated with systemic sclerosis with pulmonary hypertension, we think that systemic endothelial dysfunction played an important role in the pathogenesis (*26*), but the event synchronized with inflammatory symptoms followed by a hypercoagulable state. Although we were unable to determine the trigger for such process, infection was perhaps the most likely candidate, since the symptoms and all of the inflammatory markers were ameliorated by using antibiotics. Such synergic effects produced a transient hypercoagulable state, as shown by the elevations in thrombin-antithrombin III complex, plasmin-$\alpha_2$plasmin inhibitor complex, and D-dimer level. Because thrombocytopenia and a reduction in the fibrinogen level were also seen concomitantly, we conjecture that the underlying pathogenesis involved disseminated intravascular coagulation. Although there have been previous reports of normotensive reversible posterior leukoencephalopathy syndrome, this is the first case to be involved in coagulation abnormality (*4*, *27*). Our case was successfully treated with anticoagulation therapy using heparin, but since we have no control case, the usefulness of this regimen cannot be conclusively deter-

mined. But now reversible posterior leukoencephalopathy syndrome is considered to be possibly irreversible damaged without treatment, we have to keep in mind that it could be induced by hypercoagulable state, and cope with it by anticoagulation therapy to avoid any hangover.

In this completely normotensive case, the typical clinical findings of reversible posterior leukoencephalopathy syndrome were triggered by a hypercoagulable state without any blood pressure variation, and 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.

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Loss of Diurnal Rhythms of Blood Pressure and Heart Rate Due to High Fat Feeding

Ruri Kaneda and Kazuomi Kario

Obesity is the most prevalent nutritional disorder in developed countries[1] and plays an important role in cardiovascular morbidity through multiple mechanisms,[2] including well-known risk factors such as hypertension, diabetes, and dyslipidemia.[3–8]

Previous studies have shown that being overweight is associated with increased cardiac output[9] and resting heart rate, with decreased heart rate variability,[10] and with increased prevalence of nondipping status,[11] which is considered to be prognostic indicators of cardiovascular mortality[12,13] and morbidity[14,15] in humans.

Sympathetic nervous system activity is increased in patients with essential hypertension per se,[16] and the adrenergic factors represent one of the mechanisms involved in determining blood pressure (BP) variability[17] including the nondipping pattern of BP. We have the data that diurnal BP variation in elderly hypertensive individuals was significantly associated with neurohumoral factors regulating circulating blood volume. Nondippers appeared to have α- and β-adrenergic subsensitivity, which may be induced by their chronic exposure to high norepinephrine levels.[18]

On the other hand, overactivity of the sympathetic nervous system is a common feature of obesity in humans and in animal models. Study of regional sympathetic nerve activity in obese humans using norepinephrine spillover has demonstrated that obesity is associated with increased sympathetic activity to the kidney, a key organ of cardiovascular homeostasis.[19] Chronic hyperinsulinemia is also associated with a high output, low resistance hemodynamic state, persistent baroreflex downregulation, and episodic (postprandial) sympathetic dominance.[20] Accordingly, decrease of heart rate and BP variability or nondipping status in obese subjects might be caused by overactivity of the sympathetic nervous system.

Consistent with the report by Carroll et al,[21] which shows high fat feeding in rabbits caused immediate losses of diurnal rhythms of BP and heart rate that were independent of weight gain and BP elevation, there are some reports that show an increase of whole day mean arterial pressure and heart rate, rapid abolition the normal diurnal rhythm of mean arterial pressure and heart rate, and increase of low-frequency energy of systolic BP variabilities were shown at an early but not at a late phase after an hyperlipidic and hypercaloric diet.[22,23] Another study also reported that a high fat diet induces abdominal obesity, hyperinsulinaemia, and arterial hypertension, with a left ventricular hypertrophy associated with a biphasic change in autonomic activity. This biphasic change consists of an early and long-lasting decrease in parasympathetic nervous system activity and an early but transient increase in sympathetic activity.[10] The autonomic nervous system changes are dependent on the time course of obesity development. Therefore, the importance of immediate sympathetic nerve activation with overfeeding is clear. However, it is indispensable to investigate the association with several other factors including FFA, insulin, leptin, and the renin-angiotensin system, which might account for the increased sympathetic outflow associated with obesity.[24]

In the future, it is necessary to clarify the time course of these factors in adipose tissue or in circulation, which are strongly associated with obesity and affect the diurnal variation of BP and heart rate. Clarification of these points would shed some light on the pathophysiology of obesity–hypertension and find a new time-dependent therapeutic target.

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☐ EDITORIAL ☐

"Cocktail" Antihypertensive Chronotherapy for Perfect Control of Morning Hypertension in Diabetic Patients

Key words: hypertension, morning hypertension, diabetes, chronotherapy, target organ protection

It is well-known that cardiovascular events occur more frequently in the morning (1). Ambulatory blood pressure (BP) varies along with various physical and psychological factors and this BP variability may be a risk for cardiovascular events (2, 3). In recent years, clinical research using ambulatory BP monitoring (ABPM) or self-measured home BP monitoring has clarified that morning BP and BP surge are more closely related to target organ damage and cardiovascular risk than clinic BP (4–14). Also, in hypertensive patients treated with antihypertensive medication, even patients whose clinic BP is well controlled, the morning BP level prior to taking medication is often high (15–17). Therefore, morning hypertension is currently the 'blind spot' in the clinical practice of hypertension.

As diabetes is one of the worst conventional cardiovascular risk factors. In our recent study on asymptomatic hypertensive patients with and without type 2 diabetes, silent cerebral damage including silent cerebral infarcts, decreased functional neuronal mass, and reduced cerebrovascular reserve were advanced in hypertensive patients with diabetes (18). Hypertensive patients were classified into four groups and the risk of multiple silent cerebral infarcts was comparable between diabetic patients with white-coat hypertension (WCHT) and nondiabetic patients with sustained hypertension (19). The patients with both diabetes and sustained hypertension had the highest risk for multiple silent cerebral infarcts. Cardiac remodelling is also advanced in diabetes; in hypertensive patients, the presence of diabetes increases the relative wall thickness (20). Concentric hypertrophy, which is the worst prognosis, was more frequently found in diabetic hypertensive patients.

Nighttime and morning BP levels should be monitored more closely in diabetic patients. In a cross-sectional study in newly-diagnosed type 2 diabetic normotensive patients, morning BP levels and morning BP surge were significantly increased in patients with microalbuminuria compared to those without microalbuminuria (21). In another study on type 2 diabetic patients, those with morning BP hypertension (morning BP level measured at home >130/85 mmHg) had marked frequencies of diabetic renal disease, retinopathy, microvascular disease and vascular complications, including coronary artery disease and cerebrovascular disease (22). In this study, hypertension defined by clinic BP level was not associated with these complications. Diabetic patients, particularly those with autonomic nervous dysfunction, are also likely to have a nondipping pattern of nocturnal falls in BP, which might precede microalbuminuria, leading to a poor prognosis (23). Nighttime BP is associated with a poor prognosis in diabetic patients (24).

In the international guidelines including the guideline of management of hypertension of the Japanese Society of Hypertension, target BP levels are lower for diabetic patients than nondiabetic patients. In addition, the persistent BP control for a 24-h period achieves more effective prevention for target organ damage and cardiovascular events particularly in these patients. However, in the practical sense, 24-h BP control is very difficult in diabetic patients particularly in those with nephropathy. In this issue, Kuriyama et al tried a unique antihypertensive medication for diabetic patients with nephropathy, whose BP was poorly controlled as morning hypertension (self-measured morning BPs >130/85 mmHg) (25).

See also p 1239.

Their special medication consists of calcium channel blockers and/or diuretics given in the morning, an angiotensin receptor blocker given in the evening, together with alpha1-blockers given at bedtime. Actually, the "cocktail" medication successfully reduced morning BP levels with a significant reduction of urinary protein excretion. Considering that neurohumoral factors including sympathetic nervous activity and the renin-angiotensin-aldosterone system are activated in the morning, this sequential combined chronological medication could be physiologically considered as a specific medication for morning hypertension. In recent reports, a long-acting angiotensin receptor blocker (26), and the bedtime dosing of an alpha1-blocker (27) or an angiotensin-converting enzyme inhibitor (28) were effective for controlling morning hypertension.

In addition to the standard clinical practice of hypertension, and following the guidelines issued on the subject, an important next step should be the specific combined chronobiological management targeting the higher blood pressure in the morning in order to achieve a more beneficial outcome particularly in high-risk hypertensive patients such

as in those with diabetes and/or chronic kidney disease.

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