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Morning Blood Pressure Surge and Hypertensive Cerebrovascular Disease

Role of the Alpha Adrenergic Sympathetic Nervous System

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Background: The morning surge of blood pressure (BP) is associated with α-adrenergic activity. We studied the association between the α-adrenergic morning surge in BP and silent cerebrovascular disease in elderly patients with hypertension.

Methods: We conducted ambulatory BP monitoring three times (twice at baseline and after nighttime dosing of the α_1-blocker doxazosin) in 98 elderly hypertensive patients in whom the presence of silent cerebral infarcts (SCI) was assessed by brain magnetic resonance imaging. The morning BP surge (MBPS) was calculated as the mean systolic BP during the 2 h after waking minus the mean systolic BP during 1 h that included the lowest sleep BP. The α-adrenergic MBPS was calculated as the reduction of MBPS by doxazosin.

Results: The prevalence of multiple SCI was higher in the Surge group (top quartile: MBPS ≥45 mm Hg, n = 24) than in the Nonsurge group (MBPS <45 mm Hg, n = 74) (54% *v* 31%, P = .04), and in the higher α-adrenergic surge group (top quartile: α-adrenergic MBPS ≥28 mm Hg, n = 25) than in the lower α-adrenergic surge group (<28 mm Hg, n = 73) (68% *v* 26%, P < .0001). In the Surge group, subjects with higher α-adrenergic surge (n = 17) had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic surge group had multiple SCI (n = 7) (77% *v* 0%, P = .001). The α-adrenergic MBPS was closely associated with multiple SCI (10 mm Hg increase: OR = 1.96, P = .006), independently of age, MBPS, 24-h systolic BP, and other confounding factors.

Conclusion: The morning BP surge, particularly that dependent on α-adrenergic activity, is closely associated with advanced silent hypertensive cerebrovascular disease in elderly individuals. Am J Hypertens 2004;17: 668–675 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, elderly, morning surge, sympathetic activity, cerebrovascular disease.

Cardiovascular events occur more commonly in the morning than at other times of day, and the diurnal blood pressure (BP) variation also shows a peak early in the morning.[1,2] We have recently clarified that the morning BP surge is risk for stroke events independently of 24-h BP level in elderly individuals with hypertension.[3] It is generally accepted that the sympathetic nervous system plays a major role in the regulation of BP changes, and therefore an increase in α-adrenergic activity might be one of the major determinants of this morning BP surge.[4] In fact, the Hypertension and Lipid Trial (HALT) study disclosed that the BP reduction with an α-blocker, doxazosin, was most pronounced in the morning period.[5,6] Furthermore, it is also possible that the morning increase in α-adrenergic activity and related BP surge contribute to the morning peak of cardiovascular events.

There is some evidence indicating that aging is associated with increased sympathetic nervous activity[7] and that central nervous system mechanisms mediate this process.[8] This systemic increase in sympathetic activity in older subjects might be expected to cause or to exacerbate hypertension and cardiac and vascular hypertrophy.[9,10] Autonomic dysfunction, which is mainly related to increased sympathetic activity, is frequently present in pa-

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tients with clinical cerebrovascular disease.[11,12] In elderly persons with hypertension, silent cerebral infarcts (SCI) are commonly found and are one of the strongest predictors of strokes.[13] However, the associations between the morning increase in α-adrenergic activity and the related BP surge with silent hypertensive target organ damage have not been thoroughly investigated.

To study the association between the morning BP surge (particularly the component associated with α-adrenergic activity) and silent cerebrovascular disease, we investigated the effect of nighttime dosing of doxazosin on the morning BP surge using ambulatory BP monitoring (ABPM) in asymptomatic elderly hypertensive individuals, with or without SCI detected by brain magnetic resonance imaging (MRI).

Methods

Patient Selection

This was an open-label study of the effects of doxazosin on ambulatory BP, which included older Japanese hypertensive patients at three Japanese hospital clinics. The entry period was June 1996 to January 2001. A total of 106 patients who were either untreated or were off medication for at least 1 week at the time of entry were studied. The entry BP criterion was ≥140 mm Hg for an average of a seated clinic systolic BP (SBP) or ≥90 mm Hg for diastolic BP (DBP) during the follow-up period (3 to 5 weeks). To be included in the study, patients had to be ≥60 years of age, to have a diagnosis of essential hypertension, and to have no history of other significant medical disorders including diabetes or any clinically overt cardiovascular disease. All participants were fully ambulant.

Body mass index was calculated as weight (kg)/height $(m)^2$. Electrocardiographically verified left ventricular hypertrophy was defined by abnormally high voltages of QRS complexes (R in V5 plus S in V1 >3.5 mV) associated either with flat T waves (<10% of R) or with ST segment depression and biphasic T waves.

Study Design

Each patient was studied for a maximum of 11 weeks, with an observation period of 3 to 5 weeks, a titration period of up to 4 weeks, and 1 to 5 weeks of maintenance therapy. After the observation period, patients were started on 1 mg doxazosin daily, taken at bedtime. The dose was doubled at weekly intervals until the average seated BP had fallen 1) by at least 20/10 mm Hg from the baseline level, or 2) by at least 10/5 mm Hg from the baseline level when baseline BP was <160/90 mm Hg. If BP reduction reached the above criteria at each of two consecutive visits, if a maximal daily dose of 8 mg doxazosin had been reached, or if adverse effects had occurred, no further dose increase was attempted. After the titration phase there was a maintenance phase of 1 to 5 weeks on the same dose of doxazosin. This protocol was modified from that of the HALT study.[5,6] Informed consent was obtained from all subjects, and the study was approved by the Research Ethical Committee of Department of Cardiology, Jichi Medical School.

We excluded three patients for whom at least one of the three BP recordings was not evaluable because of the presence of artifacts in >20% of either awake or asleep measurements. One patient who refused a second ABPM and two patients who reported that their sleep was severely disturbed by the ABPM were also excluded from the analysis. Two patients who developed orthostatic dizziness (one during the observation period and one during the titration period) were also discontinued from the study. Accordingly, three complete sets of ABPM data were successfully obtained in 98 patients.

Ambulatory BP Monitoring

Noninvasive ABPM was carried out three times on a weekday with one of two automatic ABPM devices (TM-2421 or TM-2425; A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 h. The accuracy of these devices was previously validated. The first ABPM was performed at the time of entry after being unmedicated for at least 2 weeks, the second ABPM at the end of the drug-free baseline period (3 to 5 weeks), and the third at the end of the maintenance period (1 to 5 weeks). The interval between the first and second ABPM and between the second and third ABPM were 3 to 5 weeks and 4 to 6 weeks, respectively.

We defined 24-h BP as the average of all BP readings throughout 24 h. All subjects were ambulant during the day, and none reported staying in bed after waking. Sleep BP was defined as the average of BP from the time when patients went to bed until the time they got out of bed, and awake BP as the average of BP recorded during the rest of the day. Morning BP was defined as the average of BP during the first 2 h after waking (four BP readings). The lowest BP was defined as the average BP of three readings centered on the lowest nighttime reading (that is, the lowest reading plus the readings immediately before and after). Evening BP was defined as the average BP during the 2 h before going to bed (four BP readings). Preawake BP was defined as the average BP during the 2 h just before waking (four BP readings). The morning BP surge (MBPS) was calculated as the morning SBP minus the lowest SBP. Systolic pressures were used for all of these calculations. We subclassified the patients according to the extent of the MBPS as follows: the top quartile of MBPS (≥45 mm Hg, $n = 24$, the Surge group), versus all others ($n = 74$, the Nonsurge group). The α-adrenergic MBPS was calculated as the baseline MBPS (the average of the first and second MBPS) minus the third MBPS (during doxazosin therapy).

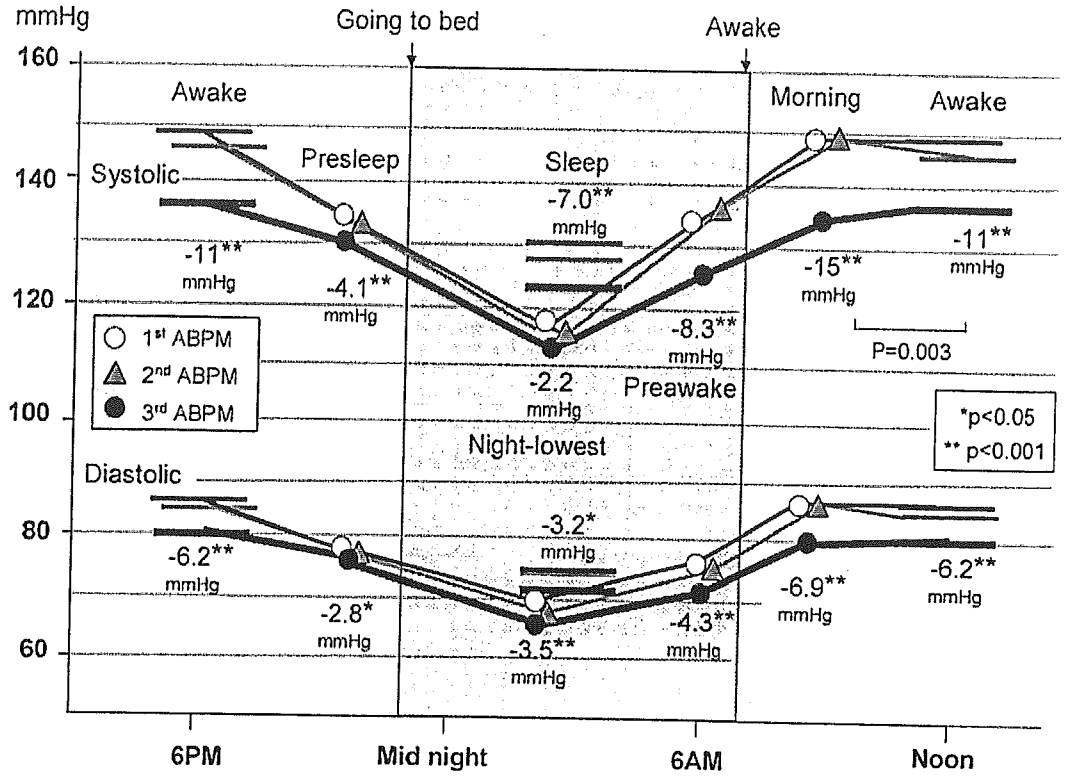

FIG. 1. Ambulatory blood pressure (BP) values during the two baseline recordings and after doxazosin therapy.

Brain MRI

Brain MRI was performed using a superconducting magnet with a main strength of 1.5 T (Toshiba MRT200FXII, Toshiba, Tokyo, Japan; SIGNA-Horizon version 5.8, General Electric Co.; or Vision, Siemens, Munich, Germany) during the period of ≤3 months before the first ABPM and the initiation of doxazosin treatment after the second ABPM. T1- and T2-weighted images were obtained in the transverse plane with sections 7.8 mm or 8.0 mm thick. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images, as previously described.[13–15] Multiple SCI was defined as two or more infarcts. All SCI detected were lacunar infarcts of <15 mm. The MRI images of the subjects were randomly stored and interpreted by a professional blind to the subjects' names and characteristics. The κ statistics assessing inter-reader and intrareader agreement (non-SCI, one SCI, and multiple SCI) were 0.70 and 0.80, respectively, in our laboratory.

Statistical Analysis

The analysis was conducted using data from the 98 patients in whom brain MRI and three ambulatory BP recordings were successfully obtained. The changes from the baseline values were analyzed statistically using paired *t* tests for each subgroup. Two-sided unpaired *t* tests and χ^2 tests were used to test differences between the two groups in the mean values of continuous measures and prevalence rates, respectively. One-way analysis of covariance (ANCOVA) (controlling for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP) were performed to detect differences among groups. Spearman correlation coefficients were calculated. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of the presence of multiple SCI (two or more per person) versus single SCI or no SCI per person was calculated using multiple logistic regression analysis (multiple SCI = 1, one or no SCI = 0). Multiple linear regression analysis was used to test the differences in the slope of the relationship of MBPS and α-adrenergic MBPS between patients with and without multiple SCI. The criterion for determining statistical significance was $P < .05$. Results are given as mean ± SD.

Results

Ambulatory BP

Figure 1 shows the ambulatory BP values during the two baseline recordings and after doxazosin therapy. Nighttime dosing of doxazosin reduced morning BP more effectively than the other ambulatory BP parameters. There was no significant effect of doxazosin on the lowest SBP at night.

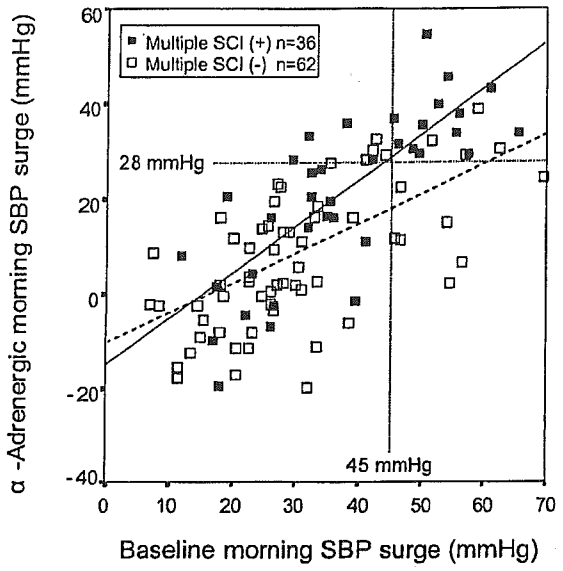

FIG. 2. Baseline morning blood pressure (BP) surge and the BP response to doxazosin. SBP = systolic BP; SCI = silent cerebral infarct.

Morning BP Surge

At baseline, the average MBPS was 33 ± 16 mm Hg for SBP and 17 ± 8.3 mm Hg for SBP (the average of the first and the second ABPM data), and the correlation coefficients between MBPS calculated from the first ABPM and the second ABPM were 0.66 for SBP and 0.42 for DBP (both $P < .0001$). The α-adrenergic MBPS (reduction of MBPS by doxazosin) was 13 ± 17 mm Hg for SBP and 3.4 ± 12 mm Hg for DBP. The α-adrenergic MBPS was significantly correlated with the baseline MBPS ($r = 0.73$, $P < .001$; Fig. 2).

The Surge group had significantly higher prevalences of left ventricular hypertrophy, multiple SCI, and number of SCI than the Nonsurge group (all $P < .05$), whereas the age and clinic and 24-h BP levels were comparable between the two groups (Table 1). Even after adjusting for possible confounding factors (age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP), the higher prevalence of multiple SCI in the Surge group remained significant ($P \leq .05$; Table 2). Both the MBPS ($P < .05$) and α-adrenergic MBPS ($P < .001$) were significantly associated with the number of SCI (Table 3). The α-adrenergic MBPS was significantly associated with smoking ($P < .01$) but with not with age or body mass index.

Silent Cerebral Infarction

The prevalence of multiple SCI was higher in the Surge group (top quartile: MBPS ≥ 45 mm Hg, $n = 24$) than in the Nonsurge group (MBPS < 45 mm Hg, $n = 74$) (54% *v* 31%, $P = .04$). Those with the highest α-adrenergic MBPS (top quartile: α-adrenergic MBPS ≥28 mm Hg, $n = 25$) had a higher prevalence of SCI (68% *v* 34%, $P = .005$) and multiple SCI (68% *v* 26%, $P < .0001$) than those with a lower α-adrenergic MBPS (α-adrenergic MBPS

Table 1. Clinical and blood pressure (BP) characteristics

Measure	Total Group ($n = 98$)	Surge Group* ($n = 24$)	Nonsurge Group* ($n = 74$)
Age (y)	70 ± 6.8	70 ± 6.7	70 ± 6.9
Male (%)	44	43	44
Body mass index (kg/m²)	23.5 ± 3.2	23.8 ± 2.8	23.2 ± 3.3
Current smoker (%)	39	43	37
Hyperlipidemia (%)	33	43	29
Duration of hypertension (y)	6.0 ± 7.0	7.8 ± 8.1	5.4 ± 6.6
Left ventricular hypertrophy (%)	16	30§	12
Dose of doxazosin (mg/day)	3.7 ± 1.9	3.5 ± 1.8	3.7 ± 1.9
Clinic systolic BP (mm Hg)†	158 ± 9.9	160 ± 11	158 ± 9.7
Clinic diastolic BP (mm Hg)†	87 ± 10	89 ± 10	86 ± 10
24-h systolic BP (mm Hg)†	142 ± 12	142 ± 8.4	141 ± 13
24-h diastolic BP (mm Hg)†	82 ± 8.0	83 ± 6.0	82 ± 8.5
Silent cerebral infarct			
Prevalence (%)	43	57	39
Average number/person	1.5 ± 2.2	2.4 ± 2.4§	1.3 ± 2.1
Multiple silent cerebral infarct‡ prevalence (%)	37	57§	31

Data shown as mean ± SD or percentages.

* Morning BP Surge (morning BP [average of 2-h systolic BP after waking] minus lowest BP during sleep [nighttime three consecutive BP including lowest systolic BP] using average of first and second ambulatory BP) ≥45 mm Hg for Surge group and <45 mm Hg for Nonsurge group.

† Average of first and second ambulatory BP.

‡ Two or more silent infarcts.

§ $P < .05$, *v* Nonsurge group.

Table 2. Adjusted silent cerebral infarct status between morning blood pressure surge and nonsurge groups

Measure	Surge Group (n = 24)	Nonsurge Group (n = 74)	P
Silent cerebral infarct			
Prevalence (%)	55	39	.184
Average number/person	2.2 ± 0.42	1.3 ± 0.24	.086
Multiple silent cerebral infarct prevalence (%)	53	31	.045

Data shown as mean ± SE or percentages after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, daily dose of doxazosin, and 24-h systolic blood pressure using analysis of covariance.

<28 mm Hg, n = 73). In the Surge group, those with higher α-adrenergic MBPS (n = 17) had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic Surge group had multiple SCI (n = 7) (77% v 0%, P = .001; Fig. 2). In addition, the slope between MBPS and α-adrenergic MBPS (Fig. 2) was significantly steeper in patients with multiple SCI than in those without multiple SCI, even after controlling for 24-h BP (P < .05).

Table 4 shows the results of adjusted MBPS and α-adrenergic MBPS using ANCOVA. Even after adjusting for possible confounding variables, MBPS and α-adrenergic MBPS were significantly higher in the multiple SCI group than in the nonmultiple SCI group. Table 5 shows the results of a logistic regression analysis using MBPS and α-adrenergic MBPS as continuous variables in the total sample. After adjusting for possible confounding variables, both MBPS (model 1) and α-adrenergic MBPS (model 2) were significantly associated with multiple SCI. However, when both were entered in the same model (model 3), only α-adrenergic MBPS remained significant. These surges were also significantly associated with SCI (one ore more SCI per person: 10 mm Hg MSBP increase: OR = 1.44, P = .03; 10 mm Hg α-adrenergic MBPS increase: OR = 1.55, P = .006). There were no significant associations between the morning surge in pulse rate and either single or multiple SCI.

Discussion

This study, has demonstrated a positive association between the MBPS, particularly the component associated with α-adrenergic activity, and silent hypertensive cerebrovascular disease in elderly individuals. This finding is supported by the relatively high reproducibility of MBPS in the two baseline recordings, and the fact that we used the average of these to reduce regression to the mean when assessing the effects of the α-adrenergic blocking drug doxazosin.

Morning BP Surge

The Surge group in this study had a higher number of SCI and higher prevalence of multiple SCI than the Nonsurge group, whereas there was no significant difference in the clinic and average 24-h BP between the two groups. In addition, when we considered the MBPS as a continuous variable, MBPS was significantly correlated with the number of SCI independent of other possible confounders including 24-h SBP level. These results indicate that factors other than persistent BP overload may be involved in the progression of SCI in hypertensive individuals. The SCI occurs predominantly in the small cerebral vessels. An excessive morning BP surge might facilitate microvascular remodeling in the small cerebral arteries through increased shear stress. In addition, platelets may be acti-

Table 3. Determinants of morning blood pressure (BP) surge

Measure	Morning BP Surge*	α-Adrenergic Morning BP Surge†
Age (y)	0.06	0.05
Male (female = 0, male = 1)	−0.11	−0.11
Body mass index (kg/m^2)	0.04	0.01
Duration of hypertension (y)	−0.003	0.12
Dose of doxazosin (mg/day)	−0.09	−0.06
Left ventricular hypertrophy (absence = 0, presence = 1)	0.06	0.10
Silent cerebral infarct (number/person)	0.26‖	0.38‡

Spearman correlation coefficients shown.
* Morning systolic BP minus lowest systolic BP during sleep.
† Reduction in morning systolic BP surge by doxazosin (average of first and second morning BP surge minus third morning BP surge).
‡ P < .001; § P < .01; ‖ P < .05.

Table 4. Adjusted morning blood pressure (BP) surge status and multiple silent cerebral infarct (SCI)

Measure	Multiple SCI Group (n = 24)	Nonmultiple Surge Group (n = 74)	P
Systolic BP			
Morning BP surge*	38.6 ± 2.5	30.1 ± 1.9	.011
α-Adrenergic morning BP surge†	21.7 ± 2.6	7.2 ± 2.0	< .001
Diastolic BP			
Morning BP surge*	19.9 ± 1.5	15.9 ± 1.1	.037
α-Adrenergic morning BP surge†	6.6 ± 2.1	1.6 ± 1.5	.073

Data shown as mean ± SE, after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, duration of hypertension, dose of doxazosin, and 24-h systolic BP, using analysis of variance.
* Morning systolic BP minus lowest systolic BP during sleep.
† Average of first and second morning BP surge minus third morning BP surge.

vated by increased shear stress[16] and by increased sympathetic tone (an α_2-receptor mediated effect).[17] Thus, in atherosclerotic arteries, platelet activation in the morning hours could contribute to the formation of microthrombus.

Determinants of Alpha Adrenergic Morning BP Surge

We defined the α-adrenergic component of the MBPS as the reduction of MBPS by doxazosin therapy. The α-adrenergic MBPS varied widely among individual patients, even within the MS group, suggesting that the mechanism of MBPS is heterogeneous. The function of the human sympathetic nervous system is altered in important ways by aging. Microneurographic recording from sympathetic fibers and studies of spillover of the sympathetic neurotransmitter norepinephrine to plasma suggest that progressive sympathetic activation occurs with aging,[7] although the sympathetic α-adrenergic vasoconstrictor responsiveness to endogenous norepinephrine release has been found to be reduced with age in healthy men.[18] Thus α_1-adrenergic blocker therapy might be especially useful for elderly hypertensive patients whose BP level is predominantly dependent on increased sympathetic activity. In fact, the previous results of the HALT study indicated that the doxazosin was more effective in older than in younger hypertensive persons.[7,8]

Alpha Adrenergic Morning BP Surge and Cerebrovascular Disease

The α-adrenergic MBPS was positively associated with the number of SCI in the multiple logistic regression analysis, independently of age, 24-h BP, and other confounding variables. A general characteristic of antihypertensive drugs is that the greater the baseline BP level, the greater the BP reduction. Thus the α-adrenergic morning BP surge, defined by the BP response to doxazosin, would partly depend on the baseline morning BP surge level. The morning surge is not exclusively mediated by the α-adrenergic sympathetic system, as it can also be controlled by a nonspecific, appropriately timed intervention such as extended release verapamil.[19] However, in our study, the difference in the slopes of the baseline morning BP surge and the BP response to doxazosin (Fig. 2) between subjects with multiple SCI and those without multiple SCI may indicate that there is some α-adrenergic role in the pathogenesis of silent hypertensive cerebrovascular disease. In addition, when we entered the MBPS and α-adrenergic MBPS into the same model, only the

Table 5. Multiple logistic regression analysis for multiple silent cerebral infarcts

Covariate	Model 1 Odds Ratio (95% CI)	Model 1 P	Model 2 Odds Ratio (95% CI)	Model 2 P	Model 3 Odds Ratio (95% CI)	Model 3 P
Morning BP surge (10 mm Hg)*	1.63 (1.13–2.34)	.008	—		0.98 (0.58–1.64)	.935
α-Adrenergic morning BP surge (10 mm Hg)†	—		1.93 (1.35–2.76)	.0003	1.96 (1.21–3.16)	.006

Adjusted odds ratios of the presence of multiple (more than two per person) silent cerebral infarcts after adjusting for age, sex, body mass index, smoking status, hyperlipidemia, 24-h systolic BP, and daily dose of doxazosin.
* Morning systolic BP minus lowest systolic BP during sleep.
† Average of first and second morning BP surge minus third morning BP surge.
BP = blood pressure; CI = confidence interval.

α-adrenergic MBPS remained significantly correlated with SCI. In the Surge group, subjects with higher α-adrenergic surge had a markedly higher frequency of multiple SCI, whereas none in the lower α-adrenergic Surge group had multiple SCI. Because this was a cross-sectional study, the causal relationships between the various factors remain unclear. Increased sympathetic activity could accelerate the progression of SCI formation through increased morning BP surge and other pathways such as platelet hyperactivation, endothelial cell dysfunction, and increased blood viscosity.[1,2] On the other hand, the presence of multiple SCI might itself increase the morning BP surge by altering central sympathovagal balance toward increased sympathetic activity. Thus sympathetic activity is increased in patients with clinically overt ischemic cerebrovascular disease, as manifested by increased plasma norepinephrine levels, which may be an independent risk factor for future cardiovascular and cerebrovascular events.[12] In a study using muscle sympathetic nervous activity recording, sympathetic nervous activity was higher in the patients with cerebrovascular disease than in control subjects, suggesting that the damage of cortical or subcortical structures might cause an increase in basal sympathetic activity.[10] In our previous study, heart rate variability, an indicator of autonomic nervous function, was diminished in hypertensive patients with multiple SCI.[20]

Study Limitation

This study lacks specific data for other antihypertensive drugs. The renin-angiotensin system,[21] which also exhibits a morning surge,[22] could also contribute to the BP surge. Thus, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, particularly if administered to patients just before they go to bed, may suppress the morning BP surge. Labetalol,[23] an α/β blocker, and extended-release verapamil taken at bedtime[19] also blunt the morning BP surge. Because our data suggest that the morning surge in sympathetic activity may have detrimental effects, it is possible that patients may benefit from treatments that inhibit this surge, either by central or peripheral blockade of the α-adrenergic limb of the sympathetic nervous system. At the same time it should be borne in mind that in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the rate of hospitalization for congestive heart failure was doubled in patients in the doxazosin arm compared with the chlorthalidone arm,[24] and there was also a slightly higher risk of stroke. However, the latter difference could be explained by the lower BP levels in the chlorthalidone group. In reality, most patients who are taking and α-blocker for lowering their BP are likely to be taking a diuretic as well.

In conclusion, our study suggests that an increased morning surge in BP, particularly that dependent on α-adrenergic activity, may be linked to the development of hypertensive cerebrovascular disease.

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Case Report

Nocturnal Onset Ischemic Stroke Provoked by Sleep-Disordered Breathing Advanced With Congestive Heart Failure

Kazuomi Kario, Masato Morinari, Mitsunobu Murata, Takaaki Katsuki, and Kazuyuki Shimada

Recently, sleep-disordered breathing and nocturnal hypoxia have been recognized to increase the risk of cerebrovascular disease.[1] Kirkham et al reported that nocturnal hypoxemia was a predictor of future cerebrovascular events in sickle-cell disease.[2] However, it remains unclear whether nocturnal hypoxemic episodes directly lead to nocturnal onset stroke, because other predisposing conditions might confound the association between sleep-disordered breathing and the risk of stroke. Congestive heart failure is often accompanied by central sleep–disordered breathing.[3] We report here a case of nocturnal onset ischemic stroke directly provoked by sleep-disordered breathing, newly developed together with congestive heart failure.

Case Report

The patient was a 67-year-old man who was diagnosed with congestive heart failure April 17, 2001. He had a history of coronary artery bypass grafting because of acute myocardial infarction (three-vessel disease) 11 months previously, as well as Leriche syndrome. He had been given anticoagulation therapy with a prothrombin time of approximately 1.6 international normalized ratio (INR), antiplatelet therapy, nitrate, and long-acting calcium antagonists, and his blood pressure (BP) levels had been controlled from 130 to 160 mm Hg for systolic BP, and from 75 to 90 mm Hg for diastolic BP. Because of the development of mild congestive heart failure, administration of a diuretic (spinoloractone) was started. Mild left hemiparesis and sensory disturbance were present when the patient awakened 15 days after starting diuretic intake, and this neurologic deficit continued until the next morning. One month after the episode, brain magnetic resonance (MR) imaging revealed multiple cerebral infarcts on T2-weighted imaging (Fig. 1A) and flair imaging (Fig. 1B). Diffusion MR imaging revealed a new infarct corresponding to the patient's neurologic deficit (Fig. 1C, arrow). Brain MR angiography showed total occlusion of left internal carotid artery (Fig. 2, arrow). When compared with the BP variables obtained from ambulatory BP monitoring 3 months before the episode, the BP variables 1 month after the episode were significantly lower (after versus before the episode, 24-h BP: 111/70 *v* 125/72 mm Hg; awake BP: 114/72 *v* 133/77 mm Hg; sleep BP: 106/67 *v* 111/66 mm Hg). In addition, over-

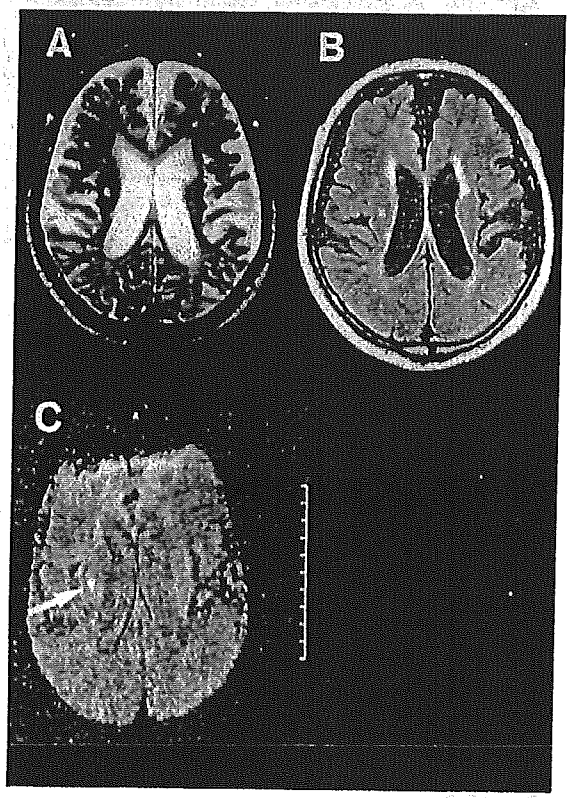

FIG. 1. Brain magnetic resonance (MR) imaging 1 month after the episode revealed multiple cerebral infarcts. (**A**) T2-weighted imaging; (**B**) flair imaging. Diffusion MR imaging revealed a new infarct corresponding to a neurologic deficit (**C, arrow**) in this patient.

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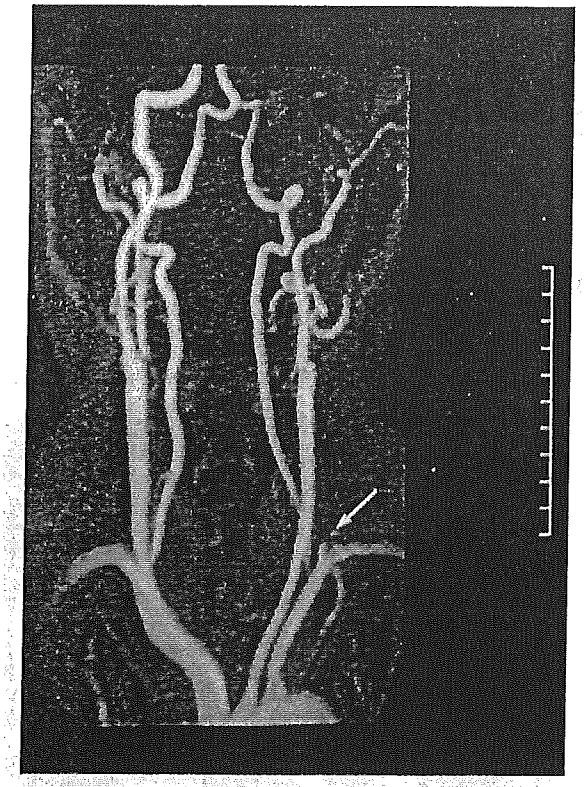

FIG. 2. Brain MR angiography disclosed total occlusion of the left internal carotid artery (**arrow**).

night pulse oximetry one month after the episode newly revealed moderate sleep-disordered breathing with a high frequency of 4% desaturation episodes (29.2/h) during sleep, whereas mean awake oxygen saturation was 97%. Polysomnography disclosed that the patient's apnea–hypopnea index was 55/h (central apnea dominant, 71% of total apnea). Three months before the episode, his frequency of 4% desaturation episodes during sleep had been only 4.8/h.

Discussion

In this patient, MR angiography examination revealed occlusion of internal carotid artery; however, he had noted no clinical neurologic deficits. Thus, we considered that nocturnal hypoxia, which developed along with congestive heart failure, directly triggered transient ischemic attack with a new infarct verified by MR imaging of the brain. A previous case-control study showed that sleep apnea was fivefold more frequent in patients with transient ischemic attack than in a normal control group (62.5% *v* 12.5%).[4] In addition, nocturnal BP reduction (5 mm Hg reduction for systolic BP) caused by a diuretic might reduce cerebral perfusion and trigger a nocturnal ischemic episode. We have recently reported that elderly hypertensive patients with marked nocturnal BP fall (extreme dipping pattern) reduction have a higher risk of stroke than with appropriate nocturnal BP fall (more normal dipping pattern).[5] During an apneic episode, cerebral perfusion pressure was found to decrease by approximately 11.2 ± 7.7 mm Hg (mean ± SD) from baseline,[6] and a significant reduction in middle cerebral artery blood flow velocity has been reported.[7] In addition to the direct effect of hypoxia, these intracranial hemodynamic changes in patients with marginal circulatory reserve would contribute to increase the risk of ischemic stroke.

In this patient, onset of congestive heart failure per se triggered nocturnal hypoxia. The use of diuretic therapy for congestive heart failure may have independently contributed to nocturnal hypoxia. Thus, this implies that initial therapy of heart failure might emphasize nondiuretic options.

In conclusion, if congestive heart failure develops in high-risk patients with severe systemic atherosclerosis, simple evaluation of nocturnal hypoxemic episodes using pulse oximetry should provide valuable information for predicting the risk of stroke.

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Sleep Pulse Pressure and Awake Mean Pressure as Independent Predictors for Stroke in Older Hypertensive Patients

Kazuomi Kario, Joji Ishikawa, Kazuo Eguchi, Masato Morinari, Satoshi Hoshide, Shizukiyo Ishikawa, and Kazuyuki Shimada

Background: It remains uncertain which is the stronger predictor for stroke in older hypertensives, ambulatory pulse pressure (PP) or mean blood pressure (MBP).

Methods: We studied the prognosis for stroke in 811 older hypertensives in whom ambulatory BP monitoring was performed. We also assessed silent cerebral infarct (SCI) by brain magnetic resonance imaging.

Results: Silent cerebral infarcts were found in 50% of 515 subjects (64% of the total population) in whom we assessed SCI using brain magnetic resonance imaging. During a mean of a 42-month follow-up period, stroke events occurred in 59 subjects. After adjustment for covariates, for each 10 mm Hg increase in sleep PP, there was an independent 43% (95% confidence interval [CI]: 16%–75%, $P = .001$) increase in the stroke risk, and sleep MBP was not a significant factor after controlling for sleep PP. On the other hand, for each 10 mm Hg increase in awake MBP, there was an independent 48% (95% CI: 21%–81%, $P = .0002$) increase in the stroke risk, and awake PP was not a significant factor after controlling for awake MBP. After adjusting for SCI (a strong predictor, $P < .0001$) at baseline, the effects of awake MBP (38% risk increase for each 10 mm Hg, $P = .007$) and sleep PP (32% risk increase for each 10 mm Hg, $P = .016$) remained significant.

Conclusions: In older hypertensives, the impacts of PP and MBP on stroke risk are different during sleep and awake periods. Sleep PP and awake MBP are both predictors of stroke events independently of SCI. Am J Hypertens 2004;17:439–445 © 2004 American Journal of Hypertension, Ltd.

Key Words: Ambulatory pulse pressure, hypertension, prognosis, silent cerebral infarct, elderly.

Recently, there is growing evidence that arterial stiffness is a predictor for cardiovascular events and death.[1–3] Pulse pressure (PP), which is a pulsatile component of blood pressure (BP), is one of the indicators of arterial stiffness. Many prospective studies have shown that PP is an important predictor of cardiovascular risk, and some studies have demonstrated that PP is a stronger predictor of cardiovascular events than mean BP (MBP; steady component), particularly in an elderly population.[4–6] However, most of these prospective studies showed that PP is an independent predictor of cardiovascular event used casual BP. Although ambulatory BP is known to be more closely associated with silent target organ damage and cardiovascular risk than clinic BP, there has been only a few prospective studies on the association between ambulatory PP (APP) and cardiovascular risk.[7–9]

Recently, silent cerebral infarct (SCI) is often detected by brain magnetic resonance imaging (MRI) in older subjects, particularly in those with hypertension.[10–12] Silent cerebral infarct is the strongest predictor of subsequent clinically overt stroke.[11,12] The association between APP and stroke risk might be related to SCI, and the stroke risk might be augmented when elevated APP is accompanied by SCI.

To investigate whether APP is a risk factor for stroke in relation to SCI in older hypertensives, we prospectively studied the stroke prognosis in 811 older hypertensive Japanese patients in whom ambulatory BP monitoring (ABPM) was performed in the absence of antihypertensive treatment.

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Methods

Subjects

This study is based on 811 older subjects (>50 years of age) diagnosed with essential hypertension, who are the participants of Jichi Medical School ABPM Study Wave 1.[12] This represents 99% of the 821 subjects who were initially enrolled in the study from six participating institutes (three clinics, two hospitals, and one outpatient clinic of the university hospital) between January 1, 1992, and January 1, 1998. No patient had taken any antihypertensive medication for at least 14 days before the ABPM study, but 51% had a prior history of antihypertensive medication. All of the subjects studied were ambulatory, and all gave informed consent for the study. We excluded from this study patients with renal failure (serum creatinine level ≥176 mmol/L) or hepatic damage, with obvious present illness, or with past history of coronary artery disease, stroke (including transient ischemic attacks [TIA]), congestive heart failure, or arrhythmia. Of the 811 patients, 515 (64%) agreed to and had a brain MRI. There were no significant differences in the age, gender, PP, or MBP parameters at the baseline, or in the incidence of cardiovascular disease between these 515 subjects and the other 296 subjects without brain MRI examination. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan. All the results of the ABPM and brain MRI were returned to the physicians who followed up the subjects.

Twenty-four-hour ABPM

Noninvasive ABPM was carried out on a weekday with one of three automatic ABPM devices (ABPM-630, Nippon Colin Co., Aichi; TM-2421 or TM-2425, A&D Co., Tokyo, Japan), which recorded BP (by the oscillometric method) and heart rate every 30 min for 24 h. We excluded the subjects in whom we obtained valid BP readings in <80% of either awake or asleep attempts, and those who reported in our post-ABPM questionnaire that their sleep was severely disturbed by wearing the ABPM. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he/she got out of bed, and awake BP as the average of BPs recorded during the rest of the day.

Brain MRI

Brain MRI was carried out using a superconducting magnet with a main strength of 1.5T (MRT200FXII, Toshiba, Tokyo; SIGNA-HorizonVer.5.8, General Electric Co., Tokyo; or Vision, Siemens, Tokyo, Japan) within 3 months of the ABPM. T1-weighted images and T2-weighted images were obtained in the transverse plane with 7.8- to 8.0-mm thick sections. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images, as described previously.[10,12,13] Multiple SCI was defined as ≥2 SCIs in a person. The MRI images of the subjects were randomly stored and interpreted blind to the subjects' name and characteristics. The interclass (non-SCI = 0, one SCI = 1, multiple SCIs = 2) kappa statistics were 0.70 and 0.80 for inter-reader and intrareader, respectively, in our laboratory.

Follow-up and Events

The patients' medical records were intermittently reviewed after the subjects entered the study for drug therapy and the occurrence of cardiovascular events. The follow-up evaluation was performed during a 20-month period from 1996 to 1998, and the mean follow-up period was 42 months, with a range from 1 to 68 months. If subjects stopped coming to the clinic, we conducted telephone interviews. Events were classified as cardiac events, stroke events, and noncardiovascular deaths. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke, but excluded TIA (transient neurologic deficits that disappear within 24-h after the onset). Cardiac events included fatal and nonfatal acute myocardial infarction, unexplained sudden death within 6 h of the abrupt onset of symptoms, and coronary revascularization. Fatal event was defined when death occurred within 1 month from the event. These events were accepted if documented in the medical records, or if confirmed by a general practitioner. We excluded 15 possible TIA from the stroke events. Of the total 821 eligible subjects at baseline, follow-up was achieved in 811 (99%) subjects, and the data analysis was restricted to these subjects.

Statistical Analysis

Data are expressed as the mean (SD). One-way ANOVA was performed to detect differences among groups in mean values, and the χ^2 test was used to detect differences among groups in prevalence rates. Adjusted odds ratio and 95% confidence intervals (95% CI) for baseline SCI were calculated using stepwise multiple logistic analysis, and adjusted relative risks (RR) and 95% CI for future stroke risk were calculated using forced or stepwise Cox regression analysis. For the subjects who experienced multiple nonfatal cardiovascular events, the analysis included only the first stroke event. These statistical analyses were performed using SPSS version 8.0 (SPSS Inc., Chicago, IL). Differences with $P < .05$, two-tailed, were considered statistically significant.

Results

During the 42-month follow-up period, 59 clinically overt stroke events (38 ischemic strokes, 9 hemorrhagic strokes, 12 unknown subtype), and 20 fatal cardiovascular events (13 fatal strokes and 7 fatal cardiac events) occurred. At the time of the final follow-up, 426 (53%) of the total 811 patients were receiving antihypertensive medications (diuretics, α- or β-blockers, calcium antagonists, or angio-

Table 1. Baseline characteristics of subjects with and without future stroke events

Measures	Total Population (n = 811)	Stroke Events	
		No Events (n = 752)	Events (n = 59)
Age (yr)	72 (9.8)	72 (9.9)	78 (7.1)*
Male (%)	49	37	51‡
Body mass index (kg/m^2)	23.9 (3.5)	24.0 (3.5)	23.0 (3.6)‡
Clinic systolic BP (mm Hg)	164 (18)	164 (18)	171 (19)*
Clinic diastolic BP (mm Hg)	90 (14)	90 (93)	93 (14)
Clinic mean BP (mm Hg)	115 (13)	115 (13)	119 (14)‡
Clinic pulse pressure (mm Hg)	74 (16)	73 (16)	78 (15)‡
Smoker (%)	20	19	41*
Diabetes mellitus (%)	12	12	17
Hyperlipidemia (%)	19	19	17
Ambulatory BP parameters (mm Hg)			
24-h systolic BP	138 (16)	137 (16)	148 (16)*
24-h diastolic BP	78 (9.7)	78 (9.7)	82 (9.7)*
24-h mean BP	98 (12)	98 (11)	104 (11)*
24-h pulse pressure	60 (9.3)	59 (9.0)	66 (11)*
Awake systolic BP	145 (18)	144 (18)	153 (17)*
Awake diastolic BP	82 (11)	81 (11)	85 (10)‡
Awake mean BP	103 (13)	102 (13)	108 (12)*
Awake pulse pressure	63 (10)	63 (9.8)	68 (11)*
Sleep systolic BP	127 (18)	126 (18)	138 (20)*
Sleep diastolic BP	72 (11)	72 (11)	76 (12)†
Sleep mean BP	90 (13)	90 (12)	97 (14)*
Sleep pulse pressure	55 (11)	54 (10)	61 (12)*

Data are shown as means (SD) or percentages.
* $P < .001$, † $P < .01$, ‡ $P < .05$ v no event group.

tensin-converting enzyme inhibitors). Strokes occurred in 32 (8.3%) of 385 untreated hypertensives, and in 27 (6.3%) of 426 treated hypertensives ($\chi^2 = 1.2$, $P = .28$).

Baseline Characteristics

Table 1 lists baseline characteristics of studied hypertensives with and without future stroke events. The mean age and clinic and ambulatory BP and PP levels and the prevalences of men and smokers were significantly higher, and body mass index (BMI) was significantly lower in the hypertensives who developed future stroke event (stroke group), than in those who did not develop stroke (nonstroke group; Table 1). The prevalences of SCI and multiple SCI were significantly higher in the stroke group (n = 43) than in the nonstroke group (n = 472) (86% v 47%, $P < .0001$; 31% v 77%, $P < .0001$, respectively).

Stroke Risk and Pulse Pressure and Mean BP

Figs. 1A and C depict the association between PP tertiles and stroke risk unadjusted and adjusted for covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication, and MBP) using Cox regression analysis, separated for clinic, 24-h, awake, and sleep BPs. There were marked positive associations between all PP parameters and unadjusted stroke risk; however, after adjustment for covariates, only the clinic and sleep PPs remained significant. Table 2 shows the results of Cox regression analysis, in which the same covariates as in Fig. 1C were included and PP and MBP parameters were considered as continuous variables. For each 10 mm Hg increase in sleep PP, there was an independent 43% (95% CI:16%–75%, P = .001) increase in the stroke risk, and sleep MBP did not yield significance after controlling for sleep PP. On the other hand, for each 10 mm Hg increase in awake MBP, there was an independent 48% (95% CI:21%–81%, P = .0002) increase in the stroke risk, and awake PP did not yield significance after adjusting for awake MBP.

Fig. 2 shows the stroke incidence in the subjects separated according to sleep PP and awake MBP. The stroke incidence was 8.7 times higher in the highest risk hypertensives with awake MBP ≥110 mm Hg (the highest tertile) and sleep PP ≥60 mm Hg (the highest tertile) than in the lowest risk hypertensives with low awake MBP <95 mm Hg (the lowest tertile) and low sleep PP <50 mm Hg (the lowest tertile). When both sleep PP and awake MBP were entered into the same model including covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication), both sleep PP (RR = 1.32, P = .04) and awake MBP (RR = 1.35, P = .01) were associated with stroke risk independently of each other (Table 3).

Fatal Cardiovascular Events

Fig. 1B shows the association between PP tertiles and fatal cardiovascular event risk unadjusted. After adjusting for the covariates listed in Table 2 (age, gender, BMI, diabe-

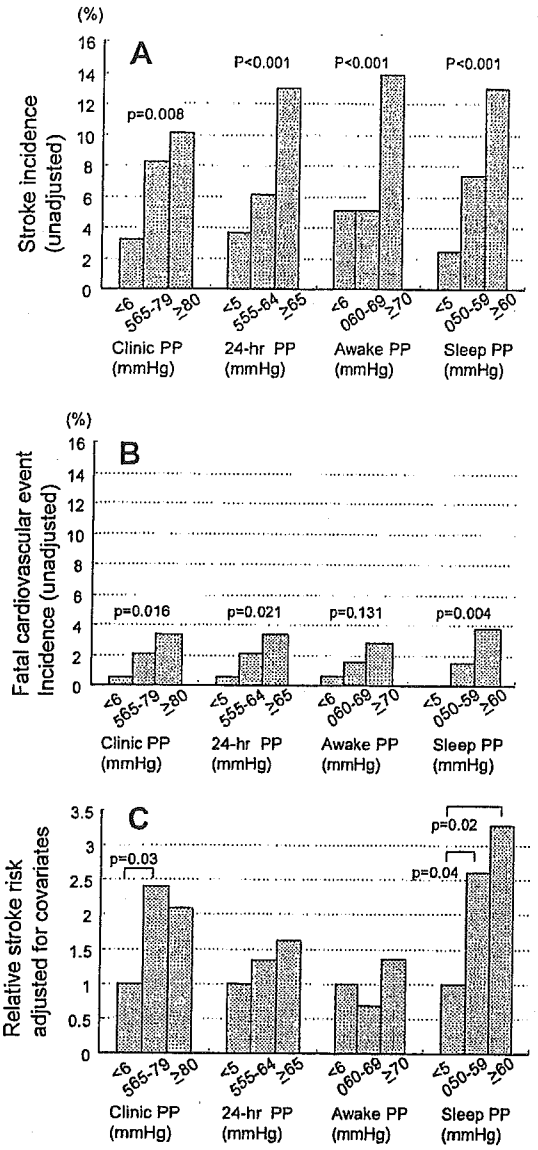

FIG. 1. **A**) Stroke incidence (unadjusted). **B**) Fatal cardiovascular event incidence (unadjusted). **C**) Relative risk for stroke event (adjusted for age, gender, body mass index, diabetes, hyperlipidemia, antihypertensive medication, and mean blood pressure) in each tertile of pulse pressure (PP) parameter.

tes, hyperlipidemia, antihypertensive medication) using Cox regression analysis, all APP parameters (clinic, 24-h, awake, and sleep) were predictors for fatal cardiovascular events (fatal stroke and cardiac events), independently of MBP parameters. For each 10 mm Hg increase in PP, there was an independent 41% (95% CI: 10%–81%, P = .007) increase for clinic BP, 71% (95% CI: 21%–141%, P = .003) increase for 24-h BP, 64% (95% CI:13–137%, p=0.01) increase for awake BP, and 63% (95% CI: 21%–121%, P = .002) for sleep BP in the stroke risk, whereas clinic, 24-h, awake, and sleep MBPs did not yield significance after controlling for PP parameters.

Table 2. Results of stepwise Cox regression analysis for clinical stroke event (n = 811)

Covariates	Relative Risk (95% CI)	P
Clinic BP		
Age (10 yr)	1.91 (1.46–2.51)	.0000
Current smoker	2.69 (1.59–4.53)	.0004
Clinic mean BP (10 mm Hg)	1.26 (1.07–1.49)	.0084
24-h BP		
Age (10 yr)	1.94 (1.48–2.53)	.0000
Current smoker	2.39 (1.42–4.03)	.0016
24-h mean BP (10 mm Hg)	1.56 (1.27–1.91)	.0000
Awake BP		
Age (10 yr)	2.01 (1.53–2.64)	.0000
Current smoker	2.55 (1.52–1.81)	.0007
Awake mean BP (10 mm Hg)	1.48 (1.21–1.81)	.0002
Sleep BP		
Age (10 yr)	1.68 (1.26–2.24)	.0003
Current smoker	2.38 (1.40–4.03)	.0020
Sleep pulse pressure (10 mm Hg)	1.43 (1.16–1.75)	.0012

CI = confidence interval. Age, gender (women = 0, men = 1), body mass index, smoking status (absence = 0, presence = 1), diabetes (absence = 0, presence = 1), hyperlipidemia (absence = 0, presence = 1), antihypertensive medication (absence = 0, presence = 1), and clinic, 24-h, awake, and sleep mean BP and pulse pressure were selected for the stepwise Cox regression analysis.

Impact of Silent Cerebral Infarct

Then we grouped the 515 subjects who had both ABPM and brain MRI into 258 subjects without SCI and 257 with SCI. There was a positive association between all PP parameters (clinic, 24-h, awake, and sleep) and SCI (data not shown). However, after adjusting for covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication) using stepwise multiple logistic regression

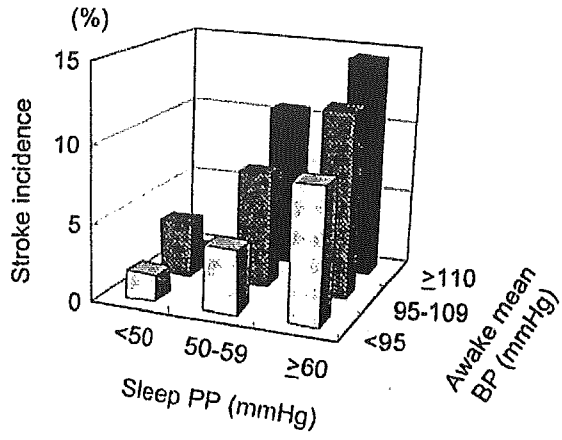

FIG. 2. Stroke incidence from the first to the third tertile of the distribution of pulse pressure (PP) parameters and awake mean blood pressure (BP).

Table 3. Results of forced Cox regression analysis for clinical stroke event

Covariates	Model 1 (n = 811) Relative Risk (95% CI)	P	Model 2 (n = 515) Relative Risk (95% CI)	P
Age (10 yr)	1.82 (1.33–2.48)	.0002	1.72 (1.13–2.61)	.01
Male	1.45 (0.81–2.59)	.21	1.19 (0.58–2.43)	.64
Body mass index (kg/m^2)	0.99 (0.92–1.08)	.87	1.01 (0.92–1.11)	.79
Current smoker	2.14 (1.18–3.87)	.01	2.06 (1.03–4.13)	.04
Diabetes	1.03 (0.51–2.10)	.93	0.91 (0.42–1.99)	.81
Hyperlipidemia	1.56 (0.76–3.20)	.23	1.14 (0.50–2.56)	.76
Antihypertensive medication	0.71 (0.41–1.24)	.23	0.51 (0.26–0.98)	.04
Silent cerebral infarct	Not included		4.49 (1.85–10.9)	.0009
Awake mean BP (10 mm Hg)	1.35 (1.07–1.69)	.01	1.30 (1.00–1.69)	.048
Sleep pulse pressure (10 mm Hg)	1.32 (1.02–1.72)	.04	1.30 (0.98–1.72)	.066

CI = confidence interval. Age, gender (women = 0, men = 1), body mass index, smoking status (absence = 0, presence = 1), diabetes (absence = 0, presence = 1), hyperlipidemia (absence = 0, presence = 1), antihypertensive medication (absence = 0, presence = 1), awake mean BP, and sleep pulse pressure were selected for the Model 1 of the forced Cox regression analysis. The silent cerebral infarct (absence = 0, presence = 1) was added in Model 2.

analysis, MBP parameters (clinic, 24-h, awake, sleep) significantly were associated with SCI (0 = absent, 1 = present); however, none of the PP parameters yielded statistical significance (Table 4).

Stroke occurred in 6 (2.3%) of the non-SCI group, and in 37 (14%) of the SCI group, indicating that SCI is a strong predictor of clinical stroke (RR = 7.1, $P < .0001$). The association between SCI (0 = absent, 1 = present) and stroke risk remained significant independently of all parameters of PP and MBP. Fig. 3 shows the positive associations between PP parameters and stroke risk in both the SCI group and non-SCI group. To study the potential mediating role of SCI in the association between PP, MBP, and stroke risk, we added SCI (0 = absent, 1 = present) into the same model as used for the results shown in Table 2. The impacts of clinic MBP (RR = 1.23, P = .03), awake MBP (RR = 1.38, P = .007), and sleep PP (RR = 1.32, P = .016) on stroke risk remained significant independently of SCI. Instead of 24-h mean BP (independent predictor for stroke event in Table 2), 24-h PP appeared to be a significant predictor for stroke event (RR = 1.41, P = .015) in this model that included SCI.

Table 4. Results of stepwise multiple logistic analysis for silent cerebral infarct detected by brain MRI (n = 515)

Covariates	Odds Ratio (95% CI)	P
Clinic BP		
Age (10 yr)	1.98 (1.59–2.49)	.0000
Male	1.80 (1.24–2.64)	.0021
Clinic mean BP (10 mm Hg)	1.19 (1.04–1.36)	.0092
24-h BP		
Age (10 yr)	2.03 (1.62–2.55)	.0000
Male	1.62 (1.10–2.39)	.0136
24-h mean BP (10 mm Hg)	1.28 (1.09–1.51)	.0021
Awake BP		
Age (10 yr)	2.07 (1.65–2.60)	.0000
Male	1.63 (1.11–2.39)	.0130
Awake mean BP (10 mm Hg)	1.31 (1.13–1.52)	.0003
Sleep BP		
Age (10 yr)	1.99 (1.59–2.49)	.0000
Male	1.67 (1.14–2.45)	.0087
Sleep mean BP (10 mm Hg)	1.20 (1.04–1.39)	.0138

Abbreviations as in Table 2.

Discussion

This study has first demonstrated that in older hypertensives, the impacts of PP and MBP on stroke risk are different during sleep and awake periods. Sleep PP and awake mean BP were independent predictors for stroke events. These associations were independent of other cardiovascular risk factors and SCI.

Sleep Pulse Pressure

All PP parameters (clinic, 24-h, awake, and sleep) were positively associated with stroke risk. However, after adjusting for covariates, only sleep PP remained significant independently of MBP. Previous studies have not studied the association of PP and MBP with cardiovascular events separately for awake and sleep periods. To consider the possible mechanism for the difference in the association of the PP and MBP with stroke events between the sleep and awake periods, we have to consider diurnal changes of neurohumoral factors. Although PP is totally considered as a global indicator of arterial stiffness, various factors such as stroke volume, rapidity of ventricular ejection, viscoelastic properties of large arteries, and timing of reflected pulse waves from the peripheral sites determine PP.[1–3] In an acute human study, pulse wave velocity was

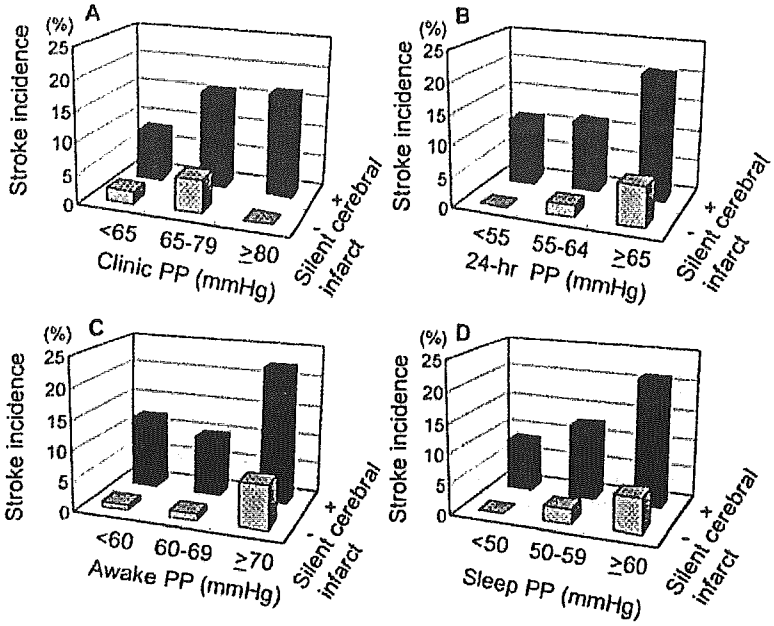

FIG. 3. Stroke incidence from the first to the third tertile of the distribution of pulse pressure (PP) parameters in the groups with and without baseline silent cerebral infarct detected by brain magnetic resonance imaging. (**A**: clinic PP; **B**: 24-h PP; **C**: awake PP; **D**: sleep PP).

unaffected by β-adrenergic blockade, but was reduced by combined α- and β-adrenergic blockade, indicating that sympathetic nervous activity affects the functional stiffness of the large artery.[14] In addition, infusion of angiotensin II increases augmentation index, which implies an augmentation of pressure during the late systolic phase, resulting in increased PP.[15] Thus, it is possible that the diurnal variation in these neurohumoral activities will change the PP during different diurnal periods. During the sleep period, parasympathetic activity increases with diminished sympathetic activity. The activity of the renin-angiotensin system also decreases during the sleep period. Thus, sleep PP may more closely reflect structural arterial stiffness with less effect on the neurohumoral factors, whereas awake PP may reflect not only structural stiffness but also functional stiffness, which is also affected by diurnal neurohumoral activation. The results of our study indicate that structural arterial stiffness might be a more powerful determinant of stroke event in the elderly hypertensives.

In addition, the marked dilatation of all peripheral arteriole, which usually occurs during night, might lead to a greater decrease in diastolic BP than systolic BP, which consequently discloses the predictive value of sleep PP (superior to that of sleep MBP) for stroke. This phenomenon might be particularly relevant in the elderly. Furthermore, an increased PP itself may be a causal mechanism for plaque disruption. A recent study (European Carotid Surgery Trial) demonstrated that PP is independently associated with carotid plaque ulceration in patients with carotid stenosis, suggesting that pulsatile hemodynamic forces are an important cause of plaque rupture leading to cardiovascular events.[16]

Awake, Twenty-four-hour, and Clinic Pulse Pressure

On the other hand, after adjusting for covariates, awake, 24-h, and clinic PPs were not associated with stroke independently of MBP. Instead, awake, 24-h, and clinic MBPs were independent predictors for future stroke. In previous prospective studies, contradictory results were obtained regarding the association between clinic PP and stroke risk.[4] In the Systolic Hypertension in the Elderly Program (SHEP), both PP and MBP were independent predictors of stroke.[17] In the recent analysis of the Medical Research Council (MRC) Mild Hypertension Trial, stroke risk was best predicted by MBP,[18] and in the European Working Party on Hypertension in the Elderly (EWPHE), MBP was a predictor for stroke even after adjusting for PP, whereas PP did not significantly predict stroke after adjusting for MBP.[4,19] In contrast, in the Systolic Hypertension in Elderly in Europe (Syst-Eur) and Systolic Hypertension in Elderly in Chinese (Syst-China) studies of elderly patients with isolated systolic hypertension, PP was a stronger predictor of stroke than MBP.[4] One prospective study using ABPM found an independent positive association between 24-h PP and cardiac events, but did not find an independent association between 24-h PP and stroke.[9] However, that study did not analyze separately for sleep and awake periods. In addition, their study population was much younger (mean age, 51 years) than our population (mean age, 72 years). In study populations with different ages, PP seems to have a different impact on stroke, because in another prospective study using ABPM, an independent impact of PP on cardiovascular events was only found in older patients aged 65 years or more. How-

ever, MBP was an independent determinant for cardiovascular events in younger adults aged <65 years.[8] It appears that when the stroke risk is analyzed separately for sleep and awake periods in older hypertensive patients, the association between APP and stroke risk might be significant, even after adjusting for MBP. The impacts of awake MBP and sleep PP on stroke risk were independent of each other, even after adjusting for covariates.

Impact of Silent Cerebral Infarcts

Silent cerebral infarct are predominantly small lacunar infarcts with various types of pathogenesis including microathoeroembolism, hemodynamic infarction, and arteriosclerosis of small penetrating arteries. In the present study, the presence of SCI was a powerful predictor of future stroke. This association was independent of all parameters of PP and MBP. On the other hand, the positive association between sleep and 24-h PPs and stroke risk was independent of the presence or absence of SCI. Thus, our study indicates that in the elderly hypertensive patients, both large vessel disease (increase in PP) and small vessel disease (SCI) determine the risk of future stroke independently of each other.

There was a positive association between all PP parameters (clinic, 24-h, awake, and sleep) and SCI. However, after adjusting for covariates, this association was not independent of MBP. In contrast, all MBP parameters were determinants for SCI independently of PP parameters. These results may imply that the steady BP overload (MBP) is main determinant for the progression of arteriosclerosis of small cerebral arteries resulting in the formation of small lacunar infarcts than the pulsatile component (PP) in hypertensive patients.

Fatal Cardiovascular Events

Because of the small number of fatal stroke events in this study, we combined the fatal stroke and cardiac events as fatal cardiovascular events. All PP parameters (clinic, 24-h, awake, and sleep) had stronger effects on the fatal cardiovascular events than MBP parameters. The impact of PP may be greater on fatal events than nonfatal cardiovascular events in elderly hypertensives.

In conclusion, in older hypertensive patients, APP, particularly during the sleep period, is an important predictor for future stroke risk, independent of age and ambulatory MBP. Antihypertensive therapy targeting the reduction of the pulsatile component of BP in addition to reducing the steady component may achieve more effective reduction of stroke risk.

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AJH 2004; 17:112–117

Comparison of Valsartan and Amlodipine on Ambulatory and Morning Blood Pressure in Hypertensive Patients

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Background: Cardiovascular events occur most frequently in the morning. We aimed to study the effects of monotherapy with the long-acting angiotensin II receptor blocker valsartan compared with the long-acting calcium antagonist amlodipine on ambulatory and morning blood pressure (BP).

Methods: We performed ambulatory BP monitoring before and after once-daily dose of valsartan (valsartan group, $n = 38$) and amlodipine (amlodipine group, $n = 38$) therapy in 76 hypertensive patients. To achieve the target BP of ≤140/90 mm Hg, valsartan was titrated from 40 mg/day to 160 mg/day (mean dose 124 mg/day) and amlodipine was titrated from 2.5 mg/day to 10 mg/day (mean dose 6.4 mg/day).

Results: Both drugs significantly reduced clinic and 24-h systolic BP (SBP) and diastolic BP (DBP) ($P < .002$). However, the antihypertensive effect of amlodipine was superior to that of valsartan in clinical SBP (−26 mm Hg *v* −13 mm Hg, $P = .001$) and 24-h SBP (−14 mm Hg *v* −7 mm Hg, $P = .008$). In addition, morning SBP was significantly reduced by amlodipine from 156 to 142 mm Hg ($P < .001$) but not by valsartan. Both agents reduced lowest night SBP to a similar extent (amlodipine 121 to 112 mm Hg, $P < .001$; valsartan 123 to 114 mm Hg, $P < .002$). Reduction in morning SBP surge (morning SBP minus lowest night SBP) was significantly greater in patients treated with amlodipine compared with those treated with valsartan (−6.1 mm Hg *v* +4.5 mm Hg, $P < .02$).

Conclusions: Amlodipine monotherapy was more effective than valsartan monotherapy in controlling 24-h ambulatory BP and morning BP in hypertensive patients. Am J Hypertens 2004;17:112–117 © 2004 American Journal of Hypertension, Ltd.

Key Words: Valsartan, amlodipine, ambulatory blood pressure, morning blood pressure surge.

Ambulatory blood pressure (BP) levels are closely associated with target organ damage and clinical cardiovascular events in hypertensive patients.[1–5] Cardiovascular events occur more frequently in the morning, and ambulatory BP exhibits a diurnal variation with increases in the morning (morning BP surge).[6,7] The morning BP surge was previously reported to be associated with cardiac hypertrophy in hypertensive patients.[8] Recently we have shown that the morning BP surge was significantly associated with an increased risk of stroke in hypertensive patients.[9] This association was independent of age and 24-h BP level. Thus, antihypertensive medication more specific for morning BP in addition to 24-h BP would be useful for the prevention of cardiovascular events in hypertensive patients.

The renin-angiotensin-aldosterone system (RAAS) is activated in the morning, and may contribute to morning BP surge[7] and to morning increase in cardiovascular risk. Valsartan, a long-acting angiotensin receptor blocker (ARB), has been reported to have a BP lowering effect similar to that of amlodipine, a long-acting calcium antagonist, for controlling ambulatory BP level without disruption of its diurnal variation in hypertensive patients.[10] However, specific comparison of the BP lowering effect on ambulatory BP, morning BP, and morning BP surge between valsartan and amlodipine has not been conducted with each single-drug therapy in hypertensive patients.

Methods

Study Patients

This study was a multicenter, open-label, randomized study of the effects of once-daily morning administration of amlodipine and valsartan on ambulatory BP, including

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Table 1. Patient baseline characteristics

Characteristics	Amlodipine Group (n = 38)	Valsartan Group (n = 38)
Age (yr)	65.7 (8.2)	65.5 (13)
Male gender (%)	32	37
BMI (kg/m^2)	25.2 (4.0)	23.7 (3.7)
Duration of HT (yr)	4.7 (3.2)	6.4 (7.0)
Hyperlipidemia (%)	29	39
Clinic SBP (mm Hg)	164 (8.4)	163 (16)
Clinic DBP (mm Hg)	93 (14)	91 (11)
Clinic PR (mm Hg)	71 (15)	72 (12)
24-h SBP (mm Hg)	147 (12)	148 (12)
24-h DBP (mm Hg)	83 (8.4)	86 (7.7)
24-h PR (mm Hg)	66 (8.4)	68 (8.3)
Awake SBP (mm Hg)	155 (12)	155 (12)
Awake DBP (mm Hg)	88 (9.2)	90 (7.7)
Awake PR (mm Hg)	70 (9.9)	72 (8.8)
Sleep SBP (mm Hg)	131 (16)	135 (19)
Sleep DBP (mm Hg)	75 (9.2)	77 (10)
Sleep PR (mm Hg)	60 (6.5)	59 (7.2)
Morning SBP (mm Hg)	156 (16)	154 (19)
Morning DBP (mm Hg)	89 (9.8)	90 (13)
Morning PR (mm Hg)	68 (10)	72 (8.6)
Lowest night SBP (mm Hg)	121 (14)	123 (19)
Lowest night DBP (mm Hg)	68 (9.1)	69 (10)
Lowest night PR (mm Hg)	59 (6.5)	60 (9.0)

Data did not show any statistical significance between the amlodipine and the valsartan group.

BMI = body mass index; DBP = diastolic blood pressure; PR = pulse rate; SBP = systolic blood pressure.

morning BP. The subjects included older Japanese hypertensive patients at four Japanese hospital clinics. The entry period was May 2002 to May 2003. A total of 76 patients (26 men and 50 women, mean age 65.6 years) with average seated clinic systolic BP (SBP) ≥140 mm Hg and < 180 mm Hg, or diastolic BP (DBP) ≥90 mm Hg and <110 mm Hg during the follow-up period (1 to 2 weeks) were recruited for this study. To be included in the study, patients were required to be ≥40 years of age, to have a diagnosis of essential hypertension, and to have no history of other significant medical disorders including diabetes, renal failure (serum creatinine ≥2.0 mg/dL), atrial fibrillation, or any clinically overt cardiovascular disease. All patients were fully ambulant. Body mass index was calculated as weight (killograms)/height (meters)^2.

Study Design

Each patient was studied for a maximum of 18 weeks, with a run-in period of 1 to 2 weeks and a treatment period of up to 8 to 16 weeks. After the run-in period, the valsartan group (n = 38) was started on 40 to 80 mg of valsartan just after breakfast, subsequently increasing the dose by 40-mg increments with an interval of 4 weeks (maximal dose 160 mg). The amlodipine group was started on 2.5 to 5 mg of amlodipine, increasing by 2.5 mg, unless the patient's BP had already been reduced to <140 mm Hg for SBP and <90 mm Hg for DBP or unless adverse events had occurred. 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.

Ambulatory BP Monitoring

Noninvasive ambulatory BP monitoring (ABPM) was carried out twice on two separate weekdays with one of two automatic ABPM devices (TM-2421 or TM-2430, A&D Co., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 hours. The first ABPM was performed at the end of the run-in period and the second ABPM at the end of the treatment period of 8 to 16 weeks.

Twenty-four-hour BP was defined as the average of all BP readings throughout 24 hours.[5] The subjects were all ambulant during the day, and no subjects reported staying in bed after waking. Sleep BP was defined as the average of BP from the time when patients went to bed until the time they got out of bed; awake BP was defined as the average of BP recorded during the rest of the day.[11] Morning BP was defined as the average of BP during the first 2 h after waking (four BP readings).[9] The lowest night BP was defined as the average BP of three readings centered on the lowest nighttime reading. The morning BP surge was calculated as the morning SBP minus the lowest night SBP.[9] No participants complained of sleep disturbance due to ABPM.

Statistical Analysis

All statistical analyses were carried out with SPSS software package, version 11.0 (SPSS Inc., Chicago, IL). A two-tailed paired t test was used to compare the mean values before and after each drug therapy. The χ^2 test was applied to examine differences between the prevalence in the two groups. Data are expressed as the mean ± SD or prevalence. A value of $P < .05$ was considered to be significant.

Results

All but one patient completed the study protocol. The clinic BP of this patient was 152/93 mm Hg at baseline and remained elevated even after valsartan was titrated to 160 mg/day, resulting in the patient discontinuing the study. However, 40 days after starting valsartan therapy, this patient's second ABPM was performed and the data were included in the analysis. Three adverse reactions were noted in the valsartan group (general fatigue in one patient, slight facial edema in one, and oral dysesthesia in one) and one adverse reaction (general fatigue) in the amlodipine group. All patients in the amlodipine group completed the study.

Baseline characteristics, including ambulatory BP of the study subjects, were comparable between the amlodip-

Table 2. Blood pressure before and after treatment

	Amlodipine Group (n = 38)			Valsartan Group (n = 38)		
	Baseline	Amlodipine	P	Baseline	Valsartan	P
Clinic SBP (mm Hg)	164 (8.4)	138 (7.3)	< .001	163 (16)	150 (19)	< .001
Clinic DBP (mm Hg)	93 (14)	83 (7.2)	< .001	91 (11)	84 (12)	.001
Clinic PR (mm Hg)	71 (15)	67 (11)	.11	72 (12)	71 (11)	.445
24-h SBP (mm Hg)	147 (12)	133 (10)	< .001	148 (12)	141 (14)	.001
24-h DBP (mm Hg)	83 (8.4)	78 (7.8)	< .001	86 (7.7)	83 (8.8)	.002
24-h PR (mm Hg)	66 (8.4)	69 (7.5)	.007	68 (8.3)	68 (8.4)	.861
Awake SBP (mm Hg)	155 (12)	140 (12)	< .001	155 (12)	148 (15)	.001
Awake DBP (mm Hg)	88 (9.2)	82 (8.1)	< .001	90 (7.7)	87 (9.0)	.005
Awake PR (mm Hg)	70 (9.9)	73 (8.8)	.004	72 (8.8)	71 (9.0)	.653
Sleep SBP (mm Hg)	131 (16)	119 (12)	< .001	135 (19)	128 (18)	.015
Sleep DBP (mm Hg)	75 (9.2)	70 (8.3)	< .001	77 (10)	73 (9.8)	.016
Sleep PR (mm Hg)	59 (6.5)	60 (7.0)	.04	59 (7.2)	60 (8.3)	.707
Morning SBP (mm Hg)	156 (16)	142 (11)	< .001	154 (19)	151 (19)	.396
Morning DBP (mm Hg)	89 (9.8)	85 (10)	.006	90 (13)	88 (13)	.437
Morning PR (mm Hg)	68 (10)	72 (9.9)	.006	72 (8.6)	70 (9.9)	.226
Lowest night SBP (mm Hg)	121 (14)	112 (11)	< .001	123 (19)	114 (18)	.002
Lowest night DBP (mm Hg)	68 (9.1)	66 (8.7)	.053	69 (10)	66 (11)	.078
Lowest night PR (mm Hg)	59 (6.5)	61 (7.8)	.218	60 (9.0)	59 (8.7)	.473

Paired t test was used for comparison between baseline and posttreatment values.
Abbreviations as in Table 1.

ine and valsartan groups (Table 1). Clinic BP, 24-h BP, awake BP, and sleep BP decreased significantly in both groups (Table 2). However, the reduction in all BP parameters (clinic SBP −26 mm Hg v −13 mm Hg, P = .001), 24-h SBP (−14 mm Hg v −7 mm Hg, P = .008), and awake SBP (−15 mm Hg v −7 mm Hg, P = .007) were significantly greater in the amlodipine group than in the valsartan group (Fig. 1).

Valsartan did not significantly reduce morning SBP, although it reduced the lowest night SBP (P = .002; Table 2). In contrast, amlodipine reduced both morning SBP and the lowest night SBP (both P < .001). The reduction of morning SBP surge (morning SBP minus lowest night SBP) was significantly greater in the amlodipine group than in the valsartan group (−6.1 mm Hg v +4.5 mm Hg, P = .02; Fig. 1).

There were no significant differences in reduction of 24-h SBP (7.7 mm Hg v 6.4 mm Hg) and morning SBP (3.0 mm Hg v 2.8 mm Hg) between the lower dose (40 to 80 mg/day) and the higher dose (120 to 160 mg/day) valsartan groups. There was no significant difference in the BP reduction of 24-h SBP (12 mm Hg v 16 mm Hg) and morning SBP (14 mm Hg v 15 mm Hg) between the lower dose (2.5 to 5.0 mg/day) and the higher dose (7.5 to 10 mg/day) amlodipine groups. With regard to both the lower and higher doses, the BP lowering effect was significantly

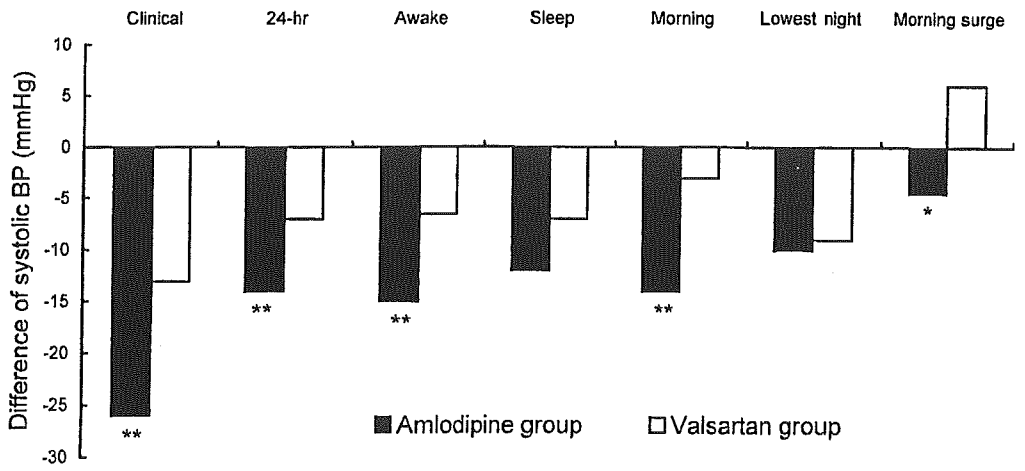

FIG. 1. Differences in clinic systolic blood pressure and ambulatory systolic blood pressure before and after amlodipine and valsartan treatment. **Black bars**, amlodipine group; **white bars**, valsartan group. BP = blood pressure. *P < .05 v valsartan group by ANOVA (between groups); **P < .01 v valsartan group by ANOVA.