is the predominant pathophysiological mechanism for orthostatic hypertension. Thus, elderly hypertensive individuals with orthostatic BP dysregulation have had a high risk of developing hypertensive cerebrovascular disease.

We investigated the relationship between diurnal and postural BP variations in asymptomatic hypertensive elderly subjects with different patterns of nocturnal BP fall. During a 70° head-up tilt test, the mean systolic BP increased 10 mmHg in the extreme dippers and decreased by 7.5 mmHg in the risers, while it did not change in the dippers (Figure 6) [41]. The heart rate increased in all four groups to a similar degree during tilt. Thus, the abnormal diurnal BP variation is closely related to the abnormal postural BP variation in elderly hypertensive patients, with extreme dippers showing orthostatic hypertension and risers showing orthostatic hypotension. The upright position during the daytime, which increases the BP in extreme dippers and decreases it in nondippers, may thus account for some of the abnormal diurnal BP variation.

Exaggerated morning surge in BP, orthostatic hypertension, and extreme dippers are closely associated with each other, and the hypertensive patients with these conditions are the high-risk group for cardiovascular events [32].

ABP and position of the body (sitting or supine position versus standing position) could be simultaneously monitored using a newly developed ABPM (TM-2425, A&D). ABPM with a potential ambulatory positional test might be useful for detecting high-risk subjects for cardiovascular events or falls and monitoring of the excessive BP lowering effect of antihypertensive medication. In addition, increase in BP reactivity to physical activity could be monitored using ABPM equipped with actigraphy. The future study of using ABPM that could evaluate an individual BP reactivity during daily life could be conducted for more beneficial management of hypertensive patients.

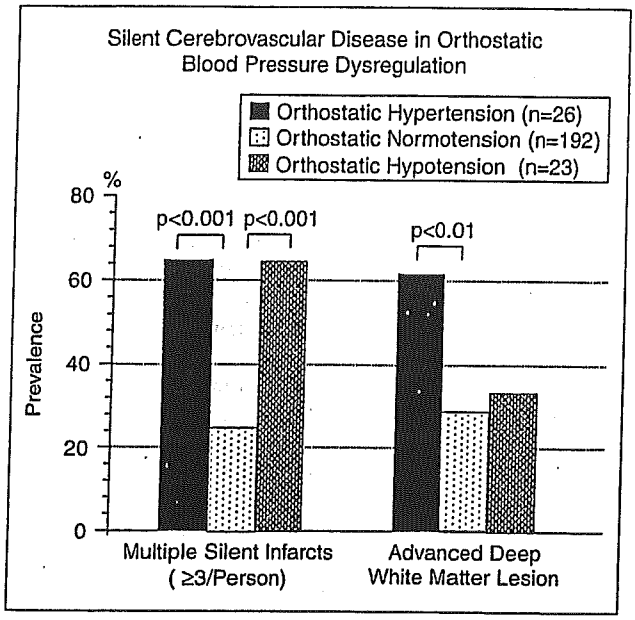


Fig. 4. Silent cerebrovascular disease in orthostatic blood pressure dysregulation.

Holter ECG Monitoring-Equipped Multifunctional ABPM

Recently developed Holter ECG monitoring-equipped multifunctional ABPM could assess the individual's more precise cardiovascular status (A&D, Tokyo; Meditech, Austria). Arrhythmia and myocardial ischemia evaluated by ST depression could be evaluated in relation to diurnal BP variation. Using heart-rate variability, cardiac autonomic function could be assessed.

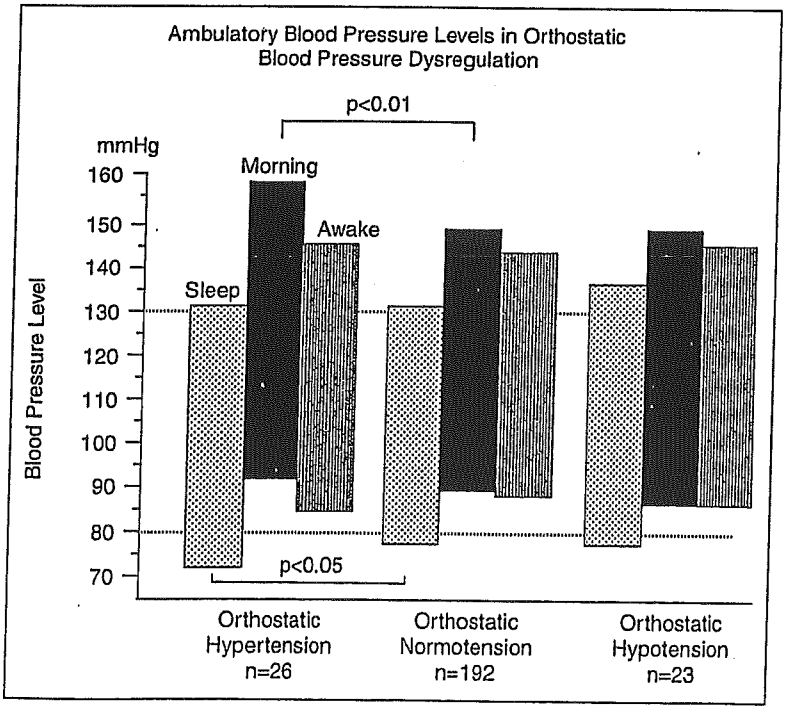


Fig. 5. Ambulatory blood pressure levels in orthostatic blood pressure dysregulation.

Myocardial Ischemia

Systemic hypertension is well recognized as a predisposing condition for coronary artery disease and sudden cardiac death. Previous reports have disclosed that myocardial ischemia is frequent even in asymptomatic hypertensive patients. When assessed by ischemic ST depression using Holter ECG monitoring, the prevalence of this silent myocardial ischemia is reported to range from 25% to 68% in hypertensive patients without clinically overt coronary artery disease (angina pectoris and myocardial infarction), while it is only 2-20% in normotensive subjects [62]-[71]. When ischemia is assessed by ECG or thallium stress testing, silent myocardial ischemia is detected in about 25-35% of hypertensive patients. This value is slightly lower than that detected by Holter ECG monitoring [66], [67]. This difference might be due to diurnal change of threshold of myocardial ischemia, although there is a possibility of a higher false positive rate with Holter ECG than with stress testing.

Several studies have concluded that silent myocardial ischemia is a powerful prognostic determinant for myocardial infarction and

Actigraphy is useful not only for objective assessment for awake physical activity but also for the assessment of sleep quality.

sudden cardiac death, including malignant arrhythmia, in patients with coronary artery disease [72]-[74]. There is a prospective report that the use of atenolol, a long acting ß-1 selective-blocking agent, decreases the frequency of silent myocardial ischemia and suppresses subsequent cardiac events in asymptomatic or minimally symptomatic patients with coronary artery disease [75]. Thus, the clinical significance of silent myocardial ischemia and therapy for this condition seems to be established in coronary artery disease patients.

In hypertensive patients without significant coronary stenosis, some authors have found that transient silent myocardial ischemia detected by Holter monitoring is also a prognostic predictor [63], [65], although the data are too limited to be conclusive. Some authors point out that ventricular arrhythmias occur frequently during ischemic episodes [63], but others do not agree [64]. Since the occurrence of myocardial ischemia is determined by the balance between the blood supply from the coronary arteries and the myocardial oxygen demand, it could occur in hypertensive patients without significant coronary artery stenosis [76], [77]. Coronary microangiopathy caused by persistent high blood pressure would reduce coronary flow reserve and lead to myocardial ischemia during an increase of physical activity and in a condition that requires increased myocardial oxygen demand such as left ventricular hypertrophy. In addition, hypertensive endothelial dysfunction of the coronary artery resulting from hypertension could trigger a coronary spasm that could lead to nonfatal and fatal myocardial ischemia.

It is well known that episodes of silent myocardial ischemia, as well as symptomatic myocardial episodes and myocardial infarction, occur more frequently early in the morning than at other times of the day both in hypertensive patients and in those with coronary artery disease [44]. Possible mechanisms of this include decreased coronary blood flow from coronary spasms resulting from withdrawal of parasympathetic activity and increase in sympathetic activity and increased myocardial oxygen demand resulting from the higher double product (BP x heart rate) occurring at this time. Some hypertensive patients show an augmented morning BP rise and some authors have reported that this augmented morning BP rise is correlated with left ventricular hypertrophy [78]. However, the relationship between the morning BP rise and silent myocardial ischemia has not yet been fully investigated.

There are only a few studies using simultaneous ambulatory 24-hr recording of BP and ECG in patients with stable angina pectoris [79], [80]. In these, the majority of myocardial ischemic episodes have been found to occur during periods when there is an increase of both BP and heart rate, even when episodes occur during the night. A recent study of hypertensive patients with coronary artery stenosis disclosed nocturnal episodes of silent myocardial ischemia more frequently in nondippers than in dippers and extreme dippers [80]. However, when antihypertensive therapy was started, nocturnal myocardial ischemia increased in the extreme dippers, who had the lowest nocturnal blood pressure values (105/58 mmHg), while it was decreased in nondippers. Although this study could not measure the exact BP at the time of the nocturnal ischemic episodes, these results suggest that there may be different mechanisms of myocardial ischemic episodes in hypertensive patients with different diurnal rhythms. Extreme dippers may be prone to nocturnal ischemia due to reduced coronary blood flow supply as a result of the excessive nocturnal BP fall, while in nondippers the persistently high nocturnal BP might increase myocardial oxygen demand. Thus, there may be a J-curve relationship between nocturnal dipping and silent myocardial ischemia.

The same J-curve relationship has been described in elderly Japanese hypertensive patients between nocturnal BP

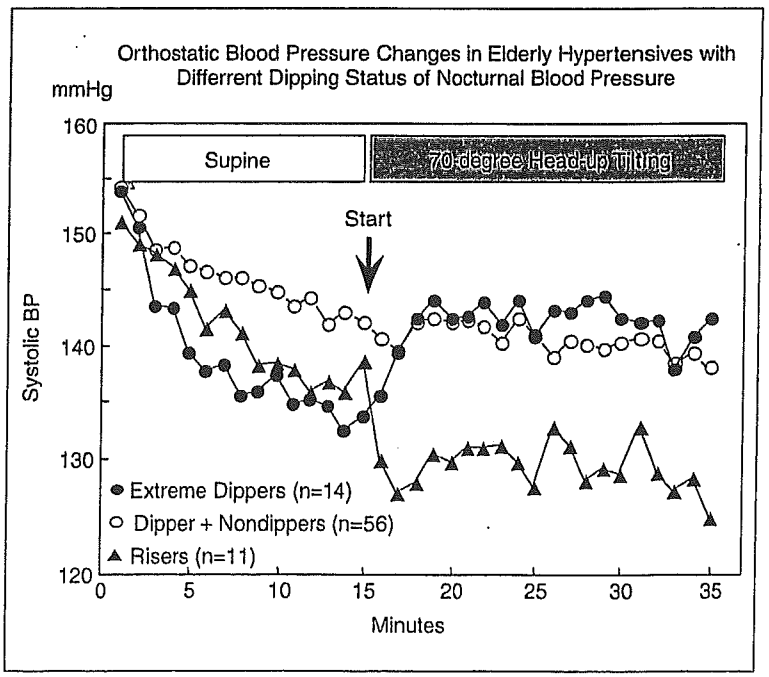


Fig. 6. Orthostatic blood pressure changes in elderly hypertensives with different dipping status of nocturnal blood pressure.

Wearable monitoring of BP and other cardiovascular variables would be useful for more effective individualized prevention and treatment of cardiovascular events.

fall and silent (detected by brain magnetic resonance imaging) and clinical cerebrovascular disease [29], [31]. Thus, both nondippers and extreme dippers have more advanced silent cerebrovascular disease than dippers. In Japan, coronary artery disease is markedly less common, while stroke is more common when compared in the United States.

Several other conditions that either reduce myocardial oxygen supply by reducing coronary blood flow (such as coronary artery stenosis or coronary spasm due to endothelial dysfunction) or by systemic hypoxic episodes (sleep apnea syndrome, congestive heart failure), or increase in myocardial oxygen demand (left ventricular hypertrophy) might be associated with silent myocardial ischemia. Both subclinical congestive heart failure due to either diastolic or systolic dysfunction and sleep apnea syndrome are frequently found in hypertensive patients, especially those with a diminished nocturnal BP fall. Although the precise mechanism remains unknown, nocturnal hypoxia in these disorders might trigger the central sympathetic nervous system to increase peripheral resistance to maintain nocturnal hemodynamics as a compensatory mechanism.

Autonomic Nervous Activity

The cardiac autonomic nervous system affects vascular tone both of the larger coronary arteries and the coronary microvascular bed to change coronary flow reserve. The circadian variations of BP and autonomic nervous activity presumably contribute to the diurnal variation of the incidence of the myocardial ischemic episodes and might partly determine the diurnal variation of threshold of myocardial ischemia. Over 80% of daily ischemic episodes during Holter ECG monitoring are preceded by an increase in heart rate [81]; however, it is unknown whether increased sympathetic nervous activity (as assessed by heart-rate variability, for example) also precedes the ischemic episode.

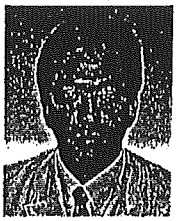
Sleep Quality

Actigraphy is useful not only for objective assessment for awake physical activity but also for the assessment of sleep quality [35], [38]. We recently found that nocturnal physical activity was increased in nondippers compared to those with a normal nocturnal BP fall [35]. This increased physical activity may partly be due to nocturnal behavior (going to the bathroom, getting a drink of water, etc.) and poor sleep quality. In addition to the possibility that increased physical activity reflects poor sleep quality and an increased frequency of unconscious microarousals, which trigger sympathetic activation, there is also the possibility that increased nocturnal physical activity per se activates autonomic nervous function and modulates endocrine functions. These neurohumoral changes could lead to the nondipping pattern. Thus, especially for nondippers, improvement of sleep quality together with a reduction of nocturnal physical activity may result in a more normal diurnal rhythm [36]. This might also reduce the risk of cardiovascular disease in the elderly population.

Subclinical depression, a newly recognized cardiovascular risk factor, is associated with poor sleep quality. In our recent study, we found that depression in men is associated with a disrupted diurnal BP variation (a tendency to the nondipping pattern) that was independent of changes of physical activity [38]. Patients with sleep-disordered breathing such as sleep apnea syndrome are likely to have nondipping patterns of nocturnal BP [37]. Increased frequency of microarousals and related sympathetic activation due to nocturnal hypoxia may contribute to nondipping patterns of BP.

Conclusion

Various valuable information on the cardiovascular system can be obtained using multifunctional ABPM. Wearable monitoring of BP and other cardiovascular variables would be useful for chronobiological strategy for risk stratification and more effective individualized prevention and treatment of cardiovascular events.



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Associations Between Nondipping of Nocturnal Blood Pressure Decrease and Cardiovascular Target Organ Damage in Strictly Selected Community-Dwelling Normotensives

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Background: In hypertensives, nondippers are more likely than dippers to suffer silent, as well as overt, hypertensive target organ damage. In this study, we investigated whether a nondipper status was associated with target organ damage in normotensives.

Methods: We performed ambulatory blood pressure (BP) monitoring, echocardiography, and carotid ultrasonography and measured natriuretic peptides and urinary albumin (UAE) in 74 normotensive subjects with the following criteria: 1) clinical BP <140/90 mm Hg; 2) average 24-h ambulatory BP <125/80 mm Hg.

Results: The left ventricular mass index (LVMI) and the relative wall thickness (RWT) measured by echocardiography, were greater in nondippers than dippers (LVMI: 103 ± 26 *v* 118 ± 34 g/m^2, $P < .05$; RWT: 0.38 ± 0.07 *v* 0.43 ± 0.09, $P < .01$). Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were higher in nondippers than dippers (ANP: 14 ± 10 *v* 36 ± 63 pg/mL, $P < .01$; BNP: 16 ± 12 *v* 62 ± 153 pg/mL, $P < .05$). There were no significant differences in UAE and intima–media thickness measured by carotid ultrasonography.

Conclusions: Normotensive nondipping may not reflect renal damage, but may have a predominant effect on cardiac damage. Nondipping of nocturnal BP seems to be a determinant of cardiac hypertrophy and remodeling, and may result in a cardiovascular risk independent of ambulatory BP levels in normotensives. Am J Hypertens 2003;16:434–438 © 2003 American Journal of Hypertension, Ltd.

Key Words: Normotensives, nondipper, left ventricular hypertrophy.

Hypertension is a potent predictor of cardiovascular events and mortality.[1] Noninvasive ambulatory blood pressure (BP) monitoring (ABPM) can now be used clinically for the evaluation of hypertensive patients. It is well known that ambulatory BP is more highly associated with target organ damage than are clinical BP readings.[2] The absence of a normal nocturnal decrease in BP is known as nondipping, in contrast to dippers who show a normal BP rhythm.[3] Previous studies have consistently shown that in hypertensive patients nondippers are more likely than dippers to suffer silent, as well as overt, hypertensive target organ damage, including cerebrovascular disease, chronic heart disease, and renal damage.[4–6] On the other hand, in normotensives, there are few studies regarding the relationship between diurnal BP variation and target organ damage.[7] The nondipping pattern, even in normotensives, might indicate a higher risk of target organ damage than that of normal BP variation.

We investigated the relationship between diurnal BP variation and target organ damage in elderly normotensive people with different nocturnal BP dipping patterns.

Methods

Subjects

This cross-sectional study was conducted in 1998, in the Miyori district in the rural community of Kinugawa, Tochigi prefecture. A total of 181 adults (33% of the 541 residents aged 20 years or older) gave their informed consent and participated in this study. Nine subjects were excluded because ABPM could not be performed. In ad-

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dition, 9 subjects were excluded because of unsatisfactory echocardiographic tracing. Seventy-four normotensive subjects satisfied the following criteria: 1) average clinical BP on two or more occasions <140 mm Hg for systolic BP (SBP) and <90 mm Hg for diastolic BP (DBP); 2) average 24-h ambulatory BP <125 mm Hg for SBP and <80 mm Hg for DBP.[8] No patients had taken antihypertensive medication, or had a history of hypertension. We excluded subjects with renal failure (serum creatinine level ≥176 μmol/L) or hepatic damage, or with a history of coronary artery disease, stroke, congestive heart failure, or arrhythmia.

Diabetes mellitus was defined by a fasting glucose level ≥7.8 mmol/L, a random nonfasting glucose level ≥11.1 mmol/L, hemoglobin A1c ≥6.2%, or the use of an oral hypoglycemic agent, and no patients used insulin. Hyperlipidemia was defined by a total cholesterol level ≥6.2 mmol/L or the lipid-lowering agents. Body mass index (BMI) was calculated as weight (kilograms)/height (meters)^2.

24-Hour ABPM

Noninvasive ABPM was carried out on a weekday with an automatic device (TM-2425, A&D Co. Inc., Tokyo, Japan), which recorded BP and heart rate every 30 min for 24 h. The accuracy of these devices had previously been validated.[9] The ambulatory BP data used in the present study were those obtained by the oscillometric method. Sleep BP was defined as the average of BP from the time when the subjects 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.

We classified the patients according to the nocturnal SBP decrease as follows: dippers, if the nocturnal SBP decrease was ≥10%; nondippers, if it was <10%.

Echocardiographic Examination

M-mode echocardiography was performed with two-dimensional monitoring. Left ventricular (LV) chamber recording was obtained at the tip of the mitral valve. The interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end-diastole. The LV internal dimensions were made at end-diastole (LVIDd) and end-systole (LVIDs), in accordance with the recommendations of the American Society of Echocardiography.[10]

The LV mass (LVM) was calculated with the regression equation described by Devereux and Reichek[11]:

$$LVM = 1.04([IVST + LVIDd + PWT]^3 - [LVIDd]^3) - 13.6.$$

The LVM index (LVMI) was calculated using standard formulas. The relative wall thickness (RWT) was calculated as 2 × PWT/LVID . Concentric hypertrophy was defined as follows: LVMI >114 g/m^2 for men and 106 g/m^2 for women, and RWT >0.44.

Carotid Ultrasonography Imaging of right and left extracranial carotid arteries was performed using a 7.5-MHz transducer with the subject supine with hyperextension of the neck. Measurement of the intimal–medial thickness (IMT) of the far wall at the end of diastole was performed in B-mode.[12]

Urinary Albumin Exertion To minimize the confounding influence of daily physical activity, and to facilitate the collection, the patients collected urine from 19:00 to 07:00. Urinary albumin exertion (UAE) was assayed using a nephelometric method.

Assays for Natriuretic Peptides Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels were measured with specific immunoradiometric assays (Shiono RIA ANP assay kit, Shiono RIA BNP assay kit, Shionogi Co., Ltd., Osaka, Japan).

Statistical Analysis

To compare mean values of the characteristics between dippers and nondippers, Student t test was used. Differences with $P < .05$ were considered to be significant.

Results

Table 1 shows the characteristics of the dipper and nondipper groups. There was no significant difference in age, BMI, and the prevalence of men, hyperlipidemia, or diabetes mellitus between dipper and nondipper groups. There was no significant difference in office BP or 24-h BP between dippers and nondippers.

Awake SBP and DBP were higher in dippers than nondippers. Sleep SBP and DBP were higher in nondippers than dippers.

Table 2 shows target organ damage of dippers and nondippers. The LVMI and RWT were higher in nondippers than dippers. The prevalence of concentric hypertrophy was also higher in nondippers than dippers. The ANP and BNP levels were higher in nondippers than dippers. There were no significant differences in UAE and IMT between the two groups.

Discussion

In this study, we found that the normotensive subjects who exhibited a nondipping pattern of nocturnal BP had more advanced LVM and LV remodeling with increased cardiac natriuretic hormones than dippers. Normotensive subjects were selected using the strict criteria of the International Society of Hypertension (average 24-h ambulatory BP <125 mm Hg for systolic and <80 mm Hg for diastolic).[8] In normotensives, the absence of a nocturnal BP decrease might be independently associated with target organ damage, as there were no significant differences in office BP levels and 24-h BP levels between the dipper and nondipper groups.

A few studies have reported a relationship between

Table 1. Characteristics of dippers and nondippers group

	Dippers	Nondippers	*P*
n	49	25	ns
age (y)	58 ± 11	62 ± 12	ns
male (%)	37	52	ns
BMI (kg/m^2)	23 ± 2.6	23 ± 3.0	ns
Hyperlipidemia (%)	30	38	ns
Diabetes mellitus (%)	0	8	ns
Office SBP (mm Hg)	122 ± 14	123 ± 10	ns
Office DBP (mm Hg)	78 ± 6.6	78 ± 9.1	ns
24-h SBP (mm Hg)	112 ± 7.1	111 ± 6.1	ns
24-h DBP (mm Hg)	69 ± 5.0	69 ± 6.3	ns
Awake SBP (mm Hg)	118 ± 8.1	113 ± 7.0	<.005
Awake DBP (mm Hg)	73 ± 5.3	70 ± 6.7	<.05
Sleep SBP (mm Hg)	98 ± 6.5	108 ± 6.5	<.001
Sleep DBP (mm Hg)	61 ± 5.1	66 ± 6.3	<.005

ns = not significant; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure. Values are shown as the mean ± SD or the number.

ambulatory BP levels and LV hypertrophy (LVH) in normotensives.[13–15] However, only one article[7] referred to the relationship between LVM and nocturnal BP decrease, dividing dippers and nondippers. In that report, there was no significant difference in LVM between dipper and nondipper groups in normotensives. This discrepancy is probably due to the difference in study subjects. In their study, normotensives were determined by rough criteria (clinical BP <160/90 mm Hg, and awake BP <134/88 mm Hg). Our subjects were selected by the criteria using lower BP levels (clinic BP <140/90 mm Hg, and average 24-h ambulatory BP <125/80 mm Hg) than used in their study. Therefore, to clarify the association between the nondipping pattern and LVM, it might be necessary to investigate a subject group with lower BP levels. The effect of high BP might overwhelm the impact of nondipping on cardiac remodeling.

In hypertensive patients, the association between nondippers and LVH had not previously been made clear.[16] Roman et al[17] reported that there was no significant difference in LVH between dipper and nondipper groups in hypertensive patients, despite the fact that 24-h ambulatory BP levels in the nondipper group were higher than in the dipper group. Ferrara et al[18] reported that the progression of LVH in the nondipper group might be blunted by the duration of hypertension. Thus, it might be possible that the progression of LVH had already occurred before the development of hypertension. Verdecchia et al[19] found that the progression of LVH in nondippers was higher than in dippers. However, there was a predominant increase in the LVM in women (mean age, 56 years), but not in men (mean age, 56 years), hypertensive nondippers.[7] They reported that in men, LV wall thickening, usually induced not only by daytime hypertension, but also by androgen hormones, progressed further regardless of the nocturnal BP decrease. However, in women, LV wall thickening may have required a longer duration of exposure to high BP levels over 24 h.[7] In our nondipper subjects, the prevalence of women was not significantly higher than that of men. Therefore, sex differences were not closely related to LVM in our study subjects.

In our study, RWT and the prevalence of concentric hypertrophy were higher in nondippers than in dippers. In hypertensives, the relationship between RWT and diurnal BP variation had not previously been made clear.[18,19] One study on hypertensive patients showed that there were no differences in LVM and RWT between dippers and nondippers.[17] Thus, the unfavorable consequences of a non-

Table 2. Target organ damages of dippers and nondippers

	Dippers	Nondippers	*P*
LVMI (g/m^2)	103 ± 26	118 ± 34	<.05
RWT	0.38 ± 0.07	0.43 ± 0.09	<.01
Concentric hypertrophy (%)	10	28	<.05
IMT (mm)	0.63 ± 0.15	0.67 ± 0.14	ns
ANP (pg/mL)	14 ± 10	36 ± 63	<.01
BNP (pg/mL)	16 ± 12	62 ± 153	<.05
UAE (mg/12 h)	4.4 ± 2.4	6.0 ± 6.1	ns

LVM = left ventricular mass index; RWT = relative wall thickness; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; UAE = urinary albumin exertion; IMT = intia-media thickness; other abbreviation as in Table 1.

dipping status might be blunted by long-standing elevated BP.[18] According to our findings, in our strictly selected community-dwelling normotensives diurnal BP variation might be one of the determinants of cardiac remodeling.

The ANP and BNP levels in the nondipper group were significantly higher than those in the dipper group. In hypertensives, increased ANP and BNP levels in patients with LVH have been reported.[20] Our present findings are consistent with the results that indicate that normotensive nondippers have more advanced cardiac hypertrophy and remodeling, compared with dippers.

The LVMI is known to be an independent risk factor for all of the cardiovascular complications of hypertension.[21] In addition, the LV geometry is also an important predictor for cardiovascular events. Concentric hypertrophy has the worst cardiovascular prognosis among other LV geometric patterns, eccentric hypertrophy, and concentric remodeling.[22] One article reported that an increased LVMI predicted a subsequent BP increase in normotensives.[23] The present study indicated that the absence of a nocturnal BP decrease, even in normotensives, might precede a BP increase and be associated with a worse cardiovascular prognosis.

We could not find any difference in the IMT between dippers and nondippers. Roman et al[17] reported that nondippers have a more increased IMT than dippers, but this difference was no longer significant after controlling for age. Age is the most important determinant of the IMT in both normotensives and hypertensives.[24] Because subjects of our group were older than those in the study by Roman et al, age might account for the effect of nondipping on the IMT.

There was no significant difference in UAE between dippers and nondippers in the normotensives. The UAE has been shown to be associated with several cardiovascular risk factors including LVH.[25] Ambulatory BP has been reported to be more closely associated with UAE than clinical BP.[26] Hypertensive patients with a nondipper status have a higher UAE than those with a dipper status.[27] However, one article[28] reported that there was no significant correlation between UAE and LVMI variables in mild hypertensives. These results suggest that renal and cardiac involvement do not occur at the same time in the initial phase of hypertension. Therefore, in our study, normotensive nondippers might not exhibit renal damage, but might exhibit cardiac damage.

The value of LVMI in this study was higher than in any other reports on Western people.[7,17] This discrepancy might be due to the following reasons. One is the difference in physical constitution between Japanese and Westerners. There was no difference between the LVMI values in our study and those of another study in our country.[23] The second is that our group is predominantly consisted of elderly subjects. Aging itself results in an increase in heart weight and myocyte size.[29]

In conclusion, nondippers were associated with increases in LVMI, RWT, and plasma levels of ANP and BNP, even in the normotensive subjects. Nondipping of nocturnal BP seems to be a determinant of cardiac hypertrophy and remodeling, and may result in a cardiovascular risk independent of ambulatory BP levels.

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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

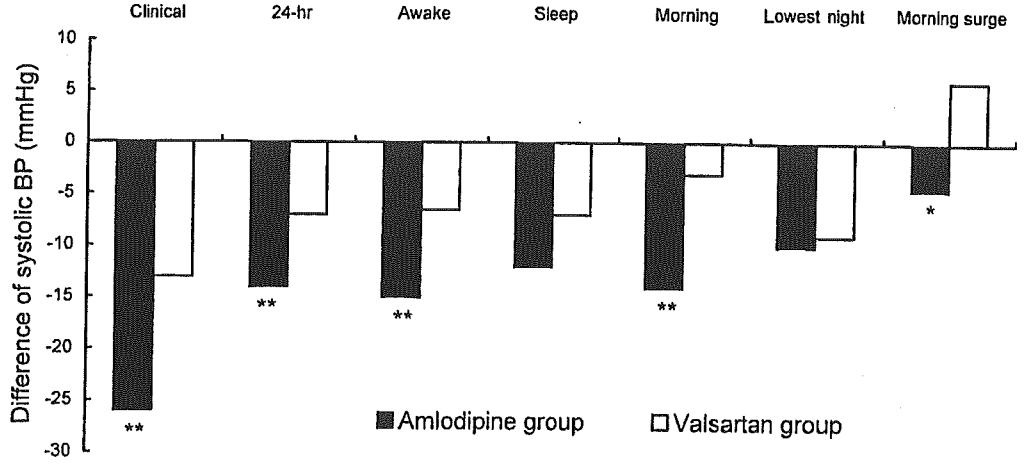

FIG. 1. Differences in clinic systolic blood pressure and ambulatory systolic blood pressure before and after amlodipine and valsartan treatment. **Black bars**, amlodipine group; **white bars**, valsartan group. BP = blood pressure. *P < .05 v valsartan group by ANOVA (between groups); **P < .01 v valsartan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

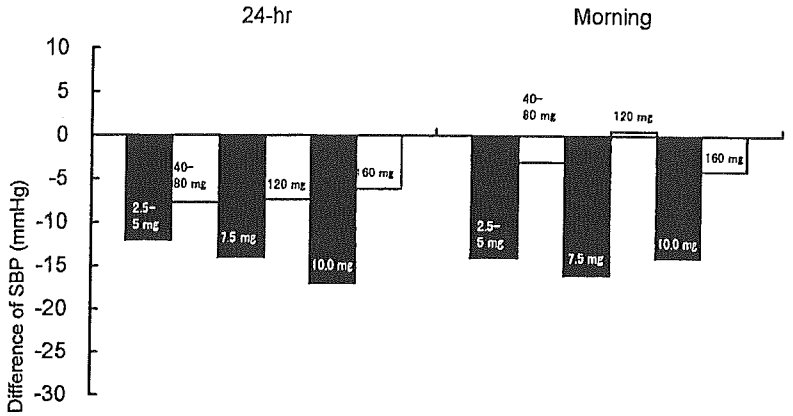

FIG. 2. Effects of amlodipine and valsartan on 24-hour and morning systolic blood pressure (SBP) by each dose. **Black bars,** amlodipine group; dose **(from left to right):** 2.5 to 5 mg (n = 21), 7.5 mg (n = 8), 10.0 mg (n = 9). **White bars,** valsartan group; dose **(from left to right):** 40 to 80 mg (n = 12), 120 mg (n = 7), and 160 mg (n = 19).

greater for amlodipine than for valsartan (both $P < .01$; Fig. 2).

To study the effect of age on the BP lowering effect, we separated the study patients into a younger age group (<65 years) and older group (≥65 years). The BP lowering characteristics of valsartan and amlodipine were essentially the same in each age group. In addition, there were no gender differences in the BP lowering effect of the two drugs.

To study the BP lowering characteristics of BP in relation to baseline BP, we graphed the scatter plot of the baseline and the reduction of 24-h BP for each group (Fig. 3). A baseline BP-dependent BP reduction was found in the amlodipine group but was not found in the valsartan group for 24-h and morning SBP.

Discussion

In this study, a once-daily morning dose of amlodipine significantly reduced morning BP and morning BP surge. In comparison, a once-daily morning dose of the long-acting ARB valsartan did not significantly reduce morning BP and morning BP surge in hypertensive patients, and its BP lowering effect on 24-h ambulatory BP was weaker and more heterogeneous independent of baseline BP level than was amlodipine. This difference was significant independent of the dose of each drug.

Twenty-four-hour BP (mean of BP throughout a 24-h period) is the most important predictor of hypertensive target organ damage (brain, heart, and kidney) and subsequent fatal and nonfatal cardiovascular events (stroke and coronary artery disease). In a recent prospective study on treated hypertensive patients, 24-h BP was an independent predictor of cardiovascular events independent of clinic BP.[12] A significant BP lowering effect as indicated by 24-h BP and morning BP is well established from our previous study in hypertensive patients.[13] In one recent study using ABPM, the BP lowering effect of valsartan 80 mg/day was comparable to that of amlodipine 5 mg in hypertensive patients.[10] However, in our study, the mean doses were 6.4 mg/day for amlodipine and 124 mg/day for valsartan, and the BP lowering effect was clearly less effective in the valsartan group than in the amlodipine group. Ethnic char-

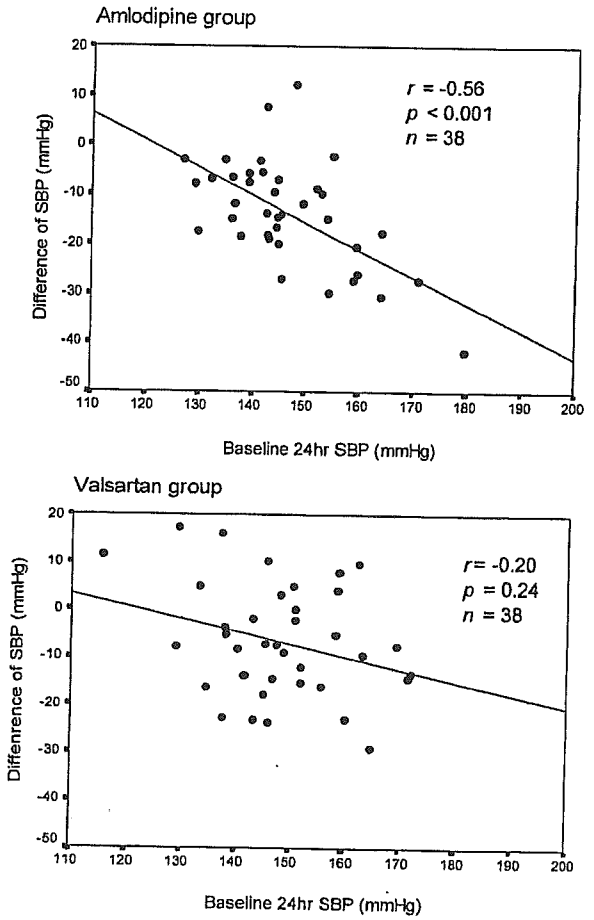

FIG. 3. Effects of amlodipine and valsartan on 24-h and morning systolic blood pressure (SBP) by each dose. **Solid lines** indicate linear regression lines.

acteristics or differences in salt intake between Asian (ie, Japanese) and white patients and may partly account for these inconsistent results. In Japan, stroke is much more common than coronary artery disease as compared the incidence in Western countries,[5] and the benefit of BP reduction for stroke is greater than that for coronary artery disease. In fact, as shown in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), relatively lower BP lowering effect of an angiotensin-converting enzyme (ACE) inhibitor was associated with increased cardiovascular risk, particularly for stroke, when compared with amlodipine.[14] In addition, the protective effect of RAAS blockade on hypertensive target organs seems limited under the BP control and is insufficient. Although a beneficial effect of valsartan in addition to ACE inhibitors on the prognosis of congestive heart failure patients whose BP is only moderately increased has been clearly demonstrated,[15] the insufficient BP lowering effect of valsartan monotherapy seems to be less beneficial than amlodipine for preventing cardiovascular events in hypertensive patients.

Recently we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients.[9] This association was independent of age, 24-h BP level, and silent cerebral infarcts,[9] which are powerful predictors of clinical stroke events.[5] In addition to morning BP surge, morning BP level is also an important predictor of stroke events in hypertensive patients.[9] Because it has recently been demonstrated that, in addition to circulating factors, tissue RAAS of the cardiovascular system exhibits diurnal variation,[16] possibly in relation to a clock gene,[17] it was unexpected that valsartan did not significantly reduce morning BP level. As both valsartan and amlodipine reduced the lowest night BP to a similar degree, the morning BP surge was slightly increased in the valsartan group. This may be due to the shorter half-life of valsartan than that of amlodipine, particularly in nonresponders.

This lower BP reduction may not be generalized to all ARBs, such as telmisartan and irbesartan, given that the BP lowering effect of valsartan is weaker than that of these drugs.[18,19] However, even in the case of valsartan, when used in combination with diuretics, the BP lowering effects would be increased.[20] In the following large clinical trials in which diuretics have been permitted, benefits of RAAS blockers have been clearly demonstrated. The Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS) has demonstrated that stroke prognosis has been demonstrated only when the long-acting ACE inhibitor perindopril is used with diuretics in stroke survivors.[21] The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial has also clearly demonstrated that the benefit of ARB losartan was greater than that of β-blockers in high-risk hypertensive patients with left ventricular hypertrophy.[22] In our study, BP reduction is dependent on baseline BP level in the amlodipine group, whereas this BP response is heterogeneous in the valsartan group (as depicted in Fig. 3), indicating that there are responders and nonresponders for RAAS blockers. With regard to nonresponders, combination therapy with diuretics would be initiated or other classes of antihypertensive medication used.

In conclusion, amlodipine monotherapy controlled ambulatory BP throughout a 24-h period including the morning hours, whereas valsartan monotherapy was limited to controlling ambulatory BP, particularly morning BP, in hypertensive patients. Combination therapy with diuretics or other classes of antihypertensive medications would be necessary to achieve target BP levels.

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Greater Impact of Coexistence of Hypertension and Diabetes on Silent Cerebral Infarcts

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Background and Purpose—Silent cerebral infarcts (SCIs), often found in the elderly and hypertensives, have been proposed as an indicator of poorer cerebrovascular prognosis. The aim of this study was to evaluate the prevalence and determinants of SCI in hypertensives with or without diabetes mellitus (DM).

Methods—We studied 360 asymptomatic hypertensive subjects with or without DM (mean age, 67.4 years; range, 41 to 88 years). We performed 24-hour ambulatory blood pressure (BP) monitoring and brain MRI. The subjects were classified into a diabetic hypertension group with DM (DHT, n=159) or a non-DM hypertension group (non-DHT, n=201).

Results—SCIs (presence of ≥1) were found in 82% of the DHT and 58% of the non-DHT ($P<0.001$) group; multiple SCIs (the presence of ≥3) were found in 62% of the DHT and 35% of the non-DHT group ($P<0.001$); and 24-hour ambulatory BP levels were comparable between groups. DM was a powerful determinant of both SCIs (odds ratio [OR], 2.95; $P<0.01$) and multiple SCIs (OR, 3.05; $P<0.001$) independently of age and 24-hour systolic BP, whereas only multiple SCIs were associated with 24-hour systolic BP. When patients were subclassified by ambulatory BP and the presence of DM (sustained hypertension [SHT]+DM, white-coat hypertension [WCHT]+DM, SHT, and WCHT groups), the prevalence of SCI and multiple SCIs was higher in the SHT+DM than in the SHT group, and only multiple SCIs were higher in the WCHT+DM than the WCHT group.

Conclusions—Diabetes was the major determinant of SCIs in both SHT and WCHT. (***Stroke.*** **2003;34:2471-2474.)**

Key Words: blood pressure monitoring, ambulatory ■ diabetes mellitus ■ hypertension ■ infarcts, silent

Diabetes mellitus (DM), which is rapidly increasing in Japan and other developed countries, is a major risk factor for stroke.[1] About 40% to 60% of DM patients are complicated with hypertension,[2] which is the strongest risk factor for stroke. When DM and hypertension coexist, the risk of a stroke further increases.

Asymptomatic or "silent" cerebral infarct (SCI) is sometimes detected incidentally by MRI or other imaging modalities in patients who demonstrate no localized neurological symptoms of stroke.[3,4] A SCI, which is now classified as a type III cerebrovascular disorder by the National Institute of Neurological Disorders and Stroke, is a specific marker of target organ damage in the brain and a powerful predictor of clinical stroke.[5-8] Ambulatory blood pressure (ABP) is superior to casual BP in predicting SCI[3,9] and cardiovascular events.[7,10] However, in diabetic patients, few reports use ABP to assess the relationship between abnormal circadian BP rhythm and cardiovascular prognosis.[11] Thus, we studied the impact of DM and ABP on SCIs in 360 asymptomatic hypertensive patients with or without DM.

Methods

Patients

We studied 360 older asymptomatic hypertensive patients (mean age, 67.4 years; range, 41 to 88 years; 134 men, 226 women): 159 with essential hypertension coexisting with diabetes (DHT group) and 201 essential hypertensives without diabetes (non-DHT group). We enrolled subjects in our study from 3 participating institutes (1 clinic, 2 hospitals). Hypertensive patients were consecutively selected according to the following criteria: (1) essential hypertension with average clinical systolic BP (SBP) >140 mm Hg and/or average clinical diastolic BP (DBP) >90 mm Hg (average for each patient on ≥2 occasions)[12] and (2) hypertensive patients >40 years old. Clinical BP was measured after resting for at least 5 minutes in patients in the sitting position. No patient had taken any antihypertensive medication for at least 1 week before the ABP monitoring study. We excluded patients with renal failure, hepatic damage, secondary or malignant hypertension, ischemic heart disease or other cardiac disease, congestive heart failure, arrhythmias (including atrial fibrillation and other arrhythmias), stroke (including transient ischemic attacks), or other severe concomitant disease. The duration of hypertension was based mainly on information from self-report and medical records, with hypertension diagnosed by a physician with or without treatment according to the patient's information. One-time hypertension was not included in the history.

We defined DM according to the criteria of the American Diabetes Association.[13] Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Left ventricular mass index (LVMI) detected by echocardiography (SSD 2200, Aloka) was calculated by the method introduced by Devereux et al.[14] This study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School (Japan). All subjects studied were ambulatory and gave informed consent for the study.

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ABP Monitoring (24 Hour)

Noninvasive ABP monitoring was carried out on a weekday with an automatic system using electric cuff inflation (TM2421, A&D), which recorded both BP (by the oscillometric method) and pulse rate every 30 minutes for 24 hours. The accuracy of this device was previously validated.[15] Sleep BP was defined as the average BP measurements from the time when the patient went to bed until the time he or she arose; awake BP was the average of the BP measurements recorded during the rest of the day. Sustained hypertension (SHT) was defined as clinical SBP >140/90 mm Hg (either) and 24-hour SBP ≥135/80 mm Hg (either); white-coat hypertension (WCHT) was defined as clinical SBP >140/90 mm Hg (either) and 24-hour SBP <135/80 mm Hg (both). The patients were subclassified into 4 groups according to ABP levels and presence of DM: 117 SHT+DM, 42 WCHT+DM, 140 SHT (without DM), and 61 WCHT (without DM).

Brain MRI

Brain MRI was carried out in all 360 patients with a superconducting magnet with a main strength of 0.5 T (Toshiba MRT50GP) within 3 months of their ABP monitoring. The brain was imaged in the axial plane at a 7-mm slice thickness. T1-weighted images were obtained with a short spin-echo pulse sequence with a repetition time of 470 milliseconds and an echo time of 15 milliseconds. T2-weighted images were obtained with a long spin-echo pulse sequence with a repetition time of 4000 milliseconds and an echo time of 120 milliseconds. The matrix size was 256×256 pixels. An SCI was defined exclusively as a low-signal-intensity area (≥3 mm, but all were <15 mm in size) depicted on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images as described previously.[8,16] The MRI images of the subjects were randomly stored and interpreted by reviewers blinded to subject names and characteristics. The interreader and intrareader interclass (non-SCI, 0; 1 or 2 SCIs, 1; multiple SCIs, 2) κ statistics were 0.70 and 0.80, respectively, in our laboratory.

Statistical Analysis

All statistical analyses were carried out with SPSS for Windows, version 11.0J (SPSS Inc). The χ^2 test was used to calculate proportions. One-way analysis of variance was performed to detect differences among groups in mean values, and unpaired *t* tests were used for comparison of variables between the DHT and non-DHT groups. Tukey's honestly significant difference test was used for multiple comparisons of the mean BPs between 2 of the 4 subgroups (SHT+DM, WCHT+DM, SHT, and WCHT groups). These data are expressed as the mean (SD) or prevalence. Odds ratios with 95% confidence intervals for no or some SCIs (0=those with no SCI; 1=those with ≥1 SCIs) and for multiple SCIs (0=those with <3 infarcts; 1=those with 3≥ infarcts) were calculated by logistic regression analysis using selected covariates for cardiovascular risk such as age, sex (0=female, 1=male), BMI, smoking (0=absent, 1=present), duration of hypertension, presence of DM (0=absent, 1=present), 24-hour SBP, and total cholesterol. A value of $P<0.05$ was considered significant.

Results

Baseline Characteristics of the Patients

The mean clinical SBP and DBP of the overall study group were 159±17 and 86±12 mm Hg, respectively, and the 24-hour SBP and DBP were 144±15 and 81±9 mm Hg. The prevalence of SCI (the presence of ≥1) was 68.6% and that of multiple SCIs (the presence of ≥3) was 46.9% in the overall study group.

Table 1 shows the characteristics of the 360 patients separated into 2 groups: hypertension with DM (DHT group; n=159) and hypertension without DM (non-DHT group; n=201). Age, BMI, prevalence of current smokers, LVMI, serum cholesterol, hematocrit, and serum creatinine were comparable between the 2 groups, but the prevalence of male sex, duration of hypertension, and serum triglycerides were significantly higher in the DHT group than in the non-DHT group. The clinic SBP, 24-hour BP, awake BP, and sleep BP were also comparable between the 2 groups; only clinic DBP was lower in the DHT group than in the non-DHT group.

TABLE 1. Baseline Characteristics

Measures	DHT Group (n=159)	Non-DHT Group (n=201)
Age, y	67.0±8.8	67.8±8.7
Male sex, %	43†	33
BMI, kg/m^2	24.4±3.9	23.9±3.1
Duration of hypertension, y	8.5±8.6*	7.0±6.9
Duration of diabetes, y	10.7±8.0	...
Current smokers, %	29	26
LVMI, g/m^2	129±35	129±35
Hematocrit, %	40.3±4.6	39.4±4.0
Total cholesterol, mmol/L	5.3±0.9	5.4±0.9
Triglyceride, mmol/L	1.6±0.8†	1.4±0.6
Creatinine, μmol/L	69.0±35.4	73.4±17.7
Clinic SBP, mm Hg	155±17	162±16
Clinic DBP, mm Hg	82±10*	89±12
24-hour SBP, mm Hg	144±16	144±15
24-hour DBP, mm Hg	80±9.0	82±9.1
Awake SBP, mm Hg	149±17	151±15
Awake DBP, mm Hg	83±9.3	86±9.8
Sleep SBP, mm Hg	135±19	132±16
Sleep DBP, mm Hg	74±10	74±9.3
SCI, n/person	4.6±4.1†	2.0±2.4
Prevalence of SCI, %	82†	58
Prevalence of multiple SCIs, %	62†	35

Data are shown as mean±SD when appropriate. Overall probability values are for 2-group comparison of means (unpaired *t* test) or percentages (χ^2 test).
*$P<0.05$ †$P<0.001$ vs non-DHT group.

Silent Cerebral Infarcts

As shown in Table 1, the number of SCIs and prevalence of SCI and multiple SCIs were significantly higher in the DHT group than in the non-DHT group regardless of background. To clarify the determinants of SCI and multiple SCIs, we performed logistic regression analysis (Table 2). The determinants of SCI were age, presence of DM, and duration of hypertension. On the other hand, the determinants of multiple SCIs were age, male sex, presence of DM, duration of hypertension, and 24-hour SBP.

WCHT Versus SHT

To clarify the impact of high ABP and DM status for SCI, we further analyzed the prevalence of SCI among the 4 subgroups classified by DM status and 24-hour BP. The number±SD of SCIs (per person) was 5.2±4.2 in the SHT+DM group, 2.8±3.5 in the WCHT+DM group, 2.3±2.6 in the SHT group, and 1.4±1.8 in the WCHT group. As shown in the Figure, the prevalence of SCI and multiple

TABLE 2. Determinants of SCI

Variables	OR (95% CI)	
	Prevalence of SCI (n=360)	Multiple SCIs (n=360)
Age (10-y groups)	2.80 (1.95–4.05)‡	2.51 (1.81–3.52)‡
Male sex	1.74 (0.87–3.50)	2.07 (1.15–3.73)*
BMI, kg/m^2	0.97 (0.89–1.05)	0.94 (0.87–1.01)
Duration of hypertension (10 y)	1.79 (1.06–2.97)*	1.88 (1.32–2.71)†
Diabetes	2.95 (1.56–5.57)†	3.05 (1.84–5.06)‡
Smoking	0.71 (0.44–1.15)	0.76 (0.45–1.29)
Total cholesterol (mg/dL)	1.01 (1.00–1.01)	1.01 (1.00–1.02)
24-hour SBP (10 mm Hg)	1.17 (0.96–1.45)	1.31 (1.10–1.54)†

The odds ratios (ORs) and (95% confidence intervals (CIs) for SCI or for silent multiple SCIs were calculated by multiple logistic regression analysis. We used the following conventional risk factors as covariates: age, sex, BMI, smoking status, total cholesterol, duration of hypertension, 24-hour SBP, and presence of DM.

*P<0.05, †P<0.01; ‡P<0.001.

SCIs was the highest in the SHT+DM group, followed by the WCHT+DM, SHT, and WCHT groups. The 24-hour SBP levels were not significantly different between the SHT+DM (151/82 mm Hg) and SHT (151/84 mm Hg) groups or between the WCHT+DM (126/74 mm Hg) and WCHT (128/76 mm Hg) groups; the prevalence of SCI and multiple SCIs was significantly higher in the SHT+DM group than in the SHT group; and the prevalence of multiple SCIs was significantly higher in the WCHT+DM group than in the WCHT group.

Discussion

SCIs assessed by brain MRI are a clinically important pathological condition relating to the incidence of future stroke events[5–8] and cerebrovascular dementia.[17] In this study, we found that the presence of DM coexisting with hypertension was the most powerful independent determinant of SCI (especially for multiple SCIs). This is the first report to use ABP monitoring to assess the impact and relationship of ABP and the presence of DM on SCIs.

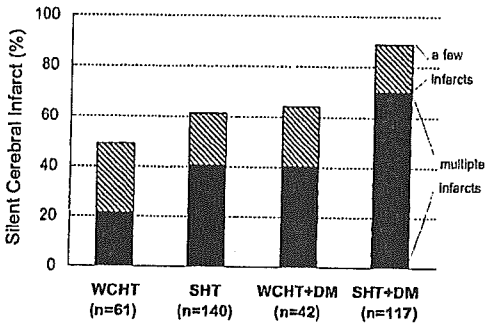
Prevalence of SCIs

In this study, the prevalences of SCI and multiple SCIs were 68.6% and 46.9%, respectively, in all patients. The prevalence of SCI in this study was higher than in previous reports: 47% in 73 patients with essential hypertension by Shimada et al,[3] 40.2% in 219 elderly patients at an outpatient clinic by Uehara et al,[18] and 65% for total SCI and 39% for multiple SCIs in essential hypertension by Kario et al.[7] The higher prevalence of SCI in this study may be due to the higher prevalence of DM (44%) in our patients.

TABLE 3. Probability Values for Comparisons of 4 Groups in the Figure

	SCI	Multiple SCIs
WCHT vs SHT	0.122	0.010
WCHT vs WCHT+DM	0.160	0.047
WCHT vs SHT+DM	<0.001	<0.001
SHT vs WCHT+DM	0.856	1.000
SHT vs SHT+DM	<0.001	<0.001
WCHT+DM vs SHT+DM	0.001	0.001

Probability values for SCI (multiple SCIs) were calculated by χ^2 test.



Prevalence of SCIs detected by brain MRI. Multiple SCIs are defined as ≥3 infarcts per person. Overall probability values for 4-group comparisons were determined by χ^2 test.

Impact of DM

As is widely known, patients with glucose intolerance are 2 to 5 times more susceptible to stroke compared with normal patients.[19] In a prospective study of Hawaiian Japanese,[20] there was twice the risk of thromboembolic stroke in DM patients compared with non-DM patients.

As shown in Table 2, the prevalence of SCI and multiple SCIs increased 3-fold in hypertensive patients with DM independently of age and ABP. This is in accordance with previous reports that DM contributes to a 2- to 4-times-greater incidence of symptomatic stroke.[20–22]

Although BP was significantly higher in the SHT group than in the WCHT+DM group, the risks for any SCI and multiple SCIs were similar among the groups (the Figure). These risks were comparably higher in the SHT and WCHT+DM groups than in the WCHT group. Therefore, DM is a powerful and independent determinant of SCI in both SHT and WCHT.

Multiple SCIs in DM

The prevalence of multiple SCIs was higher in the WCHT+DM group than in the WCHT group (the Figure). In our previous report, multiple SCIs were also significantly associated with hyperinsulinemia in hypertensive patients.[16] Although the present patients were not associated with the previous reports,[8,16] the presence of DM and accompanying hyperinsulinemia may accelerate the formation of multiple SCIs, not only when 24-hour BP is higher but also at lower 24-hour BP levels. Therefore, hypertensive target organ damage is more advanced in DM patients, even at relatively lower ABP levels (WCHT).

Impact of ABP

The strongest risk factors for stroke are hypertension and age, according to recent epidemiological report in Japan.[21] Hypertension is also the strongest risk factor for SCI.[5,6] In hypertensive patients, ABP can preferably predict the prevalence of SCI and incidence of stroke.[8] In DM subjects, Nakano et al[11]

investigated the stroke incidence of DM patients using ABP. The incidence of stroke was much higher in reverse-pattern patients whose sleep BP was higher than their waking BP. In this study, the prevalence of SCI was significantly higher in high ABP groups (SHT+DM and SHT groups). Therefore, we confirmed that ABP was useful for predicting hypertensive target organ damage not only in essential hypertension patients but also in hypertensives with DM.

Impact of Coexisting DM and Hypertension

In our study, patients with SHT and DM had the highest prevalence of SCI, particularly for multiple SCIs. The clinical impact of DM coexisting with hypertension on cardiovascular disease was recently reviewed; this status can worsen the cardiovascular prognosis.[23] The risk factors for stroke previously reported were diabetic history, SBP,[24] and insulin resistance.[25] In a report on poststroke patients,[26] hypertension and DM were closely related to multiple SCIs. We recently reported that insulin resistance–related hemostatic abnormality is associated with multiple SCIs in hypertensive patients.[16] Those subjects were not associated with the present study. Although the precise mechanism is unknown, there may be a synergistic effect between hypertension and DM for the risk of SCI involving other risk factors such as hemostatic factors.

Conclusions

These results suggest that the presence of DM is the most powerful determinant of SCI in hypertensive patients. Even in WCHT, DM is a powerful risk factor for multiple SCIs.

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