A n abnormal pattern of diurnal BP variation has been reported to carry a high risk for cardiovascular disease in hypertensive patients. Nondippers, with diminished nocturnal BP fall, have been proposed as one subgroup with abnormal diurnal BP variation characterized as associated with increased frequency of damage to all target organs (brain, heart, and kidney) and poorer prognosis for cardiovascular events, when compared with dippers with appropriate nocturnal BP fall.1–4 In addition to nondippers, recently we identified among dippers the subgroup of extreme dippers, with marked nocturnal BP fall, as having a newly recognized subtype of abnormal diurnal BP variation, and we found that among elderly hypertensive patients extreme dippers have more marked cerebrovascular damage than do dippers.5

The extreme pattern of diurnal BP variations in extreme dippers or extreme nondippers (whose sleep BP is actually higher than their awake BP) is a relatively persistent trait.5 However, the mechanism of these abnormal BP variation patterns in hypertensive patients remains unclear. A nondipper pattern has been reported in secondary hypertensive patients with endocrine abnormality and in those with autonomic nervous abnormality such as diabetic neuropathy and Shy-Drager syndrome.7 By power spectral analysis of heart rate variability using 24-hour Holter ECG, Kohara et al8 found that among adult hypertensive patients the fluctuation of autonomic nervous activity was diminished in nondippers, and we also have recently demonstrated that the sympathetic nervous activity is lower during the nighttime in extreme dippers but lower during the daytime in nondippers, who show a diminished increase of parasympathetic nervous activity during the nighttime.9 These results indicate that the abnormal diurnal BP variations are closely related to the abnormalities of autonomic nervous activity.

In normal subjects, BP shows minimal variation with postural changes because of an autoregulatory mechanism. In most hypertensive patients as well, postural BP changes do not vary much in the absence of an autonomic nervous system dysfunction. However, there have been no reports on the relationships between diurnal BP variation and postural BP change in elderly hypertensive patients.

We investigated the relationships among diurnal BP variations and postural BP variation pattern in asymptomatic hypertensive patients.
hypertensive elderly subjects with different patterns of nocturnal BP fall.

**Methods**

**Patients**

We studied 110 hypertensive outpatients aged ≥60 years, with mean office SBP of ≥140 mm Hg and/or mean office DBP of ≥90 mm Hg (average for each patient on three or more occasions). The office BP was measured in the sitting position by standard cuff methods. No patient had received any antihypertensive medication at least for 14 days before the study. For all physical and laboratory examinations that included blood and urine tests, chest x-ray, and ECG at rest, the results were normal or consistent with World Health Organization stages I and II. We excluded from this study those with renal failure or hepatic damage (serum creatinine level >130 mmol/L, urea nitrogen level >10.7 mmol/L, positive glycosuria and proteinuria detected by multistix, and aspartate aminotransferase or alanine aminotransferase level >40 IU/L). Also excluded were those with obvious present illness or with a past history of coronary artery disease, stroke including transient ischemic attack, congestive heart failure, arrhythmia, or malignancy. Those with possible diabetes mellitus (fasting glucose level >5.5 mmol/L or hemoglobin A1c >6.0%) were also excluded from this study. This study was approved by our institutional review committee, and informed consent was obtained from each subject studied.

Smokers were defined as current smokers. The body mass index was calculated as weight (kg)/height (m)^2^. LVH diagnosed by ECG was defined as abnormally high voltages of QRS complexes (R in V5 plus S in V1 greater than 3.5 mV) associated either with flat T waves (<10% of R) or with ST-segment depression and diphasic T waves.

**24-Hour Ambulatory BP Monitoring**

Noninvasive ambulatory BP monitoring was carried out on a weekday with an automatic ambulatory BP monitor with gas-powered cuff inflation (ABPM-630, Nippon Colin Co), which recorded BP and heart rate every 30 minutes for 24 hours. The accuracy of this device was previously validated. The ambulatory data used in the present study were those obtained by the oscillometric method. Each subject recorded in an activities journal information about the exact times of falling asleep and waking up. Reexamination was performed in the three hypertensive patients whose BP data were not evaluable due to the presence of artifacts in more than 10% of the total measurements. We excluded seven subjects who complained of sleep disturbance during the 24-hour monitoring.

**Definitions of White-Coat Hypertension, Extreme Dippers, Dippers, and Nondippers**

Sleep BP was defined as the mean BP from the time at which the patient went to bed until the time of awakening, and the awake BP was defined as the mean BP during the remaining portion of the day. Hypertensive patients with 24-hour SBP ≥135 mm Hg and/or 24-hour DBP ≥80 mm Hg were defined as having sustained hypertension (n=81) and those with 24-hour BP below these levels as having white-coat hypertension (n=29), as described previously. Then, the nocturnal fall in SBP was calculated as (awake SBP−sleep SBP)/awake SBP. The 81 hypertensive patients were subclassified based on the nocturnal fall in SBP, as follows: 14 extreme dippers with ≥20% nocturnal reduction of SBP; 56 dippers with ≥10% but <20% reduction; 18 nondippers with <10% reduction (higher sleep SBP level than awake SBP).

**Head-up Tilting Test and Definitions of Orthostatic Hypertension and Orthostatic BP Reduction**

After BP and heart rate were measured with the interval of 1 minute at baseline and after the subjects had been in the supine position for at least 15 minutes, the subject was then positioned upright on the tilt table at an angle of 70° with a footboard used to bear the subject’s weight. If syncope or presyncope with hypotension developed during the test, the table was lowered to the supine position; otherwise, tilt table testing was continued for the maximum of 20 minutes, after which the subject was returned to the supine position. There were no patients who developed syncope or presyncope during head-up tilting test.

Orthostatic hypertension was defined as an increase of mean SBP value of 10 mm Hg or more during 6 to 10 minutes (5 points) after the upright position was assumed, compared with the mean SBP value in the supine position during the 1 to 5 minutes (5 points) just before the assumption of the upright position. Orthostatic hypotension was defined as a decrease of mean SBP value of 20 mm Hg or more during 6 to 10 minutes after the upright position was assumed, compared with the mean SBP value in the supine position during the 1 to 5 minutes just before the assumption of the upright position.

**Laboratory Examination**

Blood samples were collected after a minimum fasting period of 12 hours. The serum total cholesterol level was determined using commercial enzyme assay kits (Wako), and the serum HDL-cholesterol level using an enzymatic procedure after precipitation with phosphotungstic acid (Wako).

**Statistical Analysis**

Data are expressed as the mean±SD. One-way ANOVA was performed to detect differences among groups, and Fisher’s protected least significant difference test was used for comparison between the mean values for pairs of groups. The χ^2 test was used to detect the differences among groups in the prevalence of male patients, smokers, and patients with target organ damage. The paired t test was used to detect the difference in the change of BP before and after the head-up tilting test in each group. Pearson’s correlation coefficient was calculated for the relationship between SBP rise by tilting and sleep/awake ratio of SBP. Differences with a value of P<.05 were considered to be significant.

**Results**

**Characteristics of Studied Hypertensive Groups**

Table 1 shows the characteristics of the white-coat hypertension group and of the three sustained hypertension subgroups of elderly hypertensive patients classified according to the magnitude of nocturnal BP fall. There were no significant differences among the groups in any demographic characteristic including age, sex, body mass index, and smoking status. ECG-diagnosed LVH was more common in dippers and nondippers than in white-coat hypertensive subjects. There were some gender differences in the white-coat hypertension group, extreme dippers, dippers, and nondippers, and we also tested the Cornell voltage criteria for the diagnosis of LVH according to the gender of the patient. The prevalence of LVH diagnosed by Cornell voltage was 6.9%, 21%, 20%, 27% for each group, respectively. There were no significant differences among these groups in the prevalence of previous antihypertensive treatment (48% for the white-coat hypertension group, 50% for extreme dippers, 46% for dippers, and 55% for nondippers) or in any other metabolic factor.

While SBP parameters and 24-hour and awake DBP were all higher in the three sustained hypertension groups than in the white-coat hypertension group, there were no significant differences among these groups in any demographic characteristic including age, sex, body mass index, and smoking status. ECG-diagnosed LVH was more common in dippers and nondippers than in white-coat hypertensive subjects. There were some gender differences in the white-coat hypertension group, extreme dippers, dippers, and nondippers, and we also tested the Cornell voltage criteria for the diagnosis of LVH according to the gender of the patient. The prevalence of LVH diagnosed by Cornell voltage was 6.9%, 21%, 20%, 27% for each group, respectively. There were no significant differences among these groups in the prevalence of previous antihypertensive treatment (48% for the white-coat hypertension group, 50% for extreme dippers, 46% for dippers, and 55% for nondippers) or in any other metabolic factor.

While SBP parameters and 24-hour and awake DBP were all higher in the three sustained hypertension groups than in the white-coat hypertension group, there were no significant differences among these groups in any demographic characteristic including age, sex, body mass index, and smoking status.
differences among the former three groups in the office or 24-hour BP, but the awake SBP in the dippers and in the nondippers was significantly lower than that in the extreme dippers. The sleep BP was significantly higher in the nondippers compared with the dippers, and in the dippers compared with the extreme dippers.

**Orthostatic BP change by Head-Up Tilting Test**

Fig 1 shows the orthostatic BP change by head-up tilting in the white-coat hypertension group and in the sustained hypertension groups with different nocturnal BP falls. In extreme dippers, the SBP levels increased during the first 3-minute period in the upright position of the tilting, and this BP rise persisted for the remaining 17-minute period, while the BP reduction in the nondippers occurred in the first 1 minute in the upright position. There was no significant orthostatic SBP change in the dippers or white-coat hypertension group. The DBP increased in the white-coat hypertension, extreme dipper, and dippers groups, while there was no change in nondippers. The degree of BP rise was greater in the extreme dippers than in the dippers and white-coat hypertension group. The heart rate was increased in all four groups 1 minute after the upright position by tilting.

Table 2 shows the mean values of BP and heart rate during the 1- to 5-minute period just before tilting, those during the 6- to 10-minute period after tilting, and their changes by tilting.
test. While the DBP in the supine position (during the 5 minute just before tilting) was significantly lower in the extreme dippers than in the dippers, there were no differences among these groups in the SBP and heart rate. By tilting, the SBP was significantly increased in the extreme dippers, while there were no significant changes in the SBP in the dippers and nondippers. The DBP was significantly increased in the extreme dippers and dippers, while no significant change by tilting was found in nondippers. There were significant differences among the three groups in the change of both SBP and DBP, while the heart rates were significantly increased to similar degrees in all three groups.

Among the dippers, those with nocturnal fall in SBP of $\leq 10\%$ but $< 20\%$ in the patterns of orthostatic changes of BP and heart rate (data not shown).

### Table 2. Changes of BP by Head-Up Tilting Test in Sustained Hypertensive Elderly Patients with Different Nocturnal Falls in BP

<table>
<thead>
<tr>
<th>Patients</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>HR, bpm</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>HR, bpm</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme-dippers (n=14)</td>
<td>132 (15)</td>
<td>70 (8.6)*</td>
<td>64 (7.3)</td>
<td>143 (17)#</td>
<td>81 (10)#</td>
<td>73 (5.6)##</td>
<td>10 (19)*</td>
</tr>
<tr>
<td>Dippers (n=56)</td>
<td>143 (15)</td>
<td>80 (10)</td>
<td>66 (8.9)</td>
<td>142 (16)</td>
<td>84 (8.9)###</td>
<td>73 (9.2)###</td>
<td>-1.5 (11)†</td>
</tr>
<tr>
<td>Nondippers (n=11)</td>
<td>139 (17)</td>
<td>78 (9.2)</td>
<td>69 (8.4)</td>
<td>132 (21)</td>
<td>79 (11)</td>
<td>77 (11)###</td>
<td>-7.5 (13)‡</td>
</tr>
</tbody>
</table>

HR indicates heart rate. Mean (SD) values are shown.

*P<.01, versus dippers; †P<.01, versus extreme-dippers by Fisher’s protected least significant difference test after ANOVA.

### Table 3. Prevalence of Orthostatic Hypertension and Hypotension by Tilting Test in Sustained Hypertensive Elderly Patients with Different Nocturnal Falls in BP

<table>
<thead>
<tr>
<th>Patients</th>
<th>Orthostatic hypertension*</th>
<th>Normal status†</th>
<th>Orthostatic hypotension‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dippers (n=56)</td>
<td>6 [11]</td>
<td>45 [80]</td>
<td>7 [64]</td>
</tr>
<tr>
<td>Nondippers (n=11)</td>
<td>1 [7]</td>
<td>5 [9]</td>
<td>3 [27]</td>
</tr>
</tbody>
</table>

The number [%] of the patients is shown. Total x² value is 29.3 (P<.0001).

*The mean SBP in the 6 to 10 minute period after the start of tilting was increased by $>10$ mm Hg compared with the mean BP during the 5-minute period just before the start of tilting.

†Those with neither orthostatic hypertension nor hypotension.

‡The mean SBP in the 6 to 10 minute period after the start of tilting was decreased by $>20$ mm Hg compared with the mean BP during the 5-minute period just before the start of tilting.

### Discussion

Various factors seem to contribute to the individual diurnal BP pattern. In the present study, we first demonstrated the close relationships between abnormal diurnal BP variation and orthostatic BP variation in asymptomatic elderly hypertensive patients with WHO Stages I and II. Extreme dippers show a marked orthostatic BP rise in the upright position with head-up tilting, while nondippers showed an orthostatic fall in BP.

Previous reports on head-up tilting indicate that SBP is not changed and DBP is slightly increased in most hypertensive patients, as well as in healthy subjects. In the present study, the white-coat hypertension group and dippers showed this nocturnal fall in SBP of $\leq 10\%$ but $<20\%$ in the patterns of orthostatic changes of BP and heart rate (data not shown).
normal orthostatic BP variation pattern, although BP was higher in the dippers and lower in the white-coat hypertension group. In the extreme dippers, orthostatic increases were found in both SBP and DBP. This increase was apparent within 3 minutes just after the upright position was assumed by tilting. During ambulatory BP monitoring, BP measurements may be made at several times during the daytime in the upright position. Thus, this positional increase in SBP and DBP would probably contribute to the increased awake BP levels in the extreme dippers. In addition, we previously reported that extreme dippers have daytime BP variability (standard deviation) than do dippers. The positional BP change during the daytime might contribute to the greater BP variation in the sustained hypertensive group. A, SBP; B, DBP. ● indicates extreme dippers; ○, dippers; and ▲, nondippers.

Orthostatic hypertension is not well-known, although a few reports have been made.13-17 Orthostatic hypertension has not been well defined. Some previous reports defined orthostatic hypertension as an orthostatic increase of DBP from below 90 to above 90 mm Hg.16 In the elderly population, SBP further increases and DBP decreases along with advancing age, resulting in isolated systolic hypertension being more common than in younger adults. In elderly subjects, SBP is more closely related to the target organ damage and related risk factors than is DBP. Thus, in the study of elderly patients with sustained hypertension, using SBP as well as the designation of extreme dippers, dippers, and nondippers, we defined orthostatic hypertension as orthostatic SBP increase of 10 mm Hg or more by the tilting test. DBP did not decrease even in the nondippers, and there was a marked increase of DBP in extreme dippers.

In previous reports, the various pathogenic mechanisms of orthostatic hypertension have been demonstrated.13-17 Frohlich et al15 studied a group of persistently hypertensive patients both in recumbent and standing postures and found that those whose orthostatic rise in DBP was greater than normal showed excessive increases in peripheral resistance during tilting and excessive increases in DBP after the Valsalva maneuver. Sapru et al16 found the excessive responsiveness to stimuli of the sympathetic nervous system. Streeter et al16 found that those with orthostatic hypertension have decreased venous return, decreased cardiac output, increased sympathetic stimulation, and excessive arteriolar constriction. Benowitz et al17 reported a case of orthostatic hypertension due to vascular adrenergic hypersensitivity. In the present study, heart rate increased by tilting in extreme dippers, dippers, and nondippers, and there were no significant differences among these groups in the degrees of heart rate rise, suggesting that there were no differences in cardiac sympathetic nervous activation. The difference of orthostatic BP changes in extreme dippers, dippers, and nondippers might be attributed to the degree of peripheral arteriolar constriction. Extreme dippers might have enhanced peripheral arteriolar constriction by peripheral sympathetic nervous activation, although further studies are necessary to clarify the pathogenic mechanism of orthostatic hypertension found in the extreme dippers.

In nondippers, orthostatic SBP were decreased within the first minute just after the upright position by tilting, while DBP levels did not change significantly. This orthostatic BP reduction might contribute to suppressed awake SBP levels in the upright position during the daytime period in ambulatory BP monitoring. Orthostatic hypotension has been reported in various diseases with autonomic nervous dysfunction.16 By spectral analysis of heart rate variability using Holter ECG, we recently found that the sympathetic nervous activity during the daytime was diminished in nondippers compared with dippers among elderly hypertensive patients.9 Thus, a nondipper pattern might be accompanied by an autonomic nervous dysfunction.

In the present study, we used the cut-off values of 0% and 20% nocturnal BP reduction for classification of extreme dippers, dippers, and nondippers. We have used cut-off values of 10 and 20% nocturnal BP in our previous studies.5,6 In the elderly hypertensive subjects we studied previously, the mean −1 SD, the mean, and the mean +1 SD values of nocturnal SBP reduction were 0%, 10%, and 20%, respectively.5,6 Thus, of elderly hypertensive patients, about 15% are extreme dippers, about half are nondippers defined by the cut-off value of 10% nocturnal BP reduction, and about 15% are nondippers defined by the cut-off value of 0% nocturnal BP reduction. On the basis of the orthostatic BP change, the classification using the cut-off values of 0% and 20% nocturnal BP reduction would be more suitable than that using 10% and 20% to define the nondippers in the elderly hypertensive patients.

There was significant negative correlation between orthostatic SBP change and the sleep/awake ratio of SBP. Similar findings were also found in DBP. However, the correlation coefficient is not so high as to conclude that the orthostatic BP change determines the diurnal BP patterns, indicating that there are some pathogenic mechanisms of BP regulation for generating these abnormal variations.

As a study limitation, there is a possibility that the frequency with which the half-hourly BP measurements awakened the
patients and might have influenced the results. However, we excluded seven subjects who complained of sleep disturbance during BP monitoring.

In conclusion, there are close relationships between abnormal diurnal BP variation and orthostatic BP variation in elderly hypertensive patients, indicating that orthostatic increase and decrease of BP in upright position during the daytime might partly contribute to the abnormal diurnal BP variation patterns of extreme dippers and nondippers, respectively.

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Relationship Between Extreme Dippers and Orthostatic Hypertension in Elderly Hypertensive Patients
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