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長寿科学研究事業


家庭血圧を用いた高齢者高血圧の早朝血圧と

その変動性の評価と管理法の確立に関する研究


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家庭血圧を用いた高齢者高血圧の早朝血圧とその変動性の評価と管理法の確立に関する研究

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**研究要旨**：新規に開発した起立性血圧調節障害を評価する家庭血圧計を用いて、家庭での起立性血圧変動と従来から行われている Head up tilting (HUT)試験との起立性血圧変動は強い相関を認めた。起立性高血圧を呈する高血圧患者は起立性正常血圧を呈する患者に比べて、高血圧性臓器障害の進行を認めた。高血圧診療にて、家庭血圧モニタリングを用いて、起立時の血圧変動を評価することにより、より有効な個別療法が可能になると思われる。

A．研究目的
【研究 1】降圧療法中の高齢者高血圧患者を対象に、著者らが開発した起立性血圧調節障害を評価する家庭血圧計(特許申請中：出願番号 2002-307787)を用いて、家庭での起立性血圧調節障害の再現性を検討し、更に起立性血圧調節障害の評価をするために従来から行われている Head up tilting (HUT)試験との再現性を検討し、本血圧計の有用性を評価する。
【研究 2】
外来通院中の高血圧患者を対象に、従来の家庭血圧計を用いた自己記入による起立時血圧変動が、高血圧性臓器障害と関連しているかを検討する。また、起立性血圧変動の再現性を検討した。

B．研究方法
【研究 1】
高血圧患者 65 名において HUT 試験で起立性血圧変動を評価し、その後、新規家庭血圧計で 2 週間、家庭血圧を測定した。HUT 試験は、臥位 10 分後、70° tilt を行い、臥位 5〜10 分の平均収縮期血圧(SBP)を臥位 SBP とし tilt 時 6〜10 分の平均 SBP を tilt SBP とし、tilt SBP から臥位 SBP を引いたものを HUT 試験での起立性血圧変動とした。新規家庭血圧計にて朝、夕また座位、立位 1 回目、2 回目の 2 週間の SBP を平均し、立位 SBP から座位 SBP を引いたものを家庭血圧での起立性血圧変動とした。
【研究 2】家庭早朝血圧 135mmHg 以上の外来通院中治療中高血圧患者 609 名においてベースラインとして、家庭にて朝、夕それぞれ座位 2 回、立位 2 回の血圧、脈拍を連続測定し、立位 SBP から座位 SBP を引いたものを起立性血圧変動とした。同様に 6 ヶ月後に血圧測定を施行した。ベースライン時に高血圧性臓器障害の評価として、脳性ナトリウム利尿ペプチド (BNP)及び、微量アルブミン尿量排泄(UAE)を測定した。

C．研究結果
【研究 1】家庭血圧による 2 週間連続測定の起立性血圧変動異常は再現性よく認められた。家庭血圧による起立性血圧変動と、HUT 試験の血圧変動の関係は、家庭血圧のどのパラメーターを用いても有意に HUT 試験との相関を認めた(p<0.001)。また、外来で新規血圧計を用いて起立性血圧変動をみた場合でも、HUT 試験の血圧変動と相関を認めた(p<0.001)。
【研究 2】
立位 2 回目の SBP から座位 2 回平均 SBP を引いた血圧差が-10mmHg 以上低下する群を起立性低血圧群 (OHYPO 群：n=174)、10mmHg 以上上昇する群を起立性高血圧群 (OHT 群：n=85)、それ以外を起立性正常血圧群 (ONT 群：n=348)とした。OHT 群は、ONT 群と比べて明らかに BNP と UAE が高値を示した(BNP; geometric mean:30.7[12.4-76.3] vs.23.3[8.9-61.2] pg/ml,p<0.05,UAE;geometric mean: 41.3 [10.0-171] vs. 27.8[7.4-105] mg/g×cre, p<0.05)。6 ヶ月後の起立性低血圧の再現性は 59%で、起立性高血圧の再現性は 29%であった。

D．考察
従来より、起立性血圧変動は、HUT 試験を用いて評価されている。しかしながら、HUT 試験は、煩雑さを伴うことが多い。一方で、近年、高血圧診療において家庭血圧の重要性が示されており、外来血圧よりも心血管イベントの関連が報告されている。今回、新規血圧計を用いて、家庭での起立性血圧変動と外来での血圧変動が簡易的に評価ができ、再現性もよく、その血圧変動は HUT 試験のそれと相関を認めた。この新規家庭血圧を用いた起立性血圧変動異常は、今後の高血圧診療に有用な測定機器となる可能性がある。また、起立性高血圧を呈する高血圧患者は起立性正常血圧を呈する患者に比べて、高血圧性臓器障害の進行を認めた。家庭血圧において起立性高血圧を呈する場合も高血圧性臓器障害の進行を認める。したがって、高血圧診療にあたっては、従来の外来血圧、家庭血圧レベルだけでなく起立時の血圧変動異常も考慮したきめ細かな診療が必要であるかもしれない。

E．結論
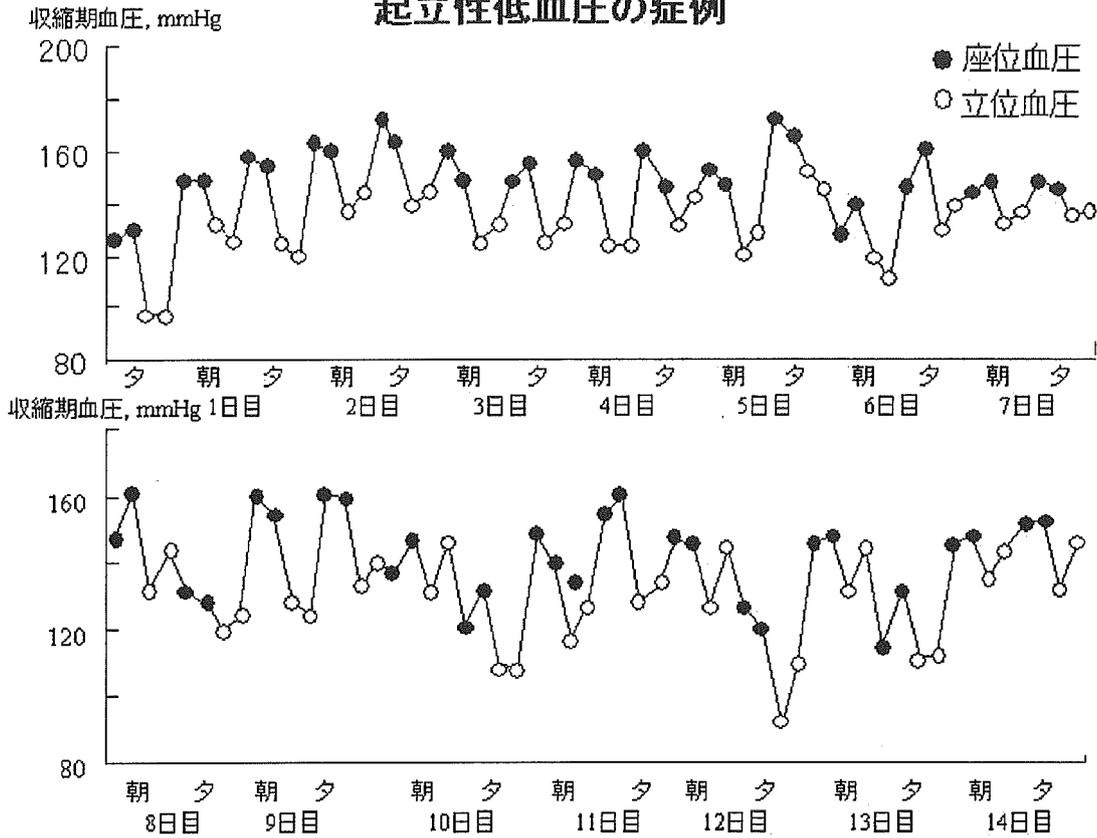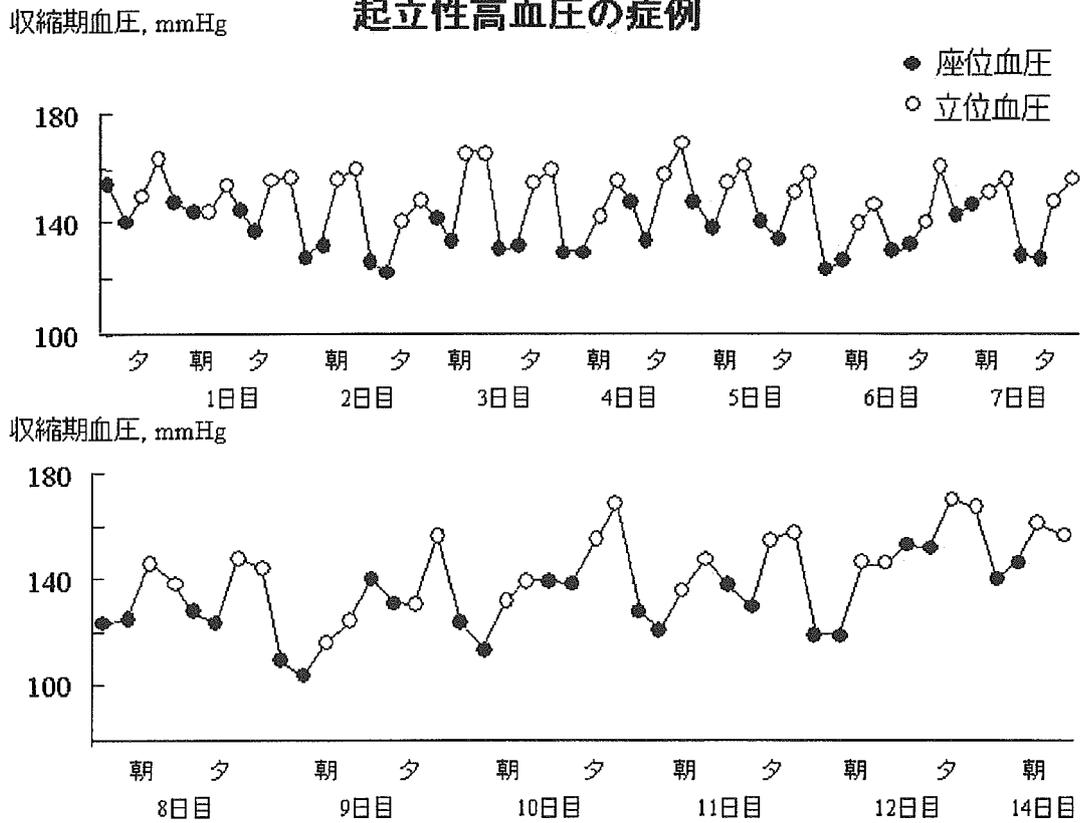高血圧診療時には、家庭血圧モニタリングを用いて、起立時の血圧変動を評価することにより、より有効な個別療法が可能になると思われる。

F．健康危険情報
なし

G．研究発表
学会発表: 2005 年度日本高血圧学会

# 起立性血圧変動の2週間の再現性

## 起立性低血圧の症例

収縮期血圧, mmHg

● 座位血圧
○ 立位血圧



夕 朝 夕 朝 夕 朝 夕 朝 夕 朝 夕 朝 夕
1日目 2日目 3日目 4日目 5日目 6日目 7日目

収縮期血圧, mmHg



朝 夕 朝 夕 朝 夕 朝 夕 朝 夕 朝 夕 朝 夕
8日目 9日目 10日目 11日目 12日目 13日目 14日目

## 起立性高血圧の症例

収縮期血圧, mmHg

● 座位血圧
○ 立位血圧



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1日目 2日目 3日目 4日目 5日目 6日目 7日目

収縮期血圧, mmHg



朝 夕 朝 夕 朝 夕 朝 夕 朝 夕 朝
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II. 研究成果の刊行に関する一覧表

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# Morning Surge in Blood Pressure as a Predictor of Silent and Clinical Cerebrovascular Disease in Elderly Hypertensives

## A Prospective Study

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*Background*—Cardiovascular events occur most frequently in the morning hours. We prospectively studied the association between the morning blood pressure (BP) surge and stroke in elderly hypertensives.

*Methods and Results*—We studied stroke prognosis in 519 older hypertensives in whom ambulatory BP monitoring was performed and silent cerebral infarct was assessed by brain MRI and who were followed up prospectively. The morning BP surge (MS) was calculated as follows: mean systolic BP during the 2 hours after awakening minus mean systolic BP during the 1 hour that included the lowest sleep BP. During an average duration of 41 months (range 1 to 68 months), 44 stroke events occurred. When the patients were divided into 2 groups according to MS, those in the top decile (MS group; MS ≥55 mm Hg, n=53) had a higher baseline prevalence of multiple infarcts (57% versus 33%, $P=0.001$) and a higher stroke incidence (19% versus 7.3%, $P=0.004$) during the follow-up period than the others (non-MS group; MS <55 mm Hg, n=466). After they were matched for age and 24-hour BP, the relative risk of the MS group versus the non-MS group remained significant (relative risk=2.7, $P=0.04$). The MS was associated with stroke events independently of 24-hour BP, nocturnal BP dipping status, and baseline prevalence of silent infarct ($P=0.008$).

*Conclusions*—In older hypertensives, a higher morning BP surge is associated with stroke risk independently of ambulatory BP, nocturnal BP falls, and silent infarct. Reduction of the MS could thus be a new therapeutic target for preventing target organ damage and subsequent cardiovascular events in hypertensive patients. (*Circulation.* 2003;107: 1401-1406.)

**Key Words:** blood pressure ■ stroke ■ hypertension ■ cerebral infarction ■ cerebral ischemia

There is growing evidence indicating that there is a marked diurnal variation in the onset of cardiovascular events, with a peak incidence of myocardial infarction, sudden cardiac death, and ischemic and hemorrhagic stroke occurring in the morning (6 AM to noon), after a nadir in these events during the night.[1-4] Further characterization of this circadian pattern has identified the hour of awakening rather than the hour in the day as being most closely related to the occurrence of cardiovascular events.[5,6]

Blood pressure (BP) shows a similar diurnal variation, reaching the highest level during the morning and then declining to reach a trough value at about midnight. In the early morning, an abrupt and steep acceleration in BP occurs, coincident with arousal and arising from overnight sleep.[7] It has been suggested that this morning surge in BP might trigger cardiovascular events, but so far there have been no studies that directly demonstrate an association between morning BP surge (MBPS) and events. However, there is considerable variation in the diurnal rhythm of BP in different patients. Our previous work has indicated that the degree to which BP falls or rises during the night, as measured by the difference or ratio of the average daytime and nighttime BPs, varies greatly from one patient to another and that these different patterns (dipping, nondipping, extreme dipping, and rising) are associated with very different risks of strokes.[8] The extreme-dipper group, whose nighttime BP is more than 20% lower than the daytime BP, is at particularly high risk, but it is not clear whether this risk is related to the fall of BP during the night, the low nighttime BP, or the morning surge of BP that occurs on waking. In the present analysis, we have attempted to determine which component of the diurnal BP rhythm (nocturnal BP dipping or MBPS) is more closely related to silent cerebral infarct (SCI) and stroke events.

## Methods

### Subjects

The present study was based on 519 elderly hypertensive patients (mean age 72 years) who were followed up prospectively for an average of 41 months. This represents 98% of the 532 patients who were initially enrolled into the study from 6 participating institutions (3 clinics, 2 hospitals, and 1 outpatient clinic of a medical school) between January 1, 1992, and January 1, 1998. These patients were selected from a larger cohort of hypertensive patients[9] by the following criteria: (1) essential hypertension with average clinic systolic BP (SBP) >140 mm Hg and/or average clinic diastolic BP >90 mm Hg (average for each patient on 2 or more occasions on different days); (2) age >50 years; (3) a successful 24-hour ambulatory BP monitoring (ABPM); and (4) assessment of the presence/absence of SCI by brain MRI. No patient had taken any antihypertensive medication for at least 14 days before the ABPM study, but 55% had a prior history of antihypertensive medication use. We excluded from the present study patients with renal failure (serum creatinine level >176 mmol/L), hepatic damage, obvious present illness, a past history of coronary artery disease, stroke (including transient ischemic attacks), congestive heart failure, arrhythmia (including atrial fibrillation), or peripheral vascular disease. All of the subjects studied were ambulatory, and all gave informed consent for the study. The results of the ABPM and brain MRI were returned to the subjects' treating physicians. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan.

Clinic BP was measured after resting for at least 5 minutes in the sitting position. 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 or insulin. Hyperlipidemia was defined by a total cholesterol level >6.2 mmol/L or the use of an oral lipid-lowering agent. Smokers were defined as current smokers. Body mass index was calculated as weight (kg)/height (m$^2$). Electrocardiographically verified left ventricular hypertrophy was defined as abnormally high voltages of QRS complexes (R in $V_5$ plus S in $V_1$ >3.5 mV) associated either with flat T waves (<10% of the R wave) or with ST-segment depression and biphasic T-waves.

### 24-Hour ABPM

Noninvasive ABPM was performed on a weekday with 1 of 3 automatic devices (ABPM-630, Nippon Colin Co, TM-2421 or TM-2425, A&D Co Inc, Japan) that recorded BP and pulse rate every 30 minutes for 24 hours. The accuracy of these devices was validated previously. The ambulatory data used in the present study were those obtained by the oscillometric method. We excluded those who obtained less than 80% of either awake or asleep valid BP readings (n=31). Patients who reported in our post-ABPM questionnaire that their sleep was severely disturbed by wearing the ABPM were also excluded from this study (n=23).

Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he or she got out of bed, and awake BP was defined as the average of BPs recorded during the rest of the day. Morning BP was defined as the average of BPs during the first 2 hours after wake-up time (4 BP readings; Figure 1). The lowest BP was defined as the average BP of 3 readings centered on the lowest nighttime reading (ie, the lowest reading plus the readings immediately before and after). Evening BP was defined as the average BP during the 2 hours before going to bed (4 BP readings). Preawake BP was defined as the average BP during the 2 hours just before wake-up time (4 BP readings). The MBPS was calculated in 2 ways: sleep-trough MBPS, defined as the morning SBP minus the lowest SBP, and prewaking MBPS, defined as the morning SBP minus the preawake SBP. The nocturnal BP fall (mm Hg) was defined as the evening BP minus the lowest BP. The systolic pressures were used for all these calculations.

We subclassified the patients according to the extent of the sleep-trough MBPS as follows: the top decile of sleep-trough MBPS (>55 mm Hg, n=53; the MS group) versus all others (n=466, the



Definition of MBPS.
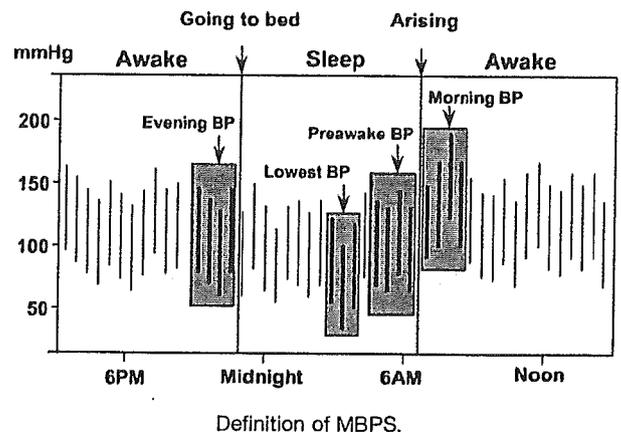
non-MS group). We also subclassified the patients according to the percentage of nocturnal SBP reduction [100×(1−sleep SBP/awake SBP)] as follows: extreme dippers if the nocturnal SBP reduction was ≥20%; dippers if the fall was ≥10% but <20%; nondippers if the fall was ≥0% but <10%; and risers if it was <0%.[8]

### Brain MRI

Brain MRI was performed with a superconducting magnet with a main strength of 1.5T (Toshiba MRT200FXII, Toshiba; SIGNA-Horizon version 5.8, General Electric Co or Vision, Siemens) within 3 months of the baseline ABPM. T1- and T2-weighted images were obtained in the transverse plane with 7.8-mm- or 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.[8-10] Multiple SCI was defined as 2 or more infarcts. All SCIs detected were lacunar infarcts with a size of <15 mm. The MRI images of the subjects were randomly stored and interpreted without knowledge of the subjects' names and characteristics. The κ-statistics in assessment of interreader and intrareader agreement (non-SCI, 1 SCI, and multiple SCIs) were 0.70 and 0.80, respectively in our laboratory.

### Follow-Up and Events

The patients' medical records were reviewed intermittently after ABPM for the use of antihypertensive drug therapy and the occurrence of cardiovascular events. The follow-up was performed during a 20-month period from 1996 to 1998; the mean follow-up period was 41 months, with a range from 1 to 68 months. When patients failed to come to the clinic, we interviewed them by telephone. There was no significant difference among the MS and non-MS groups in duration of follow-up. Stroke events were diagnosed by each physician who was caring for the patient at the time of the event, and independent neurologists reviewed the cases and confirmed the diagnosis of stroke events. Stroke was diagnosed on the basis of sudden onset of neurological deficit that persisted for >24 hours in the absence of any other disease process that could explain the symptom. Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks, in which the neurological deficit cleared completely in <24 hours from the onset of symptoms.

Of the total of 532 eligible patients at baseline, follow-up was obtained in 519 (98%) patients, and the data analysis was restricted to these patients. Of these, 292 (56%) were taking antihypertensive medication at the time of the final follow-up.

### Statistical Analysis

Data are expressed as mean±SD. Two-sided unpaired $t$ test and $\chi^2$ test were used to test differences between the 2 groups in the mean values of continuous measures and prevalence rates, respectively. Adjusted relative risks (RRs) and odds ratio with 95% CIs were calculated with Cox regression analysis and multiple logistic regres-

sion analysis, respectively. The proportional hazards assumption was checked and found to hold for the primary predictors in the Cox regression analyses. In one simultaneous model to study the effect of dipping status (extreme dippers, dippers, nondippers, and risers) and sleep-trough MBPS on stroke risk, 3 dummy variables were used to contrast the 4 dipping status groups. The statistical calculations were performed with SPSS version 8.0J (SPSS Inc). Differences with $P<0.05$, 2-tailed, were considered to be statistically significant.

## Results

### Baseline Characteristics and SCIs

The mean±SD sleep-trough MBPS in the total sample was 34±18 mm Hg. The cutoff value for identifying the top decile (the MS group) was 55 mm Hg.

The mean age and clinic BPs were significantly higher in the MS group than in the non-MS group (Table 1). Although there were no significant differences in evening and sleep BPs between the 2 groups, awake and morning BPs were significantly higher in the MS group than in the non-MS group. The mean±SD sleep-trough MBPS defined by the difference between the morning SBP and the lowest SBP was 69±12 mm Hg for the MS group and 29±13 mm Hg for the non-MS group, and prewaking MBPS (defined by the difference between morning SBP and preawake SBP) was 34±21 mm Hg for the MS group and 9.1±14 mm Hg for the non-MS group. There were no significant differences in the clinic and ambulatory pulse rates, including the morning pulse rate (MS group 77.8±11.9 bpm versus non-MS group 75.6±10.9 bpm, $P=0.25$). In addition, the higher morning surge of BP in the MS group than the non-MS group was not associated with any differences between the groups in the changes of pulse rate.

Although the MS group tended to have a higher frequency of electrocardiographically verified left ventricular hypertrophy ($P=0.08$) and higher levels of preawake SBP (by 4 mm Hg, $P=0.23$) and 24-hour SBP (by 5 mm Hg, $P=0.06$) than the non-MS group, the differences were not statistically significant. There were no significant differences among groups in the prevalence of antihypertensive medication use at the final follow-up.

At the baseline examination, SCI was more frequently detected in the MS group than in the non-MS group (Table 2), particularly when there were multiple SCIs. After age and 24-hour SBP were controlled for with multiple logistic regression analysis, MBPS was an independent determinant of multiple SCI (OR 1.91, 95% CI 1.04 to 3.51, $P=0.036$). When we identified the 145 non-MS subjects who could be matched for age (range 2 years) and 24-hour SBP level (range 4 mm Hg) to 1 or more MS subjects and weighted the controls to simulate a balanced design, the comparison of group results (Table 3) was essentially the same as in the total sample.

### Stroke Incidence

During an average duration of 41 months (range 1 to 68 months), 44 stroke events occurred. The MS group had a higher incidence of stroke events (19% versus 7.3%, $P=0.004$) than the non-MS group (Table 2). In the groups matched for age and 24-hour SBP, the RR in the MS group (versus the non-MS group) calculated from a weighted Cox

**TABLE 1. Clinical and BP Characteristics**

| Measures | MS Group (n=53) | Non-MS Group (n=466) |
|---|---|---|
| Age, y | 77±7.2* | 72±8.6 |
| Male, % | 40 | 36 |
| Body mass index, kg/m | 24.3±3.6 | 24.1±3.5 |
| Current smoker, % | 25 | 22 |
| Hyperlipidemia, % | 17 | 23 |
| Total cholesterol, mmol/L | 5.2±0.82 | 5.2±0.86 |
| LDL cholesterol, mmol/L | 3.6±0.85 | 3.6±0.85 |
| HDL cholesterol, mmol/L | 1.3±0.37‡ | 1.2±0.35 |
| Triglyceride, mmol/L | 1.5±0.74 | 1.7±1.6 |
| Diabetes, % | 21 | 14 |
| ECG-LVH, % | 30 | 20 |
| Duration of follow-up, mo | 41±14‡ | 37±14 |
| Antihypertensive medication, % | | |
| Prior history at baseline | 55 | 55 |
| At time of final follow-up | 56 | 55 |
| Calcium antagonist | 30 | 28 |
| ACE inhibitor | 16 | 21 |
| α/β-blocker | 2.6 | 3.8 |
| Diuretic | 4.5 | 5.7 |
| Others | 1.3 | 1.9 |
| Unknown | 8.8 | 5.7 |
| SBP, mm Hg | | |
| Clinic | 171±21† | 163±18 |
| 24-Hour | 143±17 | 138±17 |
| Awake | 154±19* | 145±18 |
| Evening | 139±24 | 137±20 |
| Sleep | 125±17 | 127±18 |
| Lowest | 103±16* | 114±18 |
| Preawake | 138±24 | 134±21 |
| Morning | 172±17* | 143±19 |
| Sleep-trough MS§ | 69±13* | 29±13 |
| Prewaking MS‖ | 34±21* | 9.1±14 |
| Diastolic BP, mm Hg | | |
| Clinic | 95±17‡ | 91±14 |
| 24-Hour | 80±9.3 | 78±10 |
| Awake | 86±11† | 82±11 |
| Evening | 79±13 | 78±13 |
| Sleep | 70±11 | 72±11 |
| Lowest | 65±11* | 59±11 |
| Preawake | 76±13 | 75±12 |
| Morning | 94±13* | 82±12 |
| Sleep-trough MS§ | 34±11* | 17±10 |
| Prewaking MS‖ | 17±11* | 6.5±9.3 |

ECG-LVH indicates left ventricular hypertrophy verified by electrocardiography. Data are shown as mean±SD or percentages.
*$P<0.001$, †$P<0.01$, ‡$P<0.05$.
§Morning BP minus lowest BP during sleep.
‖Morning BP minus preawake BP.

**TABLE 2. Silent Cerebrovascular Disease and Stroke Prognosis in Total Sample**

| Measures | MS Group (n=53) | Non-MS Group (n=466) |
|---|---|---|
| Baseline data | | |
| SCI | | |
| Prevalence, % | 70† | 48 |
| Average number | 2.3±2.6† | 1.3±2.6 |
| Multiple SCIs‡ | | |
| Prevalence, % | 57* | 33 |
| Prospective data | | |
| Clinical stroke incidence, % | 19† | 7.3 |

Data are shown as mean±SD or percentages.
*P<0.001, †P<0.01.
‡>2 silent infarcts.

regression analysis remained significant (RR=2.7, P=0.04; Table 3). When we divided the total group into quartiles by the sleep-trough MBPS, the stroke incidences were significantly increased in the higher quartiles (Q1=4.6%, Q2=5.5%, Q3=9.2%, Q4=14.5%, $x^2$=10.2, P=0.017).

Table 4 shows the results of a Cox regression analysis with MBPS as a continuous variable in the total sample. Age, 24-hour BP, and baseline prevalence of SCI were associated with stroke risk, whereas there were no significant other confounders (sex, body mass index, smoking status, diabetes, or hyperlipidemia). Sleep-trough MBPS (morning SBP minus lowest SBP; model 1) was significantly associated with stroke events independently of the significant confounders. When we added the prewaking MBPS (morning SBP minus preawake SBP) into model 1 instead of sleep-trough MBPS, prewaking MBPS tended to be associated with stroke risk

**TABLE 3. Silent Cerebrovascular Disease and Stroke Prognosis in Groups Matched for Age and 24-Hour Ambulatory BP**

| Measures | MS Group (n=46) | Non-MS Group (n=145) |
|---|---|---|
| Baseline data | | |
| Age, y | 76±6.9 | 76±6.9 |
| Male, % | 39 | 37 |
| Body mass index, kg/m² | 24.4±3.4 | 24.0±3.6 |
| 24-Hour SBP, mm Hg | 142±15 | 142±15 |
| SCI | | |
| Prevalence, %§ | 70‡ | 49 |
| Average number | 2.0±2.1† | 1.5±2.0 |
| Multiple SCIs‖ | | |
| Prevalence, %¶ | 54‡ | 37 |
| Prospective data | | |
| Clinical stroke incidence# | 17‡ | 7.0 |

Data are shown as mean±SD or multiple logistic regression percentages.
*P<0.001, †P<0.01, ‡P<0.05.
§OR=2.4 (95% CI 1.2–4.8), P=0.02, by multiple logistic regression analysis.
‖>2 silent infarcts.
¶OR=2.0 (95% CI 1.0–3.9), P=0.04, by weighted Cox regression analysis.
#RR=2.7 (95% CI 1.1–6.8), P=0.04, by weighted Cox regression analysis.

(10 mm Hg increase; RR 1.14, 95% CI 0.99 to 1.31, P=0.07), although the association was not significant.

To study the effect of antihypertensive medication, we added a medication term (0=absent, 1=present at follow-up) into model 1 of Table 4. Sleep-trough MBPS (10 mm Hg increase; RR 1.24, 95% CI 1.07 to 1.43, P=0.004) and antihypertensive medication (RR 0.41, 95% CI 0.22 to 0.79, P=0.007) were both significantly and independently associated with stroke risk.

### Relationships Between Different Measures of Nocturnal BP Changes

Because the definition of sleep-trough MBPS is related in part to the nocturnal BP fall, we also studied the influence of nocturnal BP dipping status. The prevalences of extreme-dippers, dippers, nondippers, and risers were 51% (n=27), 36% (n=19), 11% (n=6), and 2% (n=1), respectively, in the MS group and 18% (n=85), 46% (n=213), 27% (n=126), and 9% (n=42), respectively, in the non-MS group. Looked at another way, 24% of the extreme-dippers but only 8.1% of dippers, 4.5% of nondippers, and 2.3% of risers were classified as being in the MS group.

Because these prevalences were significantly different ($x^2$=32.0, P<0.0001), we added these 4 dipping status categories using 3 dummy variables into the same Cox regression analysis (Table 4, model 2). Stroke risk was significantly associated both with MBPS ([10 mm Hg increase; RR 1.25, 95% CI 1.06 to 1.48, P=0.008) and with being classified as a riser (RR 2.71, 95% CI 1.02 to 7.21, P=0.047 versus dipper). In this model, being classified as an extreme-dipper was not significantly associated with stroke risk independently of MBPS.

### Time of Stroke Onset and Stroke Subtype

We identified the time of stroke onset in 36 of the 44 events. Seven (78%) of the 9 stroke events in the MS group occurred in the morning period (6 AM to noon), whereas 11 (41%) of the 27 events in the non-MS group occurred in this period ($x^2$=3.70, P=0.05). In extreme-dippers, 6 (60%) of the 10 stroke events occurred during the morning period (6 AM to noon), and 3 (30%) occurred during the nighttime period (midnight to 6 AM), whereas in the other groups (dippers and nondippers), 12 (46%) of the 26 events occurred in the morning period, and 2 (7.7%) occurred during the night ($x^2$=5.48, P=0.06).

Of the 44 stroke events, 30 were ischemic, 6 were hemorrhagic, and 8 were of unknown type. There was no significant difference in the stroke subtypes between the MS and non-MS groups.

### Discussion

This study is the first to show that an excessive MPBS is a predictor of subsequent stroke events in elderly hypertensive patients independent of ambulatory BP levels and target organ damage. The MS group, with the highest sleep-trough MBPS (>55 mm Hg), had a higher stroke incidence than the non-MS group (MBPS <55 mm Hg). After they were matched for age and 24-hour SBP, the RR in the MS group versus the non-MS group was 3.2. Because the classification

**TABLE 4.    Cox Regression Analysis for Clinical Stroke Events**

| Covariates | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | Relative Risk (95% CI) | *P* | Relative Risk (95% CI) | *P* |
| Age (10 y) | 1.75 (1.20–2.55) | 0.004 | 1.69 (1.15–2.50) | 0.008 |
| 24-Hour SBP (10 mm Hg) | 1.38 (1.17–1.64) | <0.001 | 1.35 (1.13–1.60) | <0.001 |
| SCI* | 4.50 (1.99–10.2) | <0.001 | 4.02 (1.73–9.30) | 0.001 |
| Sleep-trough MS (10 mm Hg)† | 1.22 (1.05–1.40) | 0.008 | 1.25 (1.06–1.48) | 0.008 |
| Dipping status | | | | 0.025‡ |
| Extreme-dippers vs dippers | ... | | 1.43 (0.59–3.43) | 0.426 |
| Nondippers vs dippers | ... | | 1.76 (0.78–4.01) | 0.175 |
| Risers vs dippers | ... | | 2.71 (1.02–7.21) | 0.047 |

*0=absence of infarct, 1=presence of infarct.
†Morning SBP minus lowest SBP during sleep.
‡Global test of significance for differences among 4 dipping status groups.

of the MS and the non-MS groups was arbitrary, we repeated the analysis using sleep-trough MBPS as a continuous variable and again found a significant association between MBPS and stroke risk.

## Definition of MBPS

There is no consensus concerning the definition of the MBPS. We defined it in 2 ways: sleep-trough MBPS (morning SBP minus lowest SBP during the night) and prewaking MBPS (morning SBP minus preawake SBP). The sleep-trough MBPS was significantly and independently associated with stroke risk, and a 10-mm Hg increase in sleep-trough MBPS increased the stroke risk by 22%. Prewaking MBPS increased stroke by 14%, but this increase was not significant (*P*=0.07). Thus, our results suggest that sleep-trough MBPS gives a more clinically relevant definition of the MBPS.

## MBPS Versus Nocturnal BP Fall

Because the definition of sleep-trough MBPS is related in part to the nocturnal BP fall, we studied the association between MBPS and dipping status of nocturnal BP. We have previously demonstrated that in elderly hypertensive patients, extreme-dippers have more frequent SCI[8,10] and a poor stroke prognosis.[10] In the present study, 51% of the patients in the MS group were classified as extreme-dippers; thus, whereas the MS group was defined to make up only 10% of the sample (top decile), they made up 24% of the 112 extreme-dippers, and the extreme-dippers and MS groups therefore overlapped significantly. This overlap may explain in part the reason extreme-dippers not only have more frequent sleep-onset ischemic strokes but also have more strokes in the morning, which would be predominantly associated with excessive MBPS.

When we combined dipping status (extreme-dippers, dippers, nondippers, and risers) and MBPS into the same Cox regression analysis model, stroke risk was significantly associated both with MBPS (10-mm Hg increase, RR 1.25, *P*=0.008) and with being classified as a riser (RR 2.71, *P*=0.047 versus dippers). In this model, being classified as an extreme-dipper was not significantly associated with stroke risk independently of MBPS. Thus, the fall of BP that occurs

during the night appears to be of less importance than the morning surge. The mechanism underlying the increased stroke risk of extreme-dippers might depend on either an excessive morning surge of BP or on cerebral hypoperfusion due to the low nocturnal BP. Two lines of evidence argue for the former mechanism. First, in the extreme-dippers, 60% of strokes occurred during the morning period (6 AM to noon) and only 30% during the night (midnight to 6 AM), whereas in the dippers and nondippers, 46% of strokes occurred in the morning period and 7.7% during the night. Second, as shown above, extreme-dipping pattern of nocturnal BP did not predict stroke occurrence independently of MBPS.

## Time of Onset and Stroke Subtypes

Both ischemic and hemorrhagic strokes showed a greater tendency to cluster in the morning period (6 AM to noon) in the MS group than in the non-MS group. Thus, it is reasonable to suppose that an excessive MBPS might trigger strokes through some hemodynamic mechanism such as increased shear stress on the atherosclerotic cerebral vessels, but there are several other factors that change during the morning hours. These include an increase of sympathetic nervous activity, particularly α-adrenergic activity,[11,12] and other related acute risk factors such as platelet hyperactivity, hypercoagulability and hypofibrinolysis, blood viscosity, and increased vascular spasm.[6,13,14] This potentiation of acute risk factors might also be greater in the MS group than in the non-MS group and contribute to triggering the morning strokes, and it should be investigated in future research.

## Association With SCI

There are a few studies that have demonstrated an association between MBPS and target organ damage. Kuwajima et al[15] reported that in 23 elderly hypertensive patients, the SBP change after arising in the morning was significantly correlated with the left ventricular mass index and the A/E ratio, which represents diastolic function. SCI is reported to be a strong predictor of subsequent clinical stroke (approximate OR 6 to 10)[9,16] and can be considered to be the most important hypertensive target organ damage marker for stroke. In the present study, MBPS was significantly associ-

ated cross-sectionally with baseline prevalence of SCI detected by brain MRI and prospectively with stroke events. This association was particularly strong for multiple SCIs. Although SCI prevalence was a strong predictor of a subsequent stroke event in the present study population, the association between MBPS and stroke risk was independent of SCI. Thus, the identification of a "high morning surge" group in elderly hypertensive patients may have some clinical significance even after assessment of target organ damage.

## Antihypertensive Medication

Although the present study was not designed to study the effect of antihypertensive medication on stroke risk, it was found that the use of antihypertensive medication was associated with a significantly reduced stroke risk. In addition, MBPS was significantly associated with stroke risk independently of antihypertensive medication use. Thus, controlling the MBPS with antihypertensive medication might improve stroke prognosis.

## Study Limitations

Despite the relatively large size of this prospective study, the number of strokes was relatively small. In addition, there are marked differences in the epidemiology of cardiovascular disease between Japan and the United States or European countries. Among Japanese, coronary artery disease is much less common, whereas stroke is more common than among whites or blacks. Further research in a larger sample of Japanese and in the other racial populations is needed to confirm the generalizability of our new findings.

## Conclusions

In this study, an excessive MBPS was an independent predictor of stroke in elderly Japanese hypertensive patients. It extends previous work showing that extreme-dippers are at increased risk of stroke and that the principle mechanism may be the morning surge rather than an excessively low BP during the night. This suggests that the morning surge in BP could be a new therapeutic target for preventing target organ damage and subsequent cardiovascular events in hypertensive patients. This finding should be investigated in other racial populations and in a large randomized, controlled trial using antihypertensive medication aimed at suppressing the MBPS.

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# Ambulatory Blood Pressure Monitoring for Cardiovascular Medicine

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*Evaluating Blood Pressure Behavior Outside of the Clinical Setting and During Daily Activities to Identify High-Risk Subjects*

H igh blood pressure (BP) is the most powerful cardiovascular risk factor. Ambulatory BP is more closely associated with target organ damage and cardiovascular events than BP behaviors measured in the clinical setting. Due to the marked advances in technology, small-sized automated devices for ambulatory BP monitoring (ABPM) are now available for clinical practice for prevention of cardiovascular diseases. In addition to BP level, BP variability is a characteristic of the cardiovascular system to be associated with target organ damage and cardiovascular prognosis. Using a recently developed ABPM method, we were able to gather valuable information concerning the cardiovascular system. When combined with BP parameters, the recorded variables have the potential of leading to new parameters that may reflect the individual pathophysiological condition. In this article, we summarize the state of the art of ABPM and discuss information that could be recorded using future ABPM.

## Current ABPM Devices

### Small Size
The smallest ABPM device is now 215 g (including battery) in weight and 27x72x100 mm in size (TM-2431, A&D, Tokyo). The intermittent cuff-inflation pressure is set to be gradually modulated according to previous BP measures. This characteristic results in a lower cuff-inflation pressure value at night because of the lower values of BP typically recorded during sleep. A decreased cuff-inflation pressure value has the significant advantage of minimizing sleep disturbance.

### Multifunctional ABPM
In addition, recently developed multifunctional ABPM simultaneously monitors heart rate and physical activity continuously (TM-2021, A&D, Tokyo) [1]. Autonomic nervous function could be calculated using spectral analysis of heart-rate variability. These ABPM devices are typically equipped with actigraphy to allow one to perform a quantitative evaluation of physical activity. More recently developed ABPM devices are accompanied by complete Holter ECG monitors (Fukuda densi, Tokyo, Japan). Using this device, a full evaluation of arrhythmia could be achieved. Another interesting ABPM device includes triggering the system for BP measurement by ST-depression as detected by real-time analysis of Holter ECG data

(Meditech, Austria). This device could potentially be used to assess BP levels during myocardial ischemic episodes.

### Clinical Information Obtained from ABPM
Based on a more precise assessment of cardiovascular risk via ambulatory recordings, a more adequate therapeutic strategy for individualized antihypertensive therapy could be achieved by AMPM.

### White-Coat Hypertension Versus Sustained BP
Using ABPM, the "true" BP level of each individual could be measured. All previously published reports demonstrate that ABP is a better predictor of cardiovascular prognosis than clinic BP. White-coat hypertension (WCHT), defined by persistently high clinic BP levels and normal ABP, is common in clinical practice [2], particularly in older hypertensive subjects [3], in whom its frequency may be as high as 40% [4]. However, it is still controversial whether WCHT is a benign condition or not. In cross-sectional studies, some authors have found a clustering of cardiovascular risk factors or increased target organ damage in WCHT compared with normotensive subjects (NTs) [5]-[8], while others have not [9]-[14]. A way to diagnose WCHT is by using ABPM [15]. Compared with patients with WCHT, the event rates in sustained hypertension (SHT) are much higher [16]-[23]. In our prospective study on hypertensive patients, stroke prognosis is much poorer in SHT patients than in WCHT patients (Figure 1).

### Diurnal BP Variation

#### Nocturnal BP Dipping
BP has a diurnal variation, typically reaching the highest level during the morning, and then declining to reach a trough value at about midnight. This diurnal BP variation pattern is subject to random variations and could be monitored using ABPM (Figure 2).

An abnormal pattern of diurnal BP variation has been reported to be associated with both clinically overt and silent target organ damage as well as to be a predictor of subsequent cardiovascular events independently on the BP level [24]-[31]. Nondippers, with a diminished nocturnal BP fall, have been proposed as one subgroup of abnormal diurnal BP variation that is associated with increased frequency of damage to all target organs (brain, heart, and kidney) and poor

prognosis for cardiovascular events, when compared with the normal dipping pattern [25]-[27]. In addition, risers (with an increasing nocturnal BP) have the worst cardiovascular prognosis [28], [30]-[32]. The frequency of nondipping pattern increases with age, reaching 50% in the elderly population. In addition to nondippers or risers, we previously recognized extreme dippers, who have a more marked nocturnal BP fall than dippers, as another subtype of abnormal diurnal BP variation

[29], [31], and we found that among elderly patients with sustained hypertension, extreme dippers have a higher frequency of both silent and clinical cerebrovascular damage than dippers (Figure 3) [29], [31].

The precise mechanisms underlying these abnormal dipping occurrences remain unclear. Several factors are affecting the diurnal BP variation pattern. The nondipping pattern is associated with autonomic nervous system dysfunction [33], [34] and poor sleep quality due to nocturnal behavior and sleep apnea [35]-[37] and psychological factors such as depression [38]. Extreme-dippers tended to have predominant systolic hypertension and increased BP variability [29]. Extreme-dippers might have increased arterial stiffness with reduced circulating blood volume in addition to an excessive increase in orthostatic BP and morning surge due to α-adrenergic hyperactivity [39]-[41]. Antihypertensive medication that normalizes the diurnal BP variation might improve cardiovascular prognosis in high-risk hypertensive patients.

## BP Surge

There is growing evidence indicating that there is a marked diurnal variation in the onset of cardiovascular events, with a peak incidence of myocardial infarction, sudden cardiac death, and anemic and hemorrhagic stroke occurring in the morning (6 a.m. to noon), following a nadir in these events during the night [42]-[45]. It has been suggested that this morning surge in BP might trigger cardiovascular events, but so far there have been no studies that directly demonstrate an association between the morning BP surge and events.

We studied stroke prognosis in 519 older hypertensive subjects in whom ambulatory BP monitoring was performed, and silent cerebral infarct was assessed using brain MRI. Patients were followed prospectively [46]. The morning BP surge was calculated as follows: the mean systolic BP during the 2 hours after awakening minus the mean systolic BP during 1 hour that included the lowest sleep BP. During an average duration of 41 months, 44 stroke events occurred. When the patients were divided into two groups according to morning BP surge, those in the top 10% (surge group: morning BP surge $\geq 55$ mmHg, $n=53$) had a higher baseline prevalence of multiple infarcts (57% versus 33%, $p=0.001$) and a higher stroke inci-
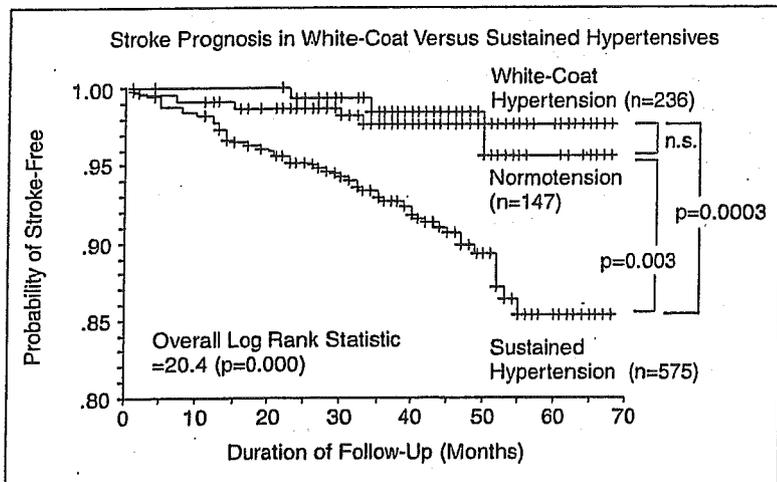


**Fig. 1.** Stroke prognosis in white-coat versus sustained hypertensives.
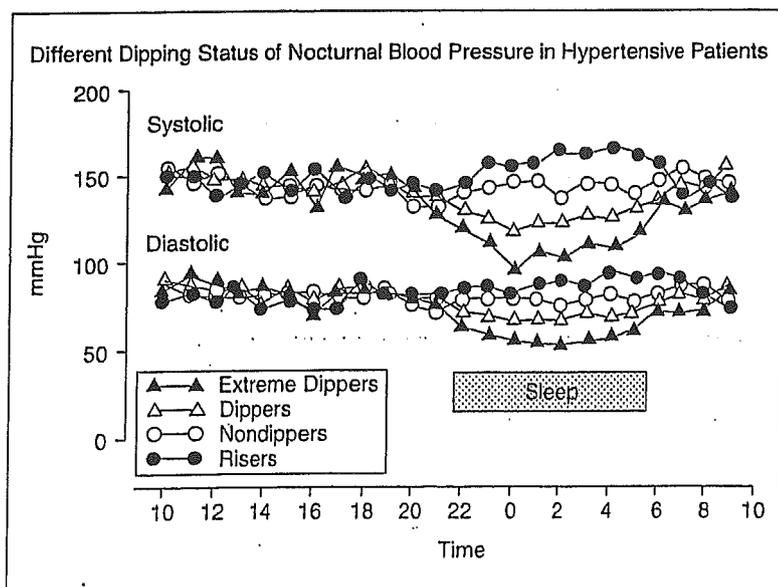


**Fig. 2.** Different dipping status of nocturnal blood pressure in hypertensive patients.

dence (19% versus 7.3%, $p=0.004$) during the follow-up period than the others (nonsurge group: morning BP surge <55mmHg, $n=466$). After matching for age and 24-hr BP, the relative risk of the surge group versus the nonsurge group remained significant ($RR=2.7$, $p=0.04$). The morning BP surge was associated with stroke events independently of the subject's 24-hr BP, nocturnal BP dipping status, and baseline prevalence of silent infarct; and thus a 10-mmHg increase in morning systolic BP surge is independently associated with a 22% increase in stroke incidence ($p=0.008$) (Table 1). In older hypertensives, a higher morning BP surge is associated with stroke risk independently of ambulatory BP, nocturnal BP falls, and silent infarct. Reduction of the morning surge could thus be a new therapeutic target for preventing target organ damage and subsequent cardiovascular events in hypertensive patients.

## BP Reactivity

BP varies widely by daily stress. Those with marked BP increase (BP reactivity) by stress such as orthostatic, physical, and psychological stress might have risk for future hypertension or cardiovascular events. Several authors report that normotensive subjects with increased BP reactivity after physical exercise very frequently develop hypertension [47], [48]. In addition, marked increase in physical activity-induced BP might lead to plaque rupture, which partly accounts for cardiovascular events that occur during exercise [49].Psychological stress also might trigger cardiovascular events through transient BP increase. A recent population-based prospective study demonstrated that men with exaggerated stress-induced SBP response (>20 mmHg) had 87% greater risk of ischemic stroke than less reactive men [50]. In a previous study by our team, cardiovascular events were triggered by external factors causing a dramatic emotional response, which were the times at which a transient BP increase was observed [51], [52].

## Orthostatic BP Dysregulation

BP reactivity during orthostatic stress is associated with stroke risk in hypertensive patients. In normal subjects, BP shows minimal variation with postural changes because of cardiovascular reflex adjustments. In most hypertensive patients as well, postural BP changes do not vary much when autonomic nervous function is intact. Orthostatic hypotension, often found in elderly hypertensive subjects, is well recognized as a risk for falls, syncope, and cardiovascular events [53]-[56]. On the other hand, there have been few reports on orthostatic hypertension, in which BP increases with orthostatic postural change [57]-[59]. Although previous reports suggested that an orthostatic BP increase predicts an increased risk of developing coronary artery disease [57] and impaired neurobehavioral function [60], the clinical significance and mechanism associated with orthostatic hypertension remain unclear.

We performed a head-up tilting test and brain MRI in 241 elderly subjects with sustained hypertension determined by ambulatory BP monitoring [61]. We classified patients into

an orthostatic hypertension group with orthostatic increase of systolic BP of $\geq 20$ mmHg ($n=26$), an orthostatic hypotension group with orthostatic systolic BP decrease of $\geq 20$ mmHg ($n=23$), and a normal group with neither of these two patterns ($n=192$). Silent cerebral infarcts were more common in the orthostatic hypertension (3.4/person, $p<0.0001$) and orthostatic hypotension groups (2.7/person, $p=0.04$), compared with the normal group (1.4/person). The multiple silent cerebral infarcts and advanced deep white matter lesion were significantly more common in the orthostatic hypertension group than in the orthostatic normotension group (Figure 4). Morning surges in systolic BP were higher in the orthostatic hypertension group than in the normal group (159 versus 149 mmHg, $p=0.007$), while there were no significant differences between the two groups in the ambulatory BP during other periods (Figure 5). The orthostatic hypertension (21 mmHg, $p<0.0001$) and hypotension (20 mmHg, $p=0.01$) groups had a higher BP variability (SD of awake systolic BP) than the normal group (17 mmHg). The associations between orthostatic BP change and silent cerebrovascular disease remained significant after controlling for confounders including ambulatory BP. The orthostatic BP increase was selectively abolished by a-adrenergic blocking, indicating that a-adrenergic activity

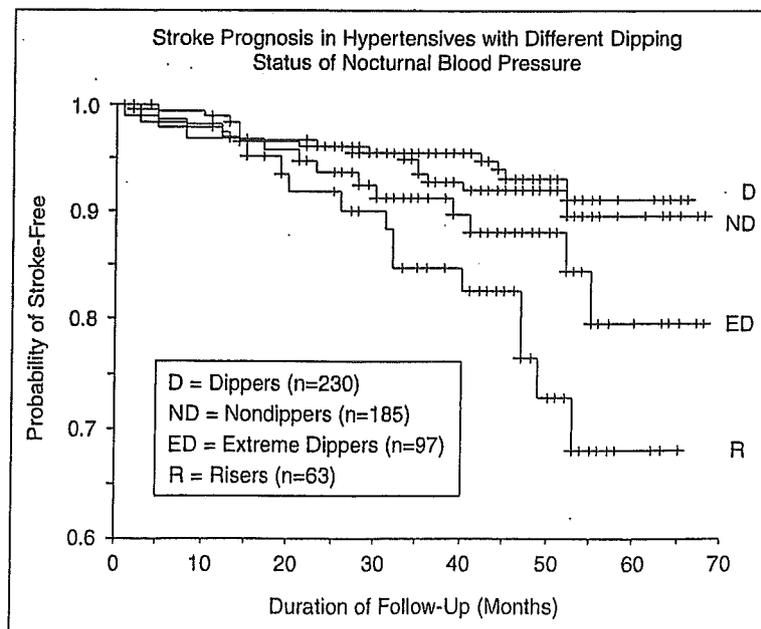| TABLE 1. Relative risk for stroke event in hypertension ($n=519$). | | |
|---|---|---|
| Covariates | Relative risk | p-value |
| Age (10 years) | 1.75 (1.20-2.55) | 0.004 |
| 24-hr SBP (10 mmHg) | 1.38 (1.17-1.64) | <0.001 |
| Silent cerebral infarct | 4.50 (1.99-10.2) | <0.001 |
| Morning SBP surge (10 mmHg) | 1.22 (1.05-1.40) | 0.008 |



Fig. 3. Stroke prognosis in hypertensives with different dipping. Status of nocturnal blood pressure.