Office Blood Pressure Variability as a Predictor of Brain Infarction in Elderly Hypertensive Patients


Large 24-h blood pressure (BP) variability and an excessive drop in BP during nighttime are associated with a higher risk of cardiovascular events. Data are lacking regarding the prognostic significance of variability in BP measured during office visits. We analyzed the relationship between office BP variability and the risk of brain infarction in elderly patients receiving antihypertensive therapy. Patients who experienced their first-ever stroke at the age of 60 years or over were registered in the study. At least 2 sex- and age-matched control patients were registered for each case patient. Office BP at each clinic visit and known cardiovascular risk factors were recorded. The BP variability was defined as the variation coefficient (VC) of office BP. In this report, we analyze the data of brain infarction patients. The VC of both systolic and diastolic BPs was significantly higher in the brain infarction patients than in the control patients. Higher office BP variability was associated with a higher risk of brain infarction after adjustment for BP level and other confounding factors. Regarding diastolic BP, the association of brain infarction with the maximal value for the difference of office BPs taken at any consecutive two visits (Max-dBP) or the difference between the highest and lowest values of office BP (BP-range) recorded during a 1-year period prior to the event was also significant. In conclusion, a retrospective case-control study suggested that office BP variability was an independent predictor of brain infarction. Either the Max-dBP or the BP-range may be surrogate indices of diastolic BP variability. (Hypertens Res 2000; 23: 553-560)

Key Words: elderly hypertension, long-term blood pressure variability, ischemic stroke, antihypertensive treatment

Introduction

Cardiovascular diseases such as stroke and myocardial infarction are the leading causes of death and disability of elderly people, so prevention of these diseases is a very important public health problem. Hypertension is a major risk factor of stroke and myocardial infarction. Antihypertensive treatment is effective in reducing cardiovascular diseases, especially strokes, and this efficacy has been proven in elderly hypertensive patients (1-6). However, our preliminary analysis suggested that the crude incidence rates of stroke and myocardial infarction were still higher in patients aged ≥50 years receiving antihypertensive therapy than in the general population (7). Therefore, current antihypertensive therapy should be im-
proved, if possible.

Analyses of circadian variation of blood pressure (BP) have shown that larger BP variability (8, 9) and excessive drops in BP during nighttime (10, 11) are associated with a higher risk of cardiovascular events. A steep BP elevation around arousal, the so-called morning surge, is believed to be associated with an increased risk of myocardial infarction (12). These results prompted us to choose a drug regimen to minimize short-term BP variability or to reduce the morning surge.

We noted, however, that the relationship between long-term variability of BP and occurrence of cardiovascular events has not been extensively examined. Therefore, in the present case-control study, we analyzed the relationship between the variability of BP measurements taken during office visits (office BP) and the occurrence of brain infarction in elderly patients receiving antihypertensive drug therapy.

Methods

Patients

Patient registration was performed at 6 hospitals, where the members of the research group had outpatient clinics. If a patient met the following conditions, he or she was registered as a case patient: 1) receiving antihypertensive drug therapy, 2) experienced first-ever stroke at the age of 60 years or over during a 10-year period from 1987 to 1996, and 3) office BP values measured at each visit were available for at least a 1-year period before the onset of the stroke. At least 2 sex- and age-matched (±5 years) control patients were registered for each case patient. The control patients were selected from the outpatients followed at the same hospital where the case patient was registered. The selection criteria for the control patients were the same as those for the case selection except that the patients had to be free from stroke or myocardial infarction.

Diagnostic Criteria of Stroke

Only cases of brain infarction and brain hemorrhage were registered. The diagnosis and classification of stroke were based on the diagnostic guidelines of the Ad Hoc Committee of the Ministry of Health and Welfare on Cerebrovascular Diseases (13), findings on computed tomography (CT), and, if available, magnetic resonance imaging (MRI) scans. In brief, the slow development of a focal neurological deficit of acute onset, usually beginning with the individual at rest, which persisted more than 24 h, with relative preservation of consciousness and absence of blood in the cerebrospinal fluid was considered suggestive of a diagnosis of brain infarction. Included in this category are cases of brain embolism with an abrupt onset of a focal neurological deficit associated with a known source for embolus in which CT or MRI revealed no evidence of hemorrhage except for hemorrhagic infarction. In cases of brain hemorrhage, there was a focal neurological deficit of acute onset that exhibited a rapid evolution, and it was frequently associated with an altered level of consciousness, headache, or elevated BP. CT or MRI demonstrated evidence of hemorrhage in the brain and/or ventricle. Patients who were found to have stroke focus/foci only through CT or MRI scans but who did not meet the clinical criteria were not included.

BP Measurement

At each visit, sitting blood pressure was measured twice by the attending physician with a standard mercury sphygmomanometer. The fifth Korotkoff sound was used as the reflection of diastolic blood pressure. The average of the two readings was recorded for that day.

Inspection of the Medical Records

By investigating the medical records of the patients, we were able to record the following on registration sheets: office BP and pulse rate measured at each visit during a 1-year period before the onset of stroke, concomitant diseases including diabetes mellitus, hypercholesterolemia and renal insufficiency, laboratory data, and electrocardiogram findings. For the control patients, data during a 1-year period prior to the registration date were recorded.

Diabetes mellitus was diagnosed when the fasting plasma glucose concentration was 140 mg/dl or more, when the diagnosis was confirmed by a 75-g oral glucose tolerance test (14), or when the patient was receiving an oral hypoglycemic agent or insulin. Hypercholesterolemia was diagnosed when the serum total cholesterol concentration was 220 mg/dl or more, or when the patient was taking an antihypercholesterolemic agent. Renal insufficiency was defined as serum creatinine concentration ≥1.4 mg/dl for men and ≥1.2 mg/dl for women. Although serum creatinine concentration may underestimate hypertensive renal involvement (15), we adopted these cutoff points based on a previous report that demonstrated that the risk of developing end-stage renal disease substantially increased when serum creatinine concentration exceeded these levels (16).

Data Analysis

We registered 171 stroke patients (138 brain infarction and 33 brain hemorrhage). Because the number of the patients with brain hemorrhage was small, we excluded these patients from the analysis. We registered 350 control patients for the brain infarction patients.

We defined the variability of office BP as the variation
Coefficient (VC) of office BP, which was calculated for each patient by using the following formula: \(100 \times (\text{SD of office BP measured at each monthly visit})/(\text{average of office BP})\). However, VC of office BP is not easy to immediately calculate in an outpatient clinic. We examined whether the following two variables could be used as surrogate indices of the variability of office BP: 1) the maximal value for the difference of office BPs taken at any consecutive two visits (Max-\(\Delta\)BP) and 2) the difference between the highest and lowest values of office BP (BP-range) recorded during a 1-year period prior to the occurrence of brain infarction.

Data are expressed as mean±SD. The statistical analysis was performed with the use of the Statistical Analysis System (SAS) (17). By using multiple logistic analysis, we examined whether the variability of office BP is a predictor of brain infarction. \(P<0.05\) was considered statistically significant.

### Results

#### Patients' Profile

The average age and men-to-women ratio were similar in the brain infarction patients and the control patients. The brain infarction patients had a lower mean body mass index and visited an outpatient clinic less frequently during the 1-year period prior to the occurrence of the event than the control patients. The brain infarction patients also had significantly higher systolic BP, a higher prevalence of atrial fibrillation (Af), lower total protein concentrations, lower total cholesterol concentrations, higher fasting plasma glucose concentrations, and higher serum creatinine concentrations. The prevalence of currently being a smoker and of having proteinuria and renal insufficiency was significantly higher in the brain infarction patients (Table 1).

#### Office BP Variability

Figure 1 shows the time course of BP and pulse rate measured at every monthly visit prior to the onset of brain infarction. \(\bullet\bullet\bullet\), brain infarction patients; \(\circ\circ\circ\), control patients. SBP, systolic blood pressure; DBP, diastolic blood pressure. The error bar represents SE of the mean. The two lines were statistically significantly different \((p<0.01)\) by two-way ANOVA.

### Table 1. Patient Profiles

<table>
<thead>
<tr>
<th></th>
<th>Control ((n=350))</th>
<th>Brain infarction ((n=138))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y.o.)</td>
<td>73.3±8.0</td>
<td>73.8±7.9</td>
</tr>
<tr>
<td>Men (%)</td>
<td>41.7</td>
<td>45.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0±3.3</td>
<td>23.2±3.4*</td>
</tr>
<tr>
<td>Frequency of hospital visits (times/1 year)</td>
<td>10.3±2.3</td>
<td>9.8±2.4*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142.2±12.2</td>
<td>148.1±14.2*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.5±8.6</td>
<td>80.2±8.0</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>73.8±9.8</td>
<td>74.7±10.5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>20.9</td>
<td>29.0</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>46.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3.7</td>
<td>16.7*</td>
</tr>
<tr>
<td>Angina pectoris (%)</td>
<td>14.6</td>
<td>13.0</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>9.7</td>
<td>17.4*</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>7.2±0.5</td>
<td>7.1±0.5*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>209.5±30.3</td>
<td>201.6±37.4*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>104.6±22.3</td>
<td>110.6±28.2*</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.9±0.3</td>
<td>1.1±0.7*</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>9.7</td>
<td>21.7*</td>
</tr>
<tr>
<td>Renal insufficiency (%)</td>
<td>6.4</td>
<td>19.4*</td>
</tr>
</tbody>
</table>

*\(p<0.05\) vs. control. †Renal insufficiency was defined as serum creatinine ≥1.4 mg/dl in men and serum creatinine ≥1.2 mg/dl in women.

### Table 2. Variability of Office Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Brain infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (%)</td>
<td>8.9±3.2</td>
<td>9.7±3.8*</td>
</tr>
<tr>
<td>Max-(\Delta)BP (mmHg)</td>
<td>31.4±13.8</td>
<td>35.3±17.7*</td>
</tr>
<tr>
<td>BP-range (mmHg)</td>
<td>40.1±15.7</td>
<td>44.5±18.9*</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (%)</td>
<td>9.2±3.8</td>
<td>10.1±4.3*</td>
</tr>
<tr>
<td>Max-(\Delta)BP (mmHg)</td>
<td>17.6±7.6</td>
<td>19.9±9.6*</td>
</tr>
<tr>
<td>BP-range (mmHg)</td>
<td>22.3±8.9</td>
<td>24.8±11.7*</td>
</tr>
</tbody>
</table>

*\(p<0.05\) vs. control.
Effects of Other Risk Factors

We examined the effects of conventional cardiovascular risk factors on the occurrence of brain infarction (Table 3). In this analysis, sex, age, and systolic or diastolic BP were adjusted. Atrial fibrillation, proteinuria, smoking habit, lower values of serum total protein and total cholesterol, and higher value of serum creatinine all independently predicted the occurrence of brain infarction. The risk associated with Af was especially high.

Table 3. Risk of Brain Infarction Assessed by Conventional Risk Factors Other than Blood Pressure and its Variability

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of hospital visits</td>
<td>0.95 (0.85-1.03)</td>
<td>0.92 (0.85-1.01)</td>
</tr>
<tr>
<td>Presence of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.50 (0.98-2.39)</td>
<td>1.57 (0.99-2.47)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.67 (0.44-1.02)</td>
<td>0.69 (0.46-1.05)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7.06 (3.26-15.3)*</td>
<td>5.82 (2.68-11.6)*</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0.99 (0.55-1.79)</td>
<td>0.93 (0.52-1.68)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.30 (1.32-4.00)*</td>
<td>2.45 (1.42-4.22)*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.01 (1.10-3.65)*</td>
<td>2.01 (1.12-3.61)*</td>
</tr>
<tr>
<td>Body mass index (every 1 kg/m²)</td>
<td>0.93 (0.87-1.01)</td>
<td>0.93 (0.87-1.01)</td>
</tr>
<tr>
<td>Total protein (every 1 g/dl)</td>
<td>0.54 (0.35-0.85)*</td>
<td>0.53 (0.34-0.84)*</td>
</tr>
<tr>
<td>Total cholesterol (every 10 mg/dl)</td>
<td>0.91 (0.85-0.98)*</td>
<td>0.92 (0.86-0.99)*</td>
</tr>
<tr>
<td>Serum creatinine (every 0.1 mg/dl)</td>
<td>1.12 (1.05-1.20)*</td>
<td>1.12 (1.05-1.20)*</td>
</tr>
<tr>
<td>Fasting plasma glucose (every 10 mg/dl)</td>
<td>1.08 (0.97-1.19)</td>
<td>1.10 (0.99-1.21)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for sex, age, and 12-month average of systolic blood pressure. Model 2: adjusted for sex, age, and 12-month average of diastolic blood pressure. *p<0.05.

Table 4. Correlation Coefficient between Office Blood Pressure Variability Expressed as VC and Other Variables

<table>
<thead>
<tr>
<th></th>
<th>VC of SBP</th>
<th>VC of DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.14*</td>
<td>0.25*</td>
</tr>
<tr>
<td>Frequency of hospital visits</td>
<td>0.15*</td>
<td>0.20*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.08</td>
<td>—</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>—</td>
<td>-0.41*</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.06</td>
<td>0.17*</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>0.04</td>
<td>0.11*</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.07</td>
<td>0.18*</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Total protein</td>
<td>-0.11*</td>
<td>-0.14*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.15*</td>
<td>-0.18*</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.12*</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

*p<0.05.

BP-range were also significantly higher in the brain infarction patients.

Effects of Other Risk Factors

We examined the effects of conventional cardiovascular risk factors on the occurrence of brain infarction (Table 3). In this analysis, sex, age, and systolic or diastolic BP were adjusted. Atrial fibrillation, proteinuria, smoking habit, lower values of serum total protein and total cholesterol, and higher value of serum creatinine all independently predicted the occurrence of brain infarction. The risk associated with Af was especially high.

Office BP Variability and Risk of Brain Infarction

The VC of BP, irrespective of systolic or diastolic, was significantly related to age, frequency of hospital visits, total protein concentration, and body mass index (Table 4). The VC of systolic BP was also significantly related to total cholesterol concentration, and the VC of diastolic BP was significantly related to diastolic BP level, pulse pressure, pulse rate, and fasting plasma glucose concentration (Table 4). Multiple logistic analysis revealed that higher BP and larger VC of BP independently increased the risk of brain infarction after adjustment of all the other risk factors measured (Table 5). When the Max-dBP or the BP-range was included in the model instead of the VC, each variable was an independent predictor of brain infarction (Table 5).

When Af is present, BP fluctuates largely beat-to-beat. Therefore, Af might increase BP variability. Readers may be concerned that the effect of Af on BP variability is a serious confounding factor that could not be appropriately adjusted by mathematical manipulation. To address this concern, we performed another set of multiple logistic analyses to reconfirm the prognostic value of BP variability after excluding the patients with Af (Table 5). Higher VC of BP again increased the odds ratio of the occurrence of brain infarction. For both systolic and diastolic BP, the Max-dBP and the BP-range were independent predictors of brain infarction.

BP Variability and Antihypertensive Drugs

We analyzed whether the VC of BP varied depending upon the class of antihypertensive drug prescribed. For this analysis, we pooled the data of brain infarction and control patients, including only the patients receiving monotherapy in this analysis. The VC of BP, irrespective of systolic or diastolic, was not significantly different...
among the patients receiving any class of antihypertensive drug (Table 6).

**Discussion**

In the present case-control study, the average systolic BP level was significantly higher and the variability of office BP was significantly larger in the brain infarction patients than in the control patients. Higher variability of office BP expressed as the VC was associated with a higher risk of brain infarction even after adjustment for other confounding factors, including the average BP level. This was true after excluding the patients with Af. Concerning diastolic BP, either the Max-dBP or the BP-range also predicted the occurrence of brain infarction.

**Higher BP in the Brain Infarction Patients**

An association between higher BP and a higher risk of cardiovascular disease has been established and was re-

confirmed in the present study. There are at least two possible explanations for the higher BP in the brain infarction patients. First, BP of the brain infarction patients remained high because of inadequate antihypertensive therapy. Second, a substantial number of brain infarction patients had resistant hypertension. We did not know the goal BP that each attending physician set up for individual patients; however, the data in Table 1 suggest that in the majority of the brain infarction patients BP was reduced to the goal recommended by the Japanese Guidelines for Hypertension in the Elderly (18). Therefore, it is unlikely that a substantial number of brain infarction patients had resistant hypertension.

**Long-Term Blood Pressure Variability as a Predictor of Brain Infarction**

To our knowledge, this is the first report of the prognostic significance of the variability of office BP. It is generally accepted that BP variability expressed as a SD of aver-

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**Table 5. Risk of Brain Infarction Assessed by Multiple Logistic Analysis**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>All subjects</th>
<th>Subjects without atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1-3:</strong> including systolic BP and its variability as independent variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Average SBP (every 5 mmHg)</td>
<td>1.16 (1.08-1.25)*</td>
<td>1.18 (1.09-1.28)*</td>
</tr>
<tr>
<td>VC of BP (every 2.0%)</td>
<td>1.15 (1.03-1.29)*</td>
<td>1.16 (1.03-1.31)*</td>
</tr>
<tr>
<td>2. Average SBP (every 5 mmHg)</td>
<td>1.14 (1.06-1.23)*</td>
<td>1.15 (1.06-1.25)*</td>
</tr>
<tr>
<td>Max-dBP (every 5 mmHg)</td>
<td>1.08 (1.01-1.15)*</td>
<td>1.09 (1.02-1.17)*</td>
</tr>
<tr>
<td>3. Average SBP (every 5 mmHg)</td>
<td>1.14 (1.05-1.23)*</td>
<td>1.15 (1.06-1.25)*</td>
</tr>
<tr>
<td>BP-range (every 5 mmHg)</td>
<td>1.07 (1.00-1.13)*</td>
<td>1.07 (1.00-1.14)*</td>
</tr>
<tr>
<td><strong>Model 4-6:</strong> including diastolic BP and its variability as independent variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Average DBP (every 5 mmHg)</td>
<td>1.26 (1.10-1.44)*</td>
<td>1.20 (1.04-1.38)*</td>
</tr>
<tr>
<td>VC of BP (every 2.0%)</td>
<td>1.25 (1.12-1.39)*</td>
<td>1.27 (1.14-1.42)*</td>
</tr>
<tr>
<td>5. Average DBP (every 5 mmHg)</td>
<td>1.16 (1.02-1.32)*</td>
<td>1.10 (0.96-1.27)*</td>
</tr>
<tr>
<td>Max-dBP (every 5 mmHg)</td>
<td>1.26 (1.12-1.41)*</td>
<td>1.29 (1.14-1.46)*</td>
</tr>
<tr>
<td>6. Average DBP (every 5 mmHg)</td>
<td>1.15 (1.01-1.31)*</td>
<td>1.09 (0.95-1.25)*</td>
</tr>
<tr>
<td>BP-range (every 5 mmHg)</td>
<td>1.23 (1.11-1.36)*</td>
<td>1.25 (1.12-1.39)*</td>
</tr>
</tbody>
</table>

*p<0.05; adjusted for sex, age, frequency of hospital visits, presence of atrial fibrillation, diabetes mellitus, proteinuria, and current smoking status. SBP, systolic blood pressure; DBP, diastolic blood pressure. In the analysis of the subjects without atrial fibrillation, sex, age, frequency of hospital visits, presence of diabetes mellitus, proteinuria, and current smoking status were adjusted.

**Table 6. VC of Office Blood Pressure by Antihypertensive Drug Prescribed as Monotherapy**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>n</th>
<th>VC of SBP</th>
<th>VC of DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker</td>
<td>257</td>
<td>8.8±3.4</td>
<td>8.9±3.4</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>35</td>
<td>8.6±2.4</td>
<td>9.8±3.4</td>
</tr>
<tr>
<td>Diuretics</td>
<td>32</td>
<td>8.4±3.3</td>
<td>7.9±3.0</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>24</td>
<td>8.1±2.6</td>
<td>8.6±3.4</td>
</tr>
<tr>
<td>Other class of antihypertensive drug</td>
<td>9</td>
<td>8.0±1.8</td>
<td>9.5±3.8</td>
</tr>
</tbody>
</table>

VC, variation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure.
age BP positively correlates with BP level (19-22). Hence we here used the VC of BP as an index of BP variability to normalize for the difference of BP level among the individual patients. In the case of diastolic BP, we noticed a significant relationship between the VC and BP level; however, the association of the VC of diastolic BP and the risk of brain infarction cannot be ascribed to a confounding effect of BP level, because an inverse relationship was noticed between the VC and BP level. That inverse correlation was also noticed in 24-h BP monitoring in a community-based study (22). Furthermore, our data suggest that either the MaxΔBP or the BP-range can be used as surrogate indices of the variability of office BP, especially for diastolic BP. These findings are of practical importance, because compared to the VC of BP these indices can be far more easily calculated in an outpatient clinic.

Several studies have suggested the prognostic value of BP variability within 24 h for the subsequent progression of cardiovascular complications. Frattolla et al. (8) demonstrated that in 73 essential hypertensive patients the degree of 24-h BP variability measured at the initial visit was significantly related to an aggregate score of end-organ damage at the follow-up visit after an average of 7.4 years. In this study (8) the ambulatory BP was monitored intra-arterially and the BP signal was sampled beat-to-beat. The BP variability was defined as the standard deviation of the average of 48 consecutive half-hour periods. However, when the BP variability was defined as the average of SD obtained for each half-hour period, this short-term BP variability did not show any association with end organ damages (8). Recently, Otsuka et al. (9) showed that in 297 subjects, including 176 treated hypertensive patients, excessive circadian amplitude of BP was associated with a higher risk of ischemic stroke and renal impairment.

Verdecchia et al. (23) failed to find any independent association between baseline BP variability, which was expressed as SD of non-invasively measured ambulatory blood pressure, and subsequent cardiovascular morbidity after correction for associated confounding factors such as aging, diabetes mellitus, and severity of hypertension. In the study of Otsuka et al. (9), there was no significant association between the excessive circadian amplitude of BP and the occurrence of coronary heart disease. Thus, the prognostic significance of the 24-h BP variability may have organ specificity. It has not been fully elucidated whether the long-term office BP variability predicts cardiac complications such as left ventricular hypertrophy and coronary heart disease. We made a preliminary analysis that showed a significant association between office BP variability and the occurrence of acute myocardial infarction (24).

### Mechanism that Links the BP Variability and Brain Infarction

In the previous studies that demonstrated the prognostic significance of 24-h BP variability, SD of the average of 48 consecutive half-hour periods (8) and the circadian amplitude of BP (9) were used as the indices of the BP variability. These variables mainly reflect the circadian BP variation. Thus, the results of these studies (8, 9) may be, at least in part, explained by the association of an excessive drop in nocturnal blood pressure and silent cerebrovascular lesions (10, 11). On the other hand, the long-term variability of office BP did not contain the component of circadian BP variation. Therefore, the mechanism that links the larger office BP variability and the occurrence of brain infarction should be different from the mechanism that links the 24-h BP variability and the cardiovascular complications.

In the present study, we did not directly focus on how the larger office BP variability increased the risk of brain infarction; however, several points deserve to be discussed. First, the significant correlation between the VC of BP and pulse pressure suggests that the larger BP variability reflected a reduced compliance of large elastic arteries due to advanced arteriosclerosis. Stiffening of the large arterial wall results in an attenuation of the baroreflex function, which then causes a larger BP variability (25). The significant correlation between the VC of BP and serum creatinine concentration, an index of hypertensive nephrosclerosis, or other cardiovascular risk factors including age and fasting plasma glucose concentration also supports the possibility that the larger BP variability was associated with advanced arteriosclerosis. Second, the negative correlation between the office BP variability and total protein concentration, body mass index, and, in the case of systolic BP, total cholesterol concentration raises a possibility that the nutritional states were impaired in the patients with larger BP variability. Third, long-term blood pressure fluctuation may be a function of patient adherence to the drug therapy. The less frequent hospital visits of the brain infarction patients compared to visits by the control patients, though the difference between the two groups was small, suggested that the larger BP variability in the brain infarction patients was, at least in part, due to poorer adherence to the drug therapy. The fact that both systolic and diastolic BPs were higher in the brain infarction patients does not seem contradictory to this possibility. However, the VC of systolic and diastolic BPs was positively correlated to the frequency of hospital visit. Even after the adjustment for possible confounding factors including the average BP level and the frequency of hospital visit, the association of larger office BP variability and higher risk of brain infarction was significant. Therefore, this association may not be solely explained by the poorer adherence to the drug...
were on antihypertensive drug therapy, we could not ex-
required. Because in the present study all the patients
therapy.
BP variability during Antihypertensive Treatment
We could not detect a significant difference of office BP
among the classes of antihypertensive drugs
prescribed. Because in the present study all the patients
were on antihypertensive drug therapy, we could not ex-
amine the effects of antihypertensive treatment on BP
variability. Mancia et al. (26) reported that several weeks
of therapy with a calcium antagonist or an angiotensin
converting enzyme inhibitor induced only a slight reduc-
tion of the BP variability expressed as the SD of average
of 24-h, daytime, and nighttime BP. In this report (26),
the BP variability expressed as VC was unchanged or
even slightly increased by antihypertensive therapy.

Study Limitations
There are several limitations to the present study. First,
the design was for a retrospective, case-control study. The
prognostic value of the long-term BP variability should be
confirmed in a prospective study. Second, the patients
were directed to visit the outpatient clinic once a month.
If the patients visited the clinic much more frequently, we
might have had different or more clear-cut results concern-
ing the relationship between the office BP variability and the
risk of brain infarction. In this context, the variability of
BP measured at home (home BP) would provide valuable
information, because home BP can be measured every
day or even twice or more times each day. Although the
variability of home BP was substantially small when com-
pared to that of ambulatory BP (27), preliminary results
from the Ohasama study suggested a U-shaped relation-
ship between home BP variability and cardiovascular
mortality (28). Third, since findings on CT or MRI were
not available in the control patients, those with asym-
tomatic cerebrovascular lesions may have been registered
as control patients. If only patients without asymptomatic
cerebrovascular lesion were registered as control patients,
we might have had different or more clear-cut results con-
cerning the relationship between the office BP variability
and the risk of brain infarction.

In conclusion, our data suggested that the larger office
BP variability expressed as VC of BP was associated with
a higher risk of brain infarction. The prognostic value of
BP variability was independent of BP level and other
known cardiovascular risk factors. Either the Max-dBP
or the BP-range may be surrogate indices of the diastolic
BP variability.

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