Determinants of Exaggerated Difference in Morning and Evening Blood Pressure Measured by Self-measured Blood Pressure Monitoring in Medicated Hypertensive Patients: Jichi Morning Hypertension Research (J-MORE) Study

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Background: Morning blood pressure (BP) surge in ambulatory BP monitoring was a risk factor for stroke in our previous study. We studied the determinants of the morning minus evening systolic BP difference (ME difference) in self-measured BP monitoring, as a possible risk factor for stroke in medicated hypertensive patients.

Methods: Nine hundred sixty-nine hypertensive outpatients receiving stable antihypertensive drug treatment were studied using self-measured BP monitoring in the morning and evening.

Results: The ME difference ranged from −37.3 to 53.3 mm Hg (mean 7.9 mm Hg). The highest quartile (Q4) of the ME difference group (>15.0 mm Hg) had older age (68.0 ± 9.8 years vs 66.2 ± 10.3 years, P = .01) and higher prevalence of men (48.3% vs 39.9%, P = .02), regular alcohol drinkers (34.7% vs 26.0%, P = .01) and β-blocker use (26.9% vs 19.9%, P = .03) than the other quartile groups (Q1 to Q3), whereas there was no significant difference in the average of morning and evening (ME average) BP. In logistic regression analysis controlling for ME average and other confounding factors, independent risks for Q4 of ME difference were older age (10 years older: odds ratio [OR] 1.21, P = .01, 95% confidence interval [CI] 1.04–1.42), regular alcohol drinker (OR 1.51, P = .04, 95% CI 1.01–2.26), and β-blocker use (OR 1.50, P = .02, 95% CI 1.06–2.12).

Conclusions: Older age, β-blocker use, and regular alcohol drinking were significant determinants of the exaggerated ME difference in medicated hypertensive patients.

Key Words: Self-measured blood pressure monitoring, hypertension, morning surge.

Recently, we reported that exaggerated morning systolic BP surge (the morning BP [average of 4 to 5 BP readings during the first 2 h after wake-up time] minus the lowest BP [average of 3 BP readings centered on the lowest night-time reading]) evaluated by ambulatory BP monitoring was an independent risk factor for the prevalence of silent cerebral infarcts and the incidence of stroke events independently of the 24-h BP level. Moreover, morning minus evening systolic BP difference (ME difference) from ambulatory BP monitoring was also shown to be an independent predictor of stroke.

Self-measured BP monitoring is a possible substitute...
for ambulatory BP monitoring. In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC7), the self-measured BP level was evaluated as the average of all BPs measured in the morning and in the evening. However, ME difference may have additional clinical usefulness for the management of hypertensive patients, and exaggerated ME difference with high morning BP and low evening BP may be a risk factor for cardiovascular disease even in medicated hypertensive patients with a well-controlled ME average.

In this study, we investigated ME difference as a possible alternative to the morning ambulatory BP surge, and examined its determinants in medicated hypertensive patients.

**Methods**

**Patients**

We studied 1027 hypertensive outpatients with stable antihypertensive drug treatment for at least 3 months. They were consecutively recruited from 43 doctors in 32 different clinics and hospitals in Japan.

Smoking was defined as having a current smoking habit. Chronic renal disease was defined as overt proteinuria or elevated serum creatinine level more than 176.8 μmol/L (2.0 mg/dL). Diabetes mellitus was defined as more than 7.0 mmol/L (126 mg/dL) of fasting blood glucose or more than 11.1 mmol/L (200 mg/dL) casual glucose level in patients who were not treated or treated for diabetes mellitus. Glucose intolerance was defined as fasting blood glucose level in the range of 6.1 to 6.9 mmol/L (110 to 125 mg/dL). Hyperlipidemia was defined as more than 5.7 mmol/L (220 mg/dL) total cholesterol level or more than 1.7 mmol/L (150 mg/dL) triglyceride level. Clinical histories of the patients were obtained from interviews by the patient’s own doctors.

All of the antihypertensive medications were classified as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, diuretics, α-blockers, and others. Patients who were taking verapamil or diltiazem and dihydropyridine calcium channel blocker were classified as taking one CCB; αβ-blocker was classified as β-blocker. The institutional review board of Jichi Medical School approved this study, and informed consent was obtained from all patients.

**Study Protocol**

Morning and evening BP were measured using commercially available self-measured BP devices of which the accuracy was validated. All of the patients were instructed to measure BP using a cuff oscillometric device on the same upper arm position for 3 days. If the patients were not using their own self-measured BP devices in daily practice, cuff oscillometric semiautomatic devices (UA-631, A&D, Tokyo, Japan) were given to them for this study. Self-measured BP was conducted twice on each occasion in a seated and relaxed position with the arm bare in the morning (within 1 h after waking, before having breakfast and taking medication) and evening (just before going to bed) for 3 consecutive days (total of six measurements). The first measurement was performed after more than 2 min of rest and the second measurement was performed after an interval of more than 30 sec. The patients were asked to document all of the self-measured BP value on the sheet and report them to their own physician.

Morning BP and evening BP were defined as the average of the first and the second self-measured BP values in the morning and in the evening, respectively, for 3 days (total of six BP measurements). The average of the morning and the evening systolic BP (ME average) was calculated. The ME difference was defined as morning systolic BP minus evening systolic BP.

Clinic BP was measured after resting for at least 5 min at two different clinic visits before and after the self-measured BP monitoring period. Clinic BP was defined as the average of the BPs measured at two visits (9 AM to 5 PM). We did not adjust the time of clinic BP measurements at trough time.

**Statistical Methods**

After excluding the 58 patients, those on night-shift work (25 patients) and incomplete data sets (33 patients), statistical analyses were conducted for 969 patients using the computer software SPSS version 11.0f (SPSS Inc., Chicago, IL). The comparisons of two parameters were performed by the two-tailed nonpaired t test and comparisons of categorical variables were performed by the χ² test. One-way analysis of variance (ANOVA) was performed to detect differences among groups, and Tukey’s honestly significant differences (HSD) test was used for multiple pairwise comparisons of means among groups. Odds ratio (OR) and the 95% confidence interval (CI) were calculated by multiple logistic regression analysis. A probability value < .05 was considered statistically significant.

**Results**

**Patient Characteristics**

The age of the total study population ranged from 32 to 95 years (mean ± SD: 66.5 ± 10.2 years) and 407 men and 562 women were enrolled. All of the 969 patients were taking one or more antihypertensive medications: CCB (71.2%), ACEI (27.3%), ARB (31.6%), β-blockers (21.7%), α-blockers (10.6%), diuretics (12.6%), and others. Thirty-three percent of the patients were taking antihypertensive medication in the evening or before going to bed. Hyperlipidemia was observed in 40.9% of patients. Diabetes mellitus or impaired glucose was observed in 15.9% of patients. Regular alcohol drinkers constituted 28.3% of all patients. Current smokers constituted 12.2%. History of cardiovascular events included angina pectoris (8.3%), myocardial infarction (5.6%), and
stroke (7.4%). Chronic renal disease was present in 5.0% of the patients.

**BP Control Status**

Clinic BP, morning BP, evening BP, and ME average were 143.0 ± 15.6/80.7 ± 10.1 mm Hg, 139.8 ± 14.6/81.7 ± 10.0 mm Hg, 131.8 ± 14.2/75.9 ± 9.8 mm Hg, and 135.8 ± 13.2/78.8 ± 9.3 mm Hg, respectively. Systolic ME average was controlled to less than 135 mm Hg in 472 patients (49.3% of all patients). We considered 140 mm Hg for clinic systolic BP and 135 mm Hg for self-measured systolic BP at home as the cutoff level, according to the JNC7.10 Well-controlled clinic systolic BP was seen in 422 patients (43.6% of all patients and 51.7% of well-controlled clinic systolic BP patients).

**ME Difference**

The ME difference ranged from −37.3 to 53.3 mm Hg (mean: 7.9 mm Hg) and the highest quartile (Q4) of ME difference was more than 15.0 mm Hg (n = 240, median: 21.3 mm Hg). Even in the 472 patients (49.3%) with well-controlled systolic ME average (≤135 mm Hg), exaggerated ME difference (>15 mm Hg) was seen in 109 patients (23.1%) (Fig. 1). The ME difference was not correlated with the ME average (r = 0.04, P = .24), although morning BP and evening BP were correlated with ME difference (morning systolic BP: r = 0.43, P < .001; evening systolic BP: r = −0.37, P < .001).

**Determinants of Exaggerated ME Difference**

We compared the Q4 group of ME difference group with the other three quartile groups (Q1 to Q3) and evaluated the determinants of the exaggerated ME difference (Table 1). The patients in the Q4 group of ME difference were older (68.0 ± 9.8 v 66.2 ± 10.3 years, P = .01) and had a higher prevalence of male gender (48.3% v 39.9%, P = .02), regular alcohol drinkers (drinker) (34.7% v 26.0%, P = .01), and β-blocker users (26.9 v 19.9%, P = .03) than those in the Q1 to Q3 groups. The prevalence of smokers tended to be lower in the Q4 of ME difference patients than that in the Q1 to Q3 patients (9.5% v 13.1%, P = .17). There was no significant difference in the ME average between the two groups (Q4 v Q1 to Q3: 137.2 ± 14.2 v 135.3 ± 12.9 mm Hg for systolic BP, P = .06; 78.8 ± 8.7 v 78.9 ± 9.5 mm Hg for diastolic BP, P = .90) (Table 2).

There was no significant difference in the prevalence of patients who were taking antihypertensive medication at night or before going to bed between the two groups (Q4 v Q1 to Q3: 32.2% v 33.6%, P = .753).

In multiple logistic regression analysis, the OR (95% CI) for the Q4 of ME difference were 1.21 (1.04–1.42) for age (10-year increase) (P = .013), 1.50 (1.06–2.12) for β-blocker use (P = .02), 1.51 (1.01–2.26) for drinkers (P = .04), and 0.52 (0.31–0.87) for smokers (P = .01) (Table 3).

**Regular Alcohol Drinkers**

Drinkers had significantly lower evening systolic BP (129.9 ± 14.0 v 132.6 ± 14.2 mm Hg, P = .01) and higher evening heart rate (70.6 ± 10.5 v 67.9 ± 8.6 beats/min, P < .001) than nondrinkers. Morning diastolic BP was significantly higher in drinkers (drinkers versus nondrinkers: 83.6 ± 10 v 81.0 ± 9.9 mm Hg, P < .001), whereas morning systolic BP did not show a significant difference (drinkers versus nondrinkers: 140.1 ± 14.4 v 139.6 ± 14.7 mm Hg, P = .66).

The increase of the ME difference in drinkers was more prominent in elderly patients (aged ≥65 years) than in younger patients (aged <65 years), although ME average was higher in both drinker and nondrinker elderly patients (Fig. 2). The morning systolic BP level was significantly higher in elderly patients than in younger patients in both drinkers and nondrinkers (elderly versus younger patients: 141.2 ± 136.9 mm Hg in nondrinkers, P < .001; 142.0 ± 137.2 mm Hg in drinkers, P < .01).

**Smokers**

Smokers had a reduced risk for ME difference in this study. Morning systolic BP (139.7 ± 14.9 v 139.9 ± 12.4 mm Hg, P = .93) and evening systolic BP (131.7 ± 14.2 v 133.0 ± 14.3 mm Hg, P = .34) were not significantly different between nonsmokers and smokers.

**Determinants of Morning BP**

The patients in the highest quartile of morning systolic BP level (>150 mm Hg) were significantly older (68.9 ± 10.0 v 65.7 ± 10.2 years, P < .001), more used antihypertensive drug classes (1.9 ± 0.9 v 1.7 ± 0.9, P = .01), had a higher prevalence of ACEI use (32.6% v 25.6%, P < .05) and α-blocker use (15.3% v 9.1%, P < .01), had higher clinic systolic BP level (147.6 ± 1.0 v
141.5 ± 0.6 mm Hg, \( P < .001 \) and higher evening systolic BP level (144.6 ± 13.6 vs 127.6 ± 11.7 mm Hg, \( P < .001 \)). In multiple logistic regression analysis, the significant determinants for the highest quartile of morning systolic BP level was older age (10-year increase: OR 1.27, 95% CI 1.06–1.52, \( P = .01 \)) and evening systolic BP level (OR: 1.12, 95% CI 1.10–1.14, \( P < .001 \)) after adjustment by use of antihypertensive drug classes, ACEI use, \( \beta \)-blocker use, and clinic systolic BP level.

### Discussion

Self-measured BP data were obtained in 969 consecutive hypertensive patients using antihypertensive medication. The

#### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>ME Difference</th>
<th>The Lower 3 Quartiles (( n = 727 )) (−37.3–14.7 mm Hg)</th>
<th>The Highest Quartile (( n = 242 )) (15–53.3 mm Hg)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.2 ± 10.3</td>
<td>68.0 ± 9.8</td>
<td>.01</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>39.9</td>
<td>48.3</td>
<td>.02</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>24.3 ± 5.0</td>
<td>23.9 ± 3.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>13.1</td>
<td>9.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Regular alcohol drinker (%)</td>
<td>26.0</td>
<td>34.7</td>
<td>.01</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>40.3</td>
<td>42.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes or IGT (%)</td>
<td>16.6</td>
<td>13.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Chronic renal disease (%)</td>
<td>5.0</td>
<td>5.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>7.4</td>
<td>7.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Angina pectoris (%)</td>
<td>8.4</td>
<td>7.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.1</td>
<td>7.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Types of drugs</td>
<td>1.7</td>
<td>1.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>71.0</td>
<td>71.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Short—Intermediate</td>
<td>13.2</td>
<td>9.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Long acting</td>
<td>59.8</td>
<td>62.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>( \beta )-Blockers (%)</td>
<td>19.9</td>
<td>26.9</td>
<td>.03</td>
</tr>
<tr>
<td>ACE Inhibitors (%)</td>
<td>27.5</td>
<td>26.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>ARBs (%)</td>
<td>31.2</td>
<td>32.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>( \alpha )-Blockers (%)</td>
<td>10.0</td>
<td>12.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>12.5</td>
<td>12.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>1.5</td>
<td>1.2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Nonpaired \( t \) test:

n.s. = not significant (\( P > .05 \)); IGT = impaired glucose tolerance;

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

#### Table 2. Blood pressure and pulse rate

<table>
<thead>
<tr>
<th>ME Difference</th>
<th>The Lower 3 Quartiles (( n = 727 )) (−37.3–14.7 mm Hg)</th>
<th>The Highest Quartile (( n = 242 )) (15–53.3 mm Hg)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic SBP (mm Hg)</td>
<td>143.1 ± 15.8</td>
<td>142.8 ± 15.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinic DBP (mm Hg)</td>
<td>80.8 ± 10.2</td>
<td>80.3 ± 9.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinic PR (/min)</td>
<td>72.9 ± 10.8</td>
<td>71.5 ± 10.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Morning SBP (mm Hg)</td>
<td>136.8 ± 13.2</td>
<td>148.8 ± 15.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Morning DBP (mm Hg)</td>
<td>80.6 ± 10.0</td>
<td>85.3 ± 9.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Morning PR (/min)</td>
<td>65.6 ± 9.0</td>
<td>64.6 ± 9.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Evening SBP (mm Hg)</td>
<td>133.9 ± 13.6</td>
<td>125.7 ± 14.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Evening DBP (mm Hg)</td>
<td>77.0 ± 9.7</td>
<td>72.5 ± 9.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Evening PR (/min)</td>
<td>68.4 ± 9.1</td>
<td>69.3 ± 9.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>ME Average SBP (mm Hg)</td>
<td>135.3 ± 12.9</td>
<td>137.2 ± 14.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>ME Average DBP (mm Hg)</td>
<td>78.8 ± 9.5</td>
<td>78.9 ± 8.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>ME Average PR (/min)</td>
<td>67.0 ± 8.6</td>
<td>66.9 ± 8.8</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are shown by mean ± standard deviation.

SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate; ME Average = average of morning and evening.
Regular Alcohol Drinking

The prevalence of regular alcohol drinkers was significantly higher in the exaggerated ME difference group (Q4) than in the other ME difference groups (Q1 to Q3). Kawano et al.\textsuperscript{12} reported that regular alcohol drinking had a biphasic effect on the self-measured BP profile at home (morning BP increase and evening BP decrease). The mechanism by which hypertension is induced by alcohol consumption is unclear; however, possible mechanisms have been reported to include an imbalance of the central nervous system, impairment of the baroreceptors, an increase in sympathetic activity, stimulation of the renin-angiotensin-aldosterone system, an increase in intracellular calcium levels with a subsequent increase in vascular reactivity, stimulation of the endothelium to release endothelin or inhibition of endothelium-dependent nitric oxide production, and chronic subclinical withdrawal.\textsuperscript{13} Evening alcohol intake at dinner may have contributed to the lower evening BP, and to increased sympathetic activity, which was expressed as increased evening pulse rate. The increased sympathetic activity could contribute to exaggerated morning BP surge, and thus to increase a ME difference.

Some prospective studies\textsuperscript{14,15} showed that regular alcohol drinking increases the risk of cerebral bleeding. Heavy alcohol drinking may lead to hypertension with exaggerated morning BP surge and this may be a trigger for cerebral bleeding. On the other hand, regular alcohol drinking increased the risk for exaggerated ME difference in this study, although many prospective studies\textsuperscript{16–19} have shown that mild-to-moderate alcohol drinking reduces the risk of cardiovascular disease. The beneficial effect of regular alcohol consumption may be partly explained by factors such as anti-inflammatory and anticoagulatory effects. The C-reactive protein (CRP), a marker of inflammation, is related to atherosclerosis\textsuperscript{20} and higher a CRP level is a risk factor for cardiovascular events.\textsuperscript{21} In regular alcohol drinkers, the CRP level had been reported to be decreased\textsuperscript{22} and alcohol might have some anti-inflammatory effects in the pathogenesis of atherosclerosis. In addition, Mukamal et al.\textsuperscript{23} reported that mild-to-moderate alcohol consumption was associated with lower coagulability.

\textbf{β-Blocker Use}

In this study, the β-blocker use was found to be a determinant of exaggerated ME difference. Most of the patients were taking antihypertensive drugs once daily in the morning, but the dosage and timing of taking drugs were different among the patients. Antihypertensive drugs changed the effects on the morning BP\textsuperscript{24–26} and Morgan and Anderson\textsuperscript{27} compared the difference in the time-dependent effects during the day among placebo, felodipine (CCB), hydrochlorothiazide (diuretic), atenolol (β-blocker), and perindopril (ACEI) users. Atenolol did not reduce BP during sleep, and it caused a significantly smaller reduction of morning BP than the other three drugs.

Morning BP is affected by circadian variation of the autonomic nerves. Panza et al.\textsuperscript{28} measured forearm vascular resistance at three different times of day (7 AM, 2 PM, and 9 PM) and found that the basal forearm vascular resistance was significantly higher and the blood flow was significantly lower in the morning than in the afternoon and evening. The vasodilator effect of phentolamine (an α-adrenergic antagonist) was also most significant in the morning, indicating that there was an α-sympathetic nerve dominant BP increase in the morning. Pickering et al.\textsuperscript{29} evaluated the effect of a single daily dose of doxazosin (an α-blocker) given at night and found that the greatest reduction of BP occurred in the morning hours. We recently found that the predominant BP reduction in the morning due to doxazosin was associated with the pro-

| Table 3. Logistic regression analysis for the highest quartile of ME difference |
|------------------------|------|------------------|
|                        | OR   | P    | 95% CI          |
| Age (10 y)             | 1.21 | .01  | 1.04–1.42       |
| Male gender            | 1.35 | .11  | 0.93–1.97       |
| β-blocker use          | 1.52 | .02  | 1.06–2.12       |
| Smoking                | 0.52 | .01  | 0.31–0.87       |
| Regular alcohol drinker| 1.51 | .04  | 1.01–2.26       |
| ME Average SBP (10 mm Hg) | 1.09 | .12  | 0.98–1.22       |

OR = odds ratio; ME average SBP = average of morning SBP and evening SBP.
Other abbreviations as in Table 2.

ME average in self-measured BP was well controlled (<135 mm Hg) in 49.3% of all patients. The independent determinants for the exaggerated ME difference (>15 mm Hg, 23.1% of the total sample) were older age, regular alcohol drinking, and β-blocker use.

FIG. 2. Impact of age and drinking on ME difference. ME difference = morning systolic blood pressure (SBP) – evening SBP; ME average SBP = average of morning SBP and evening SBP. *P < .01, **P < .001 v age <65 years and nondrinker group; †P < .01 v age ≥65 years and nondrinker group; ‡P < .01 v age <65 years and drinker group.
gression of silent hypertensive cerebral disease. Thus, the association between the exaggerated ME difference and β-blocker may be due to the predominant α-sympathetic activation due to β-sympathetic blockade. However, because of the limitations of this study, further prospective evaluations will be needed to evaluate the relationship between β-blockers and exaggerated ME difference.

**Age**

Older age was also a risk factor for exaggerated ME difference in this study. Morning BP is influenced by α-sympathetic nerve activation. Autonomic nerve function is altered with aging. In the elderly, muscle sympathetic nerve activity has been reported to be increased. Dinenno et al reported that human aging is associated with a reduction in forearm postjunctional α-adrenergic responsiveness to endogenous norepinephrine release. In addition, autonomic support of BP changes with aging are due to decreased cardiac vagal inhibition of heart rate and cardiac output and basal sympathetic activity. These imbalances of α1-sympathetic nerve and β-sympathetic nerve effects may cause increased variability of BP in the elderly.

Baroreceptor sensitivity, a regulator of BP, plays an important role in the regulation of BP and has been reported to be decreased in the elderly. Jones et al showed that aging in men was associated with a marked reduction in baroreceptor buffering of BP and that this was related to increases in basal sympathetic nerve activity and a reduction in systemic α1-adrenergic vascular responsiveness. In a study of hypertensive patients using direct BP and electrocardiogram monitoring for a 24-h period, the baroreflex sensitivity index (BRI) measured on the basis of the ratio delta RR/delta Ps (delta Ps = spontaneous decrease in systolic BP, delta RR = change in RR) was minimal early in the morning. These data show that impaired baroreceptor sensitivity is a key physiological mechanism of exaggerated ME difference in relation with the predominant α-sympathetic activity in the elderly. Actually in this study, the effect of alcohol on the ME difference was greater in elderly hypertensives than in younger hypertensives.

**Smoking**

Smoking is a risk factor for cerebrovascular disease. Smoking increases BP and heart rate during the smoking period, although the relationship between smoking and sustained hypertension is controversial. Mann et al reported that smoking is associated with increased daytime BP without causing a change in night-time BP. We expected that smoking would be associated with an increase in ME difference; however, the obtained result was the opposite.

**Study Limitations**

There is no data that show the prognostic significance of morning minus evening systolic BP difference (ME difference) by self-home BP measurements. In our preliminary analysis, which showed that the ME difference was an independent predictor for stroke, the ME difference was defined by the ambulatory BP data. Because ME difference measured using morning and evening self-home measurements (awake, seated home measurements) may have different prognostic significance from ME difference based on the ambulatory BP data, further studies will be necessary to evaluate the clinical significance of ME difference measured by self-home BP measurements.

The self-measured BP level can be a risk for target organ damage and cerebrovascular events. We showed the determinant of ME difference and how to evaluate self-home BP in treated hypertensive patients.

In addition, ME difference include two types. One is the exaggerated morning BP elevation, and the other is the large evening BP reduction. We were unable to exclude the effect of evening BP reduction (such as regular alcohol drinkers) in exaggerated ME difference. Moreover, the determinants of absolute value of ME difference was almost the same as that of ME difference (morning minus evening BP value).

In conclusion, older age, regular alcohol drinking, and β-blocker use were independent determinants of the risk of exaggerated ME difference in medicated hypertensive patients. Morning BP levels should be monitored in medicated hypertensive patients having these conditions, even if their clinic BP is well controlled.

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