Association of Ambulatory Blood Pressure and Heart Rate With Advanced White Matter Lesions in Ischemic Stroke Patients

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BACKGROUND
White matter lesions (WMLs) are a common finding in stroke patients, and the most important risk factors are old age and hypertension. Although many studies have described the association between WMLs and ambulatory blood pressure monitoring (ABPM) parameters in healthy subjects and hypertensive patients, little is known about the association in hypertensive ischemic stroke patients.

METHODS
From July 2009 to June 2012, 169 consecutive hypertensive noncardioembolic ischemic stroke patients were recruited within 1 week of suffering a stroke, and ABPM was applied 1 or 2 weeks after stroke onset. The subjects were classified into 2 groups according to the presence of advanced WMLs, and their ABPM parameters were compared. Finally, multivariable logistic regression analyses were performed to investigate the independent relationships between WMLs and ABPM parameters.

RESULTS
Seventy (41%) patients had advanced WMLs. In univariable analysis, higher 24-hour, awake, and asleep systolic blood pressure (SBP)/

diastolic blood pressure levels and 24-hour pulse pressure were associated with advanced WMLs. However, circadian blood pressure parameters such as 24-hour BP variability, morning surge, and nocturnal dipping pattern were not associated with advanced WMLs. After adjustments, old age (odds ratio (OR) = 1.063; 95% confidence interval (CI) = 1.024–1.104; P = 0.002), high 24-hour SBP levels (OR = 1.055; 95% CI = 1.028–1.082; P < 0.001), and high 24-hour heart rate (OR = 1.041; 95% CI = 1.006–1.078; P = 0.023) were independently associated with advanced WMLs.

CONCLUSIONS
In addition to old age and elevated 24-hour SBP, increased heart rate is associated with advanced WMLs in ischemic stroke patients. Heart rate deserves more attention in predicting advanced WMLs in those patients.

Keywords: ambulatory blood pressure monitoring; blood pressure; heart rate; hypertension; ischemic stroke; white matter lesions.

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Cerebral white matter lesions (WMLs) are a common finding in stroke patients and are associated with cognitive decline, depression, gait disturbance, falls, and increased risk of stroke.1 Although the origin of cerebral WMLs is not fully understood, older age and hypertension are reported to be the main risk factors.1,2 Hypertension is probably the most important modifiable risk factor for WMLs, and many studies have demonstrated the relationship between hypertension and WMLs.3–6

Ambulatory blood pressure monitoring (ABPM) is an important tool for improving the diagnosis and management of hypertension because it can provide information about blood pressure (BP) throughout the day and night.7,8

It permits evaluation of diurnal rhythms of BP and BP variability, which can be used in the diagnosis of white-coat hypertension, labile hypertension, resistant hypertension, and masked hypertension.4 ABPM is more closely associated with hypertension-related organ damage and cardiovascular events than office BP.9,10 Therefore, numerous studies using ABPM have demonstrated the positive relationship between WMLs and hypertension in hypertensive patients and the elderly,10–16 but data for ischemic stroke patients have only been reported in 1 study of lacunar infarction.17

Heart rate (HR) is another variable that can be more effectively measured by ABPM. Increased HR is associated with development of hypertension, atherosclerosis, sudden death,
and coronary heart diseases, which all increase cardiovascular morbidity and mortality. In addition, increased HR is associated with oxidative stress, subclinical inflammation, sympathetic tone, and endothelial dysfunction, all of which may lead to the development of cerebral WMLs. Although previous studies on hypertensive patients and the elderly failed to reveal an association between 24-hour HR and WMLs, such an association may have been concealed by the strong relationship between BP and WMLs. Unfortunately, similar information is not available for ischemic stroke patients.

In this study, we investigated the association between WMLs and ABPM parameters in hypertensive subacute ischemic stroke patients. In addition, we sought to assess whether HR is associated with WMLs in that population.

METHODS

Patients

We designed an observational study in a prospective registry. From July 2009 to June 2012, we identified 563 consecutive patients who were admitted to Hanyang University Hospital for acute ischemic stroke within 1 week from stroke onset. The diagnosis and treatment of stroke followed standard guidelines, and the severity of stroke was assessed using the National Institute of Health Stroke Scale. Stroke etiologies were defined according to the TOAST (Trial of Org 10172 for Acute Stroke Treatment) classification. We only included patients with hypertension, which was defined as a history of hypertension and consumption of antihypertensive medications; suffering from a hypertensive target organ disease—left ventricular hypertrophy on electrocardiography or echocardiography or hypertensive retinopathy on fundus examination; and systolic BP (SBP) > 140 mm Hg or diastolic BP (DBP) > 90 mm Hg by discharge BP at least 1 week after symptom onset. A total of 169 patients were included after exclusion of patients who had severe hypertension and were treated immediately (SBP > 220 mm Hg or DBP > 120 mm Hg), those who had secondary hypertension, those who had life threatening conditions, those who received thrombolytic therapy, those who were shift workers, those who were unable to complete the study, and those who had cardioembolic risk factors such as atrial fibrillation and other known causes of stroke. The institutional review board at Hanyang University Hospital approved the study (HYUH 2013-02-001).

Clinical information

Demographic and clinical information was collected on admission. The data included age, sex, risk factors for stroke (diabetes, hyperlipidemia, ischemic heart disease, and smoking), medication history (antihypertensives, antiplatelets, and statins), and laboratory findings. Diabetes was defined by previous use of antidiabetic medication or fasting blood glucose ≥126 mg/dl, and hyperlipidemia was defined by previous use of lipid-lowering agents, fasting serum total cholesterol level ≥240 mg/dl, and/or low-density lipoprotein level ≥160 mg/dl. Subjects were classified as either current smokers or nonsmokers. Laboratory tests, including fasting blood glucose, lipid profiles (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), C-reactive protein, and homocysteine, were measured the morning after admission after overnight fast. SBP, DBP, and HR were measured on admission. Previous medication histories, including use of antihypertensives, antidiabetics, and statins before stroke onset, were also recorded on admission.

Image analysis

Diffusion-weighted images, fluid-attenuated inversion recovery (FLAIR), T2*-gradient echo, and T2-weighted images were obtained for each subject within 48 hours of admission, with a 3-Tesla MR machine (Achieva; Philips, Best, the Netherlands) with an 8-channel SENSE head coil. Conventional diffusion-weighted images repetition time (TR)/echo time (TE) = 4,000/75 ms; slice thickness/gap = 5/2 mm), FLAIR (TR/TE = 11,000/125 ms; slice thickness/gap = 5/2 mm), T2*-gradient echo (TR/TE = 600/160 ms; slice thickness/gap = 5/2 mm), and T2-weighted images (TR/TE = 3,000/80 ms; slice thickness/gap = 5/2 mm) were obtained by using the appropriate parameters. Brain imaging studies were assessed independently by 2 experienced radiologists (Y.J.L. and Y.Y.K.) operating by consensus and without any knowledge of clinical information. Discrepancies between the 2 readers were resolved by consensus with a third rater (Y.S.K.). Following a previous proposal, WMLs were defined as punctuate, early confluent, or confluent abnormalities based on FLAIR images. Early confluent or confluent lesions were designated as advanced WMLs. Microbleeds were defined as focal homogenous areas with diameters of 2–5 mm. Silent brain infarcts were characterized as focal lesions of at least 3 mm diameter with signal intensities corresponding to liquor (hypointense on T2-weighted images and hypointense on FLAIR images). The κ statistics for concordance of advanced WMLs, microbleeds and silent infarcts indicated excellent agreement (κ = 0.90, κ = 0.87, κ = 0.88, respectively).

Twenty-four-hour ABPM

Because BP is known to rise after a stroke and resolve 7 days later, ambulatory BP was monitored (TM-2430; A&D Medical, Saitama, Japan) before discharge, 1 or 2 weeks after stroke onset. Antihypertensive medication was suspended from the ictus of a stroke unless BP reached SBP > 220 mm Hg or DBP > 120 mm Hg. BP was assessed every 15 minutes during the day and every 30 minutes during the night in the nonparetic upper extremity. Patients were free to move within the hospital area and to engage in the usual activities of inpatients not confined to bed. The following parameters were calculated from the raw data: 24-hour mean SBP/DBP awake SBP/DBP, asleep SBP/DBP, 24-hour pulse pressure, 24-hour HR, 24-hour BP variation (SBP/DBP), morning SBP surge, and nocturnal BP fall (dipper, nondipper, reverse dipper).

The individual parameters were defined as follows: asleep BP was defined as the average of the BP at the onset of sleep and awakening, based on the activity sheet. The morning SBP surge was defined as the morning SBP minus the
preambing SBP. The nocturnal SBP fall was calculated as the awake minus the asleep SBP (percentile, relative awake nocturnal fall = (1 – asleep SBP/awake SBP) × 100). According to the magnitude of the fall in BP, subjects were divided into 3 subgroups: dippers, for those who showed ordinary nocturnal falls (10% ≤ nocturnal BP reductions); nondippers, for those whose BP did not fall by the usual amount (0% ≤ nocturnal BP fall < 10%); and reverse dippers, for those whose BP increased during the night.

Statistical analyses

Patients were initially divided into 2 groups by the presence or absence of advanced WMLs. We performed Pearson’s χ² test for categorical variables, and Student t test and the Mann–Whitney U test for continuous variables, as appropriate. When comparing ABPM parameters according to the presence of advanced WMLs, Bonferroni’s correction was applied because of the multiple comparison, and the level of statistical significance was lowered in proportion to the number of comparisons made (0.05/12; P < 0.004). We also classified patients by stroke subtype (TOAST classification) and compared them according to the presence or absence of advanced WMLs by the above methods. To assess the relationship between various parameters, including the ABPM parameters and WMLs, logistic regression analyses were performed, and odds ratios (ORs) were calculated. Adjusted variables were selected from the results of the univariable analysis with P < 0.20. Because SBP was strongly associated with WMLs, we only adjusted for age, diabetes mellitus, and antihypertensive use in the initial analyses. However, we also adjusted for 24-hour SBP in the final analysis. Sex was also included in the final analysis because it could be a confounding factor for increased HR. Two-sided values of P < 0.05 were considered significant, and all statistical analyses were carried out with the SPSS 18.0 package for Windows (SPSS, Chicago, IL).

RESULTS

Of the 169 patients in this study, 105 (62%) were men and 64 (38%) were women. Participants’ ages ranged 39–89 years with a mean ± SD of 65.5 ± 10.3 years. Thirty-nine patients had diabetes (23%), 34 had hyperlipidemia (20%), and 17 were current smokers (10%). Twenty-one patients (12%) had grade 0 (absent), 78 patients (46%) had grade 1 (punctuate), 60 patients (36%) had grade 2 (early confluent), and 10 patients (6%) had grade 3 (confluent) WMLs. Seventy patients (41%) were considered to have advanced WMLs. Silent brain infarctions were noted in 71 patients (42%), and microbleeds were noted in 67 patients (40%).

Baseline characteristics according to the presence of advanced WMLs are described in Table 1. Univariable analysis revealed that advanced WMLs were more prevalent in older patients (P < 0.001) and were associated with a higher incidence of silent brain infarctions (P = 0.02) and microbleeds (P < 0.001). However, they were not associated with initial SBP/DBP, pulse pressure, HR, and other laboratory findings. The individual ambulatory BP parameters in relation to advanced WMLs are shown in Table 2. Patients with advanced WMLs had consistently higher 24-hour, awake, and asleep BPs (SBP(DBP) and 24-hour pulse pressure even after Bonferroni’s correction. Mean 24-hour HR was marginally associated with advanced WMLs without statistical significance. However, 24-hr BP variability, morning BP surge, and dipping pattern, which are regarded as circadian aspects of BP, were similar in the 2 groups. A subgroup analysis after classification by stroke subtype is shown in Supplementary Table S1. In the small vessel occlusion group, increased 24-hour HR was more significantly associated with advanced WML than in the other groups (73.7 ± 10.4 vs. 68.9 ± 7.3; P = 0.009). However, the circadian parameters of ABPM were not significantly different in these groups.

Multivariable logistic regression analysis after adjusting for potentially confounding variables excluding 24-hour SBP showed that old age (OR = 1.045; 95% confidence interval (CI) = 1.008–1.083; P = 0.002) and 24-hour pulse pressure (OR = 1.036; 95% CI = 1.036–1.069; P = 0.03) were associated with advanced WMLs. However, after additional adjustment for 24-hour SBP and sex, old age (OR = 1.063; 95% CI = 1.024–1.104; P = 0.002) as well as high 24-hour SBP levels (OR = 1.055; 95% CI = 1.028–1.082; P < 0.001), and high 24-hour HR (OR = 1.041; 95% CI = 1.006–1.078; P = 0.02) were independently associated with advanced WMLs (Table 3).

DISCUSSION

In this study, we found that increased SBP and DBP (24-hour, awake, and asleep) and increased pulse pressure measured by ABPM were consistently associated with advanced WMLs in subacute ischemic stroke patients. However, circadian aspects of BP, such as BP variability, morning surge, and nocturnal dipping pattern did not show any association. Another major finding was that increased HR measured by ABPM was also independently associated with advanced WMLs. These findings are unique to this study because we evaluated hypertensive subacute ischemic stroke patients by applying ABPM 1 week after stroke onset.

A cerebral WML is regarded as a cerebral small vessel disease and is one of the most common degenerative vessel disorders in the aging human brain.25 It is presumably caused by dysfunction of the endothelium of cerebral arterioles, which leads to chronic ischemia or breakdown of the blood–brain barrier with deposition of toxic materials.1 These brain alterations are strongly associated with old age and hypertension, which are regarded as major risk factors.2 Because other vascular risk factors such as diabetes, dyslipidemia, and smoking are less clearly associated with WMLs, the association between hypertension and WMLs has been widely investigated and established in cross-sectional14 and longitudinal15,6 studies. It is also well known that control of hypertension is effective in preventing the development of WMLs and slowing their progression.26,27 In addition to SBP and DBP, pulse pressure was associated with WMLs.12,28 However, previous studies using office BP or single BP measurements have limitations because they do not reflect true stable BP or the daily variation of BP.
Kwon et al.

Twenty-four-hour ABPM may have benefits because it measures average BP and thus minimizes bias from single measurements. It is also useful because it can evaluate dynamic BP changes throughout the day and night. Elevated 24-hour SBP and DBP are consistently associated with severe WMLs in the general population and in hypertensive patients. 

However, stroke patients may differ from these subjects because they have developed overt stroke symptoms. In this study, we found that 24-hour SBP and DBP, whether measured awake or asleep, was associated with WMLs in hypertensive subacute ischemic stroke patients. Increased 24-hour pulse pressure was also correlated with advanced WMLs. These findings are in line with previous observations in nonstroke patients. Because initial SBP, DBP, and pulse pressure were not associated with advanced WMLs, this underscores the fact that 24-hour BP monitoring is a more accurate method of evaluating BP levels. In contrast with the results for BP levels, the circadian aspects of BP (24-hour BP variation, morning surge, and nocturnal dipping pattern) were not associated with WMLs. This finding is in agreement with a number of previous reports but differs from many other studies that demonstrated a role of

Table 1. Baseline characteristics of patients according to presence of advanced white matter lesions

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without (n = 99)</th>
<th>With (n = 70)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>63.2 ± 10.5</td>
<td>68.7 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>64 (65)</td>
<td>40 (57)</td>
<td>0.32b</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>55 (56)</td>
<td>40 (57)</td>
<td>0.94b</td>
</tr>
<tr>
<td>Large artery disease</td>
<td>31 (31)</td>
<td>22 (31)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>13 (13)</td>
<td>8 (12)</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial NIHSS score</td>
<td>3.7 ± 4.0</td>
<td>3.6 ± 3.1</td>
<td>0.76c</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (18)</td>
<td>21 (30)</td>
<td>0.07c</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17 (17)</td>
<td>17 (24)</td>
<td>0.26c</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (9)</td>
<td>8 (11)</td>
<td>0.62b</td>
</tr>
<tr>
<td>Initial SBP, mm Hg</td>
<td>159.4 ± 29.4</td>
<td>160.5 ± 29.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Initial DBP, mm Hg</td>
<td>87.9 ± 15.3</td>
<td>91.2 ± 14.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Initial pulse pressure, mm Hg</td>
<td>71.4 ± 23.6</td>
<td>69.3 ± 23.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Initial heart rate, bpm</td>
<td>76.0 ± 14.5</td>
<td>79.2 ± 14.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>179.7 ± 40.6</td>
<td>183.3 ± 42.5</td>
<td>0.59</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dl</td>
<td>42.4 ± 11.7</td>
<td>44.4 ± 12.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dl</td>
<td>113.3 ± 33.9</td>
<td>112.2 ± 34.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>129.9 ± 85.4</td>
<td>127.1 ± 104.4</td>
<td>0.85</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>0.4 ± 0.7</td>
<td>0.3 ± 0.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>12.3 ± 6.6</td>
<td>12.7 ± 5.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive use</td>
<td>44 (44)</td>
<td>41 (59)</td>
<td>0.07c</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>24 (24)</td>
<td>18 (26)</td>
<td>0.83c</td>
</tr>
<tr>
<td>Statin use</td>
<td>8 (8)</td>
<td>8 (11)</td>
<td>0.46c</td>
</tr>
<tr>
<td>Radiologic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent brain infarctions</td>
<td>34 (34)</td>
<td>37 (53)</td>
<td>0.02c</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>28 (28)</td>
<td>39 (56)</td>
<td>&lt;0.001b</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%). Abbreviations: DBP, diastolic blood pressure; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure. *Student t test was used to determine P values unless otherwise noted. **Pearson χ² test. ***Mann–Whitney U test.
BP variability and nocturnal dipping status in the development of WMLs. Our patients may have differed from those in these previous studies because they were relatively young (mean aged = 65.5 years) and had ischemic stroke and hypertension simultaneously. In addition, ischemic stroke may affect BP variation even though it normalizes within a week of stroke onset. Nevertheless, we believe that 24-hour SBP, DBP, and pulse pressure play a more important role than the circadian rhythm of BP in the development of WMLs in hypertensive ischemic stroke patients.

Another interesting finding is the relationship between HR and WMLs. We found that increased 24-hour HR was associated with advanced WMLs after adjusting for possible variables including 24-hour SBP. To the best of our knowledge, 24-hour HR has only been investigated as a predictor of outcome in stroke patients, whereas the association between HR and WMLs observed in our study has not been previously reported. Although many studies have shown that HR is not associated with WMLs in hypertensive patients and the elderly, a study provided evidence that advanced WMLs are associated with a sustained increment of nighttime HR. That finding may be related to ours because we found that only 24-hour HR was clearly associated with advanced WMLs, not initial HR, which was measured during the day. A possible explanation for this finding is only speculative. Higher HR has been reported to be associated with oxidative stress, subclinical inflammation, higher sympathetic tone, and endothelial dysfunction, and these pathologic changes are known to promote hypertension, atherosclerosis, and coronary heart diseases. Because WMLs are the result of dysfunction of the endothelium of cerebral arterioles and chronic ischemia, it could be that increased HR is also associated with WMLs. This idea may be strengthened by our finding that increased HR was associated with WMLs in the small vessel occlusion subtype, which is pathologically similar to WMLs. Furthermore, it has been reported that increased HR and severe leukoaraiosis independently predict poor outcomes after ischemic stroke. These observations suggest a possible connection between HR and the severity of WMLs. However, our
data were acquired from focused hypertensive patients who suffered ischemic stroke in the subacute stage, after excluding possible cardioembolic causes such as atrial fibrillation. They should therefore be interpreted with caution.

There are some limitations to our study. First, it is a single-center, observational study, which could not avoid selection bias. However, stroke subtype and baseline stroke severity did not differ between the groups, which may have reduced selection bias. Second, we excluded patients with severe symptoms and cardioembolic causes. We believe that including those patients could lead to less clear findings because ABPM with HR monitoring may not reflect patients’ real status when they are bedridden. The inclusion of patients with atrial fibrillation with rapid ventricular responses could also confuse the results. Third, we are not able to draw any conclusions about the causative link between HR and WMLs because our study was cross-sectional and the sample was relatively small. We suggest that a prospective longitudinal study with an appropriate sample size should be undertaken to confirm our observations. Finally, ambulatory BP was monitored only once in in-patients. ABPM may reflect patients’ status more accurately when carried out repetitively in an out-patient setting because patient may have a different lifestyle when not confined to the hospital. Patient inconvenience and issues of cost prevented us from doing this.

In addition to 24-hour SBP, DBP, and pulse pressure, 24-hour HR was associated with advanced WMLs in hypertensive subacute ischemic stroke patients. On the basis of our findings and a review of literature, we propose that increased 24-hour HR may be associated with severe WMLs of our findings and a review of literature, we propose that 24-hour HR was associated with advanced WMLs in hypertensive subacute ischemic stroke patients. On the basis of our findings and a review of literature, we propose that increased 24-hour HR may be associated with severe WMLs and poor ischemic stroke outcomes. We also cautiously suggest that 24-hour HR could be an additional treatment target in ischemic stroke patients.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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