Different Impacts of Blood Pressure Variability on the Progression of Cerebral Microbleeds and White Matter Lesions

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Background and Purpose—Cerebral microbleeds (CMB) and white matter lesions (WML) are cerebral small vessel diseases. Hypertension is considered the most important risk factor. Its mechanism is not yet clarified. Our study assessed the association of blood pressure variability (BPV) with CMB and WML progression.

Methods—Patients with a history of ischemic stroke within 1 to 6 months were consecutively recruited and followed-up for 12 to 18 months. Blood pressure was measured monthly and controlled to a target level. BPV was quantified by the maximum, standard deviation, coefficient of variation, successive variation, standard deviation independent of mean, and successive variation independent of mean. Magnetic resonance imaging was performed at baseline and the end of the study. CMB and WML were rated using Microbleed Anatomic Rating Scale and Age-Related White Matter Changes scales, respectively. Multiple logistic analyses assessed BPV associations with CMB and WML development.

Results—Of 720 patients recruited, 500 and 584 had follow-up results for CMB and WML, respectively; 13.2% and 48.1% showed CMB and WML progression, respectively, over a median of 14 months. Patients with CMB had a higher mean, maximum, standard deviation, coefficient of variation, successive variation, standard deviation independent of the mean, and successive variation independent of the mean in either systolic blood pressure or diastolic blood pressure ($P < 0.05$). Systolic blood pressure variability was an independent risk factor for deep and infratentorial CMB progression, whereas diastolic blood pressure variability was independently associated with CMB development in deep regions. WML progression was not significantly associated with BPV between visits.

Conclusion—BPV independently predicts CMB progression in deep and infratentorial regions.

Clinical Trial Registration Information—Clinical Trial Registration URL: http://www.clinicaltrials.gov. Unique identifier: NCT00202020.

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Key Words: blood pressure variability ■ cerebral microbleeds ■ hypertension ■ white matter lesions

Cerebral microbleeds (CMB) and white matter lesions (WML) on magnetic resonance imaging (MRI) are generally regarded as small vessel diseases of the brain and play an important role in stroke, dementia, and normal aging. Arteriosclerosis and cerebral amyloid angiopathy are known to be mainly pathological abnormalities, but their exact pathogenesis and clinical significance require further study. Therefore, it is important to assess the risk factors for the different small vessel diseases. Hypertension is the most prevalent modifiable vascular risk factor, especially for cerebral small vessel diseases. Recent studies have proposed that the usual blood pressure (BP) hypothesis is limited, and they have indicated that visit-to-visit variability in systolic blood pressure (SBP) is a
Cohorts

The procedure used in the CASISP study (Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention, registration number NCT00202020 at ClinicalTrials.gov) was reported previously. Consecutive patients who had experienced an ischemic stroke confirmed by neuroimaging within the previous 1 to 6 months were enrolled from May 2004 to December 2004, from 12 hospitals, and were followed-up every month for 12 to 18 months. To be included, subjects had to be between 18 and 75 years old, have a score of <4 on the modified Rankin Scale, and provide informed consent. The exclusion criteria were severe disability, uncontrolled severe hypertension (>180/120 mm Hg), contraindications for antiplatelet drugs, history of intracranial hemorrhage, and cardiogenic embolism. Ethical approval was obtained at each clinical study center.

The patients were randomly divided into the antiplatelet groups of either aspirin 100 mg daily or cilostazol 100 mg twice daily for the entire follow-up period. Follow-up interviews occurred every 30 ± 5 days, and BP was measured at each visit with a mercury sphygmomanometer with the patient in a sitting position. The risk factors for stroke were evaluated by a neurologist. All patients, with hypertension, diabetes, or high-serum lipid concentration were treated according to the guidelines for the prevention of stroke. Antihypertension agents were prescribed with a target of BP <140/90 mm Hg, or <130/80 mm Hg in patients with diabetes. Statins were suggested if the lipid profile was abnormal; low-density lipoprotein cholesterol level was targeted to <100 mg/dL.

MRI

All patients underwent MRI within 2 weeks of the beginning of the study and at its end with a 1.5-T scanner. We agreed on the MRI protocol for all research sites, which was T1-weighted (scan parameters: repetition time, 400–2280 ms; echo time, 8–27 ms), some images of T1-weighted fluid-attenuated inversion recovery on GE MRI in 2 centers, T2-weighted (repetition time, 3000–4800 ms; echo time, 80–120 ms) fluid-attenuated inversion recovery (repetition time, 5000–11 000 ms; echo time, 100–146 ms), diffusion-weighted imaging (repetition time: 3000–10 000 ms; echo time, 45–112 ms), and T2 gradient echo imaging (T2*: repetition time, 300–545 ms; echo time, 3.5–23 ms). Slice thickness was 6 mm and the gap was 1 to 2 mm. Lacunar infarction was diagnosed if the T1 image showed a hypointense lesion of ≥2 mm and ≤15 mm in the area of the penetrating arterioles. CMB were defined as a focal area of signal loss in brain parenchyma <5 mm on T2*-weighted MRI. WML were ill-defined hyperintense lesions of ≥5 mm on both T2 and fluid-attenuated inversion recovery images.

A trained neurologist rated CMB and WML lesions using the Microbleed Anatomic Rating Scale (MARS) (counting CMB in deep, lobar, and infratentorial regions) and Age-Related White Matter Changes scale (score 0–3 in 5 different regions, including the frontal area, parieto-occipital area, temporal area, infratentorial area, and basal ganglia), respectively. CMB or WML progression included either newly developed lesions or the evolution of the previous lesions by the end of the study, based on the scores of the MARS or Age-Related White Matter Changes scale. Patients with microbleeds indicated at least 1 point on MARS, whereas those without microbleeds indicated no CMB lesions on MRI. Similarly, patients with WML had Age-Related White Matter Changes scale score of ≥0 and patients without WML had a score of 0.

The inter-rater reliability was determined by tests using MARS (kappa=0.94) and Age-Related White Matter Changes (kappa=0.82) scale for 20 random scans. Cerebral infarct location and the number, size, type, and distribution of the involved vessels also were evaluated by 8 trained neurologists and radiologists. All raters were blinded to the clinical data and rated at Peking University First Hospital.

Statistical Analysis

Visit-to-visit BPV was quantified by calculating the maximum (Max), standard deviation (SD), coefficient of variation (100×SD/ mean), and successive variation (SV) of the measurements. If the SD and SV were correlated to the mean BP by the Pearson correlation test, then the SD independent of the mean and SV independent of the mean with respect to variability were also calculated.

SV, SD independent of the mean, and SV independent of the mean were calculated according to the following formulas:

\[
SV = \sum_{i=1}^{n-1} \left( BP_{i+1} - BP_i \right)^2
\]

\[
\text{SD independent of the mean} = k \times \text{SD/mean}
\]

\[
\text{SV independent of the mean} = k \times \text{SV/mean}
\]

The parameter \( k \) was estimated by using the curve-fitting technique to derive the transformed variables and \( k \) was constant. BP parameters were compared between groups using the \( t \) test. The independent risk factors for CMB and WML progression during follow-up were investigated by binary logistic regression, after adjusting for other vascular risk factors. All analyses were performed with SAS version 6.1 and SPSS version 11.5 statistical software. Significance was set as \( P<0.05 \).

Results

Of 720 participants at baseline recruitment, 597 subjects finished the follow-up and underwent a second MRI at the end of the study. Patients dropped-out of the study for several reasons; 15 withdrew their consent agreements, 68 refused or failed to undergo the second MRI examination, 8 died, and 32 provided valid end points (ischemic stroke in 26, hemorrhage stroke in 6). The mean age (±SD) of the 597 subjects was 59.7±9.8 years; 182 were women (30.5%), 398 (66.7%) had a history of hypertension, 111 (18.6%) had diabetes mellitus, 44 (7.4%) had a cardiovascular disorder, 178 (29.8%) had high-serum lipid concentration, 139 (23.3%) had a history of stroke, 247 (41.4%) were current smokers, and 215 (36%) were alcohol drinkers. The patients were considered as having atherosclerosis or arteriosclerosis. Among them, small vessel disease was considered in 333 of 597 (55.8%), and large arterial involvement was confirmed by vascular imaging in 188 (31.5%). Seventy-six cases were undefined. Patients with cardiogenic embolism were excluded in this series. For the cohort, the mean SBP was 135.89±16.47 mm Hg and the mean diastolic blood pressure (DBP) was 82.86±9.48 mm Hg at baseline. Three-hundred seven patients received aspirin treatment and 290 patients received cilostazol treatment. Of 398 patients with
hypertension, 365 (91.7%) received antihypertensive therapy, which included monotherapy in 152 (38.2%); calcium-channel blockers were used in 67, angiotensin-converting enzyme inhibitors were used in 54, -blockers were used in 16, angiotension-2-receptor blockers were used in 4, diuretic drugs were used in 11, 2-drug combinations were used in 136 (34.2%), and 34.8% of 178 with abnormal lipid profile received statin therapy. The median number of BP measurements over the course of the follow-up was 8 (interquartile range, 4–12).

BP and BPV Comparison Between Patients With and Without CMB or WML at Baseline and the End of Study

Of the 597 cases, 97 were excluded because of different magnetic field strength or lack of previous comparable T2* imaging. For the 158 patients with at least 1 CMB lesion out of 500 subjects with follow-up T2*-weighted MRI, there were 77 patients (31.6%) in the cilostazol group (284) and 81 patients (31.6%) in the aspirin group (300). For the analysis of the brain WML, however, only 13 out of 597 subjects were excluded because of the lack of a T2 fluid-attenuated inversion recovery follow-up scan. As for the 440 patients with WML out of 584 patients with second T2 fluid-attenuated inversion recovery images, there were 212 patients (74.6%) in the cilostazol group (284) and 228 patients (76%) in the aspirin group (300).

We compared BP parameters between patients with and without CMB or WML at baseline and at the end of the study. The variability of SBP and DBP was significantly increased in patients with CMB (P < 0.05), but only the traditional parameters of SBP (mean, Max, and SD) were significantly associated with WML (P < 0.05; Table 1).

Progression of CMB and WML

Over a median of 14 months of follow-up, new and developing CMB were visible in 66 (13.2%) patients, including new CMB in 25 (5.0%) and a greater MARS score than at baseline.
in 41 (8.2%). The CMB lesion load increased in deep areas in 56 subjects, in lobar areas in 36 subjects, and in infratentorial areas in 23 subjects. WML progression was visible in 281 patients (48.1%), including in the infratentorial area in 35, in the lobar area in 210, and in the basal ganglia in 126 (Figure 1). The characteristics between subjects with CMB and WML progression were similar, with the exception of CMB counts at baseline.

The subjects with overall CMB progression had a higher Max SBP (153.11 ± 18.18 mm Hg) and Max DBP (93.21 ± 10.10 mm Hg) than those with stable lesions (147.19 ± 16.22 mm Hg, \(P=0.007\); and 90.43 ± 8.75 mm Hg, \(P=0.019\)), whereas other BPV parameters displayed no significant differences. The subjects with overall WML progression had a higher mean SBP compared with those with stable lesions (134.02 ± 10.24 vs 131.12 ± 11.34 mm Hg; \(P=0.001\)), mean DBP (81.39 ± 6.43 vs 79.91 ± 6.30 mm Hg; \(P=0.005\)), Max SBP (150.21 ± 15.78 vs 146.11 ± 16.83 mm Hg; \(P=0.003\)), and Max DBP (92.05 ± 9.27 vs 90.06 ± 8.75 mm Hg; \(P=0.008\)). The SD of BP measurements in patients over time are shown in Figure 2.

We next investigated the association of BPV with CMB and WML progression stratified by location.

**Impact of BPV on CMB Progression in Different Regions**

We investigated the association between the BPV and CMB progression in different regions according to MARS. The patients with CMB progression in deep areas had a significantly higher mean, Max, and SD of SBP and DBP than those with stable lesions. Similarly, there were significant differences in Max, SD, and coefficient of variation of SBP and DBP and SD independent of the mean and SV of SBP between the patients with and without infratentorial CMB progression. The subjects with lobar CMB progression had higher mean and Max SBP (Table 2 and Supplementary Table I).

To investigate which BP parameters independently predicted CMB progression, we performed multivariable logistic regression analyses after adjusting for baseline stroke risk factors (sex, age, smoking, drinking, history of cerebral infarction, hypertension, cardiovascular diseases, diabetes, and hyperlipidemia), AWMC scale score of WML load, the number of lacunar infarctions, MARS score of CMB load, cerebral infarct characteristics including location, number, size, type, and distribution of the involved vessel, type of...
antiplatelet drugs, and mean BP. The BPV was still significantly related to CMB progression in deep and infratentorial regions (Table 3). An increased Max SBP and SD DBP were significant predictors of deep CMB progression. Also, an independent association was present between Max, SD, coefficient of variation, and SD independent of mean of SBP and infratentorial CMB progression. However, there was no independent association of lobar CMB progression with BPV. In addition, CMB burden and the numbers of lacunar infarctions at baseline were risk factors for progression of deep CMB; WML at baseline and drinking alcohol were independently associated with lobar CMB progression; and WML at baseline predicted infratentorial CMB progression.

Impact of BPV on WML Progression in Different Regions

We also investigated the association of the BPV with WML progression stratified by location according to AWMC. There were significant differences in the mean SBP (135.09 ± 11.49 mm Hg vs 131.80 ± 10.65 mm Hg; P = 0.003), mean DBP (81.89 ± 7.26 mm Hg vs 80.28 ± 6.10 mm Hg; P = 0.012), and Max SBP (150.79 ± 16.62 mm Hg vs 147.34 ± 16.34 mm Hg; P = 0.037) between the patients with and without deep WML progression. The patients with lobar WML progression had higher mean SBP (133.69 ± 9.40 mm Hg vs 131.83 ± 11.66 mm Hg; P = 0.046) and Max SBP (150.04 ± 15.21 mm Hg vs 146.94 ± 17.05 mm Hg; P = 0.028) than those with stable lesions. No significant difference was observed between the BP parameters and infratentorial WML.

### Table 2. Comparing Blood Pressure Variability Between Patients With and Without Cerebral Microbleeds Progression in Different Regions

<table>
<thead>
<tr>
<th>Location of CMB</th>
<th>Progress (n=56)</th>
<th>Stable (n=444)</th>
<th>P</th>
<th>Progress (n=36)</th>
<th>Stable (n=464)</th>
<th>P</th>
<th>Progress (n=23)</th>
<th>Stable (n=477)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMB in Deep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP</td>
<td>137.0 (10.8)</td>
<td>132.3 (10.8)</td>
<td>0.003*</td>
<td>137.0 (13.1)</td>
<td>132.5 (10.7)</td>
<td>0.017*</td>
<td>136.5 (8.6)</td>
<td>132.7 (11.0)</td>
<td>0.106</td>
</tr>
<tr>
<td>Max DBP</td>
<td>82.5 (5.5)</td>
<td>80.5 (6.5)</td>
<td>0.028*</td>
<td>82.6 (6.5)</td>
<td>80.6 (6.4)</td>
<td>0.074</td>
<td>81.7 (6.1)</td>
<td>80.7 (6.4)</td>
<td>0.433</td>
</tr>
<tr>
<td>SD SBP</td>
<td>156.4 (17.3)</td>
<td>146.9 (16.2)</td>
<td>&lt;0.001*</td>
<td>155.3 (21.2)</td>
<td>147.4 (16.1)</td>
<td>0.035*</td>
<td>156.7 (15.6)</td>
<td>147.6 (16.5)</td>
<td>0.010*</td>
</tr>
<tr>
<td>CV DBP</td>
<td>9.7 (5.1)</td>
<td>8.2 (4.7)</td>
<td>0.028*</td>
<td>9.7 (5.1)</td>
<td>8.3 (4.8)</td>
<td>0.090</td>
<td>11.0 (5.2)</td>
<td>8.2 (4.7)</td>
<td>0.007*</td>
</tr>
<tr>
<td>SV SBP</td>
<td>7.9 (2.8)</td>
<td>7.1 (3.4)</td>
<td>0.126</td>
<td>7.6 (3.4)</td>
<td>7.2 (3.3)</td>
<td>0.425</td>
<td>8.8 (3.9)</td>
<td>7.1 (3.3)</td>
<td>0.019*</td>
</tr>
<tr>
<td>SDIM SBP</td>
<td>10.2 (4.2)</td>
<td>8.3 (4.6)</td>
<td>0.123</td>
<td>9.1 (4.5)</td>
<td>8.3 (4.6)</td>
<td>0.268</td>
<td>10.7 (5.3)</td>
<td>8.2 (4.5)</td>
<td>0.010*</td>
</tr>
<tr>
<td>SDIM DBP</td>
<td>10.0 (6.0)</td>
<td>8.7 (5.9)</td>
<td>0.143</td>
<td>10.1 (6.3)</td>
<td>8.8 (5.9)</td>
<td>0.188</td>
<td>11.0 (6.3)</td>
<td>8.8 (6.0)</td>
<td>0.073</td>
</tr>
</tbody>
</table>

CMB indicates cerebral microbleed; CV, coefficient of variation; DBP, diastolic blood pressure; Max, maximum; SBP, systolic blood pressure; SD, standard deviation; SDIM, standard deviation independent of the mean; SV, successive variation; SDV, successive variation independent of the mean. Blood pressure variability data are represented as the mean (standard deviation) in mm Hg (% for CV).

*P < 0.05.
†Because SD and SV for DBP were not correlated with the mean DBP by the Pearson correlation test; we did not transform SDIM and SDV in DBP.

### Table 3. Independent Associations Between Blood Pressure Variability and Cerebral Microbleeds Progression in Logistic Regression Analyses

<table>
<thead>
<tr>
<th>Location of CMB</th>
<th>Independent Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Max SBP</td>
<td>1.025</td>
<td>1.005–1.046</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Deep SD DBP</td>
<td>1.147</td>
<td>1.006–1.308</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Infratentorial Max SBP</td>
<td>1.040</td>
<td>1.008–1.072</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Infratentorial SD DBP</td>
<td>1.103</td>
<td>1.005–1.210</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>Infratentorial CV SBP</td>
<td>1.157</td>
<td>1.010–1.325</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>SDIM SBP</td>
<td>1.128</td>
<td>1.022–1.244</td>
<td>0.017</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CMB, cerebral microbleed; CV, coefficient of variation; DBP, diastolic blood pressure; Max, maximum; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; SDIM, standard deviation independent of the mean. Because SD and successive variation for DBP were not correlated with the mean DBP by Pearson correlation test, we did not transform SDIM and SDV in DBP.

Impact of BPV on WML Progression in Different Regions

We also investigated the association of the BPV with WML progression stratified by location according to AWMC. There were significant differences in the mean SBP (135.09 ± 11.49 mm Hg vs 131.80 ± 10.65 mm Hg; P = 0.003), mean DBP (81.89 ± 7.26 mm Hg vs 80.28 ± 6.10 mm Hg; P = 0.012), and Max SBP (150.79 ± 16.62 mm Hg vs 147.34 ± 16.34 mm Hg; P = 0.037) between the patients with and without deep WML progression. The patients with lobar WML progression had higher mean SBP (133.69 ± 9.40 mm Hg vs 131.83 ± 11.66 mm Hg; P = 0.046) and Max SBP (150.04 ± 15.21 mm Hg vs 146.94 ± 17.05 mm Hg; P = 0.028) than those with stable lesions. No significant difference was observed between the BP parameters and infratentorial WML.
progression. Moreover, we performed multivariable logistic regression analyses after adjusting for baseline stroke risk factors to investigate the independent association of BP parameters with WML progression. There was no BPV parameter predicting WML progression in any region.

Discussion
Among the patients with ischemic stroke in this study, the prevalence of CMB and of WML were 31.6% and 75.3%, respectively, which were quite similar to previous reports. Of these patients, 13.2% had CMB progress mainly within deep and infratentorial regions, which are vulnerable to hypertension-related effects. In contrast, 48.1% of subjects had WML progression, predominately located in the lobar area.

The visit-to-visit BPV parameters were found to be significantly related to the evolution of CMB in the deep hemispheric and infratentorial regions, which are common sites of hypertensive vasculopathy and hemorrhage. The penetrating artery branches in these sites rise directly from the large vessels and are fragile with regard to BP fluctuation. As hypertension develops, the small arteries and capillaries are exposed to a high level of pressure, which results in leaking as well as rupturing. A postmortem histopathologic imaging study confirmed the association between CMB and symptomatic cerebral hemorrhage. It is well-known that ambulatory BP is an important risk factor in the development of CMB. Our longitudinal study emphasized that the visit-to-visit BPV promoted such pathological development and evolution, although traditional parameters of hypertension were strictly controlled to target levels. The results indicate that long-term BPV should not be neglected in the prevention of CMB and symptomatic cerebral hemorrhage.

The Framingham Heart Study showed that the early elevation of SBP and DBP up to 50 years of age was consistent with increasing peripheral vascular resistance, whereas DBP in elderly subjects gradually decreased with large artery stiffness. Recent studies have highlighted the prognostic importance of long-term BPV in SBP. However, our series revealed a significantly independent association of the variability of DBP with deep CMB progression, despite the mean DBP being normal in the elderly cohort. This finding implies that controlling the variability of DBP is essential to protecting against the evolution and development of CMB or cerebral hemorrhage in the deep hemisphere.

We found a nonsignificant association between the visit-to-visit BPV and lobar CMB progression, which might imply that CMB distributed in the lobar region involved a different pathophysiology other than hypertension. The distribution of amyloid angiopathy was characteristically located at lobar and cortical–subcortical regions. The Rotterdam Scan Study showed an association of lobar distribution of CMB with APOE ε4 genotype, which is associated with amyloid angiopathy. Our results were in line with CMB in different locations representing different pathophysiology.

The mean SBP and DBP in the patients with WML progression were significantly higher than those with stable lesions. Although the traditional parameters of SBP and DBP were found to correlate to WML progression in a monovariate analysis, the multivariate analyses revealed that the impact was influenced by much more complex factors. In such a short period of follow-up, we could not show a significant effect of BPV on the progression of WML. LADIS, a population-based study, suggested that hypertension was a risk factor for WML, but only in subjects without a history of stroke. Furthermore, hypertension was not a risk factor for WML progression over a 3-year follow-up in the same cohort. Of course, we have to consider the shortage of the semiquantitative rating scales used in the present study, which is not sensitive enough to detect the slower WML progression, which would not be apparent during such a short follow-up. Recently, Holland et al showed a strong inverse correlation between hyperintensity frequency and normal perfusion in a quantitative study.

To our knowledge, this is the first study of the impact of visit-to-visit BPV on the progression of CMB and WML. We found that CMB in deep or infratentorial regions became worse as BPV increased, and the variability of DBP was specifically associated with the evolution of CMB in the deep region. The variability had a weaker association with WML progression. Because both hypertensive vasculopathy and amyloid angiopathy are age-related conditions, they commonly coexist in elderly patients; therefore, better interpretation of the pathophysiologic mechanism of CMB and WML will require validated study.

One possible limitation in this study is the small sample of subjects with CMB progression over the short follow-up period. Second, it must be considered that there were fewer patients with CMB progression than patients with WML progression. These factors might affect the study power for the association of BPV with the progression of CMB and WML. Further study is necessary to confirm our results. Third, intravisit variation was not examined in this study. It should be based on large prospective cohorts for a longer follow-up and use more sensitive techniques, such as susceptibility-weighted imaging, to detect CMB evolution and quantitative means to evaluate WML changes.

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Disclosures
None.

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SUPPLEMENTAL MATERIAL

SI. The SD of BP measurements in patients stratified by location. A–C, SD SDP in patients with CMB progression and those with stable lesions (deep region, P=0.028; lobar region, P=0.090, and infratentorial region, P=0.007). D–F, SD DBP (deep region, P=0.036; lobar region, P=0.214, and infratentorial region, P=0.011).