Baseline and Longitudinal Increases in Diastolic Blood Pressure Are Associated With Greater White Matter Hyperintensity Volume

The Northern Manhattan Study

Justin Marcus, MD*; Hannah Gardener, ScD*; Tatjana Rundek, MD, PhD; Mitchell S.V. Elkind, MD, MS, FAAN; Ralph L. Sacco, MD, MS; Charles DeCarli, MD; Clinton B. Wright, MD, MS

Background and Purpose—Elevated blood pressure (BP) is a risk factor for stroke and dementia, but the effect of BP, and change in BP over time, on white matter hyperintensity volume (WMHV) is not fully understood. Few studies have included Hispanics, who are at greater risk of stroke and dementia than non-Hispanic whites. We examined BP in relation to WMHV in a stroke-free cohort.

Methods—The Northern Manhattan Study includes 1290 stroke-free participants who had brain MRI. We examined baseline systolic and diastolic (DBP) BP, and changes in BP from baseline to MRI, and WMHV.

Results—There were 1281 participants with brain MRI and 2 BP measurements (mean age, 64 years; SD=8; range, 40 to 94 years). Baseline DBP was associated with greater WMHV (P<0.0001) independent of sociodemographic and vascular risk factors. Each 10 mm Hg above the mean baseline DBP (83±11 mm Hg) was associated with a 1.17% greater WMHV. Over 7 years average follow-up, participants with an increase >5 mm Hg DBP from baseline to MRI had 1.21% greater WMHV relative to those whose BP did not increase (P=0.02). The association between baseline DBP and WMHV was strongest for blacks compared with Hispanics and whites (interaction P=0.04).

Conclusions—Baseline DBP and longitudinal increases in DBP were independently associated with a greater WMHV, and the association between DBP and WMHV was greatest among blacks.

Key Words: blood–brain barrier ■ risk factors ■ stroke care ■ white matter disease

White matter hyperintensities (WMH) seen on brain MRI scans have been associated with stroke, cognitive decline, dementia, and mortality.1 Both diastolic and systolic blood pressures (BPs) have each been preferentially associated with greater WMH lesion load and WMH progression, but this relationship requires clarification, particularly among minorities at greater risk of stroke and dementia.2,3 We examined longitudinal BP measurements as correlates of WMH volume in the multiethnic Northern Manhattan Study (NOMAS).

Subjects and Methods

NOMAS is population-based with 3298 stroke-free participants at baseline identified through random digit dialing.4 People were eligible if never diagnosed with stroke, >40 years of age, and a Northern Manhattan resident >3 months in a household with a telephone. Data were collected from 1993 to 2001 by trained bilingual research assistants as previously described.5 Both systolic (SBP) and diastolic (DBP) BPs were measured at the right brachial artery after a 10-minute rest, in a sitting position, both at baseline, and at the time of MRI.

MRI Substudy

Participants were recruited for MRI sequentially during annual telephone follow-up if >55 years; without contraindications to MRI; and after signing Institutional Review Board-approved consent. Imaging was performed on a 1.5-T MRI system (Philips Medical Systems, Best, The Netherlands) at the Columbia University Medical Center. We processed brain MRI scans using quantitative methods to measure WMH volume using published methods.4 All analyses were performed blind to participant-identifying or risk factor information.

Statistical Analyses

We used multivariable linear regression to examine baseline SBP and DBP as well as changes in SBP and DBP between baseline and MRI in relation to WMH volume. WMH volumes were expressed as proportions of total cranial volume (WMH/total cranial volume*100) to correct for head size and log-transformed to normalize the

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distribution (WMHV). We created models that included baseline SBP and DBP and terms for increases and decreases in SBP and DBP between baseline and MRI of ≥5 mm Hg adjusting sequentially for age, sociodemographic, and vascular risk factors.

Results

There were 1281 participants who underwent brain MRI and had BP measurements at both baseline and on the day of the scan (mean interval, 7.2±2.4 years). Characteristics of the study sample are shown in Table 1. The mean (SD) for baseline SBP was 139 (20) mm Hg and for DBP was 83 (11) mm Hg. The median (interquartile range) WMHV was 0.36% (0.21% to 0.77%) of intracranial volume. Compared with the larger NOMAS cohort, the current sample was younger and healthier at baseline, but SBP and DBP were similar.

Each 10 mm Hg above the mean baseline DBP (83±11 mm Hg) was associated with a 1.17% greater WMHV (Table 2), whereas SBP was not associated with WMHV. Participants in the upper quartile of DBP had significantly greater WMHV than those with DBPs in the lower 3 quartiles (Supplemental Figure I; http://stroke.ahajournals.org). Systolic BP and DBP changes from baseline to MRI using continuous measures were not significantly associated with WMHV, suggesting nonlinear associations. However, participants whose DBP increased >5 mm Hg from baseline to MRI had a 1.21% greater WMHV relative to those whose BP did not increase (Table 2). Mean arterial pressure but not pulse pressure was associated with greater WMHV (data not shown).

We examined WMH lesion load in relation to both baseline reported hypertension duration (years since first diagnosis) and hypertension control. The median (interquartile range) years since initial diagnosis of hypertension was 9 years (3 to 17 years) and 19% were controlled. Supplemental Figure II shows that baseline duration of hypertension was more important than control in relation to WMHV. We found no difference in WMHV across medication classes, except those on multiple medications had greater WMHV (P=0.02). The association between DBP and WMHV was greatest among blacks, but also greater for Hispanics than whites (P=0.04; see stratified analysis in Supplemental Table I).

Discussion

In this stroke-free cohort, baseline DBP and increases in DBP >5 mm Hg over a mean of 7 years of follow-up were each independently associated with greater WMHV. The association between DBP and WMHV was stronger in black and Hispanic participants than non-Hispanic whites, but especially strong among blacks.

Previous studies have found associations between BP and WMHV, but results have been inconsistent regarding the relative importance of SBP and DBP.2,6,7 Differences in mechanisms of WMH damage may explain this, because large artery atherosclerosis and stiffness lead to elevated SBP and pulse pressure, whereas DBP and mean arterial pressure are more dependent on peripheral vascular resistance that may reflect small vessel damage.8 Other factors such as venous collagenosis have been associated with WMH and could also explain the association.9

Most studies on BP and WMH have been limited to white populations, and few studies have included Hispanics, but black and Hispanic people are at increased risk of stroke compared with whites.10 The distribution of WMH varies by
race/ethnicity, and blacks and Hispanics in Northern Manhattan were found to have greater WMHV compared with whites in a cohort aged >65 years.3 The current study, which also includes participants <65 years of age, suggests that the effect of DBP on WMH volume was strongest in blacks, but also greater in Hispanics compared with whites.

A limitation of this study is that MRI was done once and prospective data on WMHV are lacking. Also, BP was measured during study visits and might not reflect ambulatory values. However, in a 10% random subsample that came in annually for in-person evaluations, BP was stable over time. However, the community-based multiethnic sample, use of quantitative WMH assessments, and the prospective BP measurements are relative strengths. Additional prospective data on BP and WMH progression in race/ethnically diverse populations are needed.

### Sources of Funding
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### Disclosures
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### References
1. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ.* 2010;341:c3666.

### Table 2. BP and Log-WMHV

<table>
<thead>
<tr>
<th>Measure of BP</th>
<th>Model 1 ( \beta (P) )</th>
<th>Model 2 ( \beta (P) )</th>
<th>Model 3 ( \beta (P) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP*</td>
<td>0.02 (0.37)</td>
<td>0.02 (0.57)</td>
<td>−0.01 (0.78)</td>
</tr>
<tr>
<td>DBP*</td>
<td>0.15 (&lt;0.0001)</td>
<td>0.15 (&lt;0.0001)</td>
<td>0.16 (&lt;0.0001)</td>
</tr>
<tr>
<td>SBP increase†</td>
<td>−0.04 (0.61)</td>
<td>−0.05 (0.51)</td>
<td>−0.08 (0.29)</td>
</tr>
<tr>
<td>SBP decrease†</td>
<td>−0.03 (0.71)</td>
<td>−0.01 (0.90)</td>
<td>−0.03 (0.62)</td>
</tr>
<tr>
<td>DBP increase†</td>
<td>0.22 (0.008)</td>
<td>0.20 (0.013)</td>
<td>0.19 (0.02)</td>
</tr>
<tr>
<td>DBP decrease†</td>
<td>−0.05 (0.41)</td>
<td>−0.05 (0.43)</td>
<td>−0.07 (0.26)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age.
Model 2: adjusted for age and sociodemographic variables (sex, race/ethnicity, and high school education).
Model 3: adjusted for age, sociodemographic variables, vascular risk factors (diabetes, low-density lipoprotein cholesterol, smoking status, alcohol consumption, and use of antihypertensive medication).

BP indicates blood pressure; WMHV, white matter hyperintensity volume; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Unit: 10-mm Hg increase in BP above the baseline mean.
†Greater than 5 mm Hg.
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Supplementary Table. BP and log-WMHV stratified by race/ethnicity

<table>
<thead>
<tr>
<th>Measure of BP*</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (p value)†</td>
<td>β (p value)†</td>
<td>β (p value)†</td>
</tr>
<tr>
<td>SBP*</td>
<td>-0.07 (0.10)</td>
<td>-0.02 (0.63)</td>
<td>0.02 (0.27)</td>
</tr>
<tr>
<td>DBP*</td>
<td>0.04 (0.60)</td>
<td>0.26 (0.002)</td>
<td>0.07 (0.03)</td>
</tr>
</tbody>
</table>

†Model adjusted for sociodemographic variables (age and high school education), and vascular risk factors (diabetes, LDL, HDL, smoking status, alcohol consumption, and use of antihypertensive medication).

* The SBP and DBP rows display the change in log-WMHV (β) for every 10 mm Hg increase in BP above the mean at baseline.
Figure 1: Adjusted mean WMHV/TCV by quartile of DBP overall and across race/ethnic groups.
Figure 2: Adjusted mean WMHV/TCV by duration and control of hypertension reported at baseline