Predictors of Brain Morphology for the Men of the NHLBI Twin Study

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Background and Purpose—Cross-sectional studies show that cerebrovascular risk factors are associated with increased brain atrophy, accumulation of abnormal cerebral white matter signals, and clinically silent stroke. We extend these findings by examining the relationship between midlife cerebrovascular risk factors and later-life differences in brain atrophy, amount of abnormal white matter, and stroke on MRI.

Methods—Subjects were the 414 surviving members of the prospective National Heart, Lung, and Blood Institute Twin Study, who have been examined on 4 separate occasions, spanning the 25 years between 1969–1973 and 1995–1997. Quantitative measures of brain volume, volume of abnormal white matter signal (WMHI), and volume of stroke, when present, were obtained from those participating in the fourth examination.

Results—The mean ± SD age of the subjects was 47.2 ± 3.0 years at initial examination and 72.5 ± 2.9 years at final examination. Average blood pressure (BP) levels were normal, although 32% of the subjects had received or were currently taking antihypertensive medications. As a group, 31% had symptomatic cardiovascular disease, 11% had symptomatic cerebrovascular disease, and 8% had symptomatic peripheral vascular disease. Both systolic and diastolic BP levels at initial examination were inversely related to brain volume and positively related to WMHI volume. Multiple regression analysis identified BP-related measures and vascular risk factors as significant predictors of brain and WMHI volumes. In addition, the magnitude of orthostatic BP change was significantly associated with WMHI volume. Subjects with extensive amounts of WMHI had significantly higher systolic BP at the final examination and a higher prevalence of symptomatic cardiovascular and cerebrovascular disease, without significant differences in the prevalence of hypertension treatment.

Conclusions—Midlife BP measures are significantly associated with later-life brain and WMHI volumes and the prevalence of symptomatic vascular disease. Since WMHI share cerebrovascular risk factors and extensive WMHI are associated with symptomatic vascular disease, extensive WMHI may be a subclinical expression of cerebrovascular disease. Careful treatment of midlife BP elevations may diminish these later-life brain changes. (Stroke. 1999;30:529-536.)

Key Words: cardiovascular diseases ■ cerebrovascular disorders ■ epidemiology ■ hypertension ■ magnetic resonance imaging

Striking differences in brain morphology occur across the span of human aging. Brain growth and cerebral myelination1–7 during childhood is followed by only a brief period of morphological stability1,2 as loss of brain volume and rarefaction of cerebral white matter begins in middle age.1,7–9 Age-related differences occur even if excellent health is maintained.10 Variability in the extent of age-related brain atrophy and white matter abnormalities among older individuals, however, suggests differences in the rate of age-related change.10,11 This variability may result from differences in the health status of older individuals.10,12,13 For example, systolic blood pressure (SBP) increases with age, and approximately 44% to 53% of individuals over age 65 are treated for hypertension.14 MRI studies find associations between elevated SBP, brain atrophy, and increased amounts of abnormal white matter.10,15,16 These age-related differences are magnified in individuals with hypertension.17–20 Elevated SBP and other cerebrovascular risk factors are also associated with incidental (silent) cerebral infarctions.21–23

Associations between risk factors for cerebrovascular disease (CVA) and age-related differences in brain morphology have been examined primarily by cross-sectional methods.10,15–20 Cross-sectional studies limit conclusions regarding the impact that duration of illness may have on differ-
ences in brain morphology. For example, cross-sectional studies cannot assess the impact that midlife BP has on the extent of later-life brain atrophy, white matter hyperintensities (WMHI), or stroke. As part of a longitudinal study to assess the heredity of various vascular risk factors, subjects of the National Heart, Lung, and Blood Institute (NHLBI) Twin Study received repeated evaluations of health status and risk for CVA over a 25-year period beginning in middle age. MRI was performed at the final examination. We analyzed the impact of prospective vascular risk factors obtained in middle age on differences in brain morphology among the older individuals currently participating in this study.

Subjects and Methods
The subjects were participants in the NHLBI Twin Study. The design of this longitudinal, multicenter study involving 5 separate US research facilities has been previously described. Initial examinations were conducted on 514 intact pairs or 1028 individual subjects who were 43 to 53 years old during the period 1969–1972. Two follow-up examinations were conducted during 1979–1980 and 1985–1986 on 792 and 622 individual twin subjects, respectively. The most recent examination included the 497 survivors of this twin panel. This examination cycle began in June 1995 and was completed in April 1997. Cerebral MRI scans were obtained for 418 individual twins and included 74 intact MZ and 71 intact DZ pairs. For technical reasons, due primarily to dental-related artifact, the MRIs of 4 individuals could not be analyzed.

Health Status of Participants, Nonparticipants, and Deceased Participants
Evidence strongly suggests an increased morbidity and mortality among individuals with vascular risk factors. To place the results of the surviving members of the NHLBI Twin Study into perspective, we compared the current participants with nonparticipants and those deceased on the various initial vascular risk factors, as shown in Table 1. Nonparticipants included subjects who were examined but refused MRI, subjects followed up by questionnaire only, and subjects lost to follow-up.

Definition of Predictor Variables
Blood Pressure
Sitting BP was measured at each examination by 2 independent examiners. Diastolic BP (DBP) was recorded as the fifth phase. Linear regression analysis was performed for each subject across observations to determine the slope of time-related change and the intercept. We then examined the association between MRI measures and initial BP and slope of change in BP. Current BP was not included in our analysis, as it is the simple sum of initial BP and individual trajectories over time due to age or treatment.

Cardiovascular Disease and Risk Factors
As described previously, medical interviews and physical examinations on each member of a twin pair were performed independently by 2 trained physicians who were blinded to zygosity. Subjects’ self-reports of cardiovascular events and medical procedures were confirmed with medical and hospital records. The final diagnosis of stroke, cerebrovascular accidents, myocardial infarction, coronary insufficiency, and angina pectoris was determined by trained medical staff who reviewed the medical records and the physical examination data and uniformly coded these following standard protocols. Prevalent coronary heart disease (CHD) was ascertained on the basis of the surveillance data as well as ECG data. Data on medication use were collected at each examination by presentation of medication vials. The ankle/brachial BP ratio (ABI), in combination with patient medical and hospital records, was used as a measure of prevalent peripheral vascular atherosclerosis (PAD).

Glucose Tolerance
Glucose tolerance was measured as the level of blood glucose 1 hour after a 50-g oral glucose load. Four subjects diagnosed as diabetic, receiving insulin or treated with an oral hypoglycemic agent, were excluded from testing.

Alcohol Consumption and Cigarette Smoking
Alcohol consumption was defined as the number of alcoholic drinks consumed per week, with 1 bottle of beer equivalent to 1 glass of wine and 1 ounce of distilled liquor. Cigarette smoking was defined as the number of years that subjects smoked and whether they were currently smoking.

Orthostatic Change in BP
At the fourth examination, BP was obtained in the sitting, lying, and standing positions. The change in mm Hg between the lying and standing BPs after 3 to 5 minutes for both DBP and SBP was measured.

Cranial MRI
MRI was performed using 2 separate scanning protocols. Imaging of the initial 73 subjects was performed using a fast spin-echo, double-echo sequence in the coronal orientation with TR=4000 msec, TE=17/102 msec, echo train length=8, 24-cm field of view, 5-mm contiguous slices from nasium to occiput imaged in a 256×256 matrix with 2 excitations. An axial inversion recovery sequence was also performed on the same group of subjects. This sequence consisted of TR=4000 msec, TE/TI=32/120 msec, echo

### Table 1. Age, Education, and Initial Summary CVD Risk Factors for Individuals of the NHLBI Twin Study Who Were Deceased, Nonparticipants, or Participants at the Time of MRI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deceased (n=263)</th>
<th>Nonparticipants (n=353)</th>
<th>Participants (n=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial age, y</td>
<td>48.5±3.1*</td>
<td>48.2±3.2*</td>
<td>47.2±3.0‡</td>
</tr>
<tr>
<td>Education</td>
<td>12.7±2.6*</td>
<td>12.9±2.7*</td>
<td>13.5±3.2‡</td>
</tr>
<tr>
<td>Initial SBP</td>
<td>132.3±18.6‡</td>
<td>128.3±16.4‡</td>
<td>124.3±15.0‡</td>
</tr>
<tr>
<td>Initial DBP</td>
<td>84.0±12.0*</td>
<td>81.9±10.5*</td>
<td>79.7±10.3‡</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>32.7%</td>
<td>35.2%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>77.2%*</td>
<td>71.3%*</td>
<td>60.1%‡</td>
</tr>
<tr>
<td>Alcohol (drinks/wk)</td>
<td>6.5±2.8</td>
<td>6.6±3.1</td>
<td>6.5±2.9</td>
</tr>
<tr>
<td>Initial glucose tolerance</td>
<td>164.9±57.4*</td>
<td>161.2±54.5*</td>
<td>147.6±45.7‡</td>
</tr>
<tr>
<td>Initial mean body mass</td>
<td>26.0±3.7*</td>
<td>25.9±3.2*</td>
<td>25.4±3.0¶</td>
</tr>
</tbody>
</table>

Values are mean±SD. Nonparticipants included subjects who were examined but refused MRI, follow-up by questionnaire only, or lost to follow-up.

ANOVA model, by group, †p<0.05, ‡p<0.01, ††p<0.001.

Means with the same letter are not significantly different by Duncan’s multiple range test.

Opposite page: Method of image segmentation to determine brain, WMHI, and stroke volumes. Nonbrain elements are removed from the image by operator-guided tracing of the intracranial compartment, as indicated by the top row of the figure. Image intensity nonuniformity correction is then applied to the image (second row). Mathematical modeling of pixel intensity distributions determines optimal threshold for brain and CSF segmentation (third row). Finally, mathematical modeling of the combined image (proton density+T2) determines the optimal threshold for WMHI segmentation (last row). If stroke is present on the image, the operator indicates the general area of the stroke, and regional segmentation of stroke volume as well as stroke-related WMHI are determined. The yellow circle indicates this process.
train length = 8, 24-cm field of view, 5-mm contiguous slices from the vertex to the foramen magnum imaged in a 256×256 matrix with 2 excitations. The remaining 341 subjects were imaged with a conventional spin-echo, double-echo sequence in the axial orientation with TR=2000 msec, TE=20/100 msec, 24-cm field of view, 5-mm contiguous slices from the vertex to the foramen magnum imaged in a 256×192 matrix interpolated to 256×256 with 1 excitation. Axial images were oriented parallel to the anterior–posterior, posterior–anterior commissural line, whereas coronal images were oriented perpendicular to the same anatomic line.

MR scanning for each image was performed at 1 of the 4 site 1.5-T MR units (General Electric).

Image Analysis
After acquisition, digital image information was transferred offline from each MR machine to a central location for processing by 1 of the authors (C.D.), who was blinded to all clinical aspects of the subject. Quantitative analysis of each image was performed using a custom-written program operating on a SUN Microsystems Ultra 1 workstation. This program enables the user to read MR image files, remove nonbrain elements from the images (ie, the skull), correct image intensity nonuniformities, and segment images according to previously described mathematical modeling algorithms.31

Our image segmentation method is based on the assumption that within a given 2-dimensional image, image pixel intensities for each tissue type, such as cerebral spinal fluid (CSF) and brain matter, have a unique distribution that differs but may overlap with that of the other tissue types. The composite image can then be considered a mixture of different tissue types, each type having a specific mean and standard deviation that can be accurately modeled by parametric statistical functions.31

Image segmentation is semiautomatic after operator removal of nonbrain elements from the image as previously described.31 For segmentation of brain matter from CSF, a difference image was created by the subtraction of the second-echo image from the first-echo image. For segmentation of WMHI from brain matter, the first and second echo images were summed after removal of CSF through brain matter masking and correction of image intensity nonuniformities. The summed image was then modeled by use of a modified log-normal distribution function. The segmentation threshold for WMHI was a priori determined to be 3.5 SDs in pixel intensity level above the modeled mean of the summed brain matter distribution (see the Figure). Inter-rater reliabilities31 and normative data have been published for this method.8

After image segmentation into CSF and brain matter was completed, the operator could return to the image for analysis of the volume of brain infarction, if present. If stroke was identified, the operator traced the general area around the stroke (see circle in the Figure) and the previous segmentation threshold for brain matter, and CSF was applied within the stroke area to separate necrosis from infarction (Figure). This method also allowed for identification of WMHI surrounding an infarct.

Initial analysis of the first 73 subjects imaged with the fast spin-echo sequence revealed a low sensitivity and specificity for WMHI. Although fast spin-echo imaging was originally felt to be of equal sensitivity to conventional echo with improved imaging speed, quantitation of WMHI from fast spin-echo imaging has been recently shown to be less reliable.31 Repeat WMHI determination from these images was therefore performed using operator guided tracing. This method has been previously shown to be reliable and correlates well with WMHI quantification by the mathematical method described above.10

The total volume for each of the regions of interest (ROIs) were calculated by summing the number of pixels contained within the region of interest and multiplying by the voxel size in centimeters. To correct for differences in head size, all volumes are reported as the percent of intracranial volume (% ICV) unless otherwise stated.

MRI-Identified Stroke
The presence of cerebral infarction on MRI was determined from the size, location and imaging characteristics of the lesion. The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2-weighted image at 3 times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on the T2-weighted image, was interpreted to indicate a vessel. Only lesions ≥3 mm qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included: (1) CSF density on the subtraction image and (2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels.

Statistical Analyses
Differences in demographics and vascular risk factors among the 3 patient groups (deceased, nonparticipants, and participants) was examined by ANOVA with Duncan’s multiple range testing for post hoc differences. The distributions of WMHI, CVA volume, and WMHI-CVA were not normal and were log-transformed before analysis. Linear regression analyses were used to examine the univariate relations between potential risk factors and measures of brain morphology. Multivariate linear regression was also used to examine the combined effects of the same measures on brain morphology. Separate univariate and multivariate regression analyses were performed to identify statistically significant predictors of WMHI not associated with stroke (WMHI-CVA). Multivariate logistic regression was performed to identify statistically significant predictors of MRI-identified stroke ("MRI stroke").

Since the potential exists for twins to have an increased correlation between brain volumes and vascular risk factors related to shared genetic effects, univariate and multivariate analyses were repeated with random selection of one subject from each intact twin pair. No significant differences in the magnitude or direction of the relations were noted. Marginally significant observations for the group as a whole, however, tended to become non-significant due to the reduced number of subjects in the repeat analysis.

Statistical significance was determined at \( P < 0.05 \) unless otherwise stated. All analyses were conducted with SAS software, release 6.09 (SAS Institute, Inc.).

Results
Demographics
The subjects of this study were 72.5 ± 2.9 years of age. They achieved, on average, 1 year of post-high school education, or 13.5 ± 3.2 years. The average SBP (138.0 ± 18.0 mm Hg) and DBP (75.7 ± 9.5 mm Hg) pressures of the subjects were within the normal range, although 32% of the subjects had received or were currently prescribed hypertension medications. Many of these subjects smoked (mean number of years smoked, 19.5 ± 19.8 years) and many subjects drank regularly (mean number of alcoholic drinks consumed per week, 6.5 ± 2.9).

Symptomatic Vascular Disease
By the fourth examination, symptomatic CHD was present for 31%, symptomatic CVA was present for 11%, and evidence of peripheral vascular insufficiency was present for 8% of the subjects.

MRI Variables
The average head size (ICV) of individuals in this study was in the normal range for men at 1269 ± 103 cm³. The average cerebral brain volume was 953 ± 85 cm³. The average uncorrected WMHI volume was 3.93 ± 5.82 cm³ (median, 2.18; range, 0.022 to 46.57 cm³), and WMHI-CVA volume was 3.84 ± 5.62 cm³ (median, 2.09; range, 0.022 to 46.16 cm³). The mean CVA volume was 0.41 ± 3.77 cm³ (median, 0.0; range, 0.0 to 69.28 cm³).
Stroke was identified on the MRIs of 97 subjects (23%). Individuals with MRI stroke were the same mean age as those without MRI stroke (72.6 years versus 72.3 years) but had significantly higher mean SBP at examinations 1 and 2 (129.5 versus 124.9, P = 0.01).

Vascular Risk Factors in Deceased Participants and Nonparticipants
Table 1 summarizes comparison of initial demographic and vascular risk factor differences between subjects who participated in the fourth examination, those deceased, and those who did not participate in the fourth examination. As expected, participants were slightly younger, more educated, and in better health than the other 2 groups. Interestingly, alcohol consumption and hypertension treatment were not significantly different among the 3 groups.

Univariate Analyses
Standardized regression coefficients from analyses of the relation between potential cerebrovascular risk factors and measures of brain morphology are summarized in Table 2. Brain volume was significantly and negatively related to age, years of educational achievement, symptomatic CVA, symptomatic CHD, peripheral vascular disease (ABI), treatment of hypertension, pack-years smoked, current smoking status, initial SBP, and initial DBP. Brain volume was significantly and positively related to the slope of DBP change across the 4 examinations. WMHI was significantly and positively related to age, CHD, treatment of hypertension, pack-years smoked, current smoking status, initial SBP and DBP. WMHI was significantly and negatively related to the slope of DBP change across the 4 examinations. The relations between WMHI-CVA and brain measures were the same as WMHI with the exception of pack-years smoked. CVA volume was significantly and positively related to CVA, current smoking status, and the average amount of alcohol consumed.

Multivariate Analyses
Standardized regression coefficients from results of multivariate linear regression for each brain measure and MR stroke are summarized in Table 3. The total amount of variance explained by the model can be seen in the last row of the table. On average, these models explained between 15% and 20% of the variance in brain morphology. Brain volume was significantly and negatively related to age, ABI, and treatment of hypertension. Brain volume remained positively related to the slope of DBP change across the 4 examinations. WMHI was significantly and positively related to age, CHD, orthostatic SBP change, and initial DBP. In addition, there were trends toward positive significant relations between WMHI, CVA, and current smoking status. WMHI-CVA was significantly and positively related to age, CVA, orthostatic SBP change, and initial DBP. In addition, there was a trend toward a positive significant relation with CHD. CVA volume was significantly and positively related to CVA.

Table 3 also includes standardized coefficients from maximum likelihood estimates of a multivariate logistic regression predicting the presence or absence of MRI stroke. χ² estimates were significant only for a history of symptomatic stroke. Removing history of symptomatic stroke from the model did not improve the significance of any other variable (data not shown).

Extensive WMHI
We examined the prevalence of CVA risk factors and hypertension treatment in association with the presence or absence of extensive amounts of WMHI volume (>0.5% of ICV). Subjects with extensive WMHI had a significant increase in prevalent CVA, CHD, and PAD. SBP at the final
examination was also significantly higher for individuals with extensive WMHI. Treatment of hypertension, however, was not significantly different between these 2 groups of subjects.

Discussion

We believe this is the first prospective study to examine the relationship between cerebrovascular risk factors assessed at midlife and quantitative measures of brain volume, CVA volume, and WMHI volume obtained at later life. Interestingly, there was no significant relationship between midlife BP and CVA volume or MRI stroke, although subjects with MRI stroke did have significantly higher SBP at initial examination. Extensive WMHI were associated with significant differences in initial BP and final SBP as well as the prevalence of symptomatic vascular disease. Our segmentation algorithm allowed us to independently explore the relationship between cerebrovascular risk factors and WMHI after stroke-related WMHI had been removed. Predictors for WMHI-CVA were the same as those for WMHI, confirming that WMHI unrelated to stroke share stroke-related vascular risk factors. From these analyses we observe that vascular risk factors assessed in midlife are strong predictors of later-life brain and WMHI volumes.

Our results are consistent with those in a number of studies relating elevated BP to brain atrophy and increased WMHI. The prospective nature of our study and use of quantitative image analysis, however, enables us to address a number of issues not previously reported.

Treatment of BP

Subjects in the NHLBI Twin Study were generally healthy individuals living in the community. In this regard, treatments received by this group likely reflect general medical management. In our previous report, we noted that 78% of subjects with a midlife pattern of high BP were treated for hypertension, and treatment reduced final DBP to normal. Despite treatment, however, the SBP of individuals with a midlife pattern of high SBP remained significantly higher than that of individuals with a low or normal midlife SBP history. The pattern of high midlife SBP also was associated with significantly more brain atrophy, increased amounts of WMHI, and the highest prevalence of symptomatic vascular disease. In this study, we show that initial BP levels are strongly associated with later-life brain abnormalities, whereas the slope of change for SBP was not significantly related to any measure of brain morphology. This suggests that despite treatment, reductions in SBP may have been insufficient to reduce the later-life brain changes.

A lack of hypertension treatment benefit may also be seen from examining prevalent risk factors among individuals with extensive amounts of WMHI. Despite comparable prevalences of hypertension treatment and no significant differences in DBP, subjects with extensive WMHI had significantly higher SBP at examination 4 and were significantly more likely to have suffered from symptomatic vascular disease. These findings are consistent with other studies that show increased brain atrophy and WMHI in individuals with elevated SBP, even when the level of SBP is at the upper range of normal.

Our results are part of a body of accumulating evidence that points to the benefit of hypertension treatment as a method to reduce the risk for CHD and stroke, including treatment of “borderline” hypertension in the elderly. Our analyses suggest that a similar approach to the treatment of borderline hypertension in middle age may also reduce BP-related brain atrophy and increased WMHI. Further research, however, is clearly indicated. Orthostatic hypotension is a recognized consequence of hypertension treatment and commonly occurs in older individuals with hypertension. Our results as well as

### Table 3. Standardized Regression Coefficients From Multivariate Models Investigating the Independent Relationship Between CVD Risk Factors and MRI Measures of Brain Morphology in Individuals of the NHLBI Twin Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Brain Volume</th>
<th>WMHI</th>
<th>WMHI-CVA</th>
<th>CVA Volume</th>
<th>MR Stroke#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.197***</td>
<td>0.175***</td>
<td>0.175***</td>
<td>0.053</td>
<td>0.032</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.054</td>
<td>-0.027</td>
<td>-0.026</td>
<td>-0.002</td>
<td>-0.111</td>
</tr>
<tr>
<td>History of CVA (yes/no)</td>
<td>-0.07</td>
<td>0.097#</td>
<td>0.141**</td>
<td>0.283***</td>
<td>0.288***</td>
</tr>
<tr>
<td>History of CHD (yes/no)</td>
<td>-0.011</td>
<td>0.101*</td>
<td>0.092#</td>
<td>-0.030</td>
<td>0.108</td>
</tr>
<tr>
<td>ABI ≤0.9 (yes/no)</td>
<td>-0.164***</td>
<td>-0.028</td>
<td>-0.040</td>
<td>-0.004</td>
<td>0.107</td>
</tr>
<tr>
<td>Hypertension treatment (yes/no)</td>
<td>-0.110*</td>
<td>-0.006</td>
<td>0.003</td>
<td>-0.015</td>
<td>-0.119</td>
</tr>
<tr>
<td>Current smoking (yes/no)</td>
<td>-0.005</td>
<td>0.106#</td>
<td>0.098</td>
<td>0.102</td>
<td>-0.051</td>
</tr>
<tr>
<td>Pack-years smoked</td>
<td>-0.097</td>
<td>-0.028</td>
<td>0.031</td>
<td>0.087</td>
<td>0.004</td>
</tr>
<tr>
<td>Alcohol (drinks/wk)</td>
<td>0.059</td>
<td>-0.005</td>
<td>-0.006</td>
<td>0.064</td>
<td>0.076</td>
</tr>
<tr>
<td>Systolic orthostatic BP change</td>
<td>0.029</td>
<td>0.136*</td>
<td>0.139*</td>
<td>0.026</td>
<td>0.120</td>
</tr>
<tr>
<td>Diastolic orthostatic BP change</td>
<td>-0.027</td>
<td>-0.038</td>
<td>-0.042</td>
<td>0.066</td>
<td>0.086</td>
</tr>
<tr>
<td>DBP at exam 1</td>
<td>-0.072</td>
<td>0.073</td>
<td>-0.091</td>
<td>0.064</td>
<td>0.205</td>
</tr>
<tr>
<td>Slope in SBP across exams</td>
<td>0.132</td>
<td>0.327***</td>
<td>0.339***</td>
<td>-0.071</td>
<td>0.087</td>
</tr>
<tr>
<td>DBP at exam 1</td>
<td>0.023</td>
<td>0.094</td>
<td>0.096</td>
<td>-0.017</td>
<td>0.126</td>
</tr>
<tr>
<td>Slope in DBP across exams</td>
<td>0.145#</td>
<td>0.083</td>
<td>0.083</td>
<td>-0.064</td>
<td>-0.058</td>
</tr>
<tr>
<td>Model R²</td>
<td>0.167***</td>
<td>0.161***</td>
<td>0.152***</td>
<td>0.110***</td>
<td>28.8*</td>
</tr>
</tbody>
</table>

#P<0.10, *P<0.05, **P<0.01, ***P<0.001. #Logistic regression coefficients. Logistic model results are presented as χ² value and level of significance.
TABLE 4. Comparison of Sociodemographic and Risk Factor Characteristics to Severity of WMHI in Genetically Unrelated Individuals of the NHLBI Twin Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WMHI ≤0.5% ICV (n=211)</th>
<th>WMHI &gt;0.5% ICV (n=49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of total</td>
<td>81.1</td>
<td>18.9</td>
<td>...</td>
</tr>
<tr>
<td>Final age, y</td>
<td>72.3±2.7</td>
<td>74.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education</td>
<td>13.4±3.0</td>
<td>12.6±2.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Percent prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of CVA</td>
<td>7.1</td>
<td>16.3</td>
<td>0.03</td>
</tr>
<tr>
<td>History of CHD</td>
<td>28.0</td>
<td>53.1</td>
<td>0.002</td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
<td>8.5</td>
<td>16.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP at exam 4</td>
<td>137.1±16.8</td>
<td>142.9±23.3</td>
<td>0.048</td>
</tr>
<tr>
<td>DBP at exam 4</td>
<td>75.6±9.5</td>
<td>76.1±9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>68.7</td>
<td>55.1</td>
<td></td>
</tr>
<tr>
<td>First at exams 1–3</td>
<td>20.4</td>
<td>28.6</td>
<td>NS</td>
</tr>
<tr>
<td>First at exam 4</td>
<td>10.9</td>
<td>16.3</td>
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</tbody>
</table>

those of others\textsuperscript{39} show that the magnitude of orthostatic change in SBP is a significant predictor of the extent of WMHI. In addition, we found that slope of DBP over time was inversely related to later-life brain volume and WMHI. The importance of “balanced” BP management is supported by the observation that acute reductions in BP accompanying hypertension treatment, especially in older individuals, can sometimes have devastating consequences.\textsuperscript{40}

WMHI and Vascular Disease

It is now well established that age-related abnormalities of cerebral white matter are exacerbated in individuals with concomitant cerebrovascular risk factors.\textsuperscript{15,16,19,39} Similar to risk for stroke,\textsuperscript{41} midlife and current levels of SBP are the strongest predictors of WMHI severity.\textsuperscript{27,30} Unlike stroke, however, there is an incremental relationship between the level of SBP and the extent of WMHI.\textsuperscript{39} Moreover, history of symptomatic CVA remained a significant predictor of WMHI even when stroke-related WMHI was removed from the calculation. Because risks for stroke are similar to those for WMHI, it is tempting to conclude that they share the same pathophysiology. This notion is supported by the fact that WMHI predict risk for future cerebral infarctions.\textsuperscript{42} While such a conclusion is clearly tenable, WMHI are nonspecific and have numerous etiologies.\textsuperscript{43} Moreover, orthostatic hypotension may rarely lead to stroke.\textsuperscript{40} Our data and those of Longstreth et al\textsuperscript{39} show that orthostatic changes in SBP are significant predictors of the extent of WMHI. These results suggest that while stroke and WMHI share similar risk factors, the pathophysiology of these 2 processes may be quite different.\textsuperscript{43}

WMHI occur in the watershed zones of the deep end-arteries supplying cerebral white matter.\textsuperscript{44,45} Similar arteries supply much of the circulation to the deep nuclei of the basal ganglia.\textsuperscript{45} It is not surprising, then, that hypertensive cerebrovascular change (eg, lipohyalinosis\textsuperscript{46} may alter cerebrovascular autoregulation\textsuperscript{15,45} as well as lead to lacunar infarction\textsuperscript{46}). Altered cerebrovascular autoregulation may explain how WMHI can occur with aging and in the presence of nonocclusive CVA such as cerebral amyloid angiopathy.\textsuperscript{47} Loss of cerebral autoregulation may also explain how orthostatic hypotension might increase the severity of WMHI. Therefore, while stroke and WMHI may share elevated SBP as part of their pathogenesis, secondary effects relating to vascular size, vascular territory, and hemodynamic factors influencing atherosclerotic deposition may explain final differences in prevalence and severity between stroke and WMHI.\textsuperscript{48}

Stroke

Although hypertension is a major risk factor for stroke,\textsuperscript{41} neither the number of MRI strokes nor the CVA volume was associated with reported BP measures. Consistent with other CT and MRI studies, clinically apparent strokes had significantly larger volumes of infarcted tissue.\textsuperscript{21–23} Unfortunately, while the stochastic nature of cerebral infarction might make predicting the volume of a stroke from various risk factors unlikely, some measure of BP should be associated with the presence of MRI stroke. The lack of association between MRI stroke and BP is interesting and is consistent with at least 1 epidemiological study that found a similar prevalence of hypertension among individuals with or without stroke.\textsuperscript{49} These results suggest that small, clinically silent strokes detected by MRI may have a pathophysiology different from that of larger symptomatic strokes.\textsuperscript{49} The possibility of pathological factors other than hypertension in this population and populations examined by other MRI studies\textsuperscript{50} deserves further investigation.

Conclusions

Our observation that vascular risk factors predict age-related differences in brain morphology is consistent with a growing body of literature.\textsuperscript{10,15–23,50} Much of this research, however, is cross-sectional. Our data confirm the negative impact of current SBP and hypertension treatment on brain morphology, but our prospective data emphasize the effects of midlife BP. In fact, it is probable that this effect has been underestimated, as nonparticipants in the NHLBI Twin Study were generally more ill than the participants\textsuperscript{10,27,51} and therefore would be expected to have greater cerebral pathology. Our results also emphasize the need for further research into issues of midlife BP control\textsuperscript{10,34–39} as well as risk for future vascular disease and the benefits of treating current levels of borderline or isolated elevations in SBP.

Acknowledgment

This work was supported by grant HL51429 from the National Heart, Lung, and Blood Institute.

References

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Stroke. 1999;30:529-536
doi: 10.1161/01.STR.30.3.529

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