Association of Ambulatory Blood Pressure With Ischemic Brain Injury


Abstract—Cerebral white matter hyperintensities on brain MRI (leukoaraiosis) are associated with increased risk of stroke and dementia. To assess the relationships of blood pressure level and circadian pattern with leukoaraiosis, we obtained 24-hour ambulatory blood pressure recordings and brain magnetic resonance images in 343 white and 267 black adults who were members of sibships that had ≥2 siblings with essential hypertension. In multiple linear regression models, factors associated with greater leukoaraiosis in both racial groups included age (P≤0.002), homocysteine levels (P≤0.006), and brain volume (P≤0.008). In blacks, ambulatory blood pressure measures associated with greater leukoaraiosis were higher awake, asleep, and 24-hour systolic and diastolic levels (P≤0.009 for each). In addition, there was a trend for smaller nocturnal declines in systolic and diastolic levels (ie, nondipping patterns) to be associated with greater leukoaraiosis, and all of these associations, except nondipping of diastolic level, remained or became significant after controlling for office blood pressure (P<0.05 for each). In whites, among ambulatory blood pressure measures, only higher asleep diastolic levels trended toward association with greater leukoaraiosis. However, similar to findings in blacks, nondipping of systolic and diastolic ambulatory blood pressure levels were each associated with greater leukoaraiosis (P≤0.008), and all of these associations remained or became significant after controlling for office blood pressure (P≤0.009 for each). Higher ambulatory blood pressure levels and a nondipping circadian pattern contribute to greater leukoaraiosis volume after controlling for office blood pressure. (Hypertension. 2007;49:1228-1234.)

Key Words: ambulatory blood pressure ■ leukoaraiosis ■ predictors ■ hypertension ■ target organ injury

Cerebral hyperintensities in the subcortical and periventricular white matter on computed tomography or MRI of the brain, referred to as leukoaraiosis, are common in elderly persons.1–3 Leukoaraiosis is associated with an increased risk of stroke, cognitive dysfunction, and dementia.1,4–7 Although the pathogenesis of these lesions is not well understood, the major risk factors are age, tobacco use, elevated homocysteine, hypertension, diabetes mellitus, and a history of stroke or heart disease.1,2,8–13 In hypertensive persons, leukoaraiosis has been associated with the degree of office blood pressure (BP) elevation, as well as lack of control among those on treatment.14,15 Thus, ischemia caused by arteriolsclerosis of penetrating end arterioles may be a predominant cause.

Noninvasive ambulatory BP (ABP) monitoring provides a comprehensive assessment of BP level and variation over a 24-hour period.16 Although, in general, ABP measures have been shown to be better predictors of target organ injury than office measures,17–19 few studies have assessed the relationship between ABP and leukoaraiosis volume. In addition to measures of level, ABP provides a measure of the circadian pattern of BP that may be of clinical importance. For example, both cross-sectional and longitudinal studies have demonstrated an increased risk of cardiovascular disease events in hypertensive subjects in whom nocturnal BP fails to decline normally from daytime values (ie, nondippers).20–24

The purpose of this study was to assess the relationships of ABP level and circadian pattern with leukoaraiosis volume assessed by brain MRI. We studied a biracial sample of adults expected to be at higher risk of leukoaraiosis by virtue of having been recruited through sibships with ≥2 members with hypertension diagnosed before age 60 years.

Methods

Sample
The current study included 343 non-Hispanic white (204 women and 139 men) and 267 non-Hispanic black subjects (190 women and 77 men) who were members of sibships initially enrolled in the Genetic Epidemiology Network Of Arthritis (GENOA) of the Family Blood Pressure Program. The Family Blood Pressure Program, sponsored by the National Heart, Lung, and Blood Institute, is designed to identify and
characterize genetic determinants of hypertension and its associated cardiac and renal complications. An ancillary study to GENOA, the Genetics of Microangiopathic Brain Injury (GMBI) Study, was designed to extend the assessment of hypertension-related target organ damage to include ischemic damage to the subcortical white matter of the brain determined by MRI, referred to as leukoaraiosis. Noninvasive, 24-hour ABP was performed in a subset of GMBI participants to assess the relationship of measures of the ABP level and circadian pattern with leukoaraiosis volume.

Recruitment for the GENOA study has been described previously. Briefly, for the GENOA–Rochester cohort, the Mayo Clinic diagnostic index, and medical chart linkage system of the Rochester Epidemiology Project were used to identify non-Hispanic white residents of Olmsted County, Minn, with a diagnosis of essential hypertension made before the age of 60 years. When an eligible proband had ≥1 sibling who also reported hypertension, all of the available members of the sibships were invited to the study center for an initial visit.

For the GENOA–Jackson, Miss, cohort, sibships were recruited through hypertensive probands who had participated in the Atherosclerosis Risk in Communities cohort in Jackson was a probability sample of 45- to 64-year-old non-Hispanic black residents of the community. When an eligible proband had ≥1 sibling who also reported hypertension, all of the available members of the sibships were invited to the study center for an initial visit.

The only exclusions to recruitment for the GMBI ancillary study were a history of stroke or neurologic disease or implanted metal devices. The only exclusions to recruitment for the ABP supplement study were an upper arm circumference of the nondominant arm of ≥40 cm, atrial fibrillation, or an irregular pulse. Between December 2000 and May 2004, 2626 of 3434 original GENOA participants (ie, 1482 of 1854 blacks from Jackson [80%] and 1144 of 1580 whites from Rochester [72%]) and 27 siblings of whites from Rochester participated in a second study visit. Between August 2001 and February 2006, 1594 of these subjects also underwent MRI of the brain as part of the GMBI ancillary study. Between October 2003 and January 2006, 631 of the subjects who underwent MRI of the brain also underwent ABP as part of the GMBI supplement study. The median time between the second GENOA study visit and the subsequent performance of the MRI scans was 10.6 months. The median time between the performance of the MRI scan and the subsequent performance of ABP was 12 months.

Study protocols were approved by the human studies review board of the Mayo Clinic and the University of Mississippi. Informed consent was obtained from all of the participants.

Study Visit

At the study visit, blood was drawn after an overnight fast of ≥8 hours. Serum creatinine, glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured by standard enzymatic methods.

A diagnosis of hypertension was made at the study visit if the average systolic or diastolic BP (2 readings made after 5 minutes of rest in the sitting position) was ≥140 mm Hg or ≥90 mm Hg, respectively or if the subject reported a history of hypertension and current use of prescription antihypertensive medications. The duration of hypertension was determined by subject recall of the year of diagnosis. Diabetes was diagnosed if the subject reported treatment with insulin or oral hypoglycemic agents or if the fasting serum glucose concentration was ≥126 mg/dL. Each prescription medication was recorded at the study visit and assigned a code based on mechanism of action. The diagnosis of cardiovascular disease was made if the subject reported a history of ≥1 of the following on a questionnaire: "heart attack," "myocardial infarction," "stroke," "blocked arteries," "blocked carotid artery," "coronary artery bypass graft surgery," "percutaneous coronary angioplasty," or "carotid endarterectomy."
leukoaraiosis volume was skewed, log-transformed values were used in the regression analyses. Initially, each measure of office and ABP was added separately to the baseline model to determine whether it was associated with leukoaraiosis volume. For each ABP measure that was found to be associated with volume of leukoaraiosis (P/H11349 0.10), the regression analysis was repeated with inclusion in the model of both the ambulatory measure and the corresponding office BP to assess whether the ambulatory measure remained associated with volume of leukoaraiosis after considering the effect of office BP.

**Results**

**Descriptive Characteristics**

All of the characteristics differed significantly between the racial groups except for median age, body mass index, duration of hypertension, pack-years of smoking, total cholesterol, leukoaraiosis volume, and percentage with cardiovascular disease (Table 1). In particular, the percentages with diagnosed hypertension and who were on antihypertensive drug treatment were significantly higher in whites. Median values of office systolic and diastolic, ambulatory awake, and 24-hour systolic BP were also significantly higher in whites than in blacks (Table 2). Median asleep systolic and diastolic ABP levels did not differ significantly between the groups, but the nocturnal decline in systolic BP (ie, dipping) was significantly less in blacks.

**Factors Associated With Volume of Leukoaraiosis**

**Baseline Model**

In both racial groups, factors significantly associated with greater leukoaraiosis volume were older age, higher plasma homocysteine, and larger total brain volume (Table 3). In whites, male sex was also significantly associated with greater leukoaraiosis, whereas in blacks longer duration of hypertension was significantly associated with greater leukoaraiosis. In whites, the effect of age on leukoaraiosis volume was greater in older than in younger subjects (ie, age interaction), and the effect of male sex was less in older than in younger subjects (ie, age×sex interaction). In neither group was there an association of leukoaraiosis volume with the number of antihypertensive drugs used, pack-years of smoking, or diagnosed cardiovascular disease or diabetes.

**Office BP**

In blacks, higher levels of office systolic and diastolic BP were each significantly associated with greater leukoaraiosis volume when added to the baseline model (Table 4).
whites, this was not the case. There was a trend for lower levels of office systolic BP to be associated with greater leukoaraiosis volume ($P=0.06$).

**ABP**

In blacks, higher mean levels of ambulatory awake, asleep, and 24-hour systolic and diastolic BP were each significantly associated with greater leukoaraiosis volume when added to the baseline model (Table 4), and all of the associations remained significant when the corresponding measures of office BP were included in the models ($P\leq0.031$ for each). In whites, no measure of ABP level was significantly associated with leukoaraiosis volume when added to the baseline model (Table 4). Although a trend for higher mean levels of ambulatory asleep diastolic BP to be associated with greater leukoaraiosis volume ($P=0.064$) became significant when the corresponding measure of office BP was included in the model ($P=0.009$), this was not the case for any other measure of ABP level. Plots of the predicted leukoaraiosis volume versus 24-hour ambulatory systolic and diastolic BP levels (Figure 1) illustrate the stronger positive relationship between ABP levels and leukoaraiosis volume in blacks and the weak or nonexistent relationship in whites.

### TABLE 3. Association of Traits With Volume of Leukoaraiosis in Baseline Multiple Regression Model in Black Subjects From Jackson and White Subjects From Rochester

<table>
<thead>
<tr>
<th>Trait</th>
<th>Blacks (N=267)</th>
<th>Coefficient</th>
<th>$P$</th>
<th>Whites (N=343)</th>
<th>Coefficient</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td>0.0270</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age×age</td>
<td></td>
<td>0.0014</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>0.1215</td>
<td>0.18</td>
<td>1.5137</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Age×male sex</td>
<td></td>
<td>-0.0265</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-brain volume, cm$^3$</td>
<td></td>
<td>0.9862</td>
<td>0.008</td>
<td>1.3469</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td></td>
<td>0.0089</td>
<td>0.01</td>
<td>-0.0005</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td></td>
<td>0.0324</td>
<td>0.39</td>
<td>0.0062</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td>0.0726</td>
<td>0.61</td>
<td>0.1543</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.0645</td>
<td>0.44</td>
<td>0.1295</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Homocysteine level</td>
<td></td>
<td>0.0459</td>
<td>0.002</td>
<td>0.0275</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td></td>
<td>-0.0067</td>
<td>0.79</td>
<td>-0.0140</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.

### TABLE 2. Descriptive Characteristics of Office and ABP in Black Subjects From Jackson and White Subjects From Rochester

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Blacks (N=267)</th>
<th>Median</th>
<th>Interquartile Range</th>
<th>Whites (N=343)</th>
<th>Median</th>
<th>Interquartile Range</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td></td>
<td>136.0</td>
<td>127.5 to 149.0</td>
<td></td>
<td>148.0</td>
<td>136.0 to 161.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td>133.9</td>
<td>125.6 to 143.0</td>
<td></td>
<td>141.4</td>
<td>131.2 to 154.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Whole day</td>
<td></td>
<td>123.2</td>
<td>114.6 to 133.2</td>
<td></td>
<td>125.1</td>
<td>113.9 to 138.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Dip</td>
<td></td>
<td>131.5</td>
<td>122.7 to 140.6</td>
<td></td>
<td>138.2</td>
<td>127.7 to 150.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td></td>
<td>10.3</td>
<td>8.0 to 22.5</td>
<td></td>
<td>15.3</td>
<td>15.3 to 27.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Dip indicates dip in systolic BP.
In whites, smaller nocturnal declines in ambulatory systolic and diastolic BP levels (ie, nondipping patterns) were significantly associated with greater leukoaraiosis volume, and these associations remained significant after the corresponding measures of office BP were included in the models (P<0.01 for each). In blacks, similar trends were noted with smaller nocturnal declines in ambulatory systolic and diastolic BP levels associated with greater leukoaraiosis volume (P<0.09 for each). The trend became significant for systolic BP when the corresponding measure of office BP was included in the model (P<0.05). In regression analyses that used a combined sample of both racial groups, a significant association of nondipping of both systolic and diastolic BP with greater leukoaraiosis volume was observed (P<0.02 for both), and there was no evidence of a significant interaction between the effects of race and either systolic or diastolic BP dipping on leukoaraiosis volume. Plots of the predicted leukoaraiosis volume versus the degree of dipping of ambulatory systolic and diastolic BP (Figure 2) illustrate similar relationships in both racial groups.

Discussion

A major finding of this study was that measures of ABP level and circadian pattern were associated with the volume of leukoaraiosis after considering office BP. Some but not all studies have found an association of higher levels of office or ABP or a nondipping circadian pattern with the presence of leukoaraiosis. However, in most of these studies, sample sizes were small, and BP levels or circadian patterns were simply compared between subjects with and without leukoaraiosis. In studies that found an association between BP level and leukoaraiosis, there was no assessment of whether ABP measures made an additional contribution to the presence or quantity of leukoaraiosis after considering the effects of office BP. To our knowledge, this is the first study to demonstrate an additive, that is, “independent,” contribution of higher ABP levels to greater leukoaraiosis volume. The results of this study, along with a number of previous investigations regarding multiple target organ complications, support the notion that ABP measures provide additional prognostic information beyond that of office BP. Another major finding in this study was that the associations of measures of both office and ABP level with volume of leukoaraiosis were stronger in blacks than in whites (Figure 1). The only previous investigation that has assessed the effect of ethnicity on the relationship of BP level with leukoaraiosis is from the Atherosclerosis Risk in Communities Study. An association of higher office BP levels with greater leukoaraiosis was observed in both blacks and whites, but the association was stronger in blacks than in whites. The results of the present study are consistent with the findings in Atherosclerosis Risk in Communities and extend the observation to also include a stronger association of ABP levels with leukoaraiosis in blacks compared with whites.

That our study was carried out in a sample of mostly drug-treated hypertensive subjects may partially account for the weaker associations of measures of BP level with leukoaraiosis volume, particularly in whites, compared with that reported in studies of hypertensive subjects who were untreated or who were withdrawn from treatment. This may also account for the unexpected observation in whites that lower office systolic BP tended to be associated with greater leukoaraiosis volume (Table 4). That the majority of subjects in both racial groups were receiving antihypertensive drug therapy, yet the relationship remained significant in blacks, is consistent with the interpretation that blacks may be more sensitive than whites to vascular injury. It is noteworthy that the urinary albumin–creatinine ratio, another measure of microvascular target organ damage, was also higher in blacks than in whites despite lower median BP levels in blacks. Other studies have demonstrated that, after accounting for conventional predictors, blacks are at greater risk for hypertensive target organ complications, such as left ventricular hypertrophy and end-stage renal disease. Moreover, blacks

![Figure 1](image1.png)  
**Figure 1.** Dependence of volume of leukoaraiosis on mean 24-hour ambulatory systolic (top) and diastolic (bottom) BP level. 

![Figure 2](image2.png)  
**Figure 2.** Dependence of volume of leukoaraiosis on nocturnal decline (dipping) of mean ambulatory systolic (top) and diastolic (bottom) BP level. 

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have greater incidence rates than whites for all of the subtypes of ischemic stroke. In particular, the elevations in these relative rates are greatest for small-vessel stroke.\textsuperscript{27} Both leukoaraiosis and nephrosclerosis are manifestations of small-vessel arterial disease. The results of the present study are consistent with the notion that, in addition to a greater susceptibility to vascular injury, per se, in blacks compared with whites, blacks may be specifically more sensitive to hypertension-related small-vessel arterial disease.

Similar to some\textsuperscript{20,29,30} but not all\textsuperscript{31,32} previous studies, we found an association of smaller nocturnal declines in ambulatory systolic and diastolic BP with greater leukoaraiosis volume (Figure 2). Cross-sectional and longitudinal studies have shown that a nondipping circadian BP pattern predicts an increased risk of cardiovascular and cerebrovascular morbidity and mortality.\textsuperscript{20–24} Our findings are consistent with previous investigations and extend the association of nondipping with greater leukoaraiosis volume to a biracial sample. Also, consistent with previous studies,\textsuperscript{38} we found that the nocturnal decline in systolic BP was less in blacks than in whites (Table 2). Thus, nondipping could partially explain the relatively greater risk of target organ injury in blacks versus whites despite similar clinic BP levels.

There are several limitations of the present investigation. First, this is a cross-sectional study, and, therefore, causality underlying the statistical relationships observed cannot be determined. Second, there was a median time difference of \approx 1 year between the performance of MRI and the ABP recording. In as much as BP levels may have changed from the time of MRI, use of these BP measures could distort the “true” association of BP with leukoaraiosis volume. Third, most of the subjects in this study were taking antihypertensive medications at the time of ABP. This would tend to lessen the ability to find associations between measures of BP and volume of leukoaraiosis.

In conclusion, we found that measures of BP level and circadian pattern determined by 24-hour ABP were associated with quantitative measures of subcortical white matter ischemia determined by brain MRI in a biracial sample of mostly treated hypertensive adults. In particular, the associations of higher ABP levels and nondipping circadian patterns with greater leukoaraiosis volume were independent of the effects of office BP.

**Perspectives**

Currently, office measures of BP are used clinically to determine the risk of target organ injury and benefit of treatment in hypertensive patients. A growing body of evidence demonstrates the additive effects of ABP measures in refining the risk of target organ complications. The present study suggests that measures of BP level and circadian pattern make additive and independent contributions to the risk of leukoaraiosis, a known form of ischemic small-vessel injury to the brain that is associated with an increased risk of stroke, cognitive dysfunction, and dementia. In particular, higher levels of ABP in blacks and a nondipping circadian pattern in both blacks and whites were associated with greater leukoaraiosis volume after considering the effects of office BP. At present, more aggressive treatment may be indicated in patients identified by ABP monitoring to be at higher risk; however, definitive recommendations will require prospective treatment trials that use measures of ABP level and circadian pattern.

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**Disclosures**

None.

**References**


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