Silent Cerebrovascular Disease in the Elderly
Correlation With Ambulatory Pressure

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Does the average daily blood pressure correlate with hypertensive cerebrovascular disease better than the casual pressure, as has been reported in other target organ involvement? We investigated the associations of two abnormal findings on brain magnetic resonance imaging suggestive of a vascular etiology, low intense foci (lacunae), and periventricular hyperintense lesions on T1- and T2-weighted images, with both office and average daily blood pressure values in a population of 73 healthy normotensive and hypertensive elderly individuals (70 ± 6 years old). Lacunae were detected in 34 subjects (47%); the number per subject ranged from 0 to 19 and was significantly correlated with advancing age. Furthermore, these changes were supposedly related to the average of noninvasive ambulatory (24-hour and during awake and asleep periods) pressure recordings but not to office pressures. The grade of periventricular hyperintensity was also significantly associated with advancing age and the average of ambulatory systolic pressure recordings, particularly during sleep, but not with office blood pressure. In comparisons of normotensive, "office hypertensive," and hypertensive subgroups, abnormalities on magnetic resonance imaging were appropriate to the level of the 24-hour blood pressure measurements but not to that of clinic pressure. In hypertensive patients, the presence of electrocardiographic evidence of left ventricular hypertrophy was also associated with greater abnormalities on magnetic resonance imaging. We conclude that ambulatory blood pressure monitoring is superior to casual pressure measurements in predicting latent cerebrovascular disease, which is unexpectedly common in apparently healthy elderly subjects. (Hypertension 1990;16:692-699)

It is well known that pressures measured in the office or clinic may not be representative of the patient's blood pressure throughout the day. The correlations between target organ damage and different measures of blood pressure have been compared in several studies. In the heart, ambulatory blood pressure measurements have given better correlations than clinic readings with left ventricular hypertrophy as evaluated by electrocardiogram, chest x-ray, and echocardiography. Hypertensive retinopathy was also found to correlate more closely with ambulatory pressures than with casual pressures. These results suggest that the adverse effects of blood pressure on the heart and peripheral vessels (including the optic fundi) depend on the average level of pressure over time. To date, however, there has been no direct evidence that this is also the case with another important type of end-organ damage (i.e., cerebrovascular disease), probably because of the difficulty of detecting this condition in the preclinical stage.

Magnetic resonance imaging (MRI), which is a more advanced and sensitive technology than computerized tomographic (CT) scans in the brain, can visualize two distinct types of lesions related to hypertensive cerebrovascular disease (i.e., lacunae and periventricular white matter abnormalities). Lacunae are small, deep infarcts from penetrating arteriolar occlusive disease and can produce characteristic lacunar stroke syndromes. With the use of CT scans, however, clinically silent lacunar stroke has been shown to occur frequently among subjects from a general population investigated for acute stroke symptoms, suggesting that silent stroke is not rare. On the other hand, periventricular white matter lesions on MRI, visible in CT as diffuse subcortical hypodensity (leukoaraiosis), are also often incidental findings in the elderly. Subcortical hypertensive small vessel disease is suggested to play an etiological role in this type of lesion. This process, in some cases, may account for the development of intellectual...
impairment in the elderly, ultimately leading to a Binswanger type of vascular dementia.\textsuperscript{9,12}

In the present study, we investigated these MRI lesions in a group of active community-dwelling healthy elderly subjects and evaluated the relation between the severity of the lesions and both casual and ambulatory blood pressures.

\section*{Methods}

\subsection*{Subjects}

The study population consisted of 73 elderly subjects (24 men and 49 women) aged 59–83 years with a mean age of 70±6 (SD) years. All subjects, who were volunteers recruited from the community, maintained an active daily life. All patients either had never received antihypertensive therapy or had discontinued therapy at least 4 weeks before the study. They had no history of neurological, cardiovascular (except high blood pressure), respiratory, endocrine (including diabetes mellitus), or other major diseases. The duration of hypertension was based on the historical information about the date when each patient was first found to have high blood pressure. The average known duration of hypertension was 8.1±6.5 years, ranging from 0 to 24 years. The data may be limited to an approximation that probably underestimates the actual duration in most instances. The results of physical and laboratory examinations that included blood and urine tests, chest x-ray, and electrocardiograms at rest were normal or consistent with World Health Organization stages I and II. Electrocardiographic evidence of left ventricular hypertrophy (LVH) in hypertensive patients was graded into two classes.\textsuperscript{4} LVH was defined as abnormally high voltages of QRS complexes (R in V\textsubscript{5} plus S in V\textsubscript{1} greater than 3.5 mV) associated either with flat T waves (less than 10% of R) or with ST segment depression and diphasic T waves. None showed the more severe grade of LVH, such as prolonged ventricular activation time, depressed downsloping ST segments, and asymmetrically inverted T waves in left precordial leads. No attempt was made to distinguish between “within normal limits” and abnormally high voltages of QRS complexes alone, and “no LVH” was assigned to those subjects in this study. Blood pressure was measured in the sitting position by standard cuff methods in our clinic. The mean of three sphygmomanometric determinations at one visit was recorded as the office pressure. Informed consent was given by every participant.

\subsection*{Twenty-four–Hour Blood Pressure Monitoring}

Noninvasive ambulatory blood pressure monitoring was carried out on a weekday with the automatic ambulatory blood pressure monitor with gas-powered cuff inflation (ABPM-630, Nippon Kohrin Co., Komaki, Japan), which recorded blood pressure and heart rate every 30 minutes for 24 hours. The accuracy of this device was previously validated.\textsuperscript{13,14} The ambulatory data used in the present study were those

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Multiple lacunae on magnetic resonance imaging located in basal ganglia and white matter. Lacunae (arrows) were defined as low-intensity foci on \textit{T}_1-weighted images, which were seen as hyperintense lesions on \textit{T}_2-weighted images. Hyperintense punctate lesions on \textit{T}_2-weighted images (arrowheads) were not counted as lacunae if they were not identified as low intensities on \textit{T}_1-weighted images.}
\end{figure}
obtained by the oscillometric method. Subjects recorded a diary of action profile from which information about the precise times of falling asleep and waking up were obtained. The onset of sleep was identified as the time subjects went to bed. The average duration of sleep was 8.3±1.6 hours. The subjects whose blood pressure data were lost due to artifacts in more than 10% of the total measurements and those who documented disturbed sleep (frequent awakening during sleep) were not included in the present study.

Nuclear Magnetic Resonance Imaging
MRI was carried out on all 73 subjects with a superconducting magnet with a main field strength of 0.5 T (Hitachi G-50, Ibaragi, Japan). The brain was imaged in the axial plane at 10-mm-thick slices. \( T_1 \)-weighted images were obtained using a short spin-echo pulse sequence with a repetition time of 600 msec and an echo time of 20 msec. \( T_2 \)-weighted images were obtained using a long spin-echo pulse sequence with a repetition time of 2,000 msec and echo times of 60 and 120 msec. The matrix was 256×256 pixels. The images were evaluated for the number and location of lacunae and for the extent of periventricular signal abnormalities. Lacunae were defined as low signal intensity areas (less than 1 cm) on \( T_1 \)-weighted images, which were visible as hyperintense lesions on \( T_2 \)-weighted images (Figure 1). Periventricular hyperintensities \( (PVH) \) in \( T_2 \)-weighted images were classified into four groups (Figure 2). The first group (grade I) was defined as no abnormality or minimal periventricular signal hyperintensities in the form of caps only in the anterior horns or rims lining the ventricle. Grade II was defined as caps in both anterior and posterior horns of lateral ventricles or periventricular unifocal patches. Multifocal periventricular hyperintense punctate lesions and their early confluent stages were classified as grade III. Multiple high signal intensity areas that reached confluency in the periventricular region were defined as grade IV. One of the authors (K.M.), a neuroradiologist, interpreted all of the MRI while blinded to the clinical status of the subjects. Because only two subjects showed grade IV of PVH, these two subjects were included in grade III for the following analysis.

Subject Classification
Office blood pressure measurements greater than or equal to 140 mm Hg in systolic or 90 mm Hg in diastolic defined hypertension. The ambulatory blood pressure criteria were more arbitrary, as there are no defined standards for these data. In an attempt to accord with previously reported ambula-
tery blood pressure data in normal subjects and to make certain that there was appropriate separation among the groups, mean 24-hour ambulatory systolic and diastolic blood pressure had to be less than 135/80 mm Hg to be considered normotensive in the present study. Based on office blood pressure measurements, 40 subjects were classified as hypertensive. Fourteen of these 40 were normotensive according to the ambulatory pressure criteria and categorized as "office hypertensive." From the remaining 26 hypertensive subjects who were also hypertensive in ambulatory blood pressure measurements, 20 patients were matched to the office hypertensive group fairly closely by age and office blood pressure and designated "hypertensive." The subjects who were consistently normotensive in both office and ambulatory blood pressure measurements (28 subjects) were defined as "normotensive."

Statistical Analysis

Statistical analysis was performed with Biomedical Programs (BMDP) statistical software (University of California, Los Angeles, Calif.). Analysis of variance (ANOVA) was used to estimate the difference among groups, and significant differences were located with Student's t test. For categoric variables, Fisher's exact test or x² test was used. Both Pearson's test and nonparametric Spearman's rank correlation test were used to examine the correlation between two parameters. Results were reported as mean±SD.

Results

Characteristics of Study Group

Office systolic and diastolic blood pressure in this study population was 143±28/84±14 mm Hg on average, ranging from 90 to 226 mm Hg for systolic and from 53 to 116 mm Hg for diastolic. The average of ambulatory blood pressure measurements during the total 24-hour and the awake and asleep periods was 132±17/73±10 mm Hg (range, 101–186/57–97 mm Hg), 138±17/77±9 mm Hg (range, 102–181/61–103 mm Hg), and 123±19/67±10 mm Hg (range, 88–175/51–87 mm Hg), respectively.

Thirty-four subjects (47%) had at least one lacuna. The maximum number of lacuna was 19. There was a total of 113 lacunar lesions (average, 1.5/person as a whole or 3.3/person with lacunae). The localization of the lesions was 14 (12%) in the brain stem, 61 (54%) in the basal ganglia, and 38 (34%) in the deep white matter. No lacuna was found in the cerebral cortex. On the other hand, the number of subjects classified into PVH grades I, II, and III was 13, 41, and 19, respectively.

Magnetic Resonance Imaging Findings and Age

There was a weak, but significant, correlation between the number of lacunae and age (Figure 3). The difference in age among three different PVH groups was also significant (Figure 3). The mean age of the PVH-grade III group was significantly higher than that of the other two groups. The severity of lacunae and PVH correlated with each other. The number of lacunae was 0.7±1.7, 1.0±2.2, and 3.6±4.5 per subject in the groups with PVH grade I, II, or III, respectively (p<0.05 by analysis of variance [ANOVA]). Statistically significant differences were observed between the PVH-grade III group and the other two groups (p<0.05).

Magnetic Resonance Imaging Findings and Blood Pressure

As shown in Figure 4, the number of lacunae was significantly correlated with the means of ambulatory blood pressure readings (r=0.35, 0.31, and 0.42 for systolic and 0.33, 0.25, and 0.38 for diastolic blood pressure during the total 24-hour and the awake and asleep periods, respectively) but not with casual office blood pressure (r=0.17 and 0.06 for systolic and diastolic pressures, respectively). Both parametric and nonparametric statistical analyses gave essentially the same results. Furthermore, there were significant differences among three PVH groups in the means of systolic blood pressures during the 24-hour and asleep periods but not in the mean of ambulatory measurements during the awake period.
FIGURE 4. Plots showing correlations between number of lacunae on magnetic resonance imaging (MRI) and ambulatory (24-hour, awake, and asleep) and casual office systolic blood pressure (SBP). Correlation coefficients (R) by Pearson's test are shown. N.S., not significant. Nonparametric Spearman's rank correlation test gave essentially similar results (i.e., R=0.25*, 0.15, 0.29*, and 0.04, respectively; *p<0.05).

Hypertensive Cardiac Complications and Brain Magnetic Resonance Imaging Lesions

Thirty-four hypertensive patients were divided into two groups by the presence or absence of electrocardiographic evidence of LVH. As shown in Table 2, the two groups did not differ either for age or for the status of antihypertensive treatment. The known duration of hypertension as well as systolic and diastolic blood pressures were greater in patients with electrocardiographic evidence of LVH. The difference in the office blood pressure was significant at the 0.05 level, whereas that in the ambulatory blood pressure was significant at the 0.01 level. Thus, ambulatory blood pressure appeared to be more closely related to electrocardiographic evidence of LVH than office blood pressure. Furthermore, the number of lacunae was significantly greater in patients with LVH. The grade of PVH also tended to be greater in the LVH group, although this did not reach a statistical significance (p=0.12).

Discussion

Lacunae were strictly defined on MRI in the present study. The hyperintense punctate lesions on T2-weighted images were counted as lacunae only if they were identified as low intensities on T1-weighted images. Previous clinical investigations showed that these characteristic lesions on T1- and T2-weighted MRI are produced days to weeks after cerebral ischemic infarction and are found in patients with lacunar stroke in locations appropriate for the clinical presentation.16-18 Although they were also demonstrated on CT scan, MRI was found to be more

or in casual office systolic blood pressure (Figure 5). The average systolic blood pressure during sleep tended to increase with advancing grade of PVH (i.e., p<0.1 for differences between grades I and II and between grades II and III) and was significantly higher in the PVH-grade III group than in the PVH-grade I group. The differences in the mean diastolic blood pressure during the total 24-hour period and the asleep period among the three PVH groups were only marginal (p=0.09 and 0.06, respectively, by ANOVA), whereas there were no significant differences in office and awake diastolic blood pressures. Thus, the average of ambulatory blood pressure readings, particularly systolic blood pressure during sleep, was best associated with the severity of abnormal MRI findings. Neither 24-hour blood pressure variability as determined by standard deviations of systolic and diastolic blood pressure nor the differences between the means of awake and asleep blood pressures was correlated with the number of lacunae or the grade of PVH (data not shown). There was no correlation between age and any blood pressure in this population (correlation coefficients less than 0.01).

MRI findings were then compared among three defined blood pressure groups (Table 1). The mean age was not significantly different between the groups (ANOVA). The number of lacunae as well as the grade of PVH in the office hypertensive group were not significantly different from those in the normotensive group but significantly less than in the hypertensive group. Thus, MRI abnormalities were more appropriate to the level of 24-hour blood pressure than to that of the clinic blood pressure.
sensitive than CT imaging for detecting such deep, small lesions.\textsuperscript{18} Several neuropathological studies\textsuperscript{9,19-20} however, demonstrated that patchy subcortical hyperintensities on T$_2$-weighted images were associated with arteriosclerosis, dilated perivascular spaces, and vascular ectasia (i.e., the condition named \textit{état criblé}) resulting from chronic, low grade vascular insufficiency. Additional associated findings such as myelin pallor, gliosis, and lacunar infarctions had indistinguishable MRI appearances. \textit{État criblé} and subcortical infarctions often coexist. Thus, some of the patchy T$_2$-low and T$_2$-high intense lesions counted in this study may represent pathological processes such as \textit{état criblé}, not true lacunar infarcts. On the other hand, the CT evidence of prior lacunar stroke without a history of such an event was reported to be found in 10\% of the middle-aged (32–62 years) subjects who presented acute stroke symptoms in the Framingham cohort,\textsuperscript{11} suggesting that silent strokes occur fairly frequently. No systemic CT or MRI evaluation of fully neurologically asymptomatic members in the community, however, has yet been done. From these observations, we think that these MRI lesions incidentally detected in apparently healthy older subjects reflect silent lacunar or at least small, deep ischemic lesions. The location and the small size of lesions may explain their being silent, as most of the lacunae were found in the basal ganglia or the deep white matter areas, which are frequently asymptomatic. The specificity of these radiographic lesions, however, would have to be clarified by further pathoradiological correlation studies.

Our data have shown that the prevalence of silent lacunar stroke is unexpectedly high, as high as nearly 50\% in a free-living, apparently healthy,

### Table 1. Comparisons of Different Blood Pressure Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT (n)</th>
<th>Office HT (n)</th>
<th>HT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Office SBP (mm Hg)</td>
<td>119±13</td>
<td>152±13*</td>
<td>158±14*</td>
</tr>
<tr>
<td>Office DBP (mm Hg)</td>
<td>73±7</td>
<td>92±8*</td>
<td>91±10*</td>
</tr>
<tr>
<td>Average of 24-hour SBP (mm Hg)</td>
<td>119±10</td>
<td>124±6</td>
<td>147±8*</td>
</tr>
<tr>
<td>Average of 24-hour DBP (mm Hg)</td>
<td>66±5</td>
<td>70±5†</td>
<td>81±6†</td>
</tr>
<tr>
<td>No. of lacunae</td>
<td>1.1±1.5</td>
<td>0.6±1.2</td>
<td>2.8±4.6†</td>
</tr>
</tbody>
</table>

VALUES ARE MEAN±SD. SBP, SYSTOLIC BLOOD PRESSURE; DBP, DIASTOLIC BLOOD PRESSURE; NT, NORMOTENSIVE GROUP; HT, HYPERTENSIVE GROUP; OFFICE HT, OFFICE HYPERTENSIVE GROUP. NT, HT, AND OFFICE HT ARE DEFINED AS DESCRIBED IN METHODS. DIFFERENCE AMONG THE GROUPS IN ANY BLOOD PRESSURE VALUE AND THE NUMBER OF LACUNAE WERE SIGNIFICANT (P<0.0001 AND P<0.05, RESPECTIVELY) BY ANALYSIS OF VARIANCE.

\*P<0.0001, SIGNIFICANTLY DIFFERENT FROM NT GROUP BY STUDENT'S T TEST.

\*P<0.0001, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY STUDENT'S T TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM NT GROUP BY STUDENT'S T TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY STUDENT'S T TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY FISHER'S EXACT TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY FISHER'S EXACT TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY FISHER'S EXACT TEST.

\*P<0.05, SIGNIFICANTLY DIFFERENT FROM OFFICE HT GROUP BY FISHER'S EXACT TEST.

**FIGURE 5.** Plots showing differences in ambulatory (24-hour, awake, and asleep) and casual office systolic blood pressure (SBP) among three periventricular hyperintensity (PVH) groups. Vertical bar represents mean±SD. N.S., not significant by analysis of variance (ANOVA). **p<0.01, †p<0.001** by Student's t test.
Another interesting result is that a correlation between brain MRI abnormalities and asleep blood pressure appeared to be slightly better than those with the awake period and the total 24-hour-period blood pressure measurement. In contrast, LVH has been reported in some studies to be more closely with ambulatory blood pressures than with office pressures. Although previous results obtained by ambulatory blood pressure monitoring showed that this was indeed the case with other hypertensive target organ types of damage, including cardiac hypertrophy and retinopathy or overall severity of complications, this is the first direct demonstration of this kind. Furthermore, in hypertensive patients, the presence of electrocardiographic evidence of LVH was also associated with longer durations of hypertension and higher blood pressures (particularly ambulatory pressures), as well as a greater severity of MRI lesions (Table 2). Thus, although this study is not a longitudinal assessment that relates overt clinical outcome to ambulatory blood pressure, these cross-sectional data further support the concept that the adverse effects of high blood pressure on the function and structure of the entire cardiovascular system are more closely linked to the average level of blood pressure over time than to an isolated casual blood pressure value. The study involved both previously treated and untreated patients. The development of MRI lesions may well be affected by therapy, but once formed, these lesions are unlikely to be reversed by therapy, in contrast to the case with cardiac hypertrophy. This indicates that the potential influence, if any, of therapy on relations among normal and ambulatory blood pressure measurements and cerebrovascular damages might be less than in cardiac involvements.

Our findings on periventricular white matter signal that abnormalities (PVH) agreed with previous studies. Mild or even more extensive PVH often occur in older, normal individuals, although severe PVH is associated with intracerebral pathology, including demyelinating diseases, hydrocephalus, and subcortical arteriosclerotic encephalopathy (Binswanger's disease). Pathophysiological mechanisms of PVH in patients with demyelinating diseases or hydrocephalus (i.e., an increase in tissue water resulting from destruction of hydrophobic myelin or periventricular edema from transependymal resorption of spinal fluid) do not explain the PVH seen in normal subjects. The PVH in normal subjects may be a reflection of the higher concentration of interstitial water at the ventricular lining resulting from the normal flow of interstitial water into the lateral ventricles from the extracellular space. The progressive increase in PVH might reflect a slight increase in interstitial water caused by vascular damage with leakage of fluid into the extracellular space. In fact, pathophysiological correlation studies have suggested that they have, at least in part, a vascular etiology that can be accelerated by cerebrovascular risk factors, including hypertension. This explanation would help explain the present observation that as the extent of PVH increased, so did the number of lacunar lesions. On the other hand, caution should be exercised when relating these lesions to the cause of dementia, particularly Binswanger's subcortical arteriosclerotic encephalopathy, and other neurological symptoms, as the data on the clinical significance of these radiological lesions are conflicting.

The main as well as novel finding of this study is that the frequency and the severity of MRI abnormalities suggestive of silent cerebrovascular disease correlated more closely with ambulatory pressures than with office pressures. Although previous results obtained by ambulatory blood pressure monitoring showed that this was indeed the case with other hypertensive target organ types of damage, including cardiac hypertrophy and retinopathy or overall severity of complications, this is the first direct demonstration of this kind. Furthermore, in hypertensive patients, the presence of electrocardiographic evidence of LVH was also associated with longer durations of hypertension and higher blood pressures (particularly ambulatory pressures), as well as a greater severity of MRI lesions (Table 2). Thus, although this study is not a longitudinal assessment that relates overt clinical outcome to ambulatory blood pressure, these cross-sectional data further support the concept that the adverse effects of high blood pressure on the function and structure of the entire cardiovascular system are more closely linked to the average level of blood pressure over time than to an isolated casual blood pressure value. The study involved both previously treated and untreated patients. The development of MRI lesions may well be affected by the treatment, but once formed, these lesions are unlikely to be reversed by therapy, in contrast to the case with cardiac hypertrophy. This indicates that the potential influence, if any, of therapy on relations among normal and ambulatory blood pressure measurements and cerebrovascular damages might be less than in cardiac involvements.

Another interesting result is that a correlation between brain MRI abnormalities and asleep blood pressure appeared to be slightly better than those with the awake period and the total 24-hour-period blood pressure measurement. In contrast, LVH has been reported in some studies to be more closely related to a daytime work blood pressure than asleep
and total 24-hour blood pressure measurements, whereas data are inconsistent in other studies. Thus, two major hypertensive target organ types of damage, cardiac hypertrophy and cerebrovascular disease, might relate to different phases of normal daily activities. The former may be more closely related to blood pressure during stressful situations, whereas the latter to resting basal blood pressure. It should be noted, however, that the determination of sleep blood pressure by the noninvasive technique may be less precise than that by intra-arterial recordings, although sleep disturbance by the noise of the monitor we used is minimal because of its silent cuff inflation. Further investigations are obviously needed to prove this concept.

In conclusion, MRI lesions suggestive of silent cerebrovascular diseases are uncommonly expected in a population of community-dwelling, healthy elderly individuals, including patients with mild-to-moderate essential hypertension. Ambulatory blood pressure monitoring is superior to casual blood pressure measurements in predicting these latent cerebrovascular damages.

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