Scientific Contributions

Midlife Blood Pressure and the Risk of Hippocampal Atrophy
The Honolulu Asia Aging Study

Esther S.C. Korf, Lon R. White, Philip Scheltens, Lenore J. Launer

Abstract—Hippocampal atrophy (HA) is usually attributed to the neurofibrillary tangles and neuritic plaques of Alzheimer disease. However, the hippocampus is vulnerable to global ischemia, which may lead to atrophy. We investigated the association of midlife blood pressure (BP) and late-life HA in a sample of Japanese-American men born between 1900 and 1919. BP was measured on 3 occasions between 1965 and 1971. In 1994 to 1996 a subsample underwent magnetic resonance imaging (MRI) of the brain. Hippocampal volume was estimated by manually drawing regions of interest on relevant scan slices; HA was defined as the lowest quartile of hippocampal volume. Also assessed on the MRI were cortical and subcortical infarcts, lacunes, and white matter hyperintensities. The risk (OR, 95% CI) was estimated for HA associated with systolic (<140 versus ≥140 mm Hg) and diastolic (<90 versus ≥90 mm Hg) BP and with antihypertensive treatment. Analyses were adjusted for sociodemographic factors, other cardiovascular risk factors, apolipoprotein E allele, and correlated brain pathology. Those never treated with antihypertensive medication had a significantly increased risk for HA (OR 1.7; CI = 1.12; 2.65). The nontreated subjects with high systolic BP had an increased risk (OR = 1.98; CI = 0.89; 4.39) for HA. Results were similar for untreated men with high diastolic BP (OR = 3.51; CI = 1.26; 9.74). In conclusion, treatment with antihypertensive treatment modifies the association of BP and HA, such that high levels of BP adversely affect the hippocampus in persons never treated with antihypertensives.

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Key Words: blood pressure ■ magnetic resonance imaging ■ epidemiology ■ brain

Damage to the hippocampus may cause anterograde and retrograde memory impairment. The hippocampus and surrounding areas within the medial temporal lobe are typically involved in Alzheimer disease (AD), but are also affected in other dementias, such as vascular dementia (VaD). In AD, hippocampal atrophy (HA) is usually attributed to the deposition of neurofibrillary tangles and neuritic plaques. However, the hippocampus, particularly the CA1 area, is vulnerable to global ischemia. This vascular damage, leading to selective capillary abnormalities, neuronal necrosis, and microglial and macrophage formation may contribute to HA in both AD and VaD.

For these reasons, we investigated the association of high blood pressure (BP) and HA in a subsample of Japanese-American men participating in the longitudinal community-based Honolulu Asia Aging Study (HAAS). Previously in this cohort, we found that hypertension in midlife increased the risk for late-life cognitive impairment, AD and VaD, and neuropathological markers of AD. Results, particularly for the clinical end points of AD, were strongest in those never treated for hypertension.

Methods
The design of the HAAS has been described elsewhere. The original cohort included Japanese-American men born between 1900 and 1919 who underwent 5 exams (examination 1: 1965 to 1968; examination 2: 1968 to 1970; examination 3: 1971 to 1974; examination 4: 1991 to 1993; examination 5: 1994 to 1996). At each examination, clinical measures were made and sociodemographic and medical conditions assessed.

Dementia, Blood Pressure, and Treatment
At exams 4 and 5, cognitive status was tested with the Cognitive Abilities Screening Instrument (CASI) and prevalent (examination 4) and incident (examination 5) dementia was ascertained. Diagnostic and Statistics Manual of Mental Disorders (DSM-III-R) criteria were applied for dementia, National Institute of Neurologic Diseases and Stroke—Alzheimer’s Disease and Related Disorders for AD, and the State of California Alzheimer’s Disease Diagnostic and Treatment Centers for VaD. Stroke was identified through the ongoing hospital surveillance system. Apolipoprotein E (apoE) genotyping was performed at examination 4.

We categorized BP, measured at the 3 midlife exams, as follows: systolic BP (SBP) low (<110 mm Hg), normal (110 to 139 mm Hg), and borderline/high (≥140 mm Hg); diastolic BP (DBP) low (<80 mm Hg), normal (80 to 89 mm Hg), and borderline/high...
(≥90 mm Hg). Subjects were further classified as (n)ever treated with antihypertensive medication or report of treatment at any of the first 4 examinations. A new variable was created that combined treatment and midlife BP. The BP categories were collapsed into 2 categories: SBP ≥140 mm Hg versus <140 mm Hg; DBP ≥90 mm Hg versus <90 mm Hg. These BP categories were combined with treatment status (yes/no) to form 4 groups: never-treated–normal, treated-normal, never-treated–high, treated-high. For the analyses, the never treated–normal BP served as the reference group.

Isolated high DBP was defined as DBP ≥90 mm Hg; DBP 140 mm Hg versus DBP 90 mm Hg. Isolated high DBP was defined as DBP ≥90 mm Hg with an SBP <140 mm Hg. These categories were also combined with treatment status in the same way as described above.

Magnetic Resonance Imaging Substudy
At examination 5, a magnetic resonance imaging (MRI) study was conducted on a subsample, including an approximately 10% random sample and a randomly selected oversample of those with prevalent dementia, those who scored poorly on the CASI but did not meet criteria for dementia, those with apoE ε4 genotype, and those with clinical stroke.

Scans were acquired with a GE Signa Advantage 1.5 Tesla machine. The acquisition protocol included a T1 weighted sagittal sequence, a three-dimensional coronal spoiled gradient echo sequence, and axial T2 and proton density weighted fast-spin echo sequences.

The coronal spoiled gradient echo sequence was formatted to oblique coronal, perpendicular to the long axis of the left hippocampus. The left and right hippocampal formations were measured according to published criteria and corrected for the total intracranial volume. One reader performed all measurements. The intraclass correlation coefficient for the intrareader agreement of the hippocampal volume (HV) was 0.97. Number of lacunes, cortical and subcortical infarcts, and white matter lesions (WMLs), graded on a scale of 0 to 9, were determined.

Measures of Confounding Variables
In addition to the variables used in sample selection, other possible confounders of the association between HA and BP were considered: education (<7 years, 7 to 9 years, >9 years [reference]), smoking (never [reference], current, and past) and daily alcohol use (none [reference], <1 drink, 1 or 2 drinks, >2 drinks per day).

Analytical Sample
Of 621 MRI scans collected, 543 MRI scans could be processed successfully for all relevant variables. The MRI sample subjects are somewhat older (81.6 versus 79.6 years; P<0.001) and had fewer years of education (10.3 versus 10.9 years; P=0.01) compared with the total sample at examination 5, but did not differ with respect to BP.

Statistical Analyses
We examined the relationship between BP and HV. We also created 2 groups by dichotomizing HV at the 25th percentile; ≤25 percentile was defined as HA. ANOVA was used to test age-adjusted differences in HV by subject characteristics; Mantel-Hansel test was used to test for differences in HA. We used a linear regression approach for HV and logistic regression approach for HA. Separate adjusted models were run for SBP and DBP, treatment status, and the combined BP/treatment variables. Three models were estimated: model 1 adjusted for age and education; model 2 also included apoE genotype, dementia status, smoking, and alcohol use; model 3 added other pathologies related to BP and HA, including lacunes, WMLs, and cortical and subcortical infarcts. The interaction between high and normal levels of BP and treatment was tested by entering into model 1 the cross product between the 2 variables. Because the conclusions were similar, we present the logistic regression association (OR and 95% confidence interval [CI]) of BP with HA.

### Results
The mean age of the MRI sample was 81.6 years (SD 5.0). In this sample, the left hippocampal volumes were smaller than the right hippocampal volumes (mean difference 138 mm³; SD 270; P<0.001). The results of the analyses for the left, right, and total HV did not differ, so we only present the analyses with the total HV. HVs were significantly higher in...
nondemented men compared with those with AD, AD with cardiovascular disease, and VaD (Table 1). HV was also significantly related to the CASI score ($P<0.001$; Table 2).

The prevalence of lacunes and infarcts was high. There was 3.7% with 1 or more subcortical infarcts, 9.0% with 1 or more cortical infarcts, and 47% with 1 or more lacunes. There was 27.3% with a WML score of 4 or higher. There were no significant differences in HV between the subjects with and without subcortical infarcts, cortical infarcts, lacunes, or white matter hyperintensities. However, the percentage of subjects with HV in the lowest quartile was higher in the subjects with cortical infarcts compared with the subjects without cortical infarcts (Table 3).

In the total sample, DBP and SBP were not significantly associated with HA. Those not treated with antihypertensive medication, however, had a significantly increased risk for HA (OR=1.7; CI=1.12; 2.65), adjusting for age, education, ApoE genotype, smoking, alcohol use, and dementia. Treatment history modified the association between BP and HA. Compared with the never-treated–normal group, the treated men with normal or high SBP had a reduced risk (OR=0.56; CI=0.33; 0.97 and OR=0.74; CI=0.42; 1.32, respectively) for HA; the nontreated high SBP group had an increased risk (OR=1.98; CI=0.89; 4.39) for HA.

This same trend is seen in the DBP groups: the treated subjects with normal or with high DBP had a reduced risk (OR=0.69; CI=0.43; 1.12 and OR=0.50; CI=0.24; 1.04 respectively) and the untreated subjects with high DBP had an increased risk (OR=3.51; CI=1.26; 9.74) for HA compared with the nontreated subjects with normal DBP. The interaction between DBP and treatment was significant ($P=0.03$) as was the interaction between SBP and treatment ($P=0.02$). Adjusting for lacunes, subcortical infarcts, cortical infarcts, or WMLs did not change these associations (Table 4). Regression analyses with only the nondemented subjects resulted in essentially the same associations; the OR of untreated high DBP was somewhat higher (OR=4.76; CI=1.56; 14.5).

Isolated high SBP and isolated high DBP were not significantly associated with HA. Compared with those with untreated normal blood pressure, there were no significant differences in HA in men with isolated SBP who were treated (OR=0.9; CI=0.45;1.81) or not treated (OR=1.21; CI=0.49;3.02). Similarly, the risk for isolated DBP in treated (OR=0.17; CI=0.02;1.30) and untreated (OR=0.02; CI=0.44;8.42) men did not differ from those with untreated normal blood pressure.

### TABLE 3. Late-Age HV and HA by Midlife Blood Pressure and Treatment Group in the HAAS

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects, %</th>
<th>Mean HV, mm$^3$ (mean [SD])</th>
<th>% in Lower Quartile of HV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>74.2</td>
<td>5402 (840)</td>
<td>23.3</td>
</tr>
<tr>
<td>&gt;140</td>
<td>25.8</td>
<td>5358 (826)</td>
<td>27.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>83.1</td>
<td>5392 (860)</td>
<td>25.1</td>
</tr>
<tr>
<td>&gt;90</td>
<td>16.9</td>
<td>5384 (712)</td>
<td>20.7</td>
</tr>
<tr>
<td>Treated with antihypertensives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52.3</td>
<td>5343 (898)</td>
<td>28.6</td>
</tr>
<tr>
<td>Yes</td>
<td>47.7</td>
<td>5448 (757)</td>
<td>19.3</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not-treated–normal SBP</td>
<td>46.0</td>
<td>5369 (903)</td>
<td>26.8</td>
</tr>
<tr>
<td>Treated-normal SBP</td>
<td>28.0</td>
<td>5466 (717)</td>
<td>17.1</td>
</tr>
<tr>
<td>Not-treated–high SBP</td>
<td>6.3</td>
<td>5147 (845)</td>
<td>42.4</td>
</tr>
<tr>
<td>Treated-high SBP</td>
<td>19.7</td>
<td>5423 (813)</td>
<td>22.4</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not-treated–normal DBP</td>
<td>48.8</td>
<td>5363 (902)</td>
<td>27.5</td>
</tr>
<tr>
<td>Treated-normal DBP</td>
<td>34.1</td>
<td>5441 (790)</td>
<td>21.1</td>
</tr>
<tr>
<td>Not-treated–high DBP</td>
<td>3.5</td>
<td>5045 (792)</td>
<td>44.4</td>
</tr>
<tr>
<td>Treated-high DBP</td>
<td>13.6</td>
<td>5466 (671)</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Treatment refers to high blood pressure treatment. Normal SBP is <140 mm Hg; high SBP is ≥140 mm Hg; normal DBP is <90 mm Hg; high DBP is ≥90 mm Hg.

### Discussion

In this longitudinal, prospective, population-based study we found that men never treated for high midlife BP had an increased risk for HA compared with never-treated men with normal midlife BP. Treatment with antihypertensive medication reduced the risk associated with high BP. Several studies show that more hippocampal atrophy is associated with poorer cognitive function, AD, as well as other causes of dementia. The same trend is seen in the DBP groups: the treated subjects with normal or with high DBP had a reduced risk (OR=0.69; CI=0.43; 1.12 and OR=0.50; CI=0.24; 1.04 respectively) and the untreated subjects with high DBP had an increased risk (OR=3.51; CI=1.26; 9.74) for HA compared with the nontreated subjects with normal DBP. The interaction between DBP and treatment was significant (P=0.03) as was the interaction between SBP and treatment (P=0.02). Adjusting for lacunes, subcortical infarcts, cortical infarcts, or WMLs did not change these associations (Table 4). Regression analyses with only the nondemented subjects resulted in essentially the same associations; the OR of untreated high DBP was somewhat higher (OR=4.76; CI=1.56; 14.5).

Isolated high SBP and isolated high DBP were not significantly associated with HA. Compared with those with untreated normal blood pressure, there were no significant differences in HA in men with isolated SBP who were treated (OR=0.9; CI=0.45;1.81) or not treated (OR=1.21; CI=0.49;3.02). Similarly, the risk for isolated DBP in treated (OR=0.17; CI=0.02;1.30) and untreated (OR=0.02; CI=0.44;8.42) men did not differ from those with untreated normal blood pressure.

This study has several strengths. One is the community-based sample, which has a wide range of BP and includes persons who have never been treated with antihypertensive medication despite high levels of SBP or DBP in midlife. Second, BP was measured in midlife, years before the onset of dementia. This is crucial, because dementia, as well as other factors more prevalent in old age, may lead to a lowering of BP. This decline may begin many years before the clinical detection of dementia. Third, BP was measured at 3 different time points, 3 times at each examination, so a reasonable estimation of average BP was obtained. Furthermore, in the analyses, we controlled for WMLs and infarcts, which may mediate or confound any associations of HA to BP. Another important advantage of this study is that 1 rater which may mediate or confound any associations of HA to BP. Further, the men were very old at the time the MRI was made. As subjects with longstanding hypertension are
likely to die at a younger age because of the adverse effects of hypertension on other organs, the effects of high BP on the hippocampus may be underestimated. In addition, within subgroups that were oversampled, those in the MRI sample may have been slightly healthier compared with subgroup members randomly selected but who did not participate.

High BP was a significant risk factor for dementia in longitudinal studies. In the studies based on HAAS data we have found that higher levels of blood pressure increased the risk for cognitive impairment, and neuropathological markers of AD. In the clinical data this associations were modified by treatment status, whereby the greatest risk for adverse brain events was in those never treated with antihypertensives. The findings of a treatment with antihypertensives. The volume increase was mostly explained by volume changes in the CA1 field. The treatment effects found in these animal studies are consistent with our finding that treatment was associated with a protective effect on HV. In the HAAS we do not have information on the type of antihypertensive medication that was taken nor is it known whether the treatment effect in the animals studies was specific for the nicardipine. Further research in this area is warranted.

Also of interest in light of our findings is the study of de Jong et al, in which chronic brain hypoperfusion was found to cause selective capillary abnormalities in the CA1 region in rats, and the severity of capillary abnormalities was significantly related to cognitive performance. It is possible that the capillary changes precede neuronal changes and atrophy, and hypotension (ie, caused by long-standing hypertensive vascular changes) plays a role in the atrophy of the hippocampus.

We took vascular damage in the brain into account, because it may confound or mediate the association between the HV and BP. Lacunes, subcortical and cortical infarcts, and WMLs did not change the associations of interest. Earlier reports suggest that small vessel disease may be closely associated with hippocampal volume loss or hippocampal hypoperfusion. In this study, correction for WMLs and lacunes did not alter the relation we found between BP/treatment and HV. This is in contrast to the hypothesis that hypertension influences the white matter changes and hippocampus through similar mechanisms. That the mechanism of BP on HV is probably different from the hypertensive effect on WMLs is supported by the findings of Fein et al, who found that WMLs correlated with cortical atrophy, but not specifically with HA.

In conclusion, high levels of untreated BP was associated with HA. Treatment with antihypertensive treatment may modify this association.
**Perspectives**

HA is usually classified as a pure neurodegenerative process. This study shows that a risk factor for vascular disease, hypertension, may also be associated with HA. The precise mechanism is unknown. Our findings should stimulate more studies to explore the effect on hippocampal atrophy of elevated levels of BP and of antihypertensive treatments. Also, other clinical and experimental studies are needed to delineate the pathophysiology of how elevated blood pressure modifies brain structure and risk for neurodegeneration. Such studies may help us to understand the etiology of the prevalent types of late-life cognitive disorders.

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