Hypertension

A 32-Year Prospective Study

Robert Stewart, Qian-Li Xue, Kamal Masaki, Helen Petrovitch, G. Webster Ross, Lon R. White, Lenore J. Launer

Abstract—Studies of the association of high blood pressure (BP) with dementia are not consistent. Understanding long-term trajectories in blood pressure of those who do and do not develop dementia can help clarify the issue. The Honolulu Heart Program/Honolulu-Asia Aging Study followed a cohort of Japanese American men for an average of 32 years, with systolic BP (SBP) and diastolic BP (DBP) measured at 6 examinations and dementia assessed at the final 3. In an analysis of 1890 men who completed all 6 of the exams, 112 diagnosed with incident dementia at examination 6 were compared with the 1778 survivors without dementia. Trajectories in SBP and DBP up to and including the sixth examination were estimated with a repeated-measures analysis using 3 splines. From midlife to late life, men who went on to develop dementia had an additional age-adjusted increase in SBP of 0.26 mm Hg (95% CI: 0.01 to 0.51 mm Hg) per year compared with survivors without dementia. Over the late-life examinations, this group had an additional age-adjusted decline in DBP of 1.36 mm Hg (95% CI: 0.64 to 2.07 mm Hg) per year. These associations were strongest for vascular dementia and were reduced substantially in men who were previously taking antihypertensive medication. Similar changes in diastolic BP were observed, but only for vascular dementia, and the findings were not modified by antihypertensive treatment. Over a 32-year period, compared with men who did not, those who did develop dementia had a greater increase, followed by a greater decrease, in SBP. Both of these trends are modified by antihypertensive therapy. (Hypertension. 2009;54:233-240.)

Key Words: blood pressure ■ hypertension ■ hypotension ■ dementia ■ Alzheimer’s disease ■ vascular dementia

The association between blood pressure (BP) and dementia is complex. On the one hand, raised midlife BP is associated with an increased risk of cognitive impairment, dementia, and Alzheimer’s disease (AD) 10 to 20 years later.1,2 On the other hand, by the time dementia has developed, BP levels are relatively low compared with nondemented subjects,3 although this has not been a universal finding.4 This inverse association may reflect a decline in BP that occurs in the prodromal stage of dementia,5–7 possibly as a consequence of the weight loss or other metabolic changes that occur as a part of the dementia syndrome.8 Understanding the natural history of BP over time and by dementia status can help to interpret observational research, design prevention strategies, and make decisions about treating high BP in old age.

The 32-year follow-up for the Japanese American men who participated in the Honolulu Heart Program and later the Honolulu-Asia Aging Study provided a unique opportunity to investigate long-term BP trajectories in those who did or did not develop dementia. Based on this cohort, several reports have been published regarding the association between increased midlife BP levels and increased risk for adverse late-life cognitive and brain structure outcomes.1,2 We have found that these associations are moderated by the use of antihypertensive medications and apolipoprotein E status (the e4 allele increasing the risk for AD).9 Therefore, in this study we investigated the trajectories of BP by dementia status and the extent to which they were modified by antihypertensive treatment and genetic susceptibility.

Methods

Participants

The study design of the Honolulu Heart Program and its follow-up, the Honolulu-Asia Aging Study, has been described previously.8 Briefly, the cohort included Japanese American men identified from selective service records who were born between 1900 and 1919 and were living on the island of Oahu, Hawaii, in 1965. Participants were examined on 3 occasions between 1965 and 1971. Of survivors, 80% participated in a fourth examination between 1991 and 1993 and were followed in 2 subsequent exams in 1994–1996 and 1997–1999 (with participation rates in survivors of 84% and 90%, respectively). Dementia was ascertained at these 3 late-life exams. All of the
participants gave written, informed consent at each examination. Proxies gave permission for cases of dementia. The protocol was approved by the Kuakini Medical Center Institutional Review Board.

**BP Measurement**
BP was measured with the same standardized protocol at each examination. Briefly, after the participant had been seated for ≥10 minutes, SBP and DBPs were measured on 3 occasions 5 minutes apart on the left arm of a seated participant using a mercury sphygmomanometer with a standard cuff. Diastolic pressure was recorded as the fifth phase. Repeated readings were averaged for each BP recording (ie, longitudinal effect). Based on previous studies each BP recording was considered an individual variable.2,10

Consensus diagnoses were made by a neurologist and 2 physicians. Diagnosis was made according to the following internationally accepted criteria: dementia according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised, AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association, and vascular dementia (VaD) according to the California Alzheimer’s Disease Diagnostic and Treatment Centers criteria.11–13

The criteria for probable VaD require dementia, computed tomography/MRI evidence of ≥1 infarct outside of the cerebellum, and then either clinical/imaging evidence of ≥2 ischemic stokes or a single stroke with a clear temporal relationship to the onset of dementia. Additional support is allowed if there is evidence of multiple infarcts in brain regions known to affect cognition, multiple transient ischemic attacks, a history of vascular risk factors, and an elevated Hachinski Ischemic Scale score. Characteristics of participants with and without dementia have been described previously for an identical sample: those with dementia were older and were more likely to have had a stroke, previous hypertension, previously impaired physical function, and to carry the apolipoprotein E (APOE) e4 allele.8

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**Table 1. Characteristics of the Honolulu-Asia Aging Study Cohort at Previous and Current Examination Points**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (n=1890)</th>
<th>No Dementia (n=1778)</th>
<th>Dementia (n=112)</th>
<th>AD (n=74)</th>
<th>VaD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at exam 6, y</td>
<td>83 (3.8)</td>
<td>82 (3.7)</td>
<td>85 (5.0)</td>
<td>85 (4.9)</td>
<td>84 (5.3)</td>
</tr>
<tr>
<td>Mean (SD) education, y</td>
<td>11 (3.2)</td>
<td>11 (3.2)</td>
<td>11 (3.4)</td>
<td>10 (3.4)</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Previous stroke, %*</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension, %*</td>
<td>46</td>
<td>46</td>
<td>49</td>
<td>43</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus, %*</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>35</td>
<td>27</td>
</tr>
<tr>
<td>Smoking, %*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>36</td>
<td>36</td>
<td>38</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>Past</td>
<td>58</td>
<td>58</td>
<td>59</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Current</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Impaired physical function, %†</td>
<td>2</td>
<td>2</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Median (interquartile range) CES-D score*</td>
<td>3 (1 to 5)</td>
<td>3 (1 to 5)</td>
<td>3 (0 to 6)</td>
<td>3 (0 to 6)</td>
<td>3 (0 to 10)</td>
</tr>
<tr>
<td>APOE e4, %</td>
<td>18</td>
<td>18</td>
<td>21</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Antihypertensive use, %*</td>
<td>40</td>
<td>40</td>
<td>41</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>Mean SBP/DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination 5 (1994–1996)</td>
<td>143/76</td>
<td>143/76</td>
<td>145/77</td>
<td>145/77</td>
<td>157/82</td>
</tr>
<tr>
<td>Examination 6 (1997–1999)</td>
<td>143/73</td>
<td>143/73</td>
<td>137/72</td>
<td>138/73</td>
<td>137/70</td>
</tr>
</tbody>
</table>

*Data were classified/measured at examination 4 (1991–1993).
†Data show the inability to rise from a chair or walking speed ≤0.4 m/s.

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**Covariates**
The following factors, ascertained at the fourth examination unless stated otherwise, were also included in the analysis: age (at entry to the study), years of formal education, history of stroke (obtained through surveillance of hospital records), previous hypertension (previous treatment, SBP >160 mm Hg or DBP >95 mm Hg), diabetes mellitus (World Health Organization criteria), smoking status (current, previous, or never), impaired physical function (inability to rise from a chair or walking speed ≤0.4 m/s), and depressive symptoms (Center for Epidemiologic Studies Depression Scale). Associations of interest were also adjusted for weight change as a time-dependent covariate. Participants had been weighed at all 6 of the exams and at the first examination had also been asked about weight at the time of military service (early adulthood). Two variables were generated to investigate confounding in this respect. One was the weight recorded at the first examination (ie, cross-sectional, between-person effect) and the other was within-person weight change (kilograms per year) from the first examination at each BP recording (ie, longitudinal effect). Based on previous studies in this cohort,2,13 APOE genotype (presence or absence of the e4
allele) and antihypertensive use (up to and including examination 4) were considered as potential modifying factors.

**Statistical Analysis**

Here, we investigated trajectories in the 1890 men who participated at the sixth examination and were not diagnosed previously with dementia. As described previously, this approach was taken so as to maximize the number of previous examination points for the estimation of trajectories. Of the 3734 Honolulu-Asia Aging Study participants at the fourth examination, 226 had dementia at that time, 135 had dementia by the fifth examination, 850 died before the sixth examination, and 633 did not participate for other reasons. Those present at the fourth examination but absent at the sixth were older (mean difference in age at the fourth examination: 2.8 (95% CI, 2.5 to 3.1) years, had a higher midlife SBP (mean difference at the first examination: 4.8 (95% CI, 3.6 to 6.0) mm Hg, and had a higher late-life SBP (mean difference at the fourth examination: 1.5 (95% CI, 0.0 to 3.0) mm Hg. Individual BP changes across the 6 exams were analyzed using random-effects models (with random intercept and slope functions) to account for between-participant heterogeneity and unequal time intervals between visits. Analyses were carried out separately for SBP and DBP. BP was entered as the dependent variable, with dementia, time, and a dementia × time interaction entered as independent variables. Time intervals were calculated individually from examination dates. To model changes in trajectories flexibly, a 3-piece linear spline was used with 2 knots fixed at times when the mean ages of the sample were 61 years (consistent with the mean time gap between exams 1 and 3) and 78 years (consistent with the mean time gap between exams 1 and 4). Individual interaction terms were summed to estimate differences in slope between stratification variables (e.g., dementia status) and SEs calculated from estimated covariance matrices via the Δ method. Other independent variables were entered into the model to investigate confounding effects. The fully adjusted model was then repeated for dementia subtypes and was stratified for any previous antihypertensive medication use and presence/absence of the APOE

![Graphs plotting previous SBP adjusted for age according to whether men did or did not develop dementia between exams 5 and 6.](http://hyper.ahajournals.org/DownloadedFrom)
1B and 1C) compared with those who did not develop midlife and a significantly greater decrease in late life (Figure 2). Among those who did not receive antihypertensive treatment, SBP trajectories did not differ between those who did and those who did not develop dementia. Carrying an APOE ε4 allele. SAS (version 8) and Stata (version 6) statistical software were used.

## Results

At the first examination in 1965, the age range was 46 to 68 years; at the sixth examination, participants were between 77 and 98 years old. At the sixth examination, there were 112 cases with dementia: 74 with AD and 15 with VaD. Characteristics of the sample are summarized in Table 1. The sample as a whole had experienced an increase in SBP and DBP from midlife to late life and a decrease in SBP and DBP in late life (Figures 1 to 4). Compared with those who did not, men who developed dementia, systolic BP increased an additional 0.26 mm Hg/y from midlife to late life and decreased an additional 1.36 mm Hg/y in late life (Table 2 and Figure 1A). These changes in SBP over these 2 time periods were greater in VaD cases than in AD cases (Table 2 and Figure 2). For the whole sample, adjustment for education and previous health status at examination 4 did not have a substantial impact on these differences in slope. The decrease in late-life SBP change between those who did and did not develop dementia was reduced modestly after adjustment for baseline weight and weight change (Table 2). In general, there was little evidence for significant differences in BP level at baseline, apart from a negative coefficient for SBP in the fully adjusted model.

Antihypertensive treatment modified these observed differences in SBP trajectories. Among those who had not previously reported antihypertensive treatment, those who developed dementia had a significantly greater increase in SBP in midlife and a significantly greater decrease in late life (Figure 1B and 1C) compared with those who did not develop dementia. Among those who did receive antihypertensive treatment, SBP trajectories did not differ between those who did and did not develop dementia. Carrying an APOE ε4 did not modify the trajectories of those who did and did not develop dementia (data not shown). Differences in DBP trajectories were weaker but in the same direction as those for SBP change (Table 3 and Figure 3) and were only significant for VaD (Figure 4).

Of the 109 participants who were diagnosed with dementia at the sixth examination, 58% had experienced a fall in SBP of ≥10 mm Hg over the previous 6 years (since examination 4) compared with 39% of those without dementia (odds ratio: 2.10; 95% CI: 1.42 to 3.12). Thirty-nine percent of those who developed dementia had experienced an SBP fall of >20 mm Hg compared with 24% of those without dementia (odds ratio: 2.09; 95% CI: 1.40 to 3.11).

## Discussion

Here, in an analysis of data collected over 3 decades, we found that men who developed dementia had a greater rise in SBP from midlife to late life and a greater decrease in BP over an ~6-year period before the dementia diagnosis. For both SBP and DBP, these associations were strongest for VaD. In addition, antihypertensive medication modulated the trajectories such that differences in the change in SBP over time were greatly diminished, and levels remained relatively stable. Advantages of this study include the large sample size, the 6 BP measures acquired with a standardized protocol, the long duration of follow-up, and structured screening and diagnostic procedures for dementia on 3 occasions. In addi-
tion, any measurement error in BP is unlikely to have been different between outcome groups and will, therefore, have obscured rather than exaggerated any group differences in trajectories, eg, if SBP is easier to estimate than DBP, then this might account for more marked differences in one compared with the other. It should be noted that these results pertain to men who survived to examination 6 of the Honolulu Heart Program/Honolulu-Asia Aging Study. An advantage of this approach is that it reduces the effect of survival bias on the comparisons between demented and non-demented subjects and permits the calculation of trajectories based on complete data. However, the sample clearly limits the generalizability of findings to women and other population subgroups. Also, the analysis is based on survivors to age 77 to 98 years, ie, a relatively elderly cohort, and findings cannot necessarily be generalized to dementia of earlier onset.

These longitudinal trajectories provide important insight into research on the association of BP with the risk for dementia. A large number of studies have investigated BP level in relation to dementia with the most consistent findings for higher BP as a risk factor coming from those with the longest follow-up periods. These have been comprehensively

<table>
<thead>
<tr>
<th>Model (All Age Adjusted)</th>
<th>Difference at Baseline</th>
<th>P</th>
<th>Additional Change in Rate of Change in DBP Associated With Dementia, mm Hg/y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age 54 to 60 y</td>
</tr>
<tr>
<td>All dementia (n=1890)</td>
<td>-0.03 (-1.99 to 1.93)</td>
<td>0.98</td>
<td>0.16 (-0.16 to 0.48)</td>
</tr>
<tr>
<td>Stratified analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. . . if no previous antihypertensive treatment (n=1126)</td>
<td>0.99 (-1.28 to 3.25)</td>
<td>0.39</td>
<td>0.18 (-0.18 to 0.54)</td>
</tr>
<tr>
<td>. . . if any previous antihypertensive treatment (n=765)</td>
<td>-1.92 (-4.97 to 1.12)</td>
<td>0.21</td>
<td>0.13 (-0.44 to 0.71)</td>
</tr>
<tr>
<td>Dementia subtypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD (n=1852)</td>
<td>-0.77 (-3.03 to 1.50)</td>
<td>0.51</td>
<td>0.44 (0.07 to 0.81)</td>
</tr>
<tr>
<td>VaD (n=1793)</td>
<td>1.73 (-4.02 to 7.48)</td>
<td>0.55</td>
<td>-0.24 (-1.19 to 0.71)</td>
</tr>
</tbody>
</table>

Regression coefficients with 95% CIs.

*P value was based on likelihood ratio testing of the overall significance of the interaction terms between dementia status and time slopes.
reviewed. As far as we are aware, ours is the first report on the change in BP from midlife to late life in relation to dementia, which can help with the interpretation of extant studies. The greater rise in SBP from midlife to late life in men who later developed dementia is consistent with previous findings of associations between raised midlife BP levels and dementia, which have also been found to be strongest for untreated hypertension. Similarly, modification by previous antihypertensive treatment was most evident for the dementia-associated difference in midlife SBP trajectories rather than in midlife to late-life slopes. Although SBPs of those who developed dementia and were taking antihypertensives were lower at all of the time points compared with those who did not develop dementia, these differences were marginal.

The nature of the relation of BP to dementia remains controversial. BP decline may be a consequence of neurodegeneration. Several studies have found that people with dementia have relatively low resting and orthostatic BP levels and dementia, which have also been found to be strongest for untreated hypertension. Similarly, modification by previous antihypertensive treatment was most evident for the dementia-associated difference in midlife SBP trajectories rather than in midlife to late-life slopes. Although SBPs of those who developed dementia and were taking antihypertensives were lower at all of the time points compared with those who did not develop dementia, these differences were marginal.

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damage,\textsuperscript{24} and neuropathological studies have found that watershed infarctions and arterial stenoses are associated with Alzheimer pathology.\textsuperscript{25,26} Furthermore, worse cerebral autoregulation has been found to be associated with overexpression of the amyloid precursor protein in mice.\textsuperscript{27} When untreated, these changes may all confer vulnerability of the brain to hypotensive episodes. Our findings, therefore, raise the possibility that treatment of hypertension not only reduces dementia through the prevention of BP elevation 10 to 20 years earlier but might also reduce cerebral damage attributed to hypotension later in life. This conclusion is further supported by the stronger associations in men with VaD: although there is strong overlap between AD and VaD,\textsuperscript{28} this group will have had more severe cerebrovascular pathology, suggesting a vascular origin for both the exaggerated increase and decrease in BP (both SBP and DBP) and its possible modification (for SBP) by previous antihypertensive treatment. However, the VaD group was small in our cohort, and 2 other studies have found stronger associations between low BP and dementia in people taking antihypertensive agents\textsuperscript{29,30}; therefore, further research is required.

**Perspectives**

Although there is growing evidence that hypertension is a modifiable risk factor for VaD and AD, it is important for clinicians to be aware that a person’s BP may have begun to decline by the time he or she develops dementia. Early antihypertensive use may reduce the extent of this decline, but further research is required into the risks or benefits of BP lowering when neurodegenerative processes are at a more advanced stage.

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**References**


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