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Systolic Blood Pressure within an Intermediate Range May Reduce Memory Loss in an Elderly Hypertensive Cohort

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ABSTRACT

The objective of this study was to determine if maintenance of systolic blood pressure (BP) within a high range or low range among treated hypertensive patients increases the risk of memory decline. Biennial neuropsychological evaluations were performed on 158 hypertensive subjects. Decline/year was measured on the Cued Selective Reminding test (total free recall and delayed recall) in three systolic BP groups (low—i.e., mean systolic BP during the follow-up period < 135 mm Hg; intermediate—i.e., 135 mm Hg ≤ mean systolic BP ≤ 150 mm Hg; high—i.e., mean systolic BP > 150 mm Hg). In total free recall, the three systolic BP groups had significantly different declines per year ($P = .02$), with patients in the high subgroup showing the greatest decline. In delayed recall, the three systolic BP groups also showed significantly different declines per year ($P = .04$), with patients in the low subgroup having the greatest decline. Chronically elevated systolic BP > 150 mm Hg is associated with accelerated memory decline compared to older treated hypertensive patients with systolic BP in an intermediate range. Chronically maintained systolic BP within a low normal range < 135 mm Hg in older treated hypertensive subjects may be associated with accelerated memory decline, specifically in a test of delayed memory recall, compared to patients with systolic BP in an intermediate range. Optimal regulation of systolic BP may be a potential modifiable risk factor to prevent or minimize memory loss in older hypertensive patients. (*J Geriatr Psychiatry Neurol* 1999; 12:1–6).

Control of potential risk factors is a critical step toward the prevention of dementia in older patients. Hypertension is a major risk factor for cerebrovascular disease[1–3] and multi-infarct dementia.[4–6] In the absence of cerebrovascular disease, elevated blood pressure (BP) also may be associated with cognitive impairment.[7–11] Proposed mechanisms, in addition to cerebral ischemia, include impaired cerebral autoregulation, neuroanatomic changes (e.g., cerebral and cervical vessel atherosclerosis, atrophy, and white matter disease), and concomitant conditions such as diabetes, hyperlipidemia, cardiovascular diseases, erythrocyte changes, smoking, and genetic risk factors.[10–12] Elderly hypertensive patients with impaired cerebral autoregulation[13] and greater rigidity of cerebral blood vessels[14] potentially may develop cognitive deterioration if antihypertensive therapy is too extensive in reducing BP.[1015]

In a cross-sectional community study[16] comparing healthy older subjects with high (> 181 mm Hg), intermediate (136–181 mm Hg), and low (< 135 mm Hg) systolic BPs, cognitive impairment was observed in the high BP group relative to the other two groups. However, in a longitudinal study, Meyer et al[17] found that in hypertensive subjects with multi-infarct dementia, improved cognition correlated with control of systolic BP within the upper limits of normal (135–150 mm Hg) compared to patients with a systolic BP < 135 mm Hg. Another study in elderly hypertensive patients suggests that BP reduction does not adversely affect cognitive function.[18]

The objective of this study was to determine whether long-term maintenance of systolic BP within an intermediate range reduces the risk of memory decline and cognitive deterioration among older treated hypertensive

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patients, relative to those with consistently lower or higher BP.

METHODS

A study of hypertensive outpatients in the Baltimore Longitudinal Study of Aging (BLSA) was performed. The BLSA is an ongoing longitudinal study of normative aging in community-dwelling volunteers, funded and conducted by the National Institute on Aging since 1958 at the Gerontology Research Center.[19] Participants return to Baltimore every 2 years (± 6 months) for medical, physiologic, and neuropsychological testing. The majority of BLSA participants are white; work in or are retired from scientific, professional, or managerial positions; graduated from high school or college; and married.[19,20]

Beginning in 1986, neuropsychological tests were administered to all subjects aged 60 years or older. These tests included two screening tests: the Mini-Mental State Examination (MMSE)[21] and the Blessed Information-Memory-Concentration test.[22] The Cued Selective Reminding procedure[23] was administered as a measure of word-list memory and learning. This test assesses four-item immediate recall, three trials of free recall (total free recall), and 20-minute delayed recall of a list of 16 nouns. The Trail Making test, parts A and B,[24] was administered as a measure of attention and set shifting.

For the current study, subjects were selected from BLSA participants evaluated from July 1986 to December 1995. Inclusion criteria were as follows: (1) age > 60 years; (2) a history of hypertension by either self-report on a standardized questionnaire, medical records with a diagnosis of hypertension (defined by a BP > 160/95 mm Hg), or treatment with antihypertensive drugs; (3) a minimum of two serial neuropsychological assessments ≥ 1.5 years apart; (4) BP measurements performed on at least two separate visits; and (5) treatment with an antihypertensive medication for at least one visit during the follow-up period. Exclusion criteria were (1) hypertensive subjects without neuropsychological assessments, (2) subjects without a minimum of ≥ 1.5 years of follow-up, (3) subjects with dementia as defined by DSM-IV criteria[25] at the initial visit of neuropsychological testing, and (4) subjects without antihypertensive medication treatment during the follow-up period.

The index visit was defined as the first visit in which the neuropsychological testing battery was administered. Severity and etiology of cognitive impairment, if present, were determined by the medical history, neurologic examination, radiologic testing, appropriate serum chemistries and serologies, and neuropsychological testing results as described previously.[20]

At each biennial visit, systolic BP was measured by a physician or nurse practitioner in both the right and left arms in the seated position. Subjects were classified into one of three BP ranges based on the mean of the right and left arm BPs during the study period (combining the index visit and all subsequent visits). The high BP range was defined as a mean systolic BP > 150 mm Hg over this time period. The intermediate BP range was defined as a mean systolic BP of 135 to 150 mm Hg. The low normal BP range was defined as a mean systolic BP < 135 mm Hg.

Four neuropsychological outcomes were used to evaluate for cognitive decline: (1) Cued Selective Reminding total free recall, (2) Cued Selective Reminding delayed recall, (3) total MMSE score, and (4) Trail Making test part B time.

For data analysis, to estimate each subject's change in neuropsychological test scores per year (for each of the four cognitive measures), least-squares regression was used. The regression of cognitive scores on time was done separately for each subject and each cognitive measure. The estimated change per year (slope) was then used as the response variable for the remainder of the analysis. An analysis of covariance model adjusted for age and education was used to evaluate the association between longitudinal change per year for the neuropsychological test outcome and systolic BP group. Pairwise comparisons of two BP ranges (i.e., high vs low, high vs intermediate, intermediate vs low) were then performed. To compare baseline characteristics among the three BP range groups, analysis of variance was used for continuous variables and logistic regression was used for discrete variables. Logistic regression was also used to test for differences among the three BP groups in the development of dementia during the follow-up period. A two-tailed P value ≤ .05 was required to reject the null hypothesis.

RESULTS

Study Participants

Three hundred and fifty-four subjects above age 60 with hypertension were in the BLSA between July 1986 and December 1995, of whom 222 subjects (63%) received longitudinal neuropsychological testing. Subjects who received longitudinal neuropsychological testing were older (mean [SD] age = 74.5 [6.4] years vs 66.5 [8.2] years, $P < .01$) and more educated (mean [SD] education = 16.9 [2.8] years vs 16.3 [2.8] years, $P = .05$) than subjects without neuropsychological testing. There was no difference in gender or history of antihypertensive medication use, stroke, coronary artery disease, or hypercholesterolemia between older hypertensive subjects with and without longitudinal neuropsychological testing. Twelve subjects were excluded because they did not have BP measurements at two separate visits. Forty-nine subjects were excluded because they never received antihypertensive medication treatment during the follow-up period. Two subjects were excluded because they had dementia (probable Alzheimer's disease) at the initial visit. One subject was excluded because the follow-up

Table 1. Systolic and Diastolic BP (Mean, Range) for Low, Intermediate, and High Systolic BP Groups Over the Follow-up Period

	Low (n = 29)	*Intermediate (n = 48)*	*High (n = 81)*
Systolic BP (mm Hg)			
Mean (SD)	128.1 (5.2)	143.8 (4.4)	165.6 (12.2)
Range	116.3–134.7	135.0–150.0	150.3–207.5
Diastolic BP (mm Hg)			
Mean (SD)	78.8 (7.6)	82.6 (6.9)	88.2 (8.6)
Range	56.3–92.3	67.8–99.5	61.2–113.0

Table 3. Mean (SE) Neuropsychological Test Scores for Low, Intermediate, and High Systolic BP Groups at the Baseline Visit

	Low (< 135 mm Hg)	*Intermediate (135–150 mm Hg)*	*High (> 150 mm Hg)*	*P Value*
Total free recall	31.4 (6.5)	30.8 (5.9)	31.8 (5.3)	.64
Delayed recall	12.3 (2.7)	11.4 (2.8)	11.7 (2.3)	.32
MMSE	28.4 (1.8)	28.4 (1.4)	28.4 (1.5)	.98
Trail Making part B	105.4 (47.2)	109.3 (38.0)	103.4 (38.2)	.72

SE = standard error, MMSE = Mini-Mental State Examination.

period was only 1 year. Thus, 158 subjects were included in the analysis.

Blood Pressure Range Classification

Based on the mean of BPs taken over the follow-up period, 29 (18%) were classified in the low normal systolic BP range (< 135 mm Hg), 48 (30%) were in the intermediate range (135–150 mm Hg), and 81 (51%) were in the high range (> 150 mm Hg) (Table 1). The mean (SD) follow-up time between the initial neuropsychological testing and the most recent visit was 5.1 (2.0) years.

Demographic Characteristics

There was no difference in age, gender, race, years of education, stroke history, coronary artery disease history, or hypercholesterolemia history among the groups at baseline (i.e., the initial visit with neuropsychological testing) (Table 2). Subjects in the low normal BP group had a shorter follow-up duration (mean year [SD] = 4.2 [1.9]) than subjects in the intermediate (mean year [SD] = 5.4 [2.0]) or high BP group (mean year [SD] = 5.2 [2.0]) (P = .03). There was no difference among the three systolic BP groups at the first visit with respect to any of the four neuropsychological test results (Table 3); for example, mean (SE) MMSE scores were 28.4 (1.8) for the low, 28.4 (1.4) for the intermediate, and 28.4 (1.5) for the high systolic BP groups at the first visit of neuropsychological testing.

Table 2. Baseline Characteristics of Low, Intermediate, and High Systolic BP Groups

	Low (< 135 mm Hg)	*Intermediate (135–150 mm Hg)*	*High (> 150 mm Hg)*
Age: mean yr (SD)	74.0 (7.1)	76.6 (5.8)	76.3 (4.8)
Gender (% male)	79	71	61
Race (% Caucasian)	93	94	99
Education: mean yr (SD)	16.7 (2.8)	17.3 (2.4)	16.9 (2.7)
Follow-up duration: mean yr (SD)	4.2 (1.9)	5.4 (2.0)	5.2 (2.0)*
History of stroke (%)	3	5	5
History of coronary artery disease (%)	17	21	16
History of hypercholesterolemia (%)	3	15	12

*P = .03.

Neuropsychological Testing during the Follow-up Period

Of the 158 subjects with hypertension meeting inclusion criteria, 156 had data for the analysis of Cued Selective Reminding test total free recall and delayed recall scores, 155 had sufficient data to be included in the analysis of MMSE scores, and 146 had data for the analysis of Trail Making test part B scores.

Twelve subjects became demented during the follow-up period. One individual (3%) in the low BP range developed dementia (probable Alzheimer's disease as defined by NINCDS-ADRDA criteria[26]). Four individuals (8%) in the intermediate BP range developed dementia (three probable Alzheimer's disease, one mixed Alzheimer's/multi-infarct dementia). Seven subjects (9%) in the high BP range developed dementia (four probable Alzheimer's disease, one possible Alzheimer's disease, one mixed Alzheimer's disease/multi-infarct dementia, one dementia unspecified). There was no significant difference in the development of dementia among the groups.

After adjustment for age and education, for the neuropsychological test specific for memory, the Cued Selective Reminding test total free recall, the three systolic BP groups were found to differ significantly with respect to decline/year (P = .02) (Table 4). The high BP group (mean [SE] = 0.6 [0.2]) had significantly greater decline/year than the intermediate BP group (mean [SE] = 0.0 [0.2]) (pairwise comparison P = .04) or the low normal BP group (mean [SE] = –0.3 [0.3]) (pairwise comparison P = .02). However, for total free recall, there was no statistically significant difference between patients in the low normal BP group compared to subjects maintained in the intermediate BP group.

After adjustment for age and education, the Cued Selective Reminding test delayed recall decline/year also differed among the systolic BP groups (P = .04). The mean (SE) decline/year for delayed recall in the low BP group was 0.4 (0.1), in the intermediate BP group was 0.0 (0.1), and in the high BP group was 0.1 (0.1) (see Table

Table 4. Mean (SE) Neuropsychological Test Decline/Year for Low, Intermediate, and High Systolic BP Groups, Adjusted for Age and Education

	Low (< 135 mm Hg)	*Intermediate (135–150 mm Hg)*	*High (> 150 mm Hg)*	*P Value*
Total free recall	–0.3 (0.3)	0.0 (0.2)	0.6 (0.2)	.02
Delayed recall	0.4 (0.1)	0.0 (0.1)	0.1 (0.1)	.04
MMSE	0.2 (0.1)	0.3 (0.1)	0.2 (0.1)	.77
Trail Making part B	–0.1 (2.6)	5.4 (2.0)	5.2 (1.5)	.19

SE = standard error, MMSE = Mini-Mental State Examination.
A positive number represents a longitudinal deterioration in performance, and a negative number represents a longitudinal improvement in performance.

4). Using pairwise comparisons, delayed recall decline/year was greater for the low BP group compared to the intermediate BP group (P = .01). (A separate analysis of older hypertensive subjects with longitudinal neuropsychological testing including both individuals treated and those not treated with antihypertensive medication during the follow-up [n = 206] demonstrated similar results for the low normal BP group [mean (SE) = 0.3 (0.1)], intermediate BP group [mean (SE) = 0.0 (0.1)], and high BP group [mean (SE) = 0.2 (0.1)] [P = .05].)

There was no difference in the mean MMSE or Trail Making test part B decline/year among the three BP groups (see Table 4).

Parallel analyses were performed using diastolic BP to subdivide patients with hypertension. Patients were classified into three diastolic BP groups: low (< 80 mm Hg) (30% of the patients), intermediate (80–90 mm Hg) (43% of the patients), and high (> 90 mm Hg) (27% of the patients). Results resembled those for systolic BP in that after adjusting for age and education, total free recall decline/year was significantly greater in the high diastolic BP group (mean [SE] = 0.8 [0.3]) compared to the intermediate (mean [SE] = –0.1 [0.2]) and low (mean [SE] = 0.2 [0.2]) BP groups (P = .04). However, there was no difference in the delayed recall decline/year, MMSE decline/year, or Trail Making part B decline/year.

The effect of specific antihypertensive medications on cognitive decline was also examined. Subjects were classified into a specific antihypertensive medication subgroup if they were always taking a specific antihypertensive drug class throughout the study period. Diuretics (thiazides and nonthiazides) (n = 14), beta blockers (n = 15), calcium channel blockers (n = 15), and angiotensin converting enzyme (ACE) inhibitors (n = 6) were compared separately. Subjects who switched antihypertensive drug classes or who were on intermittent antihypertensive drug treatment were excluded from this analysis. There were no differences among the specific drug classes in decline/year for total free or delayed recall, MMSE, or Trail Making part B. However, the power to detect a difference between specific drug classes was low.

DISCUSSION

The present study was designed to evaluate whether maintenance of systolic BP within a high or a low range is associated with memory decline and cognitive deterioration compared to an intermediate BP range in older treated hypertensive patients. The three BP ranges were chosen because a previous study[17] suggested that among multi-infarct dementia patients, cognitive performance deteriorated if systolic BP was maintained below a range of 135 to 150 mm Hg. Diastolic BP ranges were not examined in this previous study by Meyer et al.[17] Therefore, the current study focused on systolic BP ranges rather than diastolic BP ranges, although the diastolic BP results were also examined.

We evaluated longitudinal performance in several different cognitive response variables: a general measure of cognition, MMSE decline/year, specific measures evaluating memory (Cued Selective Reminding test), and attention/set shifting (Trail Making test part B). The Cued Selective Reminding test and Trail Making test part B were selected because they have excellent reliability, exhibit minimal ceiling effects, were available on most BLSA subjects, and are sensitive measures of cognitive decline in the elderly.[27] The BLSA is an ideal subject population for this study because of the long duration of neuropsychological testing follow-up and the use of standardized methods for the collection of BP and medical data.

The present study demonstrates that decline in a memory test is significantly greater in hypertensive subjects chronically maintained with a systolic BP > 150 mm Hg compared to subjects maintaining an intermediate BP between 135 and 150 mm Hg. Our study agrees in part with results from a previous cross-sectional community study by Starr et al[16] demonstrating that healthy elderly (70 years and over) subjects with high (> 181 mm Hg) systolic BP had more cognitive impairment than subjects with an intermediate (136–181 mm Hg) or low (< 135 mm Hg) systolic BP. The present study is the first longitudinal study to demonstrate the specific protective effect of systolic BP control below 150 mm Hg to reduce memory decline in older hypertensive patients.

Our study also suggests the provocative finding that longitudinal change in cognitive performance on a test of memory, the delayed recall portion of the Cued Selective Reminding procedure, is worse for patients chronically maintained in a low normal systolic BP range (i.e., below 135 mm Hg), compared to subjects maintained between 135 and 150 mm Hg. Our analysis of a larger number of subjects both with and without antihypertensive medication treatment during the follow-up (n = 206) also demonstrated poorer performance in the low normal systolic BP group compared to the intermediate BP group. However, this relationship was not seen with the total free recall portion of the Cued Selective Reminding procedure as there was no difference between patients

chronically maintained in the low normal systolic BP range compared to subjects maintained in the intermediate range. Our results suggest that treatment of systolic BP to below 135 mm Hg may be associated with memory decline, specifically with a memory test with greater delays, but this result should be interpreted with caution and examined further in additional longitudinal studies before treatment practices are altered.

In our study, there was no difference among the three systolic BP groups in performance on an attention/set shifting test or a general screening test for dementia. These results are consistent with the findings of Elias et al,[28] who observed that tests that assess memory are particularly vulnerable to hypertension. The MMSE and Trail Making test part B may not be as sensitive as memory tests to assess hypertension-induced cognitive impairment.

A prior study by Meyer et al[17] found that in hypertensive subjects with multi-infarct dementia, improved cognition correlated with control of systolic BP within the upper limits of normal (135–150 mm Hg) compared to patients maintained with a systolic BP < 135 mm Hg. Our results now suggest that maintenance of systolic BP within the upper limits of normal may prevent cognitive decline specifically in a test of delayed memory recall in a nondemented subject population (mean MMSE score at the first visit = 28.4 for the entire study group).

Hypertension may influence cognitive function in the elderly by several mechanisms. Hypertension is a risk factor for both cerebral ischemia and cerebrovascular disease, resulting from large cerebral artery or cervical artery atherosclerosis or small cerebral vessel lipohyalinosis.[10–12] Furthermore, if systemic BP falls due to postural or physiologic changes, then cerebral autoregulation fails at higher mean arterial blood pressures in hypertensive subjects compared to normals because of greater rigidity of cerebral blood vessels.[10] Because of this impaired cerebral autoregulation in elderly hypertensive patients, overaggressive antihypertensive therapy could potentially produce ischemic damage and cognitive impairment.

We cannot definitively conclude from our results that dementia onset is preventable by BP control. Indeed, the incidence of dementia was low in all three of the systolic BP groups. However, given that most risk factors for dementia (e.g., age, family history, apolipoprotein E status) are fixed, a potentially modifiable risk factor for dementia such as systolic BP should be evaluated in further studies using a subject population at higher risk for dementia. Even if the development of dementia cannot be prevented by maintaining BP within an intermediate range, a delay in the time of dementia onset or a slower rate of progressive memory deterioration could have large public health implications, given the very high prevalence of both hypertension and dementia among the elderly. Follow-up of these BLSA subjects may provide additional insights on this important issue.

There are several limitations to the current study. Hypertension was diagnosed by medical history, physical examination, or a self-report of hypertension on a standardized questionnaire. Some individuals may have had a history of hypertension but maintained normal BP with intermittent use of a single medication during the observation period. Others may have had more severe hypertension, requiring multiple drugs for BP control. In addition, our study evaluated the effect of BP among older hypertensive patients with a high education level, and these results may not be generalizable to normotensive subjects, younger hypertensive patients, or subjects with a low education level. Finally, as noted earlier, the modest number of individuals developing clinical dementia in the current study limits our ability to conclude that maintenance of BP within an intermediate range can actually prevent the development of clinical dementia.

In conclusion, chronically elevated systolic BP > 150 mm Hg is associated with accelerated memory decline compared to older treated hypertensive patients with systolic BP in an intermediate range. Chronically maintained systolic BP within a low normal range < 135 mm Hg in older treated hypertensive subjects may be associated with accelerated memory decline, specifically in a test of delayed memory recall, compared to patients with systolic BP in an intermediate range. Optimal regulation of systolic BP in older hypertensive patients may be a potential modifiable risk factor to prevent or minimize memory loss.

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