Orthostatic Hypotension and Cognitive Function: The Atherosclerosis Risk in Communities Study

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Key Words

Population-based research · Orthostatic hypotension, epidemiology · Cognitive function

Abstract

Background: To examine the association between orthostatic hypotension (OH) and cognitive function in middle-aged adults. **Methods:** Participants were 12,702 men and women from the Atherosclerosis Risk in Communities Study. OH was defined as decrease in systolic blood pressure (BP) by ≥ 20 mm Hg or diastolic BP by ≥ 10 mm Hg upon standing. At the 2nd and the 4th follow-up examinations, cognitive function was assessed using the Delayed Word Recall Test, Digit Symbol Substitution Test (DSST) and Word Fluency Test (WFT). **Results:** After age adjustment, those with OH were more likely to be in the lowest quintile of the DSST (OR = 1.34, 95% CI = 1.12–1.62) and WFT (OR = 1.25, 95% CI = 1.03–1.51) than were those without OH. After adjustment for sociodemographic and cardiovascular risk factors, associations were no longer significant. In age-adjusted models only, OH was associated with increased odds of being in the greatest quintile of decline in DSST score between visits 2 and 4 (OR = 1.28, 95% CI = 1.04–1.58). **Conclusions:** OH was

associated with less favorable cognitive function, but this association was largely attributable to demographic and cardiovascular risk factors. Episodic asymptomatic hypotension in middle age may not be an independent cause of cognitive decline. Further study, including emphasis on neuroimaging, is needed.

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Introduction

Orthostatic hypotension (OH) involves a marked decrease in blood pressure (BP) after assuming the upright posture. Established guidelines define OH as a decrease in systolic BP ≥ 20 mm Hg and/or a decrease in diastolic BP ≥ 10 mm Hg [1]. Most research is based on elderly, clinical populations where symptomatic OH is associated with falls and fractures. In high-risk populations, OH is inconsistently associated with cardiovascular outcomes [2, 3] and modestly associated with mortality [2–4], and is associated with incident hypertension [5], stroke [6], coronary heart disease (CHD) [7] and mortality [8] in middle-aged healthy adults. Cognitive function is associated with diabetes [9, 10], hypertension [9, 10], CHD [9,

11] and stroke [9, 11]. Generally these conditions must be present in midlife to be associated with later life cognitive dysfunction [12].

Beyond vascular risk factors, reduced cerebral blood flow may lead to cognitive dysfunction [13]. This may explain the U-shaped association between systolic BP and cognitive performance in older populations [14, 15]. It remains unclear whether younger, otherwise healthy individuals are similarly at risk for cognitive impairment or other cerebral injury from decreased cerebral blood flow.

Because OH leads to recurrent BP drops, this could result in cerebral hypoperfusion and impact cognitive function, perhaps via cerebral small-vessel disease, which is also associated with OH [16]. However, the literature is inconclusive and limited to small studies of elderly persons [17] or others with comorbidities (e.g. Parkinson's disease) [18]. In one study of mostly diabetics, those with asymptomatic OH had lower cognitive function than those without OH [19]. However, a study of elderly Finns found no differences in cognitive performance over 2 years of follow-up by OH status [20].

We examined the association between OH and cognitive function in a large, biracial middle-aged cohort. We further examined the contribution of CVD risk factors to this association and whether cognitive decline over 6 years was greater among those with OH at baseline.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective study of middle-aged African-American and white men and women that investigates the natural history of atherosclerosis and CVD. At baseline (1987–1989), 15,792 participants were sampled from 4 US communities: Forsyth County, N.C.; Jackson, Miss.; suburbs of Minneapolis, Minn., and Washington County, Md. African-Americans were sampled exclusively in Jackson and oversampled in Forsyth to ensure race-specific estimates. The Minneapolis and Washington County subjects were predominantly white. Response rates and details about the study design are published [21, 22]. After baseline, there were 3 triennial examinations, the last occurring between 1996 and 1999.

Exclusion criteria are presented in figure 1a. Briefly, of baseline participants, we excluded those with an ethnicity other than African-American or white and African-Americans in Minneapolis and Washington County ($n = 89$), those not between the ages of 45 and 64 years ($n = 172$) and those without seated BP data ($n = 3$) or with missing data precluding the computation of baseline postural BP change ($n = 2,376$). We also excluded individuals not participating in the visit 2 examination or cognitive function testing ($n = 145$), those with prevalent/unknown baseline stroke status or those having an incident stroke between baseline and

visit 2 ($n = 257$), and those taking antiparkinsonian medications ($n = 48$). Our final sample size was 12,702.

In analyses of change in cognitive function between the 2nd and 4th examinations (fig. 1b), we further excluded 1,461 individuals not participating in the 4th examination (due to death or other reasons), 337 participants not participating in the cognitive function examinations, and 332 participants with a stroke/unknown stroke status between the 2nd and 4th examinations, leaving 10,572 participants.

Measurement and Classification of BP Response to a Change in Posture

Orthostatic BP measurements were ascertained using a Dinamap 1846 SX oscillometric device, which has high within-subject reliability and is comparable to Doppler ultrasound BP measurement [23]. Following 20 min of supine rest, automated supine BP measurements were taken approximately every 30 s for 2 min (2–5 measurements, 90% had ≥ 4 measurements). Participants were asked to stand, and as they stood, a BP measurement was taken. Measurements were repeated during the first 2 min after standing (2–5 measurements, 91% had ≥ 4 measurements). Because BP restabilization occurs during the first 30 s after standing [24], BP change was defined as the difference between the average of the standing and supine BP measurements, excluding the 1st standing measurement.

Assessment of Cognitive Function

In the 2nd (1990–1992) and 4th (1996–1999) ARIC examinations, tests were administered to assess cognitive function. The Delayed Word Recall Test (DWRT) tests verbal learning and recent memory. Participants learn a list of 10 nouns and after 5 min are asked to recall these words within 60 s. Scores range from 0 to 10, with a 6-month test-retest reliability of 0.75 reported [25]. The Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale – Revised, assesses sustained attention and psychomotor speed and is a sensitive marker of brain damage. The testee pairs numbers with corresponding symbols using a code visible during time-limited testing. Scores range from 0 to 93; short-term test-retest reliability ranges from 0.82 to 0.88 [26]. The Controlled Oral Word Association Test [Word Fluency Test (WFT)] of the Multilingual Aphasia Examination is a test of expressive language that detects frontal lobe damage [27] and early mental decline in older persons [28]. Over three 1-min trials, the testee lists as many words as possible that begin with 3 different letters. Its test-retest reliability is 0.82 [29].

Covariates

Standardized interviews were conducted to obtain participants' self-report of sociodemographic and behavioral characteristics. Education was classified as below high school diploma, high school diploma or at least some college. Smoking and alcohol status were categorized as former, current and never. Medications taken for hypertension and diabetes were based on the participants' self-reported use during the previous 2 weeks.

Participants were queried about their perception of their health compared to their peers (fair/poor or excellent/good). High-density lipoprotein and low-density lipoprotein cholesterol levels (mmol/l) were determined at a central laboratory using standardized methods [22]. Two noninvasive measures of atherosclerosis, the ankle-brachial index [dichotomized to ≤ 0.90 (indi-

Fig. 1. a Exclusion criteria for analysis of the association of baseline OH with cognitive function at the 2nd ARIC Study examination. **b** Exclusion criteria for analysis of the association of baseline OH with change in cognitive function between the 2nd and 4th ARIC Study examinations.

cator of peripheral artery disease) and >0.90] and carotid artery intima-media thickness, determined by B-mode ultrasound [30], were included.

Diabetes was defined as nonfasting plasma glucose ≥ 200 mg/dl, fasting glucose ≥ 126 mg/dl, a self-reported history of diabetes and/or current diabetes treatment. Three seated BP measurements were taken on the right arm with a random-zero sphygmomanometer after 5 min of rest, and the average of the 2nd and 3rd measurements was used. Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg and/or current use of antihypertensive medications. Resting heart rate was determined from a standard supine 12-lead electrocardiogram. Prevalence of cancer, CHD and stroke was based on self-report.

We controlled for baseline use of antihypertensive medications, but not specific classes, as in our previous work there was little association between OH and specific classes of antihypertensive agents [8]. Analyses were conducted both including and excluding 1,081 participants using selected classes of medications (benzodiazepines, benzisoxazoles, butyrophenones, tricyclic antidepressants, and other antidepressants and antipsychotic medicines).

Analyses

Logistic regression generated coefficients to calculate age-, race- and gender-adjusted proportions of risk factors and selected baseline conditions by OH status. Analysis of covariance was used to produce age-, race- and gender-adjusted means of risk factors by OH status and to estimate age-adjusted mean levels of performance (6-year change) on the cognitive examinations.

Performance on the cognitive examinations was also categorized into quintiles, with those in the lowest quintile of performance contrasted to those with more favorable performance. Higher raw scores indicated better performance on all tests. The lowest quintiles had the following cutoffs: on the DWRT, ≤ 5 ; on the DSST, 0–32; on the WFT, 0–22. For each examination, logistic regression models were run sequentially controlling for: (1) age, (2) age, gender, educational attainment and race/center, (3) same as No. 2 and systolic BP and antihypertensive medication use, and (4) same as No. 3 and current drinking, current smoking, diabetes, carotid intima-media thickness, low ankle-brachial index, low-density lipoprotein cholesterol, resting heart rate, prevalent CHD, cancer and fair/poor self-reported health. Analyses were repeated excluding those reporting use of the selected medications previously described.

Change in performance on the cognitive examinations between the 2nd and 4th examinations was calculated. Age-adjusted mean change scores were calculated as were quintiles of change (visit 2 – visit 4 performance; the quintile of largest decrease was calculated). Logistic regression analyses estimated the association between OH and change in cognitive function, using the strategy as described for cognitive function at visit 2.

Results

Baseline OH and Initial Cognitive Performance

Individuals with OH at baseline were older, more frequently African-American and of lower educational attainment than those without OH (table 1). Most vascular

Table 1. Adjusted means and percentages of selected baseline risk factors and conditions by OH status at the baseline ARIC examination (1987–1989)

	OH no (n = 12,050)	OH yes (n = 652)
Mean age, years	53.9 (53.8–54.0)	57.3 (56.8–57.7)
African-American, %	25.6 (24.8–26.4)	34.8 (31.1–38.6)
Male, %	45.1 (44.2–46.0)	44.2 (40.4–48.1)
Less than high school education, %	22.4 (21.6–23.3)	32.4 (28.7–36.3)
Mean body mass index	27.6 (27.6–27.7)	27.6 (27.2–28.0)
Mean carotid intima-media thickness, mm	0.75 (0.75–0.75)	0.82 (0.80–0.83)
Mean heart rate, beats/min	66.5 (66.3–66.7)	69.2 (68.4–69.9)
Low ankle-brachial index (≤ 0.90), %	2.9 (2.6–3.2)	7.6 (5.9–9.9)
Diabetes mellitus, %	11.5 (10.9–12.1)	18.6 (15.9–21.8)
Hypertension, %	33.3 (32.4–34.2)	53.2 (49.2–57.3)
History of coronary heart disease, %	4.8 (4.4–5.3)	7.5 (5.7–9.8)
Current smokers, %	25.6 (24.8–26.5)	34.6 (30.9–38.4)
Current alcohol use, %	56.9 (55.9–57.8)	48.7 (44.5–52.8)
Self-reported fair/poor health status	18.7 (17.9–19.5)	30.7 (27.0–34.7)

Means were adjusted for age, race and gender. Figures in parentheses are 95% CI. Body mass index is calculated by weight in kilograms per height in meters squared.

Table 2. Age-adjusted mean scores on cognitive function examinations at ARIC visit 2 (1990–1992) by baseline OH status

	n	OH no	OH yes	p value
Delayed word recall	12,657	6.6	6.4	0.003
Digit symbol	12,654	44.7	42.6	0.001
WFT	12,643	33.3	32.2	0.290

Digit symbol from the Wechsler Adult Intelligence Scale – Revised.

risk factors and comorbidities were more common or severer in those with OH compared with those without OH. Among hypertensive individuals, those with OH were modestly more likely to be using antihypertensive medications than those without OH.

Table 2 provides a comparison of cognitive performance at visit 2 by baseline OH status. Age-adjusted mean scores were significantly lower for those with baseline OH for the DWRT and DSST.

Baseline OH was associated with a 1.34-fold increased odds of poor performance on the DSST (age-adjusted OR = 1.34, 95% CI = 1.12–1.62) and a 1.25-fold increased odds of poor performance on the WFT (age-adjusted OR = 1.25, 95% CI = 1.03–1.51), with poor performance defined as the lowest quintile of each test (table 3). With further adjustment, the associations were not significant,

although point estimates indicated worse cognitive performance in those with OH compared to those without OH. The greatest absolute reduction in the association was found for demographic characteristics rather than CVD risk factors. Results were similar after: (1) excluding those on medications associated with OH and/or known to affect cognitive function, (2) limiting analyses to participants with no missing data on any covariates, and (3) analyzing the association between baseline OH and visit 4 cognitive performance (data not shown).

Baseline OH and Change in Cognitive Performance from Visit 2 to 4

Similar to baseline associations, persons with OH had less favorable change in the cognitive examinations than persons without OH. Mean age-adjusted decrease in the DSST score was 1.07 points for those with OH, whereas those without OH had a mean improvement of 1.07 points ($p = 0.012$). For the DWRT, the mean decrease for those with OH was 0.21 points, compared to a 0.06-point improvement for those without OH ($p = 0.012$). Compared to persons without OH, those with OH had a 21% (DWRT) and 28% (DSST) increased odds of being in the quintile of largest cognitive decline in age-adjusted models, but the association was statistically significant only for the DSST (table 4). Adjusting for demographic factors produced the largest absolute reduction in strength of association. Adjusting for cardiovascular risk factors produced comparable reductions (data not shown).

Table 3. Association between baseline OH and poor cognitive function at the ARIC visit 2 examination (OR, with 95% CI in parentheses)

Covariates included	Delayed word recall	Digit symbol substitution	Word fluency
(1) Age	1.18 (0.98–1.42)	1.34 (1.12–1.62)	1.25 (1.03–1.51)
(2) Model 1 + race/center, gender and education	1.11 (0.92–1.35)	1.15 (0.93–1.43)	1.12 (0.93–1.37)
(3) Model 2 + systolic BP and antihypertensive medications	1.11 (0.92–1.34)	1.16 (0.93–1.43)	1.10 (0.91–1.34)
(4) Model 3 + selected risk factors and conditions	1.07 (0.86–1.32)	1.17 (0.93–1.48)	1.09 (0.88–1.35)

Poor cognitive function defined as performance in the lowest quintile on the test. Risk factors in model 4: current drinking, current smoking, diabetes mellitus, carotid intima-media thickness, low ankle-brachial index, low-density lipoprotein cholesterol, resting heart rate, prevalent CHD, cancer and fair/poor self-reported health.

Table 4. Associations between baseline OH and cognitive decline over an approximate 6-year period of the ARIC Study (OR, with 95% CI in parentheses)

Covariates included	Delayed word recall	Digit symbol substitution	Word fluency
(1) Age	1.21 (0.99–1.48)	1.28 (1.04–1.58)	1.11 (0.90–1.38)
(2) Model 1 + race/center, gender and education	1.16 (0.95–1.42)	1.14 (0.91–1.41)	1.03 (0.82–1.28)
(3) Model 2 + systolic BP and antihypertensive medications	1.15 (0.94–1.42)	1.13 (0.90–1.40)	1.03 (0.82–1.28)
(4) Model 3 + selected risk factors and conditions	1.08 (0.86–1.35)	1.05 (0.83–1.35)	1.03 (0.80–1.31)

Cognitive decline defined as the quintile of the largest decrease on test performance. Risk factors in model 4: current drinking, current smoking, diabetes, carotid intima-media thickness, low ankle-brachial index, low-density lipoprotein cholesterol, resting heart rate, prevalent CHD, cancer and fair/poor self-reported health.

Discussion

In the ARIC cohort, those with OH generally had worse baseline cognitive function than persons without OH, as well as a larger decrement in cognitive function over a 6-year interval, but this association was largely explained by demographic and other risk factors. The DSST, which assesses motor speed, was the most consistently affected. Psychomotor speed is often affected by subcortical processes, including white matter ischemic disease [31]. OH may result in recurrent episodes of hypoperfusion of the white matter, thus leading to impaired cognitive performance. Studies suggest an association between hypotension and white matter disease [32, 33], while autopsy studies suggest that Alzheimer's disease may be associated with hypoperfusion of the deep white matter [34, 35]. OH is a form of hypoperfusion, perhaps damaging the brain via mechanisms similar to persistent hypotension [36]. This may explain associations between OH and vascular dementia [37]. OH has been associated with incident stroke [6], which might further contribute to im-

paired cognitive function. Sensitivity analyses including stroke cases, however, produced similar results (data not shown).

The minimal, nonsignificant association after adjustment for sociodemographic factors suggests that asymptomatic OH is not an important independent contributor to cognitive dysfunction in middle-aged otherwise healthy individuals. However, this does not preclude that OH has an effect on cognition in the setting of concurrent cerebrovascular disease.

Prior studies have emphasized the importance of midlife risk factors in predicting later-life cognitive impairment and dementia. In our study, associations were similar when measured within a short time frame: OH measurements were made at baseline, with initial cognitive testing at the next triennial examination. This association may exist because OH indicates earlier (before midlife) risk factor exposures that contributed to both OH and impaired cognition in midlife. Also, OH may reflect atherosclerotic disease [38] and, thus, be a marker of cerebrovascular burden. Although our findings do not

suggest a clear association between OH and cognitive dysfunction, the absence of significant associations between OH and measures of cognitive function after adjustment for sociodemographic and cardiovascular risk factors could be due to type 2 error, given the relatively small sample of individuals with OH. Alternatively, it is possible that most healthy individuals have adequate cerebral autoregulation to maintain cerebral blood flow when exposed to intermittent hypotension, and this is why on a population basis there are no apparent associations. Our lack of neuroimaging data, including information about large-vessel stenoses of the neck and brain, may limit our ability to detect subgroups in whom there may be an association between OH and cognition. It is possible that individuals with significant extra- or intracranial disease, or with significant leukoaraiosis, might be more vulnerable to cerebral effects of OH, either because of impaired cerebral autoregulation or particularly low cerebral blood flow in the presence of both OH and large-vessel stenosis.

OH and cognition were not measured concurrently but ascertained from visits a few years apart. Thus, we could not explore relationships about transient alterations in cognitive performance due to the presence of OH. However, given that OH was measured before the cognitive outcomes, this would be appropriate if OH were implicated in directly causing cognitive impairment.

The primary associations in this study became non-significant after adjustment for education, gender and race. This may partly be due to known associations with cardiovascular risk factors. Diabetes and hypertension are associated with a higher occurrence of both OH and

cognitive dysfunction. While we controlled for both conditions in our analyses, we did not have sufficient power to test for effect modification of OH-cognitive function associations by these conditions, or for the role of disease severity. However, in our earlier work, the strength of associations of OH with both CHD [7] and mortality [8] did not vary by diabetes or hypertension status. Also, as most hypertensive individuals were using antihypertensive medication, we could not exclude them from our analyses. While we statistically controlled for this, we cannot rule out residual confounding. This is of less concern for other classes of medications, since results remained similar after excluding persons using these medications.

Conclusion

Our study suggests that much of the association between asymptomatic OH and poor cognition among a middle-aged healthy population may be due to other known factors. Further studies, particularly including neuroimaging, could provide evidence of the role of OH in the pathway from risk factors to cognitive decline.

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