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# Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly

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ABSTRACT

In hypertension (HTN), cerebral blood flow regulation limits are changed, and the threshold for blood pressure (BP) at which perfusion is safely maintained is higher. This shift may increase the brain's vulnerability to lower BP in subjects with vascular disease. We investigated whether longitudinal reduction in mean arterial pressure (MAP) was related to changes in cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease in a group of cognitively healthy elderly with and without HTN. The relationships among MAP, memory decline, and hippocampal atrophy were also examined. Seventy-seven subjects (age 63.4 ± 9.4, range 44–86 years; education 16.9 ± 2.1, range 10–22 years; 60% women) were assessed twice, 2 ± 0.5 years apart. At both time points, all subjects underwent full medical and neuropsychological evaluations, lumbar punctures, and magnetic resonance imaging examinations. Twenty-five subjects had HTN. Hyper- and normotensive subjects did not differ in their CSF biomarkers, hippocampal volumes (HipVs), or memory scores at baseline. In the entire study group, the increase in tau phosphorylated at threonine 181 (p-tau$_{181}$) was associated with a decline in verbal episodic memory ($\beta = -0.30$, $p = 0.01$) and HipV reduction ($\beta = -0.27$, $p = 0.02$). However, longitudinal decrease in MAP was related to memory decline ($\beta = 0.50$, $p = 0.01$) and an increase in p-tau$_{181}$ ($\beta = -0.50$, $p = 0.01$) only in subjects with HTN. Our findings suggest that the hypertensive group may be sensitive to BP reductions.



## 1. Introduction

Hypertension (HTN) affects more than a half of the US population over the age of 60 years (Hajjar et al., 2006). It causes vascular remodeling, lumen narrowing, and rarefaction of small vessels (Levy et al., 2001), contributes to the formation of atheromatous plaques in larger arteries (Kennelly et al., 2009), and ultimately leads to the impairment of vascular function. In normal conditions, autoregulatory mechanisms maintain a constant cerebral blood flow (CBF) over a wide range of mean arterial pressure (MAP) (Zazulia, 2009). However, even in the healthy brain, cerebral regulation is better adapted to compensate for sudden increases rather than for decreases in blood pressure (BP) (Tzeng et al., 2010). In long-standing HTN, CBF regulation limits are changed and thresholds for MAP at which CBF is maintained are shifted to higher levels (Zazulia, 2009). This shift may increase the brain's vulnerability to hypoperfusion at lower BP values (van Beek et al., 2008), suggesting that higher pressure is needed to maintain an adequate flow.

Although midlife HTN is a well-documented risk factor for cognitive decline and Alzheimer's disease (AD) later in life, there is substantial evidence that low BP later in life is also related to AD and cognitive impairment (Qiu et al., 2005). The initial observation of an association between low BP and dementia in the group of oldest old (Guo et al., 1996; Verghese et al., 2003) was subsequently extended to a broader population: in a combined Swedish and Dutch sample, low baseline systolic and diastolic BP conferred a higher risk of dementia 2 years later, across all age strata. Interestingly, this association was observed only in the groups treated with antihypertensive drugs. Moreover, subjects with dementia at follow-up had greater (although nonsignificant) longitudinal BP

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decline than nondemented peers (Ruitenberg et al., 2001). In line with this observation, den Heijer et al. (2003) found that a steeper reduction in diastolic BP over a period of 20 years was related to greater cortical atrophy and that only in subjects using antihypertensive medication low diastolic BP was related to smaller hippocampal and amygdalar volumes (den Heijer et al., 2005). The use of antihypertensive medication may indicate more advanced HTN and CBF autoregulation impairment and suggest that this category of patients is susceptible to low BP.

Impairment of autoregulation may lead to hypoperfusion and hypoxia. In laboratory animals, hypoxia activates γ-secretase amyloidogenic pathway (Lee et al., 2006), increases *BACE1* gene transcription and expression (Sun et al., 2006), deposition of amyloid beta (Aβ), and formation of neuritic plaques (Sun et al., 2006). In humans, vascular disease is associated with increased neurofibrillary changes (Sparks et al., 1995), and recently, a massive surge in blood Aβ levels was seen in survivors after cardiac arrest (Zetterberg et al., 2011).

Little is known whether changes in BP relate to markers of amyloid and neurofibrillary tangles, typical of AD in humans. We investigated the relationships between longitudinal changes in BP and cerebrospinal fluid (CSF) biomarkers of AD in cognitively healthy elderly with and without HTN. Our hypothesis was that BP decreases would be associated with unfavorable dynamics of AD biomarkers in subjects with HTN, who are possibly more sensitive to MAP reduction than controls. Because hippocampal atrophy (Glodzik-Sobanska et al., 2005) and resulting memory impairment (Ball et al., 1985) are major features of AD, we also examined the relationships among BP reduction, memory decline, and hippocampal volume (HipV).

## 2. Methods

### 2.1. Participants

The study included 77 cognitively healthy individuals (age 63.4 ± 9.4, range 44–86 years; education 16.9 ± 2.1, range 10–22 years; 60% women) enrolled at the Center for Brain Health and Alzheimer Disease Center at New York University (NYU) School of Medicine. All subjects were cognitively healthy, recruited as volunteers for longitudinal studies of brain aging and memory; all signed an institutional review board–approved informed consent.

All participants received medical, neurologic, psychiatric, and neuropsychological evaluations and underwent blood tests, lumbar punctures, and magnetic resonance imaging examinations (high-resolution T1, T2, and FLAIR (fluid attenuated inversion recovery)). Patients with confounding brain pathology (e.g., tumor, neocortical infarction) were excluded. Blood tests comprised complete blood count, comprehensive metabolic panel, lipid profile, thyroid hormone tests, and urinalysis. The clinical evaluation included an interview according to the Brief Cognitive Rating Scale, rating on Global Deterioration Scale (Reisberg et al., 1993), and Clinical Dementia Rating (CDR) (Morris, 1993). Based on the clinical assessment, all subjects were diagnosed as cognitively healthy with or without subjective memory complaints but not fulfilling the criteria for mild cognitive impairment or dementia. All received a global CDR of 0. Subjects scoring ≥16 on the 17-item Hamilton depression scale were excluded (Bech et al., 1986). The mean follow-up time was 1.98 ± 0.50 years, median 1.95, minimum 1.2, maximum 3.4, range 2.2 years. At follow-up, 3 subjects received a rating of GDS = 3, and a CDR of 0.5, corresponding to a diagnosis of mild cognitive impairment (Morris, 1993; Reisberg et al., 1993). At each occasion, the presence of HTN was determined based on current antihypertensive treatment or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (Chobonian et al., 2003).

BP measurements were taken in a sitting position after 5-minute rest. If the patient was not treated but high BP was identified, the diagnosis of HTN was assigned only if high BP was further confirmed during other visits to our Center. The MAP was calculated as follows:

$$1/3 \text{ systolic BP} + 2/3 \text{ of diastolic BP}.$$

Longitudinal MAP rate of change ($R_c$) was calculated as follows:

$$R_c\text{MAP} = \left(\text{MAP}_{\text{follow-up}} - \text{MAP}_{\text{baseline}}\right) \Big/ \text{time between examinations}.$$

Hypercholesterolemia was established based on the current treatment with lipid-lowering medication and/or cholesterol levels ≥200 mg/dL (NIH Publication No. 02-5125 and US Department of Health and Human Services, 2002). Diabetes was defined as the current treatment with glucose-lowering medication and/or fasting glucose levels ≥126 mg/dL (American Diabetes Association, 2010). Smoking was determined based on clinical interview. For each individual, we calculated Framingham cardiovascular risk profile (NIH Publication No. 02-5125 and US Department of Health and Human Services, 2002). Finally, body mass index (BMI) was calculated as follows:

$$\text{weight (lb)} \times 703/\text{height (in)} \times \text{height (in)}.$$

Apolipoprotein E (ApoE) genotyping was performed using polymerase chain reaction as previously described (Main et al., 1991). Study subjects were classified as ApoE4 positive (ApoE4+) if they had one or 2 E4 alleles and otherwise negative (ApoE4−). Data were available for 76 subjects.

### 2.2. Memory testing

The measures included subtests of the Guild memory scale (Gilbert, 1970). The Guild memory scale was established in 1968 (Gilbert, 1970). It includes subscales assessing immediate and delayed recall of orally presented paragraphs and verbal paired associates, digit span, and recall of geometric design (Crook et al., 1980). In this study, we used 4 subtests pertaining to episodic verbal memory: immediate and delayed recall of orally presented paragraphs and verbal paired associates. Higher scores indicate better performance. The Guild memory test has been used at our Center for >30 years and has a good track record of predicting decline in NYU population (Kluger et al., 1999).

At both time points, test results were converted to age, education, and gender-adjusted standardized scores (*z* scores) based on a normative population from our cohort (De Santi et al., 2008). We subsequently calculated a composite score, which constituted an average of 4 tests. To analyze longitudinal change, the rate of change was calculated as follows:

$$R_c\text{memory} = \left(\text{z score}_{\text{follow-up}} - \text{z score}_{\text{baseline}}\right) \Big/ \text{time between examinations}.$$

General cognitive abilities were tested with mini-mental state examination (Folstein et al., 1975).

### 2.3. Lumbar puncture, CSF collection, and assays

Using a 25-G needle guided by fluoroscopy, 15 mL of CSF was collected into 3 polypropylene tubes. All CSF samples were kept on ice until centrifuged for 10 minutes at 1500 *g* at 4 °C. Samples were aliquoted to 0.25 mL polypropylene tubes and stored at −80 °C until