Published in final edited form as:

J Hypertens. 2012 December ; 30(12): 2352–2356. doi:10.1097/HJH.0b013e3283595651.

Interactive Relations of Blood Pressure and Age to Subclinical Cerebrovascular Disease

Shari R. WALDSTEIN, Ph.D.^{a,b,c}, Carrington R. WENDELL, Ph.D.^a, David M. LEFKOWITZ, M.D.^d, Eliot L. SIEGEL, M.D.^{d,e}, William F. ROSENBERGER, Ph.D.^f, Robert J. SPENCER, Ph.D.^a, Zorayr MANUKYAN, Ph.D., M.S.^f, and Leslie I. KATZEL, M.D., Ph.D.^{b,c}

^aDepartment of Psychology, University of Maryland, Baltimore County

^bDivision of Gerontology & Geriatric Medicine, Department of Medicine, University of Maryland School of Medicine

^cGeriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center

^dDepartment of Diagnostic Radiology, University of Maryland School of Medicine

^eDepartment of Diagnostic Radiology, Baltimore Veterans Affairs Medical Center

^fDepartment of Statistics, George Mason University

Abstract

Objective—Examine interactive relations of blood pressure (BP) and age to magnetic resonance imaging (MRI) indices of subclinical cerebrovascular disease in middle-aged to older adults.

Methods—One hundred thirteen stroke- and dementia-free, community-dwelling adults (ages 54–81; 65% male; 91% White) engaged in a) clinical assessment of resting systolic and diastolic BP; b) magnetic resonance imaging (MRI) rated for periventricular and deep white matter hyperintensities (PWMH & DWMH), silent brain infarction (SBI), and brain atrophy [i.e., ventricular enlargement (VE) and sulcal widening (SW)]. Principal components analysis of the MRI ratings yielded a two component solution – (1) PWMH, DWMH, SBI; and (2) VE, SW.

Results—Relations of systolic BP, diastolic BP, and pulse pressure (PP) (and their interactions with age) to each MRI component were examined in multiple regression analyses adjusted for age, sex, fasting plasma glucose and cholesterol, and antihypertensives. For component one, results indicated significant interactions of systolic BP and PP with age (p 's < .05); higher levels of systolic BP and PP were associated with greater white matter disease and brain infarction at younger ages (≤ 63 years). Significant interactions of systolic and diastolic BP with age were also noted for component two (p 's < .05); higher levels of BP were associated with greater brain atrophy at younger ages (≤ 63 years).

Conclusions—Higher BP and PP are associated with greater subclinical cerebrovascular disease most prominently in the “young old.” Appropriate management of hypertension and arterial stiffening may be critical to the preservation of brain structure with aging.

Correspondence to: Shari R. Waldstein, Ph.D., Department of Psychology, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, (o) 410 455-2374; (f) 410 455-1055, waldstei@umbc.edu.

Conflicts of Interest: NONE

Disclosure of Funding and Support: This work was supported by National Institutes of Health (NIH) grants R29 AG15112, 5R01 AG015112, NIH P30-AG02874, Bristol Myers Squibb Medical Imaging, Inc., NIH K24 AG00930; a VA Merit Grant, the Department of Veterans Affairs Baltimore Geriatric Research Education and Clinical Center (GRECC), and the Geriatrics and Gerontology Education and Research Program of the University of Maryland, Baltimore.

Keywords

blood pressure; hypertension; pulse pressure; subclinical cerebrovascular disease; silent cerebrovascular disease; white matter disease; brain atrophy; magnetic resonance imaging

Introduction

Subclinical or “silent” cerebrovascular disease, detected by magnetic resonance imaging (MRI), is prevalent in community-dwelling adults prior to clinical stroke. In the Cardiovascular Health Study (CHS), 28% of the stroke-free participants had evidence of silent brain infarction (lesion size > 3 mm) and 83% of those over age 64 years had white matter lesions [1, 2]. Further, some degree of brain atrophy was noted in the vast majority of CHS participants [1]. Silent cerebrovascular disease is a clinically significant public health problem with demonstrated prognostic significance for future cognitive decline, progression to dementia, and stroke [3–7]. Hypertension or higher levels of blood pressure (BP) is one of the most potent predictors of increased cerebral white matter disease [8, 9], silent brain infarction [10–12], and brain atrophy [1, 13, 14], although it is unusual for all of these endpoints to be assessed in a single investigation. Pulse pressure (PP) – the difference between systolic and diastolic BP – reflects the pulsatility component of BP and is an indirect measure of arterial stiffening particularly among those over the age of 50 years. Increased PP has been associated with stroke, dementia, and cognitive decline [15–18], but little is known about its relation to subclinical cerebrovascular disease. Among elderly men, brain atrophy has been associated with steeper increases in PP over time [19]. Recent data also indicate relations of aortic pulse wave velocity, a direct measure of arterial stiffness, to cardiovascular events, cardiovascular mortality, white matter disease, dementia, and cognitive decline [18, 20–23]. Because higher levels of BP (or hypertension) and higher PP have been related to increased risk for lowered levels of cognitive function, cognitive decline, dementia, and stroke, it is typically posited that subclinical cerebrovascular disease may be an early sign of hypertension-related progression to these clinical conditions [24].

Increasing age is another potent predictor of both subclinical and clinical manifestations of cerebrovascular disease [1]. Age and hypertension have been noted as posing independent risk for subclinical cerebrovascular disease. It is possible that the presence of high BP or PP potentiates the relation of age to subclinical cerebrovascular disease. Accordingly, here we examined relations of continuous levels of systolic and diastolic BP and PP, age, and their interaction to magnetic resonance imaging-derived ratings of subclinical cerebrovascular disease in stroke- and dementia-free older adults.

Methods

Participants were 113 healthy, community-dwelling older adults (ages 54–81; 65% men; 91% White) who engaged in an investigation of cardiovascular risk factors, brain, and cognitive function [25, 26]. Participants were recruited by local advertisement, from the Geriatric Research Education and Clinical Center at the Baltimore Veterans Affairs Medical Center (B-VAMC), and by general advertisement at the B-VAMC. Exclusionary criteria were history or clinical evidence of cardiovascular disease (other than mild-to-moderate hypertension), diabetes mellitus, other major medical disease (e.g., renal, hepatic, pulmonary), neurologic disease, stroke, known or suspected dementia (Mini-Mental State Examination score < 24), self-reported psychiatric disorder, heavy alcohol use (> 14 drinks per week), moderate-to-severe head injury, or medications affecting central nervous system function. Sample characteristics are displayed in Table 1. Participants provided written

informed consent according to the guidelines of the University of Maryland Baltimore and University of Maryland, Baltimore County's Institutional Review Boards.

Biomedical Assessment

Participants underwent a comprehensive medical evaluation that included history, physical examination, blood chemistries, a graded exercise treadmill test, and an oral glucose tolerance test. Resting BP, and fasting lipids and glucose were assessed while participants were taking their routine medications. Total plasma cholesterol and glucose levels were determined enzymatically. Clinical assessment of BP was performed on 2–3 occasions with patients in a seated position using an automated vital signs monitor (Dinamap Model # 1846SX, Critikon, Tampa, FL) and appropriately sized occluding cuff. The readings were averaged to yield an estimate of participants' resting systolic and diastolic BP. PP was computed as the average systolic BP minus the average diastolic BP (and therefore may reflect increases in systolic BP, decreases in diastolic BP, or both).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed utilizing a Philips 1.5 Tesla scanner. The imaging protocol consisted of sagittal T1 (TR/TE/thickness/matrix/FOV/averages = 465/14/6 mm/192X256/24/1) axial T1 (600/14/5 mm/192X256/23/2), dual contrast proton density/T2 (3500/16,96/5 mm/192x256/23/2), and fluid attenuated inversion recovery (FLAIR) (TR/TE/TI/thickness/matrix/FOV/averages = 8000/120/2200/5 mm/192x256/21/2) sequences. The images were rated blindly for silent brain infarction by two board-certified neuroradiologists using modified CHS criteria [2]. Infarcts manifested abnormal signal in a vascular distribution, but no mass effect. Infarcts of the deep white matter, cortical gray matter, deep nuclear regions, and capsule were hyperintense on proton-density and T2-weighted images compared with normal gray matter, and isointense or hypointense on T1-weighted images. The CHS requirement for T1 hypointensity for deep white matter infarcts was not used, as this would have resulted in sole coding of cystic lacunes, which were a small minority of the infarcts scored. As per CHS criteria, infarcts were defined as ≥ 3 mm in size and infarct-like lesions as < 3 mm in size [2]. Periventricular and deep white matter hyperintensities (WMH) were rated using the published, and extensively used, method of Fazekas [27] as follows: *Periventricular hyperintensities*: 0=absent; 1=cap; 2=band; 3=irregular hyperintensity extending into the deep white matter; *Deep hyperintensities*: 0=absent; 1=punctate; 2=beginning confluent; 3=confluent. As per prior work (25), the following method was used for topographic location of periventricular and deep hyperintensities. Anterior areas: centrum semiovale on the frontal region and white matter surrounding the frontal horn of the lateral ventricle. Posterior areas: centrum semiovale on the parietal regions, white matter surrounding the corpus of the lateral ventricle and white matter surrounding the atrium and occipital horn of the lateral ventricle. WMH were coded as present if hyperintense on T2 and proton density weighted images. Punctate lesions seen only on T2 but not proton density were generally considered to be perivascular spaces and not counted. Brain atrophy was rated according to the apparent size of the ventricles (a measure of subcortical atrophy) and sulcal widening (an indication of cortical atrophy) using the following coding scale: 0=absent; 1=mild; 2=moderate; 3=severe.

Data Analysis

We first subjected our five subclinical cerebrovascular disease endpoints – periventricular WMH, deep WMH, silent brain infarction, ventricular enlargement, and sulcal widening – to a principal components analysis. The results indicated the presence of two components with eigenvalues > 1 as indicated in Table 2. The first component reflected the two WMH variables and silent brain infarction, and the second component the two brain atrophy variables. Because of the skewness and limited variability associated with the ordinal

ratings, we transformed using normal rank scores for each of the two subclinical cerebrovascular disease components as described below.

First, we ranked the individual MRI outcome variables. Next, we transformed the rank scores to percentiles of a normal distribution, a procedure called “normal scores transformation” [28]. We then added the transformed rank scores for periventricular and deep white matter hyperintensities and silent infarction to derive a “rank sum score” reflecting the first brain component, SCD. The transformed rank scores for ventricular enlargement and sulcal widening were then added to derive a “rank sum score” reflecting brain component or BA. Subsequent statistical examination of the distributions of these rank sum scores confirmed that the distributions had been normalized and were therefore appropriate to examine as outcome variables in multiple regression analyses.

Using the rank sum scores associated with each of the two components as outcome variables in separate multiple regression models, we examined as predictors the following variables: age, sex, fasting glucose levels, total cholesterol levels, antihypertensive medications, systolic BP, and the interaction of age and systolic BP. The models were then re-computed for diastolic BP and then PP. Age was tested at three levels based on tertile distribution of the data: ≤ 63 years ($n=40$); ages 64–68 years ($n = 35$); ages ≥ 69 years ($n = 38$), with the latter group coded as the reference group.

Results

Multiple regression analyses indicated that, after covariate adjustment, there were significant interactions of BP and age as follows (see Table 3): For component one, there were significant interactions of systolic BP and age at ≤ 63 years ($t = 2.76$, $p = .007$) and PP with both age ≤ 63 years ($t = 3.81$, $p = .0003$) and at ages 64–68 years ($t=2.22$, $p = .03$) such that higher levels of systolic BP or PP were associated with greater white matter disease and brain infarction in these age groups (as compared to those aged ≥ 69 years). For component two, significant interactions of systolic BP and age ≤ 63 years ($t = 2.08$, $p = .04$), and diastolic BP and age ≤ 63 years ($t = 2.09$, $p = .04$) were noted. Higher levels of systolic BP or diastolic BP were associated with greater brain atrophy.

Discussion

Results of this study indicate that MRI ratings of silent, or subclinical, cerebrovascular disease are associated with higher levels of BP and/or PP among those in our youngest age cohort of ≤ 63 years (based on tertile distributions), which is comprised predominantly of middle-aged (range commonly defined as ages 40–59 years) to “young old” (range defined as 60–69 years) persons (see 29).. Specifically, both systolic BP and PP were associated with greater WMH and silent brain infarction among those 63 years of age or younger. PP was also related to these endpoints among those aged 64–68 years (which would be defined as “young old” [29]). Both systolic and diastolic BP was associated with greater brain atrophy in those aged 63 and younger.

Our findings are consistent with prior research linking elevated BP with greater extent of white matter disease and increased frequency of silent brain infarctions [8, 10]. In contrast, relatively little is known about relations between PP and white matter disease or silent brain infarction. Emerging evidence does suggest that pulse wave velocity, another measure of arterial stiffness, is related to degree of white matter disease and number of silent infarctions among older adults [21, 30, 31]. The present study therefore suggests that these findings extend to PP.

Previous research has also identified associations between elevated BP and hypertension and indicators of brain atrophy [1, 32, 33]. Limited evidence suggests that elevations in PP may also be associated with brain atrophy. For instance, cognitively-intact older adults with subclinical brain atrophy demonstrate steeper increases in PP with age than individuals without evidence of brain atrophy [19]. Present study findings add to this growing literature and further emphasize the possible role of BP pulsatility in the development of multiple aspects of subclinical cerebrovascular disease.

Associations between elevated BP/PP and subclinical cerebrovascular disease noted here were most apparent among those ages 63 or younger. This pattern of findings is consistent with longitudinal research noting midlife BP to be a potent predictor of late-life brain-related endpoints, including cognitive function and dementia [34, 35]. When age cohorts are compared directly, however, BP levels are predictive of poor brain health across adulthood. For instance, Elias and colleagues found similar detrimental effects of elevated BP on longitudinal cognitive change among both younger and older adult cohorts in the Maine-Syracuse Longitudinal Study of Hypertension [36]. Further, elevated BP is significantly associated with vascular and overall mortality among both middle-aged and older adults [37]. Present study findings may therefore be attributable, in part, to a healthy survivor effect among our older participants, given the rather stringent inclusion and exclusion criteria utilized and increased hypertension/cardiovascular disease incidence with age. It has also been noted that mildly elevated BP may be beneficial to brain status among elderly persons.

Several neurophysiological mechanisms posited to underlie BP- and PP-brain associations include regional or global cerebral hypoperfusion, disruption of the blood-brain barrier, and/or endothelial dysfunction [38, 39]. With respect to PP, increased pulsatility associated with arterial stiffness may directly and negatively impact cerebral vessel integrity, particularly in watershed areas of the cerebral circulation. These neurophysiological mechanisms have been linked with both subclinical and clinical cerebrovascular diseases, including white matter disease, silent infarctions, cortical atrophy, and micro- and macro-vascular diseases [40, 41], which are in turn predictive of brain-related endpoints including cognitive dysfunction and decline, dementia, and stroke.

Our work extends prior research in three major ways. First, our PP findings suggest that the pulsatility component of BP may be particularly important to the development of WMH and silent brain infarction. Second, the relations of BP or PP to subclinical cerebrovascular disease are most pronounced for our middle-aged to “young old” cohort. This may, in part, reflect a healthy survivor effect on the oldest members of our sample. Third, it is rare to find simultaneous examination of BP, PP, age moderation, and multiple indicators of subclinical cerebrovascular disease in the existing literature. Lastly, the derived principal components and their transformation using normal scores represents a new methodological development that could be useful in future studies that utilize categorical ratings of brain pathology.

The present investigation had several limitations. First is use of a cross-sectional design. It is critical to determine the prognostic significance of BP and PP with respect to subclinical cerebrovascular disease. Second, the small, relatively homogeneous, and non-representative sample limits the generalizability of these findings. Third, because only those with mild to moderate hypertension, either untreated or on monotherapy, were studied in this protocol, associations of BP to subclinical cerebrovascular disease are likely underestimated in the present analyses. Fourth, the small sample size limits our statistical power. Fifth, use of ordinal MRI ratings limits power to detect associations.

To conclude, results of the present study demonstrate interactive relations of continuous levels of BP and PP with subclinical cerebrovascular disease such that those at middle-aged to “young old” ages showed the greatest pathology on MRI. Such subclinical cerebrovascular disease may confer risk for future cognitive decline, dementia, and stroke as a function of higher BP.

References

1. Manolio TA, Kronmal RA, Burke GL, Poirier V, O’Leary DH, Gardin JM, et al. Magnetic resonance abnormalities and cardiovascular disease in older adults. The cardiovascular health study. *Stroke*. 1994; 25:318–327. [PubMed: 8303738]
2. Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, et al. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The cardiovascular health study. Chs collaborative research group. *Stroke*. 1997; 28:1158–1164. [PubMed: 9183343]
3. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, Price T. Silent mri infarcts and the risk of future stroke: The cardiovascular health study. *Neurology*. 2001; 57:1222–1229. [PubMed: 11591840]
4. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: A systematic review. *Lancet Neurol*. 2007; 6:611–619. [PubMed: 17582361]
5. De Groot JC, De Leeuw FE, Oudkerk M, Van Gijn J, Hofman A, Jolles J, Breteler MM. Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol*. 2002; 52:335–341. [PubMed: 12205646]
6. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: The rotterdam scan study. *Stroke*. 2003; 34:1126–1129. [PubMed: 12690219]
7. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003; 348:1215–1222. [PubMed: 12660385]
8. Liao D, Cooper L, Cai J, Toole JF, Bryan NR, Hutchinson RG, Tyroler HA. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The aric study. Atherosclerosis risk in communities study. *Stroke*. 1996; 27:2262–2270. [PubMed: 8969791]
9. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. *Stroke*. 2005; 36:56–61. [PubMed: 15569873]
10. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based rotterdam scan study. *Stroke*. 2002; 33:21–25. [PubMed: 11779883]
11. Hougaku H, Matsumoto M, Kitagawa K, Harada K, Oku N, Itoh T, et al. Silent cerebral infarction as a form of hypertensive target organ damage in the brain. *Hypertension*. 1992; 20:816–820. [PubMed: 1452297]
12. Shintani S, Shiigai T, Arinami T. Subclinical cerebral lesion accumulation on serial magnetic resonance imaging (mri) in patients with hypertension: Risk factors. *Acta Neurol Scand*. 1998; 97:251–256. [PubMed: 9576640]
13. Salerno JA, Murphy DG, Horwitz B, DeCarli C, Haxby JV, Rapoport SI, Schapiro MB. Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension*. 1992; 20:340–348. [PubMed: 1516953]
14. Heijer T, Skoog I, Oudkerk M, de Leeuw FE, de Groot JC, Hofman A, Breteler MM. Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging*. 2003; 24:307–313. [PubMed: 12498964]
15. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: The rotterdam study. *Circulation*. 2006; 113:657–663. [PubMed: 16461838]

16. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of alzheimer disease in persons aged 75 years and older: A community-based, longitudinal study. *Stroke*. 2003; 34:594–599. [PubMed: 12624277]
17. Abhayaratna WP, Barnes ME, O'Rourke MF, Gersh BJ, Seward JB, Miyasaka Y, et al. Relation of arterial stiffness to left ventricular diastolic function and cardiovascular risk prediction in patients > or =65 years of age. *Am J Cardiol*. 2006; 98:1387–1392. [PubMed: 17134635]
18. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the baltimore longitudinal study of aging. *Hypertension*. 2008; 51:99–104. [PubMed: 18025297]
19. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Carmelli D. Biobehavioral characteristics of nondemented older adults with subclinical brain atrophy. *Neurology*. 2000; 54:2108–2114. [PubMed: 10851372]
20. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005; 111:3384–3390. [PubMed: 15967850]
21. Hatanaka R, Obara T, Watabe D, Ishikawa T, Kondo T, Ishikura K, et al. Association of arterial stiffness with silent cerebrovascular lesions: The ohasama study. *Cerebrovasc Dis*. 2011; 31:329–337. [PubMed: 21212664]
22. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, et al. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke*. 2005; 36:2193–2197. [PubMed: 16151027]
23. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006; 113:664–670. [PubMed: 16461839]
24. Waldstein, SR.; Katzel, LI. Hypertension and cognitive function. In: Waldstein, SR.; Elias, MF., editors. *Neuropsychology of cardiovascular disease*. Mahwah, NJ: Erlbaum; 2001. p. 15-36.
25. Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. *Int J Obes (Lond)*. 2006; 30:201–207. [PubMed: 16231030]
26. Waldstein SR, Lefkowitz DM, Siegel EL, Rosenberger WF, Spencer RJ, Tankard CF, et al. Reduced cerebral blood flow in older men with higher levels of blood pressure. *J Hypertens*. 2010; 28:993–998. [PubMed: 20408259]
27. Fazekas F, Niederkorn K, Schmidt R, Offenbacher H, Horner S, Bertha G, Lechner H. White matter signal abnormalities in normal individuals: Correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke*. 1988; 19:1285–1288. [PubMed: 3051534]
28. Conover, WJ. *Practical nonparametric statistics*. New York: Wiley; 1980.
29. Burnside, IM.; Ebersole, P.; Monea, HE. *Psychosocial caring throughout the life span*. New York: McGraw Hill; 1979.
30. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, et al. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension*. 2008; 52:1120–1126. [PubMed: 18852384]
31. Kuo HK, Chen CY, Liu HM, Yen CJ, Chang KJ, Chang CC, et al. Metabolic risks, white matter hyperintensities, and arterial stiffness in high-functioning healthy adults. *Int J Cardiol*. 2010; 143:184–191. [PubMed: 19261342]
32. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain atrophy in the healthy elderly. *Neurology*. 2002; 59:713–719. [PubMed: 12221162]
33. Nagai M, Hoshida S, Ishikawa J, Shimada K, Kario K. Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens*. 2008; 26:1636–1641. [PubMed: 18622243]
34. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The honolulu-asia aging study. *Journal of the American Medical Association*. 1995; 274:1846–1851. [PubMed: 7500533]
35. Launer LJ, Ross GW, Petrovitch H, KM, DF, RWL, JHR. Midlife blood pressure and dementia: The honolulu-asia aging study. *Neurobiology of Aging*. 2000; 21:49–55. [PubMed: 10794848]

36. Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: Does age make a difference? *Hypertension*. 2004; 44:631–636. [PubMed: 15466661]
37. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002; 360:1903–1913. [PubMed: 12493255]
38. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab*. 2008; 7:476–484. [PubMed: 18522829]
39. Waldstein, SR.; Wendell, CR.; Hosey, MM.; Seliger, SL.; Katzel, LI. Cardiovascular disease and neurocognitive function. In: Armstrong, C.; Morrow, LA., editors. *Handbook of medical neuropsychology: Applications of cognitive neuroscience*. New York: Springer; 2010.
40. Meyer JS, Rogers RL, Mortel KF. Progressive cerebral ischemia antedates cerebrovascular symptoms by two years. *Ann Neurol*. 1984; 16:314–320. [PubMed: 6486737]
41. Hoth KF, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, et al. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. *Stroke*. 2007; 38:308–312. [PubMed: 17204686]

Table 1

Sample Characteristics

Characteristic	M (SD) or %
Age (years)	66.0 (6.3)
Education (years)	16.4 (2.7)
Sex (% male)	64.6%
Race (% White)	91.2%
Resting Clinic SBP (mm Hg)	132.7 (18.3)
Resting Clinic DBP (mm Hg)	75.4 (9.2)
History of Hypertension	29%
Antihypertensive Medication Use	16%
Fasting Total Cholesterol (mg/dl)	197.9 (30.9)
Fasting Glucose (mg/dl)	96.4 (13.3)
Periventricular White Matter Hyperintensities (rating)	0.88 (0.61)
Deep White Matter Hyperintensities (rating)	0.89 (0.62)
Silent Brain Infarction (#)	3.7 (6.8)
Ventricular Enlargement (rating)	0.92 (0.76)
Sulcal Widening (rating)	1.09 (0.57)

Table 2

Principal Component Analysis: Component Loadings for Each MRI-Assessed Outcome Variable

	Component 1	Component 2
Periventricular white matter hyperintensities	0.713	−0.441
Deep white matter hyperintensities	0.751	−0.394
Silent brain infarction	0.790	−0.173.
Ventricular enlargement	0.616	0.614
Sulcal widening	0.522	0.707

Table 3

Results of Multiple Regression Analyses*

Significant Interaction Terms	Component 1 (Periventricular and Deep White Matter Hyperintensities, Silent brain infarction)			Component 2 (Ventricular Enlargement, Sulcal widening)		
	b (SE)	p	r ²	b (SE)	p	r ²
Systolic blood pressure x age1**	0.09 (0.03)	0.007	0.075	0.04 (0.02)	0.041	0.033
Systolic blood pressure x age2***	0.05 (0.03)	0.152	0.021	0.03 (0.02)	0.168	0.018
Diastolic blood pressure x age1	-0.03 (0.06)	0.632	0.003	0.08 (0.04)	0.040	0.031
Diastolic blood pressure x age2	-0.08 (0.06)	0.193	0.019	0.04 (0.03)	0.228	0.013
Pulse pressure x age1	0.15 (0.04)	<0.001	0.130	0.04 (0.03)	0.174	0.013
Pulse pressure x age2	0.09 (0.04)	0.029	0.046	0.03 (0.03)	0.318	0.007

* Analyses adjusted for age, sex, plasma glucose, total cholesterol, and antihypertensive medication use;

** age1: age <=63;

*** age2: age=64-68

b = beta coefficient

SE = standard error

p = significance level

r² = the proportion of unique variance associated with the predictor variable