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Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease

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Abstract

The present study examined the relationship between multiple blood pressure (BP) indices and white matter hyperintensities (WMH) in a sample of 39 older adults with cardiovascular disease (CVD). Resting BP was measured using an automated monitor every 10 min for 2 h. WMH were quantified on FLAIR images and separate indices were generated for neocortical, periventricular and subcortical brain regions. Correlation analyses revealed systolic BP variability was related to neocortical and total WMH. A function of systolic BP variability and average diastolic pressure showed the strongest relationships, including significant correlation to neocortical, subcortical and total WMH. No BP index was related to WMH in periventricular regions. Exploratory analyses showed only the function of systolic BP variability and average diastolic pressure predicted total WMH, whereas as age, CVD conditions and psychosocial factors did not. These findings demonstrate BP variability is an important contributor to WMH in older adults with CVD and suggests it may have differential relationships to WMH in different brain regions. Additional studies are needed to examine the role of autoregulatory systems in the development of WMH, particularly those using beat-to-beat measures of BP.

Keywords

Blood pressure; cardiovascular disease; cerebrovascular disease

Introduction

Hypertension is one of the most common medical conditions in the world and more than 60 million persons have high blood pressure (BP) in the USA alone (1). Hypertension has long been associated with increased risk for stroke and vascular dementia (2). More recently, researchers have identified cognitive deficits associated with hypertension long before onset of stroke or dementia (3-6).

A likely explanation for these cognitive deficits involves the structural brain abnormalities associated with high BP, as hypertensive individuals exhibit more white matter hyperintensities (WMH) than non-hypertensives on neuroimaging (7-11). WMH are increasingly viewed as an important contributor to normal age-related and pathological cognitive decline (12-16). Both average systolic pressure and the variability of systolic

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pressure have linked to the presence of WMH, though findings vary somewhat across studies (17-21).

No study to date has examined the relationship between BP variability and WMH in older adults with cardiovascular disease (CVD). These persons often have comorbid hypertension, exhibit WMH on neuroimaging, and show cognitive deficits on neuropsychological testing (1,22-25). Determining the relationship between BP variability and WMH may clarify relative contribution of BP and other forms of CVD contribute to the observed cerebrovascular and cognitive changes in this population. To further extend past literature, we also quantified WMH separately for neocortical, periventricular and subcortical regions. Past studies often report values only for periventricular or subcortical regions, though it is possible that BP may have differential effects across brain regions. Based on past findings, we expected average BP and BP variability would be related to WMH in older adults with CVD.

Materials and methods

Participants

A total of 39 participants enrolled in a larger, prospective study of the neurocognitive consequences of CVD were included in the current study. Only a subset of participants in the parent study completed magnetic resonance imaging (MRI) due to the many MRI contraindications found in older adults with CVD (e.g. pacemakers). For inclusion, participants must have a documented history of CVD, be between the ages of 55 and 85, have a Mini-Mental Status Exam score >24 (26), and have no history of neurological (e.g. seizure, stroke) or severe psychiatric disorder (e.g. schizophrenia, bipolar disorder). Sixty-seven per cent were male and participants averaged 71.41±7.38 years of age. See Table I for demographic and medical information.

Instrumentation

BP. BP was measured with an automatic noninvasive BP Monitor Press-Mate 8800 (Colin Medical Instruments Corp, San Antonio, TX, USA). BP was measured from the left arm of subjects resting in a fasted state in a quiet, darkened room every 10 min for 2 h. Eight BP indices used in past studies were generated, including average resting pressure, standard deviation, coefficient of variability (standard deviation divided by average resting pressure) for both systolic and diastolic BP. Pulse pressure and mean arterial pressure was also used. Finally, a function of systolic variability and average diastolic pressure (systolic standard deviation divided by average diastolic pressure) was generated to determine their possible interaction.

Brain MRI and WMH quantification—Brain MRI was obtained using a Siemens Symphony 1.5 Tesla unit. A standard imaging protocol consisting of sagittal T1 (TR/ TE=500/30)- and T2 (TR/TE=2500/80)-weighted conventional spin-echo localizer images as well as axial T1-, T2- and FLAIR-weighted (TR/ TE=6000/105) images were obtained. Only the FLAIR sequences were used in this study given the ability of this sequence to suppress the signal of the CSF and the sensitivity of this sequence to visualize hyperintensity. The slice thickness for all images was 5 mm with a 2-mm intersection gap, using a 192×256 matrix with one excitation. Each scan was screened for other confounding neurological disorders.

FLAIR images were used to quantify hyperintensities utilizing semi-automated threshold methods with good intra- and inter-rater reliability (>0.90). For each participant, hyperintensities were quantified separately for three anatomical regions: (i) hyperintensities

observed in the neocortical white matter (i.e. white matter of the corona radiata), (ii) hyperintensities confluent with the lateral ventricles (i.e. periventricular areas) and (iii) hyperintensities adjacent to subcortical gray matter nuclei (i.e. caudate, lentiform nuclei and thalamus). Briefly, the raw FLAIR imaging data was imported into the commercially available Mayo Clinic software program ANAYLZE®. First, the skull was stripped and the brain stem and cerebellum were removed leaving only the total cerebral brain parenchyma. Second, using the threshold tool in ANAYLZE®, we isolated the hyperintense regions from surrounding parenchyma for each patient. Using anatomical landmarks, hyperintensities were separated and labeled for the three regions. The total number of pixels from each anatomical region was then summed across the slices. Finally, total cerebral brain volume was quantified using threshold histogram values that were only consistent with brain parenchyma. Total cerebral brain volume was used to correct each of thehyperintensity values from each anatomical region and this ratio was the primary dependent variable [(hyperintensity pixel total/brain pixel total)×100)]. This method provides a ratio of hyperintensity load relative to the total amount of brain tissue for each patient and reflects the degree or extent of brain volume impacted by hyperintensity abnormalities. It also allows for a more direct comparison between patients controlling for variability in brain size and generalized atrophy.

Procedure

All procedures were approved by the local Institutional Review Board. After providing written informed consent, participants completed neuropsychological testing, echocardiogram and MRI on separate days.

Data analysis

Analyses were modeled after past studies examining BP variability and WMH (17,18). Bivariate Pearson correlation was used to examine the relationship of BP indices to neocortical, periventricular, subcortical and total hyperintensities. Finally, exploratory stepwise regression analyses were used to determine the relative contribution of BP indices, cardiovascular conditions and psychosocial factors to total hyperintensities.

Results

Relationship between BP and WMH

Average resting systolic and diastolic BP were unrelated to hyperintensities on MRI (Table II). Variability in systolic BP was related to hyperintensities in the neocortical region (r=0.34) and total hyperintensities (r=0.39), though no relationship emerged for variability of diastolic pressure. A similar pattern emerged for the coefficient of systolic variability, being related to neocortical (r=0.37) and total hyperintensities (r=0.35). No significant relationships emerged for the coefficient of diastolic pressure, pulse pressure or mean arterial pressure. The function of systolic variability divided by average resting diastolic pressure was most closely related to MRI findings, showing significant relationships with neocortical (r=0.39), subcortical (r=0.31) and total hyperintensities (r=0.38).

Predicting total hyperintensites

Exploratory stepwise regression analyses showed significant prediction of total WMH [F(1, 34) =5.52, p=0.025], with the final model accounting for 14% of the variance (Table III). Only the function of systolic variability and average diastolic BP remained significant, as age, CVD conditions and psychosocial factors were not retained in the final model.

Discussion

Results from the present study show variability in systolic BP is related to WMH in older adults with CVD, particularly when examined as a function of average diastolic BP. Though past findings are mixed, greater systolic BP variability has been linked to risk of both hyperintensities and lesions (17,18). Several mechanisms for this relationship have been proposed, including possible breakdown in cerebral autoregulatory systems and disruption of the blood– brain barrier (18,27). Finding that a function of systolic variability and average diastolic pressure is most closely related to hyperintensities implicates reduced autoregulation as a possible mechanism, but further examination in larger samples is needed to clarify this possibility.

In the present study, no relationship emerged between average pressure and WMH for either systolic or diastolic BP. Though community samples often show a relationship between hypertension andWMH, past findings for this relationship vary widely across studies and samples. A number of factors likely contribute to these inconsistent findings. Studies using continuous measures of BP often show smaller relationships to brain changes than those that dichotomize participants into hypertensive groups (e.g. ≤160/95 mmHg; (18,20,27,28)). Sampling method is another important consideration, with studies with the widest range of BP values (e.g. community samples) often showing the largest effects (19,28). Although a majority of our sample of older adults with CVD had been diagnosed with hypertension (77%), they were carefully monitored and treated, which may explain their average BP of 133/69. However, past studies indicate that even treated hypertensive individuals exhibit substantial white matter changes and that methods of diastolic pressure reduction can predispose persons to greater risk of cerebrovascular disease (29,30). Future studies should look to more closely examine the relationship between BP and structural brain changes, particularly those using beat-to-beat measures of BP.

Despite significant findings for other brain regions, no BP index was related to periventricular hyperintensities. This finding supports the belief that hyperintensities arise from different processes, with periventricular hyperintensities typically resulting from reduced myelin, gliosis, and extracellular fluid and subcortical hyperintensities from vascular changes (31,32). Should it be replicated, this finding may also help explain the cognitive deficits often found in older persons with hypertension, as periventricular and subcortical hyperintensities may have differential effects on cognition (33,36).

Our exploratory analyses suggested that systolic BP variability is an important contributor to hyperintensities in older adults with CVD. Only a function of systolic BP variability and diastolic resting pressure was retained in the regression model, whereas age, depression and comorbid CVD conditions were rejected. It is possible that this index taps into the known effects of the differential systolic and diastolic blood flow velocities on white matter lesions in past studies (i.e. pulsatility index; 37). Though they need replication in a larger sample, these findings highlight the importance of adequate BP management in persons with CVD, including regular monitoring of both systolic and diastolic levels.

Several aspects of the present study should be considered when interpreting the above results. Persons with a known history of stroke were excluded from participating in the current study. Although excluding such persons reduces internal threats to validity, our findings may not be fully generalizable to other samples of older CVD patients with stroke. Another possible limitation involves our sample size. The relatively small sample precludes determining the possible differential preventive effects of various anti-hypertensive medications (38). Finally, findings are also limited by examining only older adults with

CVD. Future studies that examine CVD patients across the adult lifespan will provide key insight into the role of BP in the development of WMH.

Taken in sum, the present study extends past research in three important ways. First, results demonstrate that systolic BP variability is an important contributor to the WMH found in older adults with CVD. Second, this relationship variesacross brain regions, with little or no relationship to periventricular hyperintensities. Finally, we provide preliminary evidence that BP variability may be an important contributor to hyperintensities in older adults with CVD, though replication in larger samples is needed.

Future studies examining the possible mechanisms for the relationship between BP variability and structural brain changes are needed, particularly those examining alternative neuroimaging modalities and cognitive functioning across multiple domains. Functional imaging (fMRI, PET) and diffusion tensor imaging (DTI) studies would complement the knowledge gained from standard MRI and prospective examinations of cognitive function may yield considerable insight into the effects of BP variability on the brain. Such studies may provide key insight into the underlying mechanisms for the relationship between BP and morphological brain changes in older adults with and without CVD.

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References

1. American Heart Association. Heart Disease and Stroke Statistics – 2005 Update. American Heart Association; Dallas, TX: 2004.
2. Posner H, Tang M, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology. 2002; 58:1175–1181. [PubMed: 11971083]
3. Morris M, Scherr P, Hebert L, Bennett D, Wilson R, Glynn R, et al. Association between blood pressure and cognitive function in a biracial community population of older persons. Neuroepidemiology. 2002; 21:123–130. [PubMed: 12006775]
4. Harrington F, Saxby B, McKeith I, Wesnes K, Ford G. Cognitive performance in hypertensive and normotensive older subjects. Hypertension. 2000; 36:1079–1082. [PubMed: 11116128]
5. Ostrosky-Solis F, Mendoza V, Ardila A. Neuropsychological profile of patients with primary systemic hypertension. Int J Neurosci. 2001; 110:159–172. [PubMed: 11912866]
6. Knopman D, Boland L, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001; 56:42–48. [PubMed: 11148234]
7. Schmidt R, Fazekas F, Koch M, Kapeller P, Augustin M, Offenbacher H, et al. Magnetic resonance imaging cerebral abnormalities and neuropsychologic test performance in elderly hypertensive subjects: A case control study. Arch Neurol. 1995; 52:905–910. [PubMed: 7661729]
8. van Swieten J, Geyskes G, Derix M, Peeck B, Ramos L, van Latum J, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol. 1991; 30:825–830. [PubMed: 1789694]
9. Schmidt R, Fazekas F, Offenbacher H, Lytwyn H, Blemtl B, Niederkorn K, et al. Magnetic resonance imaging white matter lesions and cognitive impairment in hypertensive individuals. Arch Neurol. 1991; 48:417–420. [PubMed: 2012517]
10. de Leeuw F, de Groot J, Oudkerk M, Witteman C, Hofman A, van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain. 2002; 125:765–772. [PubMed: 11912110]

11. Swan G, DeCarli C, Miller B, Reed T, Wolf P, Jack L, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology. 1998; 51:986–993. [PubMed: 9781518]
12. Oosterman J, Sergeant J, Weinstein H, Scherder E. Timed executive functions and white matter in aging with and without cardiovascular risk factors. Rev Neurosci. 2004; 15:439–462. [PubMed: 15656288]
13. Van Petten C, Plante E, Davidson P, Kuo T, Bajuscak L, Glisky E. Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. Neuropsychologia. 2004; 42:1313–1335. [PubMed: 15193940]
14. Cook I, Leuchter A, Morgan M, Conlee E, David S, et al. Cognitive and physiologic correlates of subclinical structural brain disease in elderly healthy control subjects. Arch Neurol. 2002; 5:1612–1620. [PubMed: 12374500]
15. Soderlund H, Nyberg L, Adolfsson R, Nilsson L, Launer L. High prevalence of white matter hyperintensities in normal aging: Relation to blood pressure and cognition. Cortex. 2003; 39:1093–1105. [PubMed: 14584568]
16. Gootjes L, Teipel S, Zebuhr Y, Schwarz R, Leinsinger G, Scheltens P, et al. Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease, and healthy aging. Dement Geriat Cog Dis. 2004; 18:180–188.
17. Puisieux F, Monaca P, Deplanque D, Delmaire C, di Pompeo C, Monaca C, et al. Relationship between leukoaraiosis and blood pressure variability in the elderly. Eur Neurol. 2001; 46:115–120. [PubMed: 11598328]
18. Havlik R, Foley D, Sayer B, Masaki K, White L, Launer L. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: The Honolulu-Asia Aging Study. Stroke. 2002; 33:26–30. [PubMed: 11779884]
19. Gomez-Angelats E, de La Sierra A, Sierra C, Parati G, Mancia G, Coca A. Blood pressure variability and silent cerebral damage in essential hypertension. Am J Hyperten. 2004; 17:696–700.
20. Fabregas M, Valencia J, Pujol J, Garcia-Sanchez C, Roca-Cusachs A, et al. Blood pressure variability and leukoaraiosis amount in cerebral small-vessel disease. Acta Neurol Scand. 2001; 104:358–363. [PubMed: 11903090]
21. Sierra C, de la Sierra A, Mercader J, Gomez-Angelats E, Urbano-Marquez A, Coca A. Silent cerebral white matter lesions in middle-aged essential hypertensive patients. J Hyperten. 2001; 20:519–524.
22. Cohen R, Moser D, Clark M, Aloia M, Cargill B, Stefanik S, et al. Neurocognitive functioning and improvement in quality of life following participation in cardiac rehabilitation. Am J Cardiol. 1999; 83:1374–1378. [PubMed: 10235098]
23. Moser D, Cohen R, Clark M, Aloia M, Tate B, Stefanik S, et al. Neuropsychological functioning among cardiac rehabilitation patients. J Cardiopulm Rehab. 1999; 19:91–97.
24. Manolio T, Burke G, O'Leary D, Evans G, Beauchamp N, Knepper L, et al. Relationships of cerebral MRI findings to ultrasonic carotid atherosclerosis in older adults: TheCardiovascular Health Study. CHS Collaborative Research Group. Arter Thromb Vasc Biol. 1999; 19:356–365.
25. Marstand J, Garde E, Rostrup E, Ring P, Rosenbaum S, Mortensen E, et al. Cerebral perfusion and cerbrovascular reactivity are reduced in white matter hyperintensities. Stroke. 2002; 33:972–976. [PubMed: 11935046]
26. Folstein M, Folstein S, McHugh P. Mini-mental state. J Psychiat Res. 1975; 12:189–198. [PubMed: 1202204]
27. van Dijk E, Breteler M, Schmidt R, Berger K, Nilsson L, Oudkerk M, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: Cardiovascular Determinants of Dementia study. Stroke. 2004; 44:625–630.
28. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung H. MRI white matter hyperintensities: Three-year follow-up of the Austrian Stroke Prevention Study. Neurology. 1999; 53:132–139. [PubMed: 10408549]

29. Heckbert S, Longstreth W, Psaty B, Murros K, Smith N, Newman A, et al. The association of antihypertensive agents with MRI white matter findings and the modified Mental State Examination in older adults. J Am Geriatr Soc. 1997; 45:1423–1433. [PubMed: 9400550]

30. Smulyan H, Safar M. The diastolic blood pressure in systolic hypertension. Ann Intern Med. 2000; 132:233–237. [PubMed: 10651605]

31. Fazekas F, Schmidt R, Scheltens P. Pathophysiologic mechanisms in the development of age-related white matter changes of the brain. Dement Geriat Cog Dis. 1998; 9:2–5.

32. Lazarus R, Prettyman R, Cherryman G. White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders. Int J Geriat Psychiat. 2005; 20:274–297.

33. De Groot J, De Leeuw F, Oudkerk M, Van Gijn J, Hofman A, Jolles J, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol. 2002; 52:335–341. [PubMed: 12205646]

34. Kuo H, Sorond F, Iloputaife I, Gagnon M, Milberg W, Lipsitz L. Effect of blood pressure on cognitive functions in elderly persons. J Gerontol. 2004; 59:1191–1194.

35. Raz N, Rodrigue K, Acker J. Hypertension and the brain: Vulnerability of the prefrontal regions and executive functions. Beh Neurosci. 2003; 117:1169–1180.

36. Waldstein S. The relation of hypertension to cognitive function. Curr Direct Psychol Sci. 2003; 12:9–12.

37. Sierra C, de la Sierra A, Chamorro A, Larrousse M, Domenech M, Coca A. Cerebral hemodynamics and silent cerebral white matter lesions in middle-aged essential hypertensive patients. Blood Press. 2004; 13:304–309. [PubMed: 15545154]

38. Wang J, Staessen J, Birkenhager W. Antihypertensive treatment and prevention of stroke and dementia. Semin Cerebrovasc Dis Stroke. 2003; 3:155–160.

Table I

Demographic and medical characteristics of cardiovascular disease patients undergoing magnetic resonance imaging.

Demographic	Mean	SD	Frequency (%)
Age, years	71.49	7.43	
Mini Mental Status Exam	28.90	1.19	
Medical			
Systolic BP, average	133.41	16.90	
Systolic BP, standard deviation	10.67	6.87	
Systolic BP, coefficient	0.80	0.05	
Diastolic BP, average	68.79	9.07	
Diastolic BP, standard deviation	6.84	4.20	
Diastolic BP, coefficient	0.10	0.06	
Pulse pressure	64.63	13.60	
Mean arterial pressure	90.31	10.43	
Atrial fibrillation			14
Coronary artery bypass graft/Aortic valve repair or replacement			42
Depression			13
Hypertension			77
Myocardial infarction			46
Transient ischemic attack			11
Type 2 diabetes			13

BP, blood pressure.

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Table II

Relationship between blood pressure (BP) and hyperintensities on magnetic resonance imaging.

	Neocortical	Periventricular	Subcortical	Total
Systolic BP, average	−0.04	0.09	−0.10	−0.01
Systolic BP, SD	0.34*	0.23	0.23	0.39*
Diastolic BP, average	−0.16	−0.08	−0.24	−0.15
Diastolic BP, SD	−0.17	−0.14	−0.13	−0.17
Pulse pressure	0.05	0.17	0.03	0.08
Mean arterial pressure	−0.11	0.01	−0.19	−0.10
Systolic SD/diastolic average	0.39**	0.23	0.31*	0.38**

SD, standard deviation. Values represent Pearson correlation coefficients.

* denotes significance v.05.

** denotes significance v.01.

Table III

Predicting total hyperintensities in older adults with cardiovascular disease.

Included variables	*B*	*β*	*p*
Systolic SD/diastolic average	0.04	0.38	0.025 R^2=0.14, Adjusted R^2=0.12 R=0.38

Excluded variables	*B*	*p*	Partial correlation
Age	0.28	0.17	0.24
Atrial fibrillation	−0.15	0.36	−0.16
Coronary artery bypass graft/aortic valve repair or replacement	0.03	0.85	0.03
Depression	−0.11	0.50	−0.12
Myocardial infarction	0.19	0.26	0.20
Transient ischemic attack	−0.03	0.85	−0.04
Type 2 diabetes	−0.02	0.90	−0.02

B, unstandardized regression coefficients; *β*, standardized coefficients; *p*, significance value; SD, standard deviation.

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