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THE ROLES OF ARTERIAL STIFFNESS AND BLOOD PRESSURE IN HYPERTENSION-ASSOCIATED COGNITIVE DECLINE IN HEALTHY ADULTS

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Abstract

Although there is strong evidence that hypertension leads to cognitive decline, especially in the executive domain, the relationship between blood pressure and cognition has been conflicted. Hypertension is characterized by blood pressure elevation and increased arterial stiffness. We aimed at investigating if arterial stiffness would be superior to blood pressure in predicting cognitive decline and explaining the hypertension-executive decline association. A randomly selected asymptomatic population (N=591, age=49.2 years, 70% women, 27% Black, education=18 years) underwent annual vascular and cognitive assessments. Cognition was assessed using computerized versions commonly used cognitive tests and principal component analysis was used for deriving cognitive scores for executive function, memory and working memory. Arterial stiffness was measured by carotid-femoral pulse wave velocity (PWV). Higher PWV, but not blood pressure, was associated with a steeper decline in executive ($p=0.0002$), memory ($p=0.05$) and working memory ($p=0.02$) scores after adjusting for demographics, education, and baseline cognitive performance. This remained true after adjusting for hypertension. Hypertension was associated with greater decline in executive score ($p=0.0029$) and those with combined hypertension and elevated PWV (>7 m/sec) had the greatest decline in

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executive score (p-value hypertension*PWV=0.02). PWV explained the association between hypertension and executive function (p-value for hypertension=0.0029 vs 0.24 when adjusting for PWV). In healthy adults, increased arterial stiffness is superior to blood pressure in predicting cognitive decline in all domains and in explaining the hypertension-executive function association. Arterial stiffness, especially in hypertension, may be a target in the prevention of cognitive decline.

Keywords

hypertension; arterial stiffness; executive function; memory; blood pressure

Introduction

Hypertension is associated with cognitive decline, mild cognitive impairment and dementia, including Alzheimer's disease.¹ Arterial stiffness, measured as pulse wave velocity (PWV), precedes and may further exacerbate the elevation of blood pressure in hypertension.^{2, 3} Increased PWV is a predictor of adverse cardiovascular and cerebrovascular events, independent of blood pressure elevation.⁴⁻⁷ The relative contribution of increased PWV with and without hypertension to cognitive decline, compared to elevated blood pressure, has not been fully described.

Although hypertension may eventually impact all domains, executive function is commonly affected early and may predict future dementia.⁸ The impact of increased arterial stiffness alone or in combination with hypertension on executive function is unknown.

Therefore, we aimed at investigating if arterial stiffness would be superior to blood pressure level in predicting cognitive decline in an otherwise healthy and relatively young population. We also examined the impact of PWV specifically on executive function and in explaining the hypertension-executive function association in otherwise asymptomatic healthy adults.

Methods

Study description

A cohort of healthy employees from Emory University were randomly recruited into the Center for Health Discovery and Well Being cohort as part of the Emory University/Georgia Tech Predictive Health Institute (<http://predictivehealth.emory.edu>).^{9, 10} Exclusion criteria were a history in the past year of non-accident related hospitalization, severe psychosocial disorder, or addition of new prescription medications to treat a chronic disease (except for changes in anti-hypertensive or anti-diabetic agents), active drug abuse or alcoholism, a current active malignant neoplasm, uncontrolled or poorly controlled autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, infectious, inflammatory, musculoskeletal, neurological, psychiatric, or respiratory disease, and any acute illness in the 2 weeks before baseline studies.

Participants were assessed annually through a combination of surveys, assessments and standardized clinical or research testing. Measurements included evaluation of

cardiovascular risk factors including blood pressure, heart rate, body mass index, smoking history, medication profiles and cognitive function. Blood pressure was measured while seated in the right arm using an automatic blood pressure monitor (A&D Medical, Model TM-2655). Participants were evaluated yearly. The Emory University Institutional Review Board approved the protocols, and informed consents were obtained from all participants.

Arterial stiffness

Carotid-femoral pulse-wave velocity (PWV) was measured in the supine position after an overnight fast using the Sphygmocor device (Atcor Medical, Australia).¹¹ Pressure waveforms at the carotid and femoral arterial sites were acquired using tonometry and electrocardiographic gating. Velocity (distance/time in meters/second) was calculated using the “foot-to-foot” method, measuring the interval between the R wave on the ECG and the foot of the recorded pressure waveform at each site, whereas distance between the sites was measured manually by the operator. Distance was measured as the number of meters between the area of femoral pulse to the area of the carotid pulse. Reproducibility studies in our laboratory on consecutive days have demonstrated a coefficient of variation of 3.8% for PWV.

Cognitive Assessment

Commonly employed versions of neuropsychological measures were administered via computer to 601 participants at baseline and then each visit, using software developed by Aharonson and colleagues.^{12–14} The measures included memory delayed recall, memory recognition, visual spatial learning, spatial short term memory, pattern recall, delayed pattern recall and recognition of pattern, executive function test, mental flexibility, digit symbol substitution test, forward and backward digit span, symbol spotting, and focused and sustained attention (computerized score:0–100% adjusted for computer skill levels)

Cognitive scores

We derived orthogonally distinct scores for cognitive domains using principal component analysis with Varimax (orthogonal) rotation and Kaiser normalization.^{15, 16} Our factor analysis results are shown in an online supplement (Table S1). Three factors provided the best solution, explaining 90% of variance in cognitive performance. Scree plots showed that solutions with more than 3-factors added little to the explanation of the variance. The three factors showed a low magnitude of correlation: Factor 1 vs 2= 0.28; Factor 1 vs 3=0.04; Factor 2 vs 3=0.02 (a value less than 0.32 suggests less than 10% variance overlap and is an accepted cutoff of distinct factors¹⁵). Factor 1 was predominantly loaded on tests that assess executive function; Factor 2 loaded on memory; and Factor 3 loaded on backward and forward digit span suggestive that it is reflective of working memory. We then used the derived scoring coefficients to calculate the factor-saved scores (unitless) in the sample: predominantly executive, predominantly memory, and predominantly working memory domains. We used these 3 scores as our cognitive outcomes.

Statistical Considerations

Mixed Models with repeated measures were used with cognitive performance as the outcome and history of hypertension, blood pressure (systolic and diastolic: SBP, DBP) and arterial stiffness (PWV) as predictors (fixed effects). In additional analyses, we investigated the impact (interaction) of PWV on the relation between hypertension and cognition by including an interaction term (arterial stiffness* HTN*visit). Models were adjusted for age, gender, race, body mass index, educational level, and the corresponding baseline cognitive performance. Analyses were conducted using SAS (Carey, NC) V9.3.

Results

At baseline, 591 subjects (mean age=48.8, range 18–82 years) underwent vascular and cognitive function assessments. Of those, 558 (94%) had a follow-up at year 1 and 511 (87%) had at least one additional follow-up visit (range: 2–4 years). At baseline, 32% had hypertension. Table 1 describes the baseline characteristics of the cohort and the comparison between the 2 hypertension groups.

Over the follow-up period, the mean increase in blood pressure was 1.6/0.6 mm Hg 95% CI [−0.6/−0.9, 3.7/2.1] and in PWV was 0.28 m/sec [0.08, 0.48]. The mean decrease in the executive derived score was −2.4 [−4.6, −0.2], in the memory derived score was −2.3; [−8.7, 3.8] and in the working memory derived score was −2.7; [−5.5, 2.3].

Blood pressure, hypertension and cognitive performances

At baseline, hypertension was not associated with cognitive performance on any of the derived scores, Table 1. Longitudinally, hypertension was associated with greater decline in the executive derived score ($p=0.0029$ for hypertension*Time, Figure 1), but not memory ($p=0.94$) or working memory ($p=0.34$). In addition, systolic, diastolic or pulse pressure levels were also not associated with the change in cognitive function after adjusting for age, gender, race, BMI, educational level and baseline cognitive scores except for diastolic blood pressure and the executive derived score ($p=0.05$) as shown in Table 2.

Arterial stiffness and cognitive performance

In contrast to blood pressure, higher PWV was associated with a steeper decline in the executive cognitive score ($p=0.0002$), the working memory score ($p=0.02$), and the memory score ($p=0.05$), Table 2. The associations between PWV and declines in cognitive scores were independent of hypertension status and systolic or diastolic blood pressure levels as shown in Table 2. Additional adjustments for use of antihypertensive therapy, diabetes status, statin use and CIMT did not alter the results (p -value=0.004 for executive score, 0.039 for memory score, and 0.018 for working memory).

PWV, hypertension and cognition

The combined effects of PWV and hypertension, we found significant interaction between hypertension status and PWV (divided into high and low at the median value of 7.0 m/sec). Those with hypertension and higher PWV had the greatest decline in executive function compared to any other group (p -value hypertension*PWV=0.02). Figure 2.

Lastly we compared the contribution of PWV vs blood pressure in predicting/explaining the relationship between hypertension and executive function. As opposed to SBP, PWV explained the association between hypertension and executive function (p-value for hypertension=0.0029 vs 0.24 when adjusting for PWV) and increased the explained variance from 1% to 10%. This was not true for blood pressure level, as shown in Table 3.

Discussion

Our study demonstrates that higher arterial stiffness, measured as PWV, but not blood pressure levels predicts a greater decline in cognitive function across multiple domains for healthy adults. Although hypertension is traditionally associated with a greater decline in executive function, this relationship was better explained by higher PWV rather than elevated blood pressure. Finally, we identified a significant interaction between a history of hypertension and PWV such that subjects with hypertension and higher PWV had the greatest 4-year risk for decline in executive function.

The relationship between blood pressure level and cognition has been inconsistent.^{17, 18} In our study of healthy adults, whereas blood pressure level failed to predict cognitive decline, PWV was a significant predictor, suggesting that the cognition in hypertensive individuals is more likely related to the underlying pathophysiological changes in the systemic arterial structure. Further, PWV was related to declines in all cognitive domains, whereas hypertension was linked only to executive function decline in this healthy population. Taken together, our study supports the use of PWV as a vascular biomarker for future cognitive decline and may perform better than blood pressure in predicting future cognitive decline.

Our study is novel because we demonstrate that increased arterial stiffness explains the association between hypertension and executive function. We also demonstrate that PWV predicts cognitive decline beyond executive function in a highly educated population, even after adjusting for blood pressure. Prior studies have demonstrated that higher PWV is associated with greater cognitive decline but are limited because they have used a non-specific measure of cognition (eg mini-mental status exam).^{6, 19–21} Although Waldstein and colleagues administered a comprehensive neuropsychological battery to stroke and dementia free persons aged 20–96 years old who were enrolled in the Baltimore Longitudinal Study of Aging, their findings were restricted to declines in memory.²² We extend their findings to include executive functioning and working memory, domains that are especially susceptible to cardiovascular disease and hypertension.²³ The use of derived cognitive scores and the use of repeated measures of PWV and cognitive testing at all occasions may explain these differences. Our ability to detect relationships between PWV and the domains of executive functioning and working memory may reflect the importance of changes in PWV as predictors of cognitive decline as opposed to a single time point measurement.

Our study has both clinical and research implications for the prevention of cognitive impairment and cognitive aging. Specifically, clinical interventions and research studies that focus on lowering blood pressure may not be sufficient in preventing cognitive decline. Whether improvement of markers of vascular function such as PWV impact on cognitive decline needs to be further investigated. Moreover, the pathway from increased arterial

stiffness to cognitive decline is still unknown. Future studies need to identify potential mechanisms underlying the relationship between arterial stiffness and cognition including inflammation, oxidative stress, cerebral hypoperfusion or impaired cerebral vasoreactivity.

The strengths of our study are the longitudinal design, the multiple follow-up exams which allow for examination of non-linear trends, and the large cognitive test battery. Limitations of this study include a relatively short follow-up period, the smaller magnitude of decline in cognition over this period, and the lack of direct measurement of cerebrovascular stiffness or neuroimaging confirmation. In addition, our sample consisted of a healthy cohort of individuals, which limits its generalizability.

Perspectives

Arterial stiffness, measured as PWV, is superior to blood pressure in predicting cognitive decline in healthy adults. Increased arterial stiffness may explain the association between hypertension and executive function and further exacerbates the impact of hypertension on this domain. Interventions that may lower PWV may be considered as therapeutic targets for prevention of cognitive impairment and dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

1) What's New?

This study demonstrate that the increase arterial stiffness seen in hypertension is an important factor in cognitive decline seen in hypertension, and possibly more important than blood pressure levels.

2) What is Relevant?

This study addresses an important aspect related to the markers that might link systemic hypertension to cognition.

3) Summary

In healthy adults, increased arterial stiffness may be superior to blood pressure in predicting cognitive decline.

Figure 1.
The trajectory over the study period of executive function score in hypertensive vs non-hypertensive participants.
HTN: hypertension; NTN: No hypertension.

Figure 2.

The impact of hypertension and pulse wave velocity (low vs high at the median 7.0 m/sec) on the executive function score decline from baseline to the end of the study.

PWV: pulse wave velocity, NTN: no hypertension, HTN: hypertension

*: P-value=<0.0001 for the within group change in executive function score

P-value for the hypertension*PWV was adjusted for. age, gender, race, education, body mass index, and baseline executive score

Values=score_{final visit} – score_{baseline}.

Table 1

Baseline characteristics of the overall sample and the hypertensive and non-hypertensive groups

Characteristic	Total sample	No hypertension	Hypertension	
N	591	402(68%)	189(32%)	<i>p-value</i>
Age, years	48.8 (0.4)	47.4(0.5)	51.9(0.7)	<.0001
Gender, women	400(68%)	277(69%)	123(65%)	0.35
Race, African American	142(24%)	79(20%)	63(33%)	
White	415(70%)	292(73%)	123(65%)	<.0001
Other	34(6%)	31(7%)	3(2%)	
Body Mass Index, kg/m ²	27.99 (0.27)	26.35(0.26)	31.48(0.54)	<.0001
Education, years	18.8(0.2)	19(0.2)	18.5(0.3)	0.18
Current/past smokers	36(6%)	22(5%)	14(7%)	0.36
Systolic BP, mm Hg	121 (1)	115(1)	135(1)	<.0001
Diastolic BP, mm Hg	77 (0.5)	73(0.4)	84(1)	<.0001
Controlled hypertension (<140/90 mm Hg)	488(83%)	402 (100%)	86 (46%)	<.0001
Hypertension severity, >160/100 mmHg	26 (4%)	0	26 (14%)	<.0001
Median Duration of hypertension (range), years	NA	NA	7 (0–38)	NA
Heart rate, bpm	68.7(0.4)	67.7(0.5)	70.6(0.7)	0.0012
<i>Medical History</i>				
Depression	11(2%)	8(2%)	3(0.7%)	0.12
Diabetes*	34(6%)	11(3%)	23 (12%)	<.0001
Heart disease	5(0.8%)	2(0.5%)	3(2%)	0.1
Stroke	10(2%)	7(2%)	3(2%)	0.89
<i>Medications</i>				
Antihypertensive therapy	126 (21%)	0	126 (66%)	<.0001
Diuretics	47 (8%)	0	47 (25%)	<.0001
Angiotensin converting enzyme inhibitors	50 (8%)	0	50 (26%)	<.0001
Angiotensin receptor blocker	32 (5%)	0	32 (17%)	<.0001
Calcium channel blocker	13 (2%)	0	13 (7%)	<.0001
Beta blocker	27 (5%)	0	27 (14%)	<.0001
Memory score, mean	65.4 (0.7)	65.5(0.8)	65.3(1.2)	0.92
Executive score, mean	83.7(0.3)	83.6(0.4)	83.9(0.4)	0.6
Working memory score, mean	54.5(0.4)	55.1(0.5)	53.5(0.9)	0.079
Pulse Wave Velocity, m/sec	7.20(0.06)	6.98(0.06)	7.68(0.12)	<.0001
Carotid intima media thickness, mm	0.64(0.01)	0.61 (0.01)	0.69 (0.01)	<.0001
High Pulse Wave Velocity, m/sec (>7.00 m/sec)	288 (49%)	167 (42%)	121 (64%)	<.0001

Numbers are mean (standard error) or count (percentage). P-values compare hypertensive vs. non-hypertensive groups and are obtained from t- or Chi-square tests Diabetes Mellitus is defined as self report of diabetes or receiving antidiabetic agents

DBP: diastolic blood pressure; SBP: systolic blood pressure; PWV: pulse wave velocity; HTN: hypertension; NTN: no hypertension

Table 2

Association between baseline hypertension, pulse wave velocity and blood pressure with the yearly change in the 3 cognitive scores

Baseline measure	Memory			Executive Function			Working memory		
	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P
HTN (vs NTN)	0.35	0.68	0.61	-1.03	0.34	0.0029	0.35	0.45	0.44
SBP, per 10 mm Hg	-0.06	0.20	0.77	-0.12	0.10	0.26	-0.07	0.14	0.59
DBP, per 10 mm Hg	0.35	0.31	0.26	-0.31	0.16	0.05	0.05	0.21	0.82
PWV, per 1 m/sec	-0.45	0.24	0.05	-0.44	0.12	0.0002	-0.36	0.16	0.02
PWV (adjusted for SBP)	-0.54	0.25	0.035	-0.44	0.13	0.0004	-0.35	0.17	0.04
PWV (adjusted for DBP)	-0.41	0.12	0.0009	-0.61	0.25	0.01	-0.38	0.17	0.02

Estimates are change per year for each unit of increase in blood pressure or PWV. (except for hypertension where the value is the difference between the 2 groups in the yearly change). By mixed model after adjusting for baseline cognitive score, age, gender, race, education, and BMI

Table 3

The impact of including pulse wave velocity vs systolic blood pressure in the models relating executive function score with hypertension.

Model 1			Model 2			Model 3		
Effect	F-Value	Pr > F	Effect	F-Value	Pr > F	Effect	F-Value	Pr > F
HTN*TIME	4.09	0.0029	HTN*TIME	1.36	0.24	HTN*TIME	2.72	0.028
			PWV*TIME	6.92	<.0001	SBP*time	0.99	0.41
R ²	1%			10%				1%

Model 1 includes hypertension, age, gender, race, education and baseline executive score

Model 2 includes Model 1 + PWV

Model 3 includes Model 1 + SBP

HTN: hypertension, PWV: Pulse wave velocity; SBP: systolic blood pressure