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Pulse Wave Velocity and Cognitive Function in Older Adults

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Abstract

Arterial stiffness may be associated with cognitive function. In this study, pulse wave velocity (PWV) was measured from the carotid to femoral (CF-PWV) and from the carotid to radial (CR-PWV) with the Complior SP System (Alam Medical, Vincennes, France). Cognitive function was measured by six tests of executive function, psychomotor speed, memory, and language fluency. A total of 1433 participants were included (mean age 75 years, 43% men). Adjusting for age, sex, education, pulse rate, hemoglobin A1C, HDL cholesterol, hypertension, CVD history, smoking ,drinking, and depression symptoms, a CF-PWV > 12 m/s was associated with a lower Mini-Mental State Examination score (coefficient: −0.31, se: 0.11, p=0.005), fewer words recalled on Auditory Verbal Learning Test (coefficient: −1.10, se: 0.43, p=0.01), and lower score on the composite cognition score (coefficient: −0.10, se: 0.05, p=0.04) and marginally significantly associated with longer time to complete Trail Making Test-B (coefficient: 6.30, se: 3.41, p=0.06), CF-PWV was not associated with Trail Making Test-A, Digit Symbol Substation Test, or Verbal Fluency Test. No associations were found between CR-PWV and cognitive performance measures. Higher large artery stiffness was associated with worse cognitive function, and longitudinal studies are needed to confirm these associations.

Keywords

pulse wave velocity; cognitive function; epidemiology; arterial stiffness

INTRODUCTION

Dementia is an important public health issue (1). Cardiovascular disease and its risk factors have been suggested to be associated with dementia, although the biological mechanism is not entirely clear (2). Aortic pulse wave velocity (PWV) is the gold standard for arterial

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stiffness measurement, and also an independent predictor of stroke(3, 4). Because PWV is the direct measurement of arterial wall properties, and is associated with a wide range of CVD risk factors (such as hypertension, lipids, and so on)(3), assessing the association of PWV and cognitive function may help to understand the associations of cardiovascular factors and brain function.

There have been relatively few studies examining the association of PWV and cognitive function. Many studies were patient-based studies with relatively small sample sizes (5-9), and included only one cognitive function test which limited their ability to determine effects on different cognitive domains(5, 6, 8, 10, 11). Larger studies often had sample sizes less than a thousand, data available on only a subset of the cohort, or may not have been representative of the general population(12-15). The Rotterdam study included a large sample size, but PWV and cognitive function were not measured currently (16). Some studies found that PWV was independently associated with cognitive decline (12, 15), but PWV was not an independent risk factor of cognitive decline and dementia in the Rotterdam Study (16).

The association of PWV and cognitive function may be due to the detrimental effects of arterial stiffness within the cardiovascular system. With increased stiffness, the pulse waves travel faster in arteries, and the reflected pulse waves arrive in early systole. The early arrival of the reflected pulse waves increases the pressure load and myocardial oxygen consumption, and also decreases the diastolic pressure and coronary perfusion, both of which are harmful to the cardiovascular system, and eventually result in insufficient blood supply to the brain. In addition, the high pulsations cannot be absorbed well in the large “stiffened” arteries, and would be transmitted to small vessels, and cause damage. The brain may be especially susceptible because it has more dilated small vessels, and the small vessel damages caused by high pulsations may contribute to impaired cognitive function (17, 18).

The aim of this study was to assess the association of PWV and cognitive function in a large cohort of older adults, and to determine whether the effect of PWV is independent of other CVD risk factors. In this large population-based study, PWV and multiple cognitive domains were measured concurrently and many traditional CVD risk factors were also measured.

METHODS

Study Population

The Epidemiology of Hearing Loss Study (EHLS) is a longitudinal study of aging among residents of Beaver Dam, WI. The details have been described previously(19). In brief, Beaver Dam residents aged 43 to 84 years were invited to participate in the Beaver Dam Eye Study (BDES) baseline exam in 1989-1990. Participants in the BDES were invited to participate in the EHLS baseline examination in 1993-1995 (n=3753) when the BDES 5-year follow-up examinations were conducted. Since then the EHLS was conducted currently with BDES every five years. In the EHLS 15-year follow-up examination in 2009-2010 (n=1812, 80.8% of surviving baseline participants), pulse wave velocity was measured from carotid to femoral (CF-PWV) and from carotid to radial (CR-PWV), and cognitive function was measured with multiple tests. The EHLS study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board; all participants provided informed consent.

Measurements

Data were collected through interviews, health examinations, and laboratory tests using standardized protocols. PWV was measured with the participants in a supine position, using

the Complior SP System (Alam Medical, Vincennes, France). This device has been widely used and validated; the intra-observer and inter-observer repeatability were 0.935 and 0.890, respectively (20, 21). The carotid-radial distance was measured from the sternal notch to the styloid process of the right wrist; and the carotid-femoral distance was from the sternal notch to the right femoral artery sampling site, measured in the plane over the body to avoid being affected by body size or shape. The pulse waves were measured at the right common carotid artery, the right femoral artery, and the right radial artery. The examiner would monitor signal quality directly (through graphics about amplitude and upstroke provided in the software), and select the segment to be captured when the signal was good (clean, fast rising systole, sufficient systolic amplitude and a relatively flat diastole) for at least ten cycles. The device then automatically calculated PWV and the tolerance. The examiners would repeat the measurement if the participant moved, or the PWV value or the tolerance were high. Although the examination only causes minimal discomfort from the pressure of the sensors, participants were advised not to be examined if they had transient ischemic attack or stroke within the past 6 months or had bilateral carotid arterial bruits on auscultation. Participants weighing more than 400 lb were not examined due to the weight limit of the examination table.

A total of 1436 (79%) out of the 1812 participants had PWV data available. The main reasons for not having PWV were participants did not come to the office for examination (home bound or nursing home residents), and physical limitations of participants (for example, unable to lie on the table). Compared to those without PWV data, participants with PWV data were younger (age: 74.9 vs. 79.5 years, p<.0001), had lower body mass index (30.6 vs. 31.7 kg/m^2, p=0.03), were healthier (CVD history: 16% vs. 25%, p=.0001, diabetes: 20% vs. 30%, p=.0001), were more likely to be men (43% vs. 33%, p=.0008), and had better cognitive function (Mini-Mental State Examination score: 27.9 vs. 26.5, p<. 0001).

Cognitive function was measured by six tests. The Mini-Mental State Examination (MMSE) is a test of general cognitive function which measures orientation to time and place, attention and calculation, language, and memory (22). Trail Making Test -part A and -part B (TMT-A and TMT-B, respectively) are tests of executive function, attention and speed (23). The tests require the subject to connect targets (the targets are numbers in TMT-A, and are numbers and letters in TMT-B) as fast as possible. The score for each task was the time (in seconds) taken to complete the test; a score of 301 was given if the test was not completed within 5 minutes. The Digit Symbol Substitution Test (DSST) is a test of psychomotor speed and sustained attention, which requires the participant to translate digits (1-9) to symbols as quickly as possible (23). The score was the total number of correct symbols that the participant filled in within 90 seconds. Rey Auditory Verbal Learning Test (AVLT) is a test of memory (23), and was modified in our study due to limited exam time with four learning trials instead of five. In the test, a 15-word list was read to the participant, and he/she was asked to recall as many words as possible. After three repeated trials, an interruption word list was introduced. Then the participant was immediately asked to recall the original 15-word list again. The total number of words recalled from the original 15-word list (all 4 trials summed) was used as the score. The Verbal Fluency Test (VFT) measures spontaneous production of words under restricted search conditions (23). In this test, the participant was asked to give as many words beginning with the letter (F, A, S) as possible in one minute per letter. The score of VFT was the total number of words given by the participant. Except for the TMT-A and TMT-B scores, higher test scores reflected better cognitive function.

Age, gender, education, and lifestyle factors were self-reported through questionnaires. Participants were asked to bring their current medications, and the medication information

was recorded. Heavy drinking was defined as reporting a period when 4 or more drinks were consumed daily. Physical activity was defined as current exercise at least once a week long enough to sweat. Height (m), weight (kg) and pulse rate were measured. Seated blood pressure was measured using the Hypertension Detection and Follow-up Program protocol(24). Hypertension was defined as measured systolic pressure ≥ 140 mmHg, or diastolic pressure ≥ 90 mmHg or current use of antihypertensive medications. Mean arterial pressure was approximately calculated as diastolic pressure+ one third of pulse pressure. Blood samples were drawn, and total cholesterol, HDL cholesterol, and hemoglobin A1C (HbA1C) were measured at the Fairview Laboratory at the University of Minnesota. CVD history was defined as self-reported physician diagnosed angina, myocardial infarction, stroke, or transient ischemic attack. Diabetes was defined as self-reported physician diagnosis of diabetes, or HbA1C ≥ 6.5, or self-reported suspected diagnosis with current medications for diabetes. The Center for Epidemiologic Studies Depression Scale (*CES-D*) was administered, and a CES-D score >15 (possible range: 0-60) was classified as positive of depression symptoms(25).

Statistical Analyses

All the analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC). The association of pulse wave velocity and cognitive function test performance was assessed with ordinary linear regressions. The individual test scores were used as outcomes. Age, sex and education were included in the models, and interactions of age*PWV, sex* PWV were tested. No significant interactions were detected. In the final multivariable models, the following selected CVD risk factors were included: pulse rate, BMI, smoking and drinking, physical activity, HDL cholesterol, A1C, CVD history, hypertension, and depression symptoms. Several sensitivity analyses were performed with the final models to assess whether the associations were independent of other CVD risk factors. In one sensitivity analysis, we included a marker of duration of hypertension which was a count of the number of times the participant was considered hypertensive at each of the examinations (maximum of five during a 20-yr period). The CF-PWV was dichotomized using >12 m/s as a cutoff because this level is recommended as a marker for significant change in arterial stiffness (26). For the CR-PWV, there are no recommended cut-points so we chose >10.6 m/s, the same percentile (68%) as the CF-PWV >12 m/s in our population. The original continuous CF-PWV and CR-PWV were also tested.

A composite score was derived from these test scores using principal component analysis to reflect the composite cognitive function. This composite score was then analyzed as an additional outcome with ordinary linear regression. There was only one eigenvalue greater than one, and one principal component was kept as the composite score (mean: 0, sd: 1). The loadings on each test were 0.70, −0.77, −0.83, 0.72, 0.84, and 0.60 for the MMSE, TMT-A, TMT-B, AVLT, DSST and VFT, respectively. We also calculated the average of the z-scores of these individual tests as an outcome. Results from analyzing the average z-score were not different; therefore they were not reported here.

RESULTS

A total of 1433 participants were included in the analyses (those with both PWV data and cognition test scores). The mean (sd) of CF-PWV and CR-PWV were 11.0 (3.6) m/s and 10.0 (2.3) m/s, and the distributions were not strictly normal. Based on the CF-PWV >12 m/s cutoff, about 32% of the population had high CF-PWV. They were older, had more comorbidities, and had lower cognitive scores compared to the rest of the population (Table 1).The CF-PWV and the CR-PWV were correlated with each other (correlation coefficient:

0.4, p<0.01). The CF-PWV but not the CR-PWV was correlated with age (correlation coefficient: 0.3, p<0.0001, and 0.02, p=0.4, respectively).

High CF-PWV (>12 m/s) was associated with worse MMSE, TMT-B, AVLT scores, and the composite cognition score when adjusting for age, sex and education. The effect sizes decreased a little but largely remained significant after further adjusting for pulse rate, BMI, HDL cholesterol, A1C, smoking and drinking, CVD history, hypertension, physical activity, and depression symptoms (Table 2). No significant associations were found when CF-PWV was tested continuously (Supplemental Table 1).

In the final model, when participants with CVD history were excluded, the associations largely remained similar (effect sizes and p-values were: −0.28, p=0.02 for MMSE, 6.98, p=0.06 for TMT-B, −1.10, p=0.03 for AVLT, and −0.11, p=0.06 for composite score, no other significant associations were detected). When those on antihypertensive medications were excluded, and the model was additionally adjusted for mean arterial pressure, the sample size for analyses were significantly reduced, and the associations became borderline non-significant although the effect sizes increased a bit (effect sizes and p-values were: −0.35, p=0.07 for MMSE, 8.68, p=0.1 for TMT-B, −1.47, p=0.047 for AVLT, −2.28, p=0.056 for VFT, and −0.15, p=0.10 for composite score). No other significant associations were detected. When the duration of hypertensive status was included to replace hypertension status, the results were similar (effect sizes and p-values were: −0.28, p=0.01 for MMSE, 5.78, p=0.09 for TMT-B, −1.10, p=0.01 for AVLT, and −0.09, p=0.07 for composite score).

No significant associations with cognitive function were found for high CR-PWV (>10.6 m/s) (Table 3), or for continuous CR-PWV (Supplemental Table 2).

DISCUSSION

In this population-based study, high arterial stiffness was associated with poorer cognitive function in multiple domains, including executive function, psychomotor speed, and memory. These results were generally consistent with the few previous large studies (12-15). Our study provides further support for the association between arterial stiffness and cognitive function. However, as a cross-sectional nature, this study does not allow for conclusions about temporality; longitudinal studies are needed to determine if higher CF-PWV predicts cognitive decline.

The finding that CF-PWV >12 m/s but not the continuous CF-PWV was associated with cognitive function seems to suggest that there is a threshold effect in this older population. This threshold was chosen because it has been recommended as a conservative estimate of significant alterations of aortic stiffness by the European Society of Hypertension and the European Society of Cardiology (26), although there are different opinions (27-29) . However, the absence of a significant association between the continuous CF-PWV and cognitive function does not ensure that the brain is protected when CF-PWV is below this cut-point. There are studies which found that the CF-PWV in continuous form was associated with cognitive function in middle-aged to older adults (12) and well-functioning older adults (13). The absence of a continuous effect could be related to our study population. As would be expected, in our older population-based cohort which included home-bound and nursing home residents, there was a high prevalence of arterial stiffness which may have prevented the detection of continuous effects. The distribution of cognitive test scores, some of which were skewed and truncated may also have limited our ability to detect continuous effects. Younger or healthier cohorts followed over time may be better able to detect continuous effects of arterial stiffness.

Our sensitivity analyses suggested that the effect of CF-PWV on cognitive function was largely independent of conventional CVD risk factors. The effects were not changed by excluding participants with CVD history, which suggests that the associations were not completely due to the increased risk of CVD disease. Because some antihypertensive medications may reduce arterial stiffness, we repeated the analysis by excluding participants on antihypertensive medications. The slightly increased effect sizes suggest that the associations with arterial stiffness might be attenuated by use of medications. Although the associations became statistically borderline non-significant, it was probably due to the decrease of sample size. When the model was adjusted for the duration of hypertension, the strength of the associations decreased slightly but largely remained, which suggests that the associations were unlikely to be simply downstream from hypertension. Therefore, increased arterial stiffness may operate through pathways in addition to hypertension, to decrease cognitive function. It has been suggested that the high pulsatility from the arterial tree may directly cause damage to small brain vessels (17, 18). In MRI studies, PWV predicted white matter brain atrophy, cerebral microbleeds and lacunar brain infarcts independent of conventional CVD risk factors (30, 31).

In contrast to CF-PWV, CR-PWV has not been extensively studied, and even less is known about its association with cognitive function. One patient-based study found that the CR-PWV was not statistically different between the dementia and control groups(35); our study is consistent with that report. CR-PWV measures the medium-sized muscular arteries (the brachial artery), which are different from the large elastic arteries (such as the aorta). Medium-sized muscular arteries may be able to compensate for the loss of compliance due to aging (36). Our study also found that CR-PWV was not correlated with age. Therefore, CR-PWV may not be a good marker for age-related arterial stiffness, and was not associated with cognitive function. Further studies are needed to understand the role of CR-PWV in the cardiovascular system and brain function.

Understanding the role of arterial stiffness in dementia may also be useful for developing dementia prevention strategies because arterial stiffness can be modified by interventions (3). Habitual exercise may improve vascular endothelial function, increase nitrous oxide bioavailability, and reduce oxidative stress, thus slowing down arterial aging (32). Treatments including anti-hypertensive and anti-diabetic medicines may decrease PWV independent of blood pressure reduction (33). Use of statins may also reduce arterial stiffness although the evidence has been inconclusive (34).

Our study had several strengths. It was a large population-based study. Pulse wave velocity was measured with a validated and widely-used device. Cognitive function was measured by multiple well-established tests on different cognitive domains. A wide range of CVD risk factors were collected and evaluated to assess the independent effect of PWV. All interviews and examinations were conducted using standardized protocols.

Our study also had limitations. The cross-sectional design provides limited evidence for causal inference, although it also avoids problems in longitudinal studies, such as loss to follow-up and regression to the mean. Secondly, about 20% of participants did not have PWV data which may be a source for bias. However, since these participants were older, less healthy, and had worse cognitive function, the bias would be toward null, which suggests that the associations in our study might be underestimated. Thirdly, some cognitive variables, especially the MMSE score, have values skewed toward the high end of the distribution, which may have limited measurement sensitivity in that range. Fourthly, although we have collected a variety of CVD risk factor data, we did not measure endothelial function. Finally, the small differences in the cognitive task performance found in our study may not be clinically significant.

In summary, our large population-based study found that carotid to femoral PWV greater than 12 m/s was associated with cognitive function in multiple domains in older adults. Carotid to radial PWV was not associated with cognitive performance. Our results suggest that arterial stiffness in large vessels is associated with worse cognitive function. Future longitudinal studies are needed to understand the role of arterial stiffness in age-related cognitive decline and dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the study population by the CF-PWV <12 m/s.

CF-PWV >12 m/s or not	No (n=952)	Yes (n=442)
Age (years, sd)	73.3 (6.4)	78.4 (7.5)
Male %	42.4	43.7
Education Years %		
<12	11.2	13.9
12	48.6	49.6
13-15	17.9	18.0
16+	22.3	18.5
Smoker %		
-current	9.0	4.8
-past	45.5	48.1
Heavy drinking %	24.0	28.7
Physical activity %	51.0	35.2
Hypertension %	61.4	75.8
CVD history %	17.2	23.4
Diabetes %	19.0	23.3
BMI (kg/m2)	30.7 (5.7)	30.0 (5.5)
Total cholesterol (md/dl)	193.3 (38.5)	191.8 (42.0)
HDL cholesterol (md/dl)	54.1 (16.7)	53.5 (15.3)
Hemoglobin A1C	5.9 (0.7)	5.9 (0.8)
Antihypertensive Medications.	65.1	77.1
Use of Aspirin	58.1	61.5
Use of Statins	46.2	49.7
Depression symptoms %	16.2	21.2
MMSE score	28.2 (1.8)	27.3 (2.7)
TMT-A score	45.2 (22.9)	53.5 (38.1)
TMT-B score	114.8 (58.3)	145.8 (70.3)
DSST score	43.1 (11.1)	38.3 (11.3)
AVLT score	25.6 (7.8)	22.2 (6.9)
VFT score	33.8 (11.8)	30.5 (11.3)

Table 2

High CF-PWV (>12 m/s) and the cognitive test scores.

	Age-sex-education adjusted model				Multivariable model			
	n	**coefficient**	**se**	**p**	**n**	**coefficient**	**se**	**p**
MMSE	1364	−0.32	0.12	0.01	1227	−0.31	0.11	0.005
TMT-A	1348	1.11	1.58	0.5	1215	−0.08	1.31	0.9
TMT-B	1314	8.89	3.39	0.009	1192	6.30	3.41	0.06
DSST	1331	−0.87	0.57	0.1	1205	−0.69	0.59	0.2
AVLT	1312	−1.21	0.41	0.003	1189	−1.10	0.43	0.01
VFT	1353	−1.23	0.67	0.07	1221	−1.17	0.72	0.1
Composite score	1262	−0.12	0.05	0.02	1150	−0.10	0.05	0.04

Multivariable model further adjusted for pulse rate, hemoglobin A1C, HDL cholesterol, hypertension, CVD history, smoking and drinking, and depression symptoms.

Table 3

High CR-PWV (>10.6 m/s) and the cognitive test scores.

	Age-sex-education adjusted model				Multivariable model			
	n	coefficient	se	p	n	coefficient	se	p
MMSE	1401	0.10	0.11	0.4	1258	0.10	0.10	0.3
TMT-A	1385	−1.47	1.48	0.3	1246	−1.63	1.22	0.2
TMT-B	1349	1.14	3.23	0.7	1222	0.70	3.18	0.8
DSST	1368	−0.42	0.55	0.4	1236	−0.25	0.55	0.6
AVLT	1348	0.09	0.39	0.8	1220	0.15	0.40	0.7
VFT	1390	0.68	0.63	0.3	1252	0.78	0.67	0.2
Composite score	1297	−0.01	0.05	0.9	1180	0.01	0.05	0.8

Multivariable model further adjusted for pulse rate, hemoglobin A1C, HDL cholesterol, hypertension, CVD history, smoking and drinking, and depression symptoms.