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Arterial Stiffness is Correlated with Cognitive Decline Independent of Silent Brain Ischemia

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Abstract

Objective: Arterial stiffness is a measure of cerebrovascular disease. We analyzed the association between arterial stiffness, cognitions and silent brain ischemia.

Methods: We performed a cross sectional study in 2055 neurologically normal subjects in brain checkup system. We estimated periventricular hyperintensity (PVH), white matter hyperintensity (WMH) and silent brain infarction (SBI) as silent brain ischemia in MRI with brachial-ankle pulse wave velocity (baPWV) as arterial stiffness. Kohs' block design test, Okabe's Intelligence Scale and frontal assessment battery (FAB) were assessed as measures of cognitive function.

Results: The baPWV was higher in PVH+(grade 2 and 3) and WMH+(grade 3) groups than in PVH- and WMH- groups ($p<0.01$). The baPWV was also higher in SBI group than in non SBI group ($p<0.001$). The baPWV was inversely correlated with Kohs test ($p<0.01$, $\beta=-0.066$) and FAB test ($p<0.01$, $\beta=-0.084$) independently after adjusted for age, education level, presence of PVH, WMH and SBI. The middle and high tertiles of baPWV were not correlated with silent brain ischemia after adjusted for age, and vascular risk factors.

Conclusions: The baPWV is not only a biomarker of arterial stiffness, but also index of cognitive impairment independent of silent brain ischemia.

Introduction

The marker for arterial stiffness, brachial-ankle pulse wave velocity (baPWV) is independently associated with silent ischemic brain lesions including white matter hyperintensity [1,2], silent brain infarction [3] and acute ischemic stroke [4,5]. Elevated baPWV reveals stiffened vascular wall caused by intracranial cerebral atherosclerosis, so it could be a biomarker for ischemic brain lesions [4,6]. Aortic PWV is also a prognostic factor for vascular dementia and is higher in vascular dementia than in Alzheimer disease, mild cognitive impairment and normal cognitive subjects [7,8]. It has been reported that baPWV is correlated with cognitive decline including memory disturbance, activity of daily living, visuospatial and executive function [8,9]. We examine baPWV, ischemic brain lesions in MRI and cognitive functions in our brain checkup system for 8 years, and analyzed the possibility of baPWV for biomarkers and predictors of brain functions. We also hypothesized that baPWV could be biomarkers for early diagnosis of dementia with or without brain ischemic lesions.

Materials and Methods

Subjects

We studied 2055 Japanese subjects (1145 males and 910 females) aged 27-92 years (mean, 61.1 ± 11.0 years) participated in the brain checkup system in the Shimane Institute of Health Science from January 2008 to June 2016. All the participants provided informed consent. They are all neurologically diagnosed normal by an experienced neurologist. Based on detailed medical interview and medical history taking, we excluded any history of neurologic diseases including cerebrovascular diseases, any history of psychiatric diseases such as depressive, drug abuse, or other psychiatric diseases, and use of medications affecting cognitive function. The checkup system includes MRI scans of the head, neuropsychological testing, blood tests and baPWV.

Magnetic resonance imaging and silent brain ischemia

Head MRIs were obtained using conventional pulse sequences for T2-weighted image, T1-weighted image, and fluid-attenuated inversion recovery (FLAIR) image in the transverse plane with a slice thickness of 7 mm by a 1.5-Tesla MRI (Symphony, Siemens). Silent brain infarction (SBI) was defined as a focal hyper intensity lesion 3 mm or large in diameter in the T2-weighted image corresponding to a hypointensity lesion in the T1-weighted image. Periventricular hyperintensity (PVH) were evaluated separately based on their distinct subcortical distributions and graded on a scale of 0 to 4 as described [10]. We defined grades 0 to 4 PVH as PVH-, grades 2 to 4 PVH as PVH+. We also defined deep and subcortical white matter hyperintensity (WMH) as grades 0 to 4 with Fazekas grading scale [11].

Measurement of baPWV

The brachial-ankle pulse wave velocity (baPWV) was measured by Form PWV/ABI: OMRON COLIN Co Ltd, Tokyo, Japan. This device simultaneously measures bilateral and posterior tibial arterial pulse waveforms and arterial blood pressure by the oscillometric method. The baPWV on each side were automatically calculated and the average values of the baPWV obtained bilaterally were used for the analysis.

Cognitive function

Okabe's intelligence scale (Okabe scale), which is a shortened and modified Wechsler Adult Intelligence Scale-Revised for the Japanese aged population, was used for assessing general intelligence, including orientation, semantic memory, calculation, forward and backward digit

span, and paired association memory [12]. The Kohs' block design test (Kohs test) is a popular bedside screening test of constructional function and reflects elderly's cognitive function. The subjects are shown cards with a variety of colored designs and ask to reproduce them using a set of colored blocks, yielding an intelligence quotient. The Kohs test assessed the visuospatial ability in addition to executive function [13]. And we assessed the frontal assessment battery (FAB) for frontal lobe function as it was previously reported by us [14].

Statistical analysis

The association between baPWV and demographics, vascular risk factors, MRI imaging finding with ischemic brain lesion and cognitive function was investigated using analysis of covariance and chi-squared test for categorical variables. We performed the analyses with baPWV levels categorized in tertiles of the baseline distribution. After adjusting for age, gender, hypertension, diabetes and hyperlipidemia, logistic regression analysis was used to determine the relationship between baPWV levels and the presence of silent brain infarctions, PVH and WMH. We defined PVH grades 0-1 as PVH- and grades 2-3 as PVH+; similarly, WMH grades 0-1 were defined as WMH- and grades 2-3 as WMH+. Multiple regression analysis is used to assess the statistical correlation between baPWV and cognitive tests, Okabe scale, Kohs test and FAB test adjusting for age, education level (years), presence of PVH, WMH and SBI. A value of $p<0.05$ was considered statistically significant.

Results

At first the baPWV is significantly positive correlated with age in our 2055 subjects, so we need to adjust for age while analyzing baPWV and any other factors ($r=0.605$, $p<0.0001$). In our 2055 participants, the value of baPWV ranged from 847 to 4405 cm/sec with a median of 1591cm/sec.

Table 1 shows that demographics, our participants' characteristics, vascular risk factors, and cognitive functions in three tertiles of PWV levels. The subjects with higher baPWV had a significantly higher systolic and diastolic pressure ($p<0.0001$). The frequency of vascular risk factors, hypertension, diabetes and hyperlipidemia were significantly higher in third tertile of baPWV level ($p<0.0001$). Furthermore, the difference of cognitive test including Okabe scale, Kohs test and FAB test was also statistically significant among three groups ($p<0.0001$).

Characteristics	Tertile of baPWV (cm/sec), mean (SD)			p Value
	1st tertile (n=680)	2nd tertile (n=689)	3rd tertile (n=686)	
Age, Year	52.5 (10.0)	62.4 (8.3)	68.2 (8.2)	p<0.0001
Gender, male, %	56	55.8	52.2	ns
Hypertension, %	13.3	34.4	55.5	p<0.0001
Systolic BP, mmHg	118.6 (13.9)	129.5 (14.6)	139.2 (16.6)	p<0.0001
Diastolic BP, mmHg	70.2 (10.4)	75.2 (10.4)	78.0 (11.5)	p<0.0001
Diabetes, %	4.8	9.4	14.7	p<0.0001
HbA1C, %	5.3 (0.5)	5.4 (0.5)	5.6 (0.8)	ns
Hyperlipidemia, %	36	50.5	47.3	p<0.0001
Total chlolesterol, mg/dl	208.8 (32.6)	214.6 (75.9)	208.2 (31.3)	p<0.05
Triglyceride, mg/dl	106.3 (73.8)	120.2 (74.0)	119.7 (70.5)	p<0.001
HDL cholesterol, mg/dl	64.2 (16.3)	63.5 (16.5)	62.8 (16.4)	ns
LDL cholesterol, mg/dl	120.5 (30.4)	122.8 (29.7)	118.5 (29.1)	p<0.05
Okabe scale	47.4 (6.7)	44.9 (6.7)	43.6 (7.3)	p<0.0001
Kohs test	111.0 (16.2)	101.2 (18.0)	95.1 (18.3)	p<0.0001
FAB test	16.5 (1.3)	16.1 (1.4)	15.6 (1.6)	p<0.0001

Table 1: Demographics, risk factors, magnetic resonance imaging findings and cognitive functions according to three tertiles of baPWV levels.
baPWV: Brachial-ankle pulse wave velocity (cm/sec); BP: Blood pressure; FAB: Frontal assessment battery

In table 2 the value of difference in three tertiles of PWV levels were shown by presence of silent brain infarction and grades of PWV or WMH. The baPWV was significant between 4 groups of PVH grades after adjusted for age ($F=3.605$, $p<0.01$). The baPWV in WMH grade 3 was significantly higher than WMH grade 0 ($p<0.01$), WMH grade 1 ($p<0.01$) and WMH grade 2 ($p<0.05$). The baPWV was significant between 4 groups of WMH grades after adjusted for age ($F=3.5873$, $p<0.01$). And it is significantly higher in SBI group than non SBI group after adjusted for age ($F=10.846$, $p=0.001$). As shown in table 3, the associations between the tertiles of baPWV and the presence of severe WMH (Fazekas grades 2 and 3) or silent brain infarctions were not statistically significant after adjusting for age, gender, hypertension, diabetes and hyperlipidemia.

After adjusted for age, the level of education (year), presence of PVH, WMH and SBI, the baPWV was inversely correlated with the IQ score of Kohs test ($p<0.01$, $\beta=-0.066$) and FAB test ($p<0.01$, $\beta=-0.084$) independently by multiple regression analysis (Table 4). Other cognitive tests, Okabe scale was not significantly correlated with baPWV. The associations between all of three cognitive tests and the presence of severe WMH (Fazekas grades 2 and 3) were not correlated. Otherwise silent brain infarctions were inversely correlated with Okabe scale ($p<0.05$, $\beta=-0.049$) and FAB test ($p<0.01$, $\beta=-0.060$) independently, and severe PVH (grades 2 and 3) is also inversely correlated with Kohs test ($p<0.0001$, $\beta=-0.074$) independently by multiple regression analysis (Table 4).

Discussion

The aortic stiffening is caused by various phenomena, including breaks in elastin fibers, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis and calcifications within the arterial wall [15]. The measurement of PWV is generally accepted as the most simple, non-invasive method to determine arterial stiffness. The advantage of the regional evaluations of arterial stiffness by peak wave velocity is that they are based on direct measurements of parameters strongly linked to arterial wall stiffness [16]. The presence of arteriosclerosis or lipohyalinosis of

Silent brain lesions	baPWV(cm/sec), mean (SD)	Tertile of baPWV (cm/sec)			
		1 (n=680)	2 (n=689)	3 (n=686)	
Grades of PVH					Total
PVH grade 0	1555(508)	533	422	297	1252
PVH grade 1	1744(377)	113	162	218	493
PVH grade 2	1843(355)	30	86	134	250
PVH grade 3	1989(571)	4	19	35	58
PVH grade 4	2068(376)	0	0	2	2
Grades of WMH					Total
Fazekas grade 0	1534(540)	467	329	217	1013
Fazekas grade 1	1695(356)	164	234	247	645
Fazekas grade 2	1838(372)	45	117	191	353
Fazekas grade 3	2081(578)	4	9	30	43
Fazekas grade 4	2205	0	0	1	1
SBI					Total
SBI Negative	1622(363)	668	658	604	1930
SBI Positive	1953(422)	12	31	82	125

Table 2: Presence and grading of three silent brain lesions in MRI according to three tertiles of baPWV levels.
PVH: Periventricular hyperintensity; WMH: White matter hyperintensity with Fazekas grade; SBI: Silent brain infarction; baPWV: brachial-ankle pulse wave velocity (cm/sec)

	Presence of grade 2 and 3 PVH (n=310)			Presence of grade 2 and 3 WMH (n=397)			Presence of SBI (n=125)		
baPWV level	n	OR(95% CI)	P value	n	OR(95% CI)	P value	n	OR (95%CI)	p value
1st tertile	34	Reference		49	Reference		12	Reference	
2nd tertile	105	0.62 (0.39-0.98)	0.04	126	0.93 (0.61-1.40)	ns	31	0.72 (0.35-1.47)	ns
3rd tertile	171	0.99 (0.73-1.33)	ns	222	0.95 (0.71-1.27)	ns	82	0.71 (0.44-1.13)	ns

Table 3: Association between baPWV levels in three tertiles and the presence of silent brain ischemia including PVH, WMH and SBI.
PVH: Periventricular hyperintensity; WMH: White matter hyperintensity with Fazekas grades; SBI: Silent brain infarction; baPWV: brachial-ankle pulse wave velocity; OR: odds ratio, CI: Confidence interval, ns: Not significant

Cognitive function	Okabe scale		Kohs test		FAB test	
	β	p value	β	p value	β	p value
Age	-0.242	<0.0001	-0.438	<0.0001		<0.0001
Education	0.181	<0.0001	0.148	<0.0001	0.141	<0.0001
PVH grade 2 and 3	-0.043	0.06	-0.074	<0.0001	-0.035	0.118
WMH Fazekas grade 2 and 3	0.006	0.802	0.018	0.406	0.033	0.15
Presence of SBI	-0.049	0.024	-0.037	0.055	-0.06	0.005
baPWV	-0.045	0.087	-0.066	0.005	-0.084	0.001
1st tertile of baPWV (n=680)	47.4 (6.7)		111.0 (16.2)		16.5 (1.3)	
2nd tertile of baPWV (n=689)	44.9 (6.7)		101.2 (18.0)		16.1 (1.4)	
3rd tertile of baPWV (n=686)	43.6 (7.3)		95.1 (18.3)		15.6 (1.6)	

Table 4: After adjusted for age, the level of education, presence of PVH, WMH and SBI, the baPWV was inversely correlated with the IQ score of Kohs test and FAB test in multiple regression analysis. The mean (SD) of three cognitive tests are also presented according to three tertiles of baPWV levels.
PVH+: Periventricular hyperintensity grade 2-3; WMH+: White matter hyperintensity with Fazekas grade 2-3; SBI: Silent brain infarction; baPWV: brachial-ankle pulse wave velocity (cm/sec)

cerebral small vessels contributes to chronic hypoperfusion of the white matter [8]. Arterial stiffness promotes microvascular disease including impaired cerebral perfusion, lacunar infarctions and cerebral white matter lesions [17]. The measurement of aortic stiffness integrating the alterations of the arterial wall may also reflect parallel lesions present at the site of cerebral vascular and coincides with the prevalence and severity of cerebral white matter lesions [17]. Our results reveals that elevated aortic stiffness in peripheral artery could predict intracranial arteriosclerosis and finally could cause cognitive decline in categorized tertiles analysis in table 1. Although the baPWV and vascular risk factor, age is significantly correlated, we could not find correlation between baPWV and three patterns of silent brain ischemia after adjusted these factors in table 3. Our result is equal to Matsumoto's report about baPWV being not associated with SBI in multivariate analysis [6]. The baPWV analysis could not be an effective predictor of silent brain ischemia as much as we expected.

Many reports are reported about association aortic stiffness and cognitive decline [8,9,18-20]. Their conclusions are almost early intervention to prevent arterial stiffness could contribute to the delaying cognitive decline. Higher PWV are related to decline on the Mini-Mental State Examination (MMSE) in healthy elderly or persons who had memory deficits and are caused by impaired microcirculatory damage in brain due to hypertension, hyperlipidemia, elevated blood coagulation which are related to the atherosclerotic process [9,21,22]. It is also inversely associated with functional outcome in acute ischemic stroke patients [5]. Waldstein et al. [18] reported that higher pulse wave velocity exhibited prospective decline on tests of verbal learning and delayed recall, nonverbal memory and working memory in non-demented, stroke-free persons. In a prospective population-based cohort of the Rotterdam study about 2767 persons, Poels et al. [20] reported that participants with high PWV showed poorer performance only in the Stroop test, but not showed no decline in other cognition with word fluency test. It is partially equals to our results in preserved verbal IQ and study size of participants [20].

For the purpose of estimating the association between arterial stiffness and the Intelligence Quotient with verbal IQ (VIQ) or performance IQ (PIQ), we utilized Okabe's intelligence scale for VIQ and Kohs' test for PIQ. We did not analyze MMSE that is influenced by the level of education [23]. The baPWV is highest in vascular dementia than other groups of Alzheimer disease, mild cognitive impairment and normal cognitive subjects [8]. We thought that baPWV could be a predictive examination associated with cognitive test, especially, performance IQ and frontal lobe function. It is not clear why performance IQ test is correlated with aortic stiffness in our participants. We could find a few reports about the association between arterial stiffness and nonverbal memory indicated by performance IQ. Tasmoc and Elias reported that PWV was a predictor for cognitive impairment measured by Trail Making Test Part-A assessing attention, perceputo-motor speed, visuomotor scanning and executive function [19,24]. Waldstein also reported that higher PWV displayed decline in nonverbal memory with the Benton Visual Retention Test [18]. Aortic stiffness might have an influence on brain lesions regulating nonverbal memory widely. The presence of SBI and PVH declined general intelligence, performance IQ and frontal lobe function. This results are very similar to our previous reports about same study in brain checkup system [14,25]. We need prospective study about arterial stiffness and performance IQ while aging and progression of intracranial atherosclerosis.

Study limitations

There were several limitations of our study. Our study is only cross sectional analysis, so it would not be clear in prognosis of elevated baPWV. We need prospective study about association between arterial stiffness analyzed by baPWV and cognitive function and ischemic brain lesions in our brain checkup system.

Conclusion

The brachial-ankle pulse wave velocity (baPWV) is not only a biomarker of arterial stiffness, but also index of cognitive impairment, especially performance IQ and frontal lobe function independent of silent brain ischemia. Intervention to prevent arterial stiffness may be effective in delaying cognitive dysfunction and baPWV could be a biomarker for early diagnosis of dementia.

Conflict of Interest

The authors confirm that this chapter contents have no conflict of interest.

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