Cardio-Ankle Vascular Index as a Predictor of Cognitive Impairment in Community-Dwelling Elderly People: Four-Year Follow-Up

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Key Words

Cardio-ankle vascular index • Cognitive decline • Clinical aspects • Elderly

Abstract

Background/Aim: The relation between markers of generalized atherosclerosis and cognitive impairment in old age is controversial. The aim of the study was to evaluate the cardio-ankle vascular index (CAVI) as a predictor of longitudinal changes in cognitive function in older individuals. **Methods:** We evaluated the cognitive function in elderly people with high (AS(+)) and low (AS(–)) values of CAVI each year over 4 years. **Results:** The changes in the Hasegawa Dementia Scale Revised (HDS-R) and the mini-mental state examination (MMSE) at 4 years were significantly larger in the AS(+) group (AS(+) vs. AS(–) = -1.8 ± 4.4 vs. 0.3 ± 2.8 points and -1.1 ± 3.0 vs. 0.1 ± 2.3 points, $p = 0.008$ and 0.03 , respectively). The annual changes in the HDS-R were significantly decreased from baseline at 1 year later to 4 years later in AS(+) (baseline vs. 1, 2, 3, 4 years = 26.5 vs. 25.0, 25.5, 25.7, 24.8 points, $p < 0.001$); in comparison, the annual changes in MMSE significantly decreased from the baseline over the 4 years in AS(+) (baseline vs. 1, 2, 3, 4 years = 26.8 vs. 26.2, 25.8, 26.4, 25.7

points, $p = 0.002$). **Conclusion:** The results of this study suggest that elderly people with a high CAVI value are at a greater risk of cognitive decline.

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Introduction

Cognitive dysfunction is an important problem related to the activity of daily living and mortality in elderly people [1]. Evidence suggests that the presence of symptomatic cardiovascular disease, including myocardial infarction and stroke as well as peripheral artery disease, is associated with cognitive impairment in elderly people [2–4]. However, many individuals with significant atherosclerotic disease remain asymptomatic in terms of coronary or cerebrovascular events [5]. The relationship between markers of generalized atherosclerosis, including subclinical disease, and cognitive impairment in old age is controversial. A longitudinal public health challenge is, therefore, to identify people with a high risk of cognitive impairment who might benefit from preventive, therapeutic, or supportive measures. Results of earlier studies have demonstrated that arterial stiffness,

Fig. 1. Assessment and follow-up of the study. A total of 117 people participated in this study. Fifty-four subjects (11.9%) died and 8 subjects (6.8%) dropped out during follow-up. Finally, 95 people were included in the analysis. ASO = Arteriosclerosis obliterans.

measured as the brachial-ankle pulse wave velocity (baPWV), is associated with lower cognitive performance [6, 7]. Results of several cross-sectional studies have indicated that the baPWV correlates with cognitive function and is affected by blood pressure. Measurement of baPWV is affected by stress as a result of the pressurization of 4 limbs with cuffs because the regions include muscular blood vessels of upper and lower limbs [8]. The blood pressure might participate as a confounding factor in the relationship between baPWV and cognitive function in a cross-sectional study. Therefore, to evaluate a parameter of arterial stiffness which is unaffected by blood pressure for that parameter's connection to cognitive function, it is important to investigate the relationship between arterial stiffness itself and cognitive function in elderly people. We developed a novel blood pressure-independent arterial stiffness parameter: the cardio-ankle vascular index (CAVI) [9]. It is superior to baPWV as an index of arterial stiffness [9, 10] because it clarifies measurement regions, indicates the blood pressure-independent characteristic function of blood vessels, and minimizes the effect on circulatory dynamics throughout the whole body. Furthermore, CAVI has simplicity and good reproducibility. The aim of the present

study was to evaluate CAVI as a predictor of longitudinal changes in cognitive function in older individuals reporting memory problems. We evaluated the cognitive function among high and low values of CAVI each year over 4 years in elderly people.

Methods

Subjects

Data were collected in August 2004 as part of a comprehensive health examination conducted in Tosa town, a western Japanese town. Based on a long-term care insurance program launched in 2004, the healthcare center of Tosa town promotes comprehensive health examinations for residents aged 75 years and older. Patients with Alzheimer's disease, cerebrovascular dementia, symptomatic cerebral infarction, myocardial infarction, or symptomatic myocardial ischemia were excluded. Written informed consent was obtained from all 121 subjects who participated in this study. A laboratory examination and a self-administrated questionnaire were used to collect data on the years of education, lifetime smoking history, and history of past illness. A laboratory examination in a fasting state was performed by the same company over the 5 years (BML Inc., Saitama, Japan). The CAVI was measured between both arms and ankles in a supine position using a VaSera CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) [8]. We divided the subjects into 2 groups based on the

Table 1. Baseline characteristics

Variable	AS(–) (n = 49)	AS(+) (n = 46)	p value
Age, years	78.2 ± 3.3	80.9 ± 4.7	0.01
Female ratio, %	70.4	67.4	0.83
Body mass index	23.2 ± 3.0	23.6 ± 3.3	0.58
SBP, mm Hg	152.8 ± 20.5	156.3 ± 22.2	0.43
DBP, mm Hg	86.3 ± 8.6	90.1 ± 10.0	0.03
Heart rate, beats/min	62.6 ± 9.1	68.8 ± 15.4	0.02
Hemoglobin, g/dl	12.7 ± 1.3	13.1 ± 1.3	0.25
Albumin, g/dl	4.3 ± 0.2	4.3 ± 0.3	0.69
ALT, U/l	23.4 ± 5.7	24.8 ± 8.6	0.36
AST, U/l	16.7 ± 6.5	18.7 ± 9.2	0.22
Gamma-GTP, U/l	21.4 ± 10.8	36.0 ± 72.5	0.17
Total cholesterol, mg/dl	196.4 ± 27.9	197.4 ± 32.0	0.87
Triglyceride, mg/dl	127.3 ± 78.9	144.1 ± 64.3	0.26
HDL, mg/dl	58.7 ± 17.7	50.2 ± 12.8	<0.01
FPG, mg/dl	112.7 ± 21.2	111.8 ± 25.8	0.86
HbA1c, %	5.3 ± 0.6	5.3 ± 0.4	0.85
Creatinine, mg/dl	0.79 ± 0.17	0.81 ± 0.19	0.69
Urinary acid, mg/dl	5.4 ± 1.3	5.7 ± 1.4	0.23
HDS-R, points	26.5 ± 1.0	26.4 ± 0.9	0.81
MMSE, points	26.8 ± 2.5	26.9 ± 2.6	0.89
Education, years	9.5 ± 0.2	9.6 ± 0.3	0.90
Up and Go, s	14.4 ± 4.6	14.9 ± 5.3	0.60
FR, cm	27.9 ± 7.4	26.3 ± 7.4	0.28

Variables expressed as mean ± SD. SBP = Systolic blood pressure; DBP = diastolic blood pressure; ALT = alanine transaminase; AST = aspartate transaminase; HDL = high-density lipoprotein cholesterol; Gamma-GTP = gamma-glutamyl transpeptidase; FPG = fasting plasma glucose. Statistical analysis was conducted using the Student's t test between the AS(–) group and AS(+) group.

CAVI value at baseline. Subjects with a CAVI at baseline ≥10 were defined as the AS(+) group, and those with a CAVI <10 as the AS(–) group. Four subjects were excluded from the study as the CAVI could not be measured because of arteriosclerosis obliterans (fig. 1).

Neuropsychological Assessment

Trained physicians administered global cognitive function tests, including the Japanese mini-mental state examination (MMSE) and the Hasegawa Dementia Scale Revised (HDS-R) [11], and a physical function test, including the Up and Go [12] and functional reach (FR) [12] tests, to each subject in both groups every year during the period 2004–2008. The Up and Go test is a simple measure of physical mobility and demonstrates the subject's balance, gait speed, and functional ability. A lower time score indicates better physical mobility. The FR test is used to evaluate balance and represents the maximal distance a subject can reach forward beyond arm's length while maintaining a fixed base of support in the standing position. A higher score indicates better balance.

Statistical Analysis

Paired t test, two-way ANOVA, and logistic analysis were used for analysis by JMP (SAS Institute Inc., Cary, N.C., USA). A p value <0.05 was considered statistically significant.

Results

A total of 117 people participated in the study. Six subjects in the AS(–) group and 8 subjects in the AS(+) group died during follow-up. The mortality between the 2 groups in this study was not statistically significant (AS(+) vs. AS(–) = 13.8 vs. 9.8%, $p = 0.82$). One subject died in 2004, 4 subjects died in 2005, 5 subjects died in 2006, 3 subjects died in 2007 and 1 subject died in 2008. Forty-nine subjects (83.0%) in the AS(+) group and 46 subjects (79.3%) in the AS(–) group were included in the analysis (fig. 1). Baseline characteristics are presented in table 1. The mean age, the diastolic blood pressure and the heart rate were significantly higher at baseline in the AS(+) group (AS(+) vs. AS(–) = 78.2 ± 3.3 vs. 80.9 ± 4.7 years, $p = 0.02$; 86.3 ± 8.6 vs. 90.1 ± 10.0 mm Hg, $p = 0.03$; 62.6 ± 9.1 vs. 68.8 ± 15.4 beats/min, $p = 0.02$, respectively). The high-density lipoprotein cholesterol was significantly lower in the AS(+) group (58.7 ± 17.7 vs. 50.2 ± 12.8 mg/dl, $p < 0.01$). The HDS-R and MMSE at baseline did not differ between both arms (AS(+) vs. AS(–) = 26.5 ± 1.0 vs. 26.4 ± 0.9 points, 26.8 ± 2.5 vs. 26.9 ± 2.6 points, respectively). Two-way ANOVA showed that the HDS-R score in the AS(+) group decreased significantly from baseline at 1 year later to 4 years later (baseline vs. 1, 2, 3, 4 years later = 26.5 ± 0.9 vs. 25.0 ± 1.0 , 25.5 ± 1.1 , 25.7 ± 1.3 , 24.8 ± 1.3 points, $p < 0.001$) (fig. 2a). The MMSE score in the AS(+) group decreased significantly from the baseline over 4 years (baseline vs. 1, 2, 3, 4 years later = 26.8 ± 0.7 vs. 26.2 ± 0.9 , 25.8 ± 1.0 , 26.4 ± 1.1 , 25.7 ± 1.0 points, $p = 0.002$) (fig. 2b). The annual changes in HDS-R and MMSE at 4 years were, respectively, significantly larger in the AS(+) group (AS(+) vs. AS(–) = -1.8 ± 4.4 vs. 0.3 ± 2.8 points, $p = 0.008$ and -1.1 ± 3.0 vs. 0.1 ± 2.3 points, $p = 0.03$) (fig. 2a, b). A stepwise regression analysis showed that the AS(+) state at baseline was independently related with the quantity of HDS-R change after 4 years [standardized β value = 0.24, 95% confidence interval (CI) 0.07–1.77, $p = 0.03$] (table 2). A stepwise regression analysis showed that the FR test, body mass index, triglycerides, heart rate, fasting plasma glucose and glycosylated hemoglobin (HbA1c) at baseline were independently related to the quantity of MMSE change after 4 years. The quantity of MMSE change

Fig. 2. Annual change of cognitive function during 4 years' follow-up between the AS(+) group and AS(-) group. **a, b** Annual points of HDS-R and MMSE between the AS(+) group and AS(-) group. The x axis represents the time dimension and the y axis represents the cognitive function scale: HDS-R scale (**a**) and

MMSE scale (**b**). Circles with a bar represent the mean with 95% CI (lower-upper). Two-way ANOVA was used for the statistical analyses. * $p < 0.05$ [AS(+) group vs. AS(-) group]; † $p < 0.05$ (vs. baseline); ‡ $p < 0.01$ (vs. baseline).

Table 2. Stepwise regression analysis of baseline values on longitudinal change in cognitive function

Variables	HDS-R change			MMSE change		
	β	95% CI	p value	β	95% CI	p value
Age	0.11	-0.10, 0.29	0.34	0.11	-0.07, 0.21	0.32
Female	0.02	-1.08, 1.21	0.91	-0.23	-1.46, 0.11	0.09
Body mass index *	0.18	-0.06, 0.50	0.11	0.27	0.04, 0.42	0.02
SBP	-0.25	-0.09, 0.00	0.07	-0.23	-0.06, 0.00	0.08
DBP	0.23	-0.02, 0.20	0.11	0.15	-0.03, 0.12	0.28
Heart rate*	-0.10	-0.09, 0.04	0.40	-0.27	-0.10, -0.01	0.01
Hemoglobin	-0.22	-1.50, 0.21	0.14	-0.27	-1.15, 0.01	0.05
Albumin	-0.12	-5.58, 1.91	0.33	-0.05	-3.03, 1.98	0.69
ALT	-0.30	-0.37, 0.06	0.15	0.17	-0.08, 0.21	0.40
AST	0.36	-0.01, 0.36	0.07	-0.19	-0.19, 0.06	0.31
Gamma-GTP	0.06	-0.02, 0.03	0.74	0.17	-0.00, 0.03	0.32
T-chol	-0.18	-0.05, 0.01	0.15	0.11	-0.01, 0.03	0.35
Triglycerides*	-0.12	-0.02, 0.01	0.44	-0.45	-0.03, 0.00	0.00
HDL	0.00	-0.07, 0.07	0.99	-0.11	-0.07, 0.03	0.42
FPG*	-0.21	-0.08, 0.01	0.09	-0.24	-0.06, 0.00	0.04
HbA1c*	0.17	-0.75, 3.35	0.21	0.26	0.07, 2.91	0.04
Creatinine	-0.05	-6.78, 4.63	0.71	0.06	-0.43, 0.77	0.57
Urinary acid	-0.07	-0.88, 0.50	0.58	-0.15	-0.77, 0.17	0.21
Education	0.10	-4.40, 9.70	0.36	0.06	-4.08, 7.03	0.53
Up and Go	-0.15	-0.28, 0.05	0.17	-0.07	-0.15, 0.08	0.50
FR*	-0.12	-0.18, 0.06	0.32	-0.40	-0.23, -0.06	0.00
AS(+)**	0.24	0.07, 1.77	0.03	0.25	-0.01, 1.22	0.05

SBP = Systolic blood pressure; DBP = diastolic blood pressure; ALT = alanine transaminase; AST = aspartate transaminase; Gamma-GTP = gamma-glutamyl transpeptidase; T-chol = total cholesterol; HDL = high-density lipoprotein cholesterol; FPG = fasting plasma glucose; β = standardized regression coefficient. Stepwise regression analysis was used between the quantity of cognitive change and the baseline value. * $p < 0.05$ of MMSE, ** $p < 0.05$ of HDS-R.

showed the strongest correlation with the FR test (standardized β value = 0.40, 95% CI 0.06–0.23, $p < 0.01$). The AS(+) state at baseline tended to relate with the quantity of MMSE change, but the relationship was not statistically significant.

Discussion

In the current sample of community-dwelling elderly people who were free of symptomatic vascular disease and dementia, the high CAVI value group, AS(+), showed a greater cognitive decline than the lower CAVI value group, AS(–). The mechanism leading to the association between the CAVI and cognitive function is uncertain. However, since the CAVI is a marker of functional and structural change in the arterial vessels [9], possible explanations can be proposed based on vessel wall pathology and the pathway to cognitive decline. High brain artery stiffness is associated with white matter lesions; these are common in vascular-related cognitive decline and are generally considered to be a consequence of chronic ischemia associated with microvessel lesions [13]. The 2 potent pathological mechanisms underlying atherosclerosis might impart an effect on cognitive function. First, the blood-brain barrier is disrupted in early atherosclerotic patients via the decreasing endothelial function. Therefore, neurotoxins and other substances might easily influence losses in cognitive abilities [14]. Second, the diminished delivery of oxygen resulting from reductions in blood flow is another possible mechanism by which atherosclerosis might affect cognition

[15]. Chronic cerebral hypoperfusion might precede and contribute to the onset of cognitive dysfunction and dementia in animal models [16]. Our stepwise regression showed that atherosclerotic disease and cognitive impairment share common generic or environmental risk factors, such as diabetes mellitus, obesity and dyslipidemia.

Moreover, our data showed that the HDS-R decreased more remarkably than the MMSE after follow-up. In fact, the HDS-R was more robust to demographic influences than the MMSE because it has measures for assessing frontal function and higher relative weight of memory than the MMSE and has added or strengthened measures examining the cognitive domains that are known to be impaired early in the development of dementia [11, 17]. Subjects of the present study were selected specifically as community-dwelling people without dementia. Therefore, the HDS-R might show a more remarkable decline than the MMSE. From a different perspective, the MMSE annual changes strongly influenced motor behavior, represented here as FR. The MMSE contains performance tests such as visuospatial ability and praxis tests that can be administered to disabled elderly people who have motor impairments [17]. Consequently, the FR was diminished in both the AS(+) and AS(–) groups equally with aging. The cognitive discrepancy between the AS(+) and AS(–) groups assessed using MMSE might be influenced by the motor impairment. In conclusion, the results of this study support the hypothesis that elderly people with a high CAVI value are at a greater risk of cognitive decline.

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