Original Article

Arterial Stiffness Predicts Cognitive Decline in Japanese Community-dwelling Elderly Subjects: A One-year Follow-up Study

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Aim: The purpose of this study was to determine whether arterial stiffness can be used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects.

Methods: A total of 103 Japanese community-dwelling elderly patients joined this study. Information regarding the age, height, weight, gender and past medical history of each participant was obtained. Additionally, arterial stiffness was determined according to the cardio-ankle vascular index (CAVI), and the cognitive function was assessed with the Mini-Mental State Examination (MMSE). One year later, we performed the MMSE in the same subjects. After dividing the cohort according to the 80th percentile of the CAVI (normal and arterial stiffness [AS] groups), we examined whether the degree of cognitive decline, as determined using the pre- and post-MMSE, was significantly different based on the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE scores.

Results: Of the 103 subjects who participated in the pre-data collection, 74 (38 men and 36 women, 73.4 ± 4.0 years) joined the post-data collection. We found a significant difference in the change in the post-MMSE scores between the normal and AS groups (pre-MMSE: normal group [27.4 ± 2.1] and AS group [26.9 ± 2.4] and post-MMSE: normal group [27.2 ± 2.1] and AS group [25.5 ± 2.3], $F=5.95$, $p=0.02$). For each domain of the MMSE, the changes in MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) and MMSE-language ($F=4.32$, $p=0.04$) were significantly different according to an ANCOVA.

Conclusions: We found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects regardless of the initial level of the global cognitive function. This finding indicates the potential use of the degree of arterial stiffness as an indicator for preventing or delaying the onset of dementia in the elderly.

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Key words: Arterial stiffness, Cognitive impairment, Elderly, Dementia

Introduction

Dementia is a serious issue, especially in community-dwelling elderly subjects¹. Thirty-five million people worldwide suffered from dementia in 2012

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according to the World Health Organization. Approximately 48% of patients with Alzheimer's disease (AD), the most common form of dementia, are estimated to live in Asia, and this percentage is expected to increase to 59% by 2050². Elderly people with dementia are typically frail due to their poor mobility and body composition, and the transitional stage between normal aging and AD, called mild cognitive impairment (MCI), results in frailty³, depression⁴, lower levels of physical activity¹ and higher mortality⁵. Preventing cognitive decline is therefore crucial.

Of risk factors for cognitive decline, cardiovascular risk factors have received more attention in recent years^{6, 7}. High blood pressure⁸, dyslipidemia⁸, obesity⁹ and diabetes mellitus⁹ have been proposed to be risk factors for cognitive decline. Among these factors, arterial stiffness is a comparatively easy-to-modify risk factor in community-dwelling elderly subjects. Madden *et al.* reported that three months of aerobic training reduces the degree of multifactorial arterial stiffness without generating any significant improvements in aerobic fitness, weight, BMI, waist-to-hip ratio or blood pressure in community-dwelling older individuals¹⁰. Additionally, previous studies have demonstrated the effectiveness of antihypertensive agents in improving arterial stiffness in both short- and long-term trials¹¹. Community-dwelling elderly can improve their arterial stiffness; therefore, focusing on treating arterial stiffness may be effective for preventing cognitive decline.

Most older adults with MCI live in the community, and more than half of MCI cases progress to dementia within five years¹². Therefore, a desired goal is the early detection of cognitive decline, especially in the community-dwelling elderly. When evaluating the degree of arterial stiffness in community-dwelling elderly subjects, the most important property is the ease of measurement. Arterial stiffness is one of the most easily measured vascular risk factors in community-dwelling elderly patients due to its non-invasive nature; therefore, it can be used as a predictor of cognitive decline in this population. Previous studies have also shown arterial stiffness to be a predictor of cognitive decline. However, the subjects in these studies were not elderly individuals living in the community^{13, 14}. Additionally, other authors have reported that they were unable to validate arterial stiffness as an independent risk factor for cognitive decline, as measured according to the global cognitive function using the Mini-Mental State Examination (MMSE)¹⁵⁻¹⁷. Yamamoto *et al.* reported a relationship between the cognitive function and arterial stiffness determined according to the CAVI in community dwelling elderly¹⁸, although the mean age was approximately 80 years, which is a bit high considering the mean age of community-dwelling elderly individuals in Japan. It may be more important to focus on healthier and younger older adults when discussing community-dwelling elderly¹⁹. The efficacy of arterial stiffness as a predictor of cognitive decline, especially in community-dwelling elderly patients, is less well investigated⁴.

The purpose of this study therefore was to address whether the degree of arterial stiffness can be

used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects. We used the CAVI to assess arterial stiffness, as this parameter was found to significantly correlate with cognitive decline in a cross-sectional study^{18, 19}.

Methods

Participants

Participants were recruited for this study through local press that requested healthy community-dwelling volunteers 65 years of age or older, and data collection was performed on two occasions: November 2012 (pre-data collection) and November 2013 (post-data collection). Interviews were conducted to exclude participants from both data collections based on the following exclusion criteria: severe cardiac, pulmonary or musculoskeletal disorders; comorbidities associated with a higher risk of falls, such as Parkinson's disease or stroke; and the use of psychotropic drugs. Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995 during both data collection periods. The study protocol was approved by the ethics committee of Kyoto University Graduate School of Medicine.

Measurements — Pre-data Collection

Demographic Data

Each patient's age, height, weight, gender, past medical history (cardiovascular disease, hypertension, diabetes mellitus and hyperlipidemia), smoking status (number of cigarettes smoked per day and total number of years smoked) and educational background (elementary school, junior high school, high school, career college or university) were obtained as demographic data. All data were collected at the first data collection time point. We directly asked about each participant's age and gender and measured their height and weight using standardized height and weight scales.

Arterial Stiffness

The degree of arterial stiffness was determined based on the CAVI using the VaSera-1500 device (Fukuda Denshi Co., Ltd., Tokyo, Japan). The details of this procedure have been described previously^{20, 21}. After the participants had rested for five minutes in the sitting position, we obtained these measurements as previously described. Higher CAVI values indicate a higher degree of arterial stiffness. The measurements were obtained once, and the mean values of the right

Table 1. Baseline characteristics and post-MMSE scores in the study population

	All (<i>n</i> = 74)		<i>p</i>
	Normal group <i>n</i> = 59	AS group <i>n</i> = 15	
Demographic data			
Age, year	72.8 ± 3.8	76.1 ± 3.6	< 0.01
BMI, kg/m ²	23.2 ± 2.6	23.2 ± 3.2	0.99
Gender, male	28 (47.5%)	10 (66.7%)	0.25
Mean CAVI	8.83 ± 0.61	10.6 ± 0.51	< 0.01
Cognitive function			
Pre-MMSE	27.4 ± 2.1	26.9 ± 2.4	0.40
Post-MMSE	27.2 ± 2.0	25.5 ± 2.3	< 0.01
Pre-MMSE (orientation)	9.6 ± 0.6	9.7 ± 0.5	0.89
Post-MMSE (orientation)	9.7 ± 0.7	9.7 ± 0.5	0.89
Pre-MMSE (registration)	2.9 ± 0.4	3.0 ± 0.0	0.53
Post-MMSE (registration)	2.9 ± 0.3	3.0 ± 0.0	0.49
Pre-MMSE (attention and calculation)	3.2 ± 1.7	2.9 ± 1.8	0.55
Post-MMSE (attention and calculation)	3.4 ± 1.7	2.3 ± 1.5	0.03
Pre-MMSE (recall)	2.6 ± 0.6	2.4 ± 0.8	0.30
Post-MMSE (recall)	2.5 ± 0.6	2.4 ± 0.7	0.69
Pre-MMSE (language)	8.9 ± 0.3	8.9 ± 0.4	0.73
Post-MMSE (language)	8.7 ± 0.5	8.2 ± 1.3	0.15
Comorbidities			
Cardiovascular disease	6 (10.2%)	4 (26.7%)	0.11
Hypertension	23 (39.0%)	8 (53.3%)	0.39
Diabetes mellitus	5 (8.5%)	4 (26.7%)	0.08
Hyperlipidemia	9 (15.3%)	2 (13.3%)	1.00
Brinkman index	0 (0-800)	0 (0-400)	0.63
Educational background			n.s.
Elementary school	0 (0.0%)	1 (6.7%)	
Junior high school	16 (27.1%)	4 (26.7%)	
High school	35 (59.3%)	9 (60.0%)	
Career college	3 (5.1%)	0 (0.0%)	
University	5 (8.5%)	1 (6.7%)	

Mean CAVI = mean value of the right and left CAVI scores. The mean ± SD is shown for age, BMI, mean CAVI and pre- and post-MMSE. n (%) is shown for gender, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia and educational background. The median (25% quartile-75% quartile) is shown for the Brinkman index. AS: arterial stiffness; n.s.: not significant.

and left CAVI scores for each patient were used for the analysis¹⁹⁾.

Cognitive Function Measurements

The cognitive function was assessed using the Mini-Mental State Examination (MMSE)²²⁾. The MMSE is a short screening test that consists of the following five areas for detecting cognitive impairment: orientation, registration, attention and calculation, recall and language. The scores range from 0 to 30, with higher scores indicating better cognitive performance. The MMSE was performed at both the pre-

and post-data collection time points.

Measurements—Post-data Collection Cognitive Function Measurements

One year later, the cognitive function was also assessed using the MMSE²²⁾. We performed the MMSE using the same inclusion and exclusion criteria as that used at the pre-data collection time point.

Statistical Analysis

The patients were divided into two groups based on the 80th percentile of the CAVI values: the normal

Fig. 1. Two-way analysis of variance showing the differences in the changes in the post-MMSE scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.95$, $p=0.02$).

and arterial stiffness [AS] groups. We analyzed the differences between these two groups using the unpaired t -test for age, body mass index (BMI), mean CAVI values on both sides and the pre- and post-MMSE scores (total score and scores for each domain), the χ^2 test for gender, past medical history and educational background and the Mann Whitney U -test for the Brinkman index (number of cigarettes smoked per day $\times$ total number of years smoked). A repeated measures two-way analysis of covariance (ANCOVA) was used to analyze whether the degree of cognitive decline determined according to the pre- and post-MMSE scores (total score and scores for each domain) differed significantly according to the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE score. A p value of <0.05 was considered to be statistically significant for all analyses.

Results

In total, 74 individuals (38 men and 36 women, 73.4 ± 4.0 years) participated in both data collection events. Of these individuals, none were excluded. We assigned 59 elderly individuals (28 men and 31 women) to the normal group and 15 (10 men and five women) to the AS group. **Table 1** shows the differences in each variable between the two groups. While there were no significant differences in BMI, gender, pre-MMSE, educational background or past medical history, we found significant differences in age ($p < 0.01$) and the mean CAVI values ($p < 0.01$). Additionally, the normal group had a significantly higher total post-MMSE scores (normal group: 27.2 ± 2.1 , AS group: 25.5 ± 2.3 , $p < 0.01$) and higher post-MMSE scores for the attention-and-calculation domain (normal group: 3.4 ± 1.7 , AS group: 2.3 ± 1.5 , $p = 0.03$) than the AS group.

The ANCOVA adjusted for age, BMI, gender

Fig. 2. Two-way analysis of variance showing the differences in the changes in the post-MMSE (attention and calculation) scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.11$, $p=0.03$).

and pre-MMSE showed a significant difference in the changes in the post-MMSE scores between the normal and AS groups ($F=5.95$, $p=0.02$) (**Fig. 1**), indicating that elderly individuals with a higher degree of arterial stiffness may experience greater levels of cognitive decline, even after adjusting for age, BMI, gender and the pre-MMSE score. Additionally, the changes in the MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) (**Fig. 2**) and MMSE-language ($F=4.32$, $p=0.04$) (**Fig. 3**) domains were shown to be significantly different according to the ANCOVA. The other areas did not show any differences between the two groups (orientation; $F=0.27$, $p=0.60$; registration; $F=2.69$, $p=0.11$, recall; $F=0.16$, $p=0.69$).

Discussion

In this study, we analyzed whether the degree of cognitive decline differs significantly according to the severity of arterial stiffness, adjusted for age, BMI,

gender and the cognitive function at baseline and at the one-year follow-up. Consequently, we found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects, regardless of the initial level of the global cognitive function. Previous studies have demonstrated that arterial stiffness has a predictive effect on cognitive decline in the non-community-dwelling elderly^{13-15, 18}; however, few reports have found arterial stiffness to be a predictor of cognitive decline in this group.

There are hypotheses regarding pathways linking arterial stiffness and cognitive decline, wherein augmented pressure pulses penetrate and damage small cerebral vessels in the global brain²³. Brain lesions, such as ischemic lesions and white matter abnormalities resulting from augmented pressure, are thought to cause cognitive decline, thereby leading to dementia²⁴. The augmented pressure caused by arterial stiffness independently predicts cognitive performance²⁵, and many previously published studies evaluating the

Fig. 3. Two-way analysis of variance showing the differences in the changes in the post-MMSE (language) scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=4.32$, $p=0.04$).

association between arterial stiffness and the cognitive function have discussed the causal relationship with this phenomenon^{14, 17, 18, 23}.

Several studies have examined whether the severity of arterial stiffness longitudinally predicts cognitive decline. For example, one study targeting people older than 80 years of age in nursing homes showed results similar to the current findings¹³. The mean baseline MMSE score of these subjects was 23.7 ± 4.9 , which is lower than that observed in the current study. Another study, in which the subjects were older patients in the hospital with complaints of memory loss, also reported that arterial stiffness has a strong predictive ability for cognitive decline¹⁴. Furthermore, Yamamoto *et al.* performed a similar analysis in community-dwelling elderly patients; however, the mean age was higher than that noted in our study¹⁸. Notably, we found that arterial stiffness predicts cognitive decline in community-dwelling elderly subjects with a comparably preserved cognitive function, even after adjusting for

age, gender, BMI and the baseline cognitive function. In addition, we observed the scores for the attention-and-calculation and language domains of the MMSE to be significantly decreased in the AS group. It has been reported that these MMSE domains are not affected by impairment of the hippocampus²⁶. Therefore, we assume that the cognitive dysfunction resulting from arterial stiffness is not attributed to dysfunction of the hippocampus. However, other studies have reported that measurements of arterial stiffness do not predict performance for the global cognitive function, as measured according to the MMSE¹⁵⁻¹⁷. There are various possible reasons for this discrepancy: 1) the mean age of the subjects was 57.1 years and the participants were relatively high functioning (ceiling effect of the MMSE)¹⁵; 2) many participants dropped out from the follow-up survey and selection bias may have affected the results for the change in the cognitive function¹⁶; 3) memory tasks that are more demanding for the executive function and attention

may be more sensitive to cerebrovascular alterations due to aging and the MMSE may be too insensitive to accurately detect cognitive changes^{17, 27)}. As a result, further studies are needed to establish evidence clarifying the association between arterial stiffness and the cognitive function.

The most important clinical implication of our findings is that one of the most easily measured and non-invasive parameters, especially in community-dwelling elderly individuals, arterial stiffness, predicted cognitive decline after one year. These results imply that maintaining the arterial function may prevent or delay the onset of dementia in the community-dwelling elderly. Additionally, it may be possible to identify individuals at risk of dementia by evaluating the degree of arterial stiffness. Interventional and longitudinal studies examining improvements in arterial stiffness with the aim of preventing cognitive decline are required to establish effective strategies for inhibiting the onset of dementia.

This study is associated with several limitations. First, because we were unable to perform neuroimaging assessments, it was not possible to make a specific diagnosis of dementia subtypes. In addition, we only performed MMSE as a cognitive test, and the cognitive function was not fully investigated. There may be asymptomatic brain lesions and specific cognitive domains that exhibit a strong relationship with arterial stiffness. Second, the age at baseline in the AS group was significantly higher than that observed in the normal group. Although we tried to minimize the impact of this difference by adjusting for age, the effect may have been insufficient. Third, the small number of subjects may also have affected the results, and more samples are needed to confirm the results of this study. Finally, many studies have investigated the relationship between arterial stiffness and the cognitive function; therefore, this study may not have adequate novelty. Nevertheless, we regard our findings as providing evidence that strengthens the close relationship between arterial stiffness and cognitive decline.

Conclusions

This study showed that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects regardless of the initial level of the global cognitive function. These findings indicate the potential of improving arterial stiffness in order to prevent or delay of the onset of dementia in the elderly.

Acknowledgments

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Conflicts of Interest

None.

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