Arterial Stiffness Determined According to the Cardio-Ankle Vascular Index (CAVI) is Associated with Mild Cognitive Decline in Community-Dwelling Elderly Subjects

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Aims: The purpose of this study was to determine the cross-sectional relationship between the cognitive function and cardio-ankle vascular index (CAVI) in Japanese community-dwelling elderly subjects.

Methods: A total of 179 Japanese community-dwelling elderly subjects were recruited for this study. The age, height, weight, gender and past medical history (cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia) of each participant was recorded. In addition, the degree of arterial stiffness was determined according to the CAVI, while the cognitive function was assessed using the Mini-Mental State Examination (MMSE). After dividing the cohort into two groups according to the MMSE score (≤26, >26), we used a multiple regression analysis to assign the level of the cognitive function as a dependent variable.

Results: The data were statistically analyzed for the 174 participants (84 men and 90 women) who completed the data collection process without omissions. A multivariate logistic regression analysis showed that a higher weight (Odds Ratio [OR]: 1.05, 95% Confidence Interval [95% CI]: 1.00-1.11, p = 0.03), male gender (OR: 3.13, 95% CI: 1.05-9.34, p = 0.04) and lower CAVI (OR: 0.68, 95% CI: 0.48-0.96, p = 0.03) were significantly correlated with a higher MMSE score. We also found significant correlations between the MMSE and weight (OR: 1.11, 95% CI: 1.03-1.19, p = 0.01) and CAVI (OR: 0.57, 95% CI: 0.33-0.98, p = 0.04) in elderly men only using a gender-specific analysis.

Conclusions: We found that the elderly subjects with a high CAVI exhibited a worse cognitive function even after adjusting for age, height, weight and gender. This finding therefore indicates the usefulness of the CAVI in the early detection of dementia.


Key words: Cognitive function, Arterial stiffness, Community-dwelling elderly

Introduction

Dementia can drastically influence daily life and is currently one of the most common diseases in the elderly. The World Health Organization estimated that 35 million people worldwide suffered from dementia in 2012, and people with dementia have been shown to be frail due to their poor mobility and body composition. Approximately 48% of people with Alzheimer’s disease (AD), the most common form of dementia, are estimated to live in Asia, and this percentage will grow to 59% by 2050. The transitional stage between normal aging and AD is called mild cognitive impairment (MCI), and more than half of MCI cases progress to dementia within five years. Therefore, preventing cognitive decline is crucial.
Identifying risk factors that can predict cognitive decline will help to prevent such decline. Although many studies have attempted to address this issue, evidence supporting the role of modifiable risk factors remains limited. Meanwhile, vascular risk factors have received attention in recent years. High blood pressure, dyslipidemia, obesity and diabetes mellitus have been proposed to be risk factors for cognitive decline. Among these factors, arterial stiffness, specifically, is a comparatively easy-to-modify risk factor. It has been reported that systemic atherosclerosis plays a role in the cognitive function and is directly linked to the pathology of Alzheimer’s disease. In one European study, it was found that functional changes in the arterial system may be involved in the onset of dementia.

Arterial stiffness is one of the most easily measured vascular risk factors in community-dwelling elderly subjects due to its noninvasive nature. The brachial-ankle pulse wave velocity (baPWV) is widely used for this purpose. In a cross-sectional study of 370 middle-aged Korean participants, the baPWV was found to be significantly correlated with the cognitive function. In addition, in a Japanese study, a high baPWV was shown to be a risk factor for a poor cognitive function in 352 community-dwelling elderly subjects. However, there are several problems associated with the measurement of baPWV, as the value of the parameter depends on the blood pressure at the time of measurement. Therefore, it is difficult to evaluate arterial stiffness in patients treated with antihypertensive medications or those with masked hypertension. In contrast, the cardio-ankle vascular index (CAVI) is a novel BP-independent parameter of arterial stiffness. This parameter is adjusted for the PWV according to the systolic and diastolic blood pressure and blood density and is therefore a theoretically BP-independent index. Clinicians can ensure the validity of arterial stiffness measurements using this parameter. However, no studies have so far evaluated the relationship between the cognitive function and arterial stiffness using the CAVI. In addition, few studies have evaluated this relationship in community-dwelling elderly patients.

The purpose of this study, therefore, was to determine the cross-sectional relationship between the cognitive function and the CAVI in Japanese community-dwelling elderly subjects.

**Methods**

**Participants**

Participants were recruited for this study through local press requesting healthy community-dwelling volunteers, resulting in a total of 179 Japanese participants 65 years of age or older and currently living in the community. Interviews were then performed to exclude participants based on the following exclusion criteria: severe cardiac, pulmonary or musculoskeletal disorders; comorbidities associated with a greater risk of falls, such as Parkinson’s disease and stroke; and the use of psychotropic drugs. Written informed consent was obtained from each participant for the trial in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995. The study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

**Measurements**

**Demographic Data**

Age, height, weight, gender, past medical history (cardiovascular disease, hypertension, diabetes mellitus, 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 and university) were recorded as demographic data. All data were collected at the onset of data collection. We surveyed age and gender from the participant directly and measured the height and weight using standardized height and weight scales.

**CAVI**

The CAVI was determined using the VaSera-1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan). The procedure has been detailed previously. Briefly, after the participants had rested for five minutes in a sitting position, they were placed in a supine position. Then, cuffs were wrapped around both brachia and ankles to detect the brachial and ankle pulse waves. Electrocardiograms and heart sounds were monitored. The PWV from the heart to the ankle was calculated by measuring the length from the aortic valve to the ankle and dividing by time, which was determined according to the heart sounds and the rise of the brachial and ankle pulse waves. Blood pressure was also measured at the brachial artery. Finally, scale conversion was performed using the following formula:

\[
\text{CAVI} = a\{(2\rho/\Delta P) \times \ln(P_s/P_d)\text{PWV}^2\} + b \text{ (no unit)}
\]

\(\rho\): blood density, \(P_s\): systolic blood pressure, \(P_d\): diastolic blood pressure, \(\Delta P\): \(P_s\)-\(P_d\), PWV: pulse wave velocity, \(a\) and \(b\): constants.

The validity, reproducibility and blood pressure-independent nature of this experiment have been well...
Table 1. Differences in each variable between the MMSE high/low score groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 174)</th>
<th>Men (n = 84)</th>
<th>Women (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low MMSE (≤26)</td>
<td>High MMSE (&gt;26)</td>
<td>p</td>
</tr>
<tr>
<td>MMSE</td>
<td>24.6 ± 1.3 n = 56</td>
<td>28.7 ± 1.1 n = 118</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>Age, year</td>
<td>74.2 ± 4.6 n = 56</td>
<td>73.4 ± 4.3 n = 118</td>
<td>0.26</td>
</tr>
<tr>
<td>Height, cm</td>
<td>155.5 ± 8.7 n = 56</td>
<td>156.1 ± 8.1 n = 118</td>
<td>0.65</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>54.0 ± 8.8 n = 56</td>
<td>57.3 ± 9.7 n = 118</td>
<td>0.03*</td>
</tr>
<tr>
<td>Gender, male</td>
<td>30 (53.6%) n = 56</td>
<td>54 (45.8%) n = 118</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean CAVI</td>
<td>9.61 ± 1.30 n = 56</td>
<td>9.13 ± 1.16 n = 118</td>
<td>0.02*</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>8 (14.3%) n = 56</td>
<td>8 (6.8%) n = 118</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (37.5%) n = 56</td>
<td>50 (42.4%) n = 118</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (10.7%) n = 56</td>
<td>14 (11.9%) n = 118</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (14.3%) n = 56</td>
<td>18 (15.3%) n = 118</td>
<td>1.00</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>0 (0-762.5) n = 56</td>
<td>0 (0-356.3) n = 118</td>
<td>0.70</td>
</tr>
<tr>
<td>Educational background</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Elementary school</td>
<td>2 (3.6%) n = 56</td>
<td>1 (0.8%) n = 118</td>
<td>n.s.</td>
</tr>
<tr>
<td>Junior high school</td>
<td>26 (46.4%) n = 56</td>
<td>28 (23.7%) n = 118</td>
<td>0.70</td>
</tr>
<tr>
<td>High school</td>
<td>26 (46.4%) n = 56</td>
<td>69 (58.5%) n = 118</td>
<td>0.70</td>
</tr>
<tr>
<td>Career college</td>
<td>0 (0%) n = 56</td>
<td>7 (5.9%) n = 118</td>
<td>0.70</td>
</tr>
<tr>
<td>University</td>
<td>2 (3.6%) n = 56</td>
<td>13 (11.0%) n = 118</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Mean CAVI = the mean value of the right and left CAVI scores; Mean ± SD values are shown for age, height, weight and mean CAVI; n (%) is shown for gender, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia and educational background; Median (25% quartile-75% quartile) is shown for the Brinkman index; n.s.: not significant.

*: p < 0.05, **: p < 0.01
documented by several studies\textsuperscript{15, 16}. The measurements were obtained once, and the mean value of the right and left CAVI scores for each patient was used for the analysis\textsuperscript{17}.

Cognitive Function Measurement
The cognitive function was assessed using the Mini-Mental State Examination (MMSE)\textsuperscript{18}. The MMSE is a short screening test that consists of five areas of possible cognitive impairment: orientation; registration; attention and calculation; and language. The scores ranged from 0 to 30, with a higher score indicating a better cognitive performance. We tested the participants individually based on the generalized method and used 26/27 as the cutoff score, according to Spering CC et al.\textsuperscript{19}.

Statistical Analysis
The participants were divided into two groups based on the MMSE score: \( \leq 26 \) or \( > 26 \). This cutoff of 26/27 has been shown to be a better balanced score of estimates of diagnostic accuracy for educated individuals\textsuperscript{19}. Because our participants were community-dwelling and highly educated and all lived independently, we adopted this 26/27 cutoff.

We statistically analyzed the differences between the two groups using the unpaired \( t \)-test for age, height, weight and the mean CAVI on both sides, the \( \chi^2 \) 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 multivariate logistic regression model was performed to investigate whether the CAVI was independently associated with the MMSE score. We assigned a high MMSE score as the dependent variable adjusted for age, height, weight and gender. A value of \( p < 0.05 \) was considered to be statistically significant for all analyses.

Results
In total, there were 179 elderly participants (85 men and 94 women) in this study. Of the 179 patients, 84 men and 90 women completed the data collection without omissions, for a total of 174 data points.

We assigned 56 elderly subjects (30 men and 26 women) into the low MMSE group and 118 elderly subjects (54 men and 64 women) into the high MMSE group. Table 1 shows the differences in each variable between the two groups. While there were no significant differences in age, height, gender or past medical history, a higher weight was associated with a higher MMSE score (\( p = 0.03 \)). In addition, the low MMSE group had significantly higher CAVI values than the high MMSE group (Fig. 1, the low group: 9.61 \( \pm \) 1.30, the high group: 9.13 \( \pm \) 1.16, \( p = 0.02 \)).

The multivariate logistic regression analysis showed that a higher weight (odds ratio [OR]: 1.05, 95\% confidence interval [95\% CI]: 1.00-1.11, \( p = 0.03 \)), female gender (OR: 3.13, 95\% CI: 1.05-9.34, \( p = 0.04 \)) and lower CAVI (OR: 0.68, 95\% CI: 0.48-0.96, \( p = 0.03 \)) were significantly correlated with a higher MMSE score (Table 2), indicating that elderly subjects with a higher CAVI have a lower cognitive function, even after adjustment for age, height, weight and gender. In the multivariate logistic regression analysis of each gender, we found a significant correlation between the MMSE score and weight (OR: 1.11, 95\% CI: 1.03-1.19, \( p = 0.01 \)) and CAVI (OR: 0.57, 95\% CI: 0.33-0.98, \( p = 0.04 \)) in the elderly men only (Table 2).

Discussion
We analyzed the relationship between the cogni-
CAVI and Cognitive Decline

Table 2. Multivariate logistic regression model to determine the association with a high MMSE score

<table>
<thead>
<tr>
<th></th>
<th>All (n=174)</th>
<th>Male (n=84)</th>
<th>Female (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>1.00 (0.92-1.09)</td>
<td>1.08 (0.95-1.12)</td>
<td>0.96 (0.85-1.09)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>1.04 (0.97-1.12)</td>
<td>0.97 (0.88-1.08)</td>
<td>1.13 (1.00-1.28)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.05 (1.00-1.11)</td>
<td>1.11 (1.03-1.19)</td>
<td>1.01 (0.94-1.09)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.00 (0.92-1.09)</td>
<td>1.08 (0.95-1.12)</td>
<td>0.96 (0.85-1.09)</td>
</tr>
<tr>
<td>men</td>
<td>1 [Reference]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>women</td>
<td>3.13 (1.05-9.34)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean CAVI</td>
<td>0.68 (0.48-0.96)</td>
<td>0.57 (0.33-0.98)</td>
<td>0.73 (0.44-1.23)</td>
</tr>
</tbody>
</table>

Mean CAVI = the mean value of the right and left CAVI scores; OR = Odds Ratio, 95% CI = 95% confidence interval.

*: p < 0.05

tive function and the CAVI in Japanese community-dwelling elderly subjects. In this study, we found a negative correlation between the CAVI and the cognitive function, even after adjusting for age, height, weight and gender. Many studies have demonstrated a relationship between arterial stiffness and a decreased cognitive function; however, there are no reports using the novel index of arterial stiffness, the CAVI, in community-dwelling elderly subjects.

Several mechanisms may potentially explain why arterial stiffness is associated with cognitive function. First, the development of dementia is associated with organic brain lesions, such as ischemic lesions and white matter abnormalities. Because stiff blood vessels lose their capacity to buffer pulse pressure, the pulsatile flow is increased, causing damage to the fragile small vessels in the brain. This phenomenon has been demonstrated in animal studies, in which locally induced isolated alterations in pressure pulsatility have been shown to have major effects on the cerebral microvascular structure and function. Pase et al. reported that the augmented pressure caused by arterial stiffness independently predicts the cognitive function. In addition, some studies have shown evidence that asymptomatic cerebral microvascular lesions caused by augmented pressure are associated with an increased risk of AD. Our major finding indicating a correlation between the CAVI and the cognitive function is consistent with the results of these previous reports. However, this relationship was found only in elderly men in a gender-specific analysis; therefore, cognition may be more strongly affected by arterial stiffness in men than in women. Larger studies should address the effects of the CAVI on the cognitive function in elderly women.

The peculiarity of the CAVI is that it indicates BP-independent arterial stiffness, unlike the baPWV. Therefore, it is conceivable that the CAVI is a useful parameter in patients who are subject to variation in BP at various times due to masked hypertension or the use of antihypertensive medications. Masked hypertension is defined as a normal BP in the clinic and office (<140/90 mmHg) with an elevated BP out of the clinic (ambulatory daytime BP or home BP > 135/85 mmHg). This phenomenon can occur in up to 8-38% of the general population and is observed at all ages. In addition, antihypertensive medication use has recently increased. Men have seen the greatest increase in antihypertensive medication use (47.5%, 1988-1994 versus 57.9%, 1999-2002) among hypertensive adults. Moreover, Takaki et al. demonstrated the superiority of the CAVI to the baPWV in measurement sensitivity. They found that the CAVI was better correlated with the parameters of left ventricular diastolic indices, low-density lipoprotein cholesterol and angina pectoris than the baPWV.

When evaluating arterial stiffness in community-dwelling elderly subjects, the most important properties of an instrument for assessment are ease of measurement and validation. The clinical advantage of our study is the indication of a significant relationship between arterial stiffness and the cognitive function in community-dwelling elderly subjects based on the use of a better arterial stiffness index, the CAVI. In order to early detect cognitive decline, clinicians should conduct screening exams for community-dwelling elderly patients. This is why we adopted the 26/27 cutoff point for our patients, all of whom lived independently and were highly educated. This index has the potential to be used to detect cognitive decline earlier in community-dwelling elderly subjects due to its validity and noninvasive nature.

This study is associated with several limitations. First, because this study is a cross-sectional study, the
cause-effect relationship between the CAVI and the cognitive function is unknown. Second, we were unable to perform neuroimaging procedures. The participants may have had asymptomatic brain lesions that we could not fully investigate. In addition, we did not distinguish between the types of dementia. Different types of dementia may affect the results. Further investigations, such as prospective studies, are required to confirm the findings of the present study.

Conclusion
This is the first study to determine the relationship between the cognitive function and the CAVI in community-dwelling elderly subjects. We found a significant relationship between a higher CAVI and mild cognitive decline. This finding indicates the usefulness of the CAVI in the early detection of dementia.

Conflicts of Interest
None.

References
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