Original Article

Cardio-Ankle Vascular Index Elevation in Patients with Exudative Age-Related Macular Degeneration

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Aim: To clarify whether the cardio-ankle vascular index (CAVI) independently contributes to the development of exudative age-related macular degeneration (AMD) compared with carotid arteriosclerosis parameters and other risk factors.

Methods: Eighty-eight consecutive patients with exudative AMD were enrolled. A control group (40 age-matched men, 65 years of age or older) was also evaluated, and the parameters were compared between the two groups. A logistic regression analysis was used to determine independent factors for the diagnosis of AMD. In addition, simple linear and multiple regression analyses were used to determine the relationships between the CAVI and other parameters.

Results: The carotid intima-media thickness and plaque scores in the AMD group did not differ significantly from those observed in the control group. The CAVI in the AMD group was significantly ($p=0.01$) higher than that observed in the control group. A logistic regression analysis showed that the CAVI (odds ratio [OR], 1.91; 95% confidence interval [CI], 1.26-7.20; $p=0.007$) and the use of lipid-lowering drugs (OR, 0.29; 95% CI, 0.10-0.86; $p=0.03$) independently contributed to the diagnosis of AMD. Age, the high-sensitivity C-reactive protein level and the incidence of exudative AMD each independently contributed to the CAVI.

Conclusions: The CAVI is more significantly associated with exudative AMD than carotid arteriosclerosis parameters. The overall arterial stiffness is correlated with the pathogenesis of exudative AMD. The CAVI is a useful marker of exudative AMD in elderly patients with arteriosclerosis risk factors.

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Key words: Age-related macular degeneration, Aging, Cardio-ankle vascular index, High-sensitivity C-reactive protein

Introduction

Aging is significantly associated with the development of arteriosclerosis and constitutes a major risk factor for cardiovascular disease¹. In the eye, aging is a risk factor for the development of choroidal and retinal vascular diseases, such as age-related macular degeneration (AMD)^{2, 3}.

AMD is a major cause of blindness and severe visual loss in older people in developed countries⁴⁻⁶, while the incidence of exudative choroidal neovascularization (CNV) is associated with more severe visual loss^{7, 8}. The Hisayama cohort study showed that the 9-year cumulative incidence of exudative AMD is 1.4%⁹. As the population ages in developed countries, AMD will increasingly become a public health problem; therefore, it is crucial that the factors contributing to the development of exudative AMD be identified. Many of the documented risk factors for exudative AMD also represent a cardiovascular risk profile. Smoking¹⁰, hypertension¹¹, the chole-

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terol level¹²⁾, obesity¹³⁾, the high-sensitivity C-reactive protein (Hs-CRP) level¹⁴⁾, an increased wall thickness of the carotid artery and the presence of plaque¹⁵⁾ are associated with an increased risk of AMD.

Recently, an arterial stiffness parameter, the cardio-ankle vascular index (CAVI), was developed as a marker related to arteriosclerosis, including that of the aorta, femoral artery and tibial artery¹⁶⁾. The CAVI has previously been reported to reflect the degree of coronary artery stenosis¹⁷⁾. Therefore, we hypothesized that the CAVI may contribute to the development of exudative AMD. The purpose of the current study was to evaluate whether the CAVI independently contributes to the development of exudative AMD compared with carotid atherosclerosis parameters obtained from high-resolution B-mode ultrasonography and other risk factors.

Materials and Methods

The institutional review board of Toho University Sakura Medical Center approved the current study. All participants provided their informed consent in accordance with the Declaration of Helsinki. A total of 88 consecutive Japanese men with exudative AMD were included. The patients received injections of intravitreal antivascular endothelial growth factor or the application of photodynamic therapy for exudative AMD between April 1, 2011 and April 1, 2012 at the Department of Ophthalmology, Toho University Sakura Medical Center. Forty men 65 years of age or older were evaluated as age-matched controls for patients with exudative AMD from among the consecutive cases of 101 men who visited the Vascular Function Section of the Department of Cardiovascular Center of our hospital between April 1, 2007 and October 1, 2010. The control group had some risk factors for arteriosclerosis but no choroidal or retinal diseases. Patients with the following conditions were excluded because these conditions can affect the CAVI: chronic atrial fibrillation, a decreased left ventricular function (ejection fraction <50%) and peripheral arterial disease defined as an ankle-brachial index less than 0.9. Ultimately, seven patients in the control group and eight patients in the AMD group were excluded. All evaluations were conducted before the AMD treatment was administered.

Diagnosis of Exudative AMD

Exudative AMD was diagnosed primarily on ophthalmoscopy and fluorescein angiography according to the definition of the International Classification System for Age-Related Maculopathy¹⁸⁾; however, indo-

cyanine green angiography was also used to establish the diagnosis. Briefly, exudative AMD was diagnosed in patients who were 50 years of age or older and exhibited the following abnormalities in the macular area: retinal pigment epithelium and/or associated neurosensory detachment, retinal hemorrhaging or retinal fibrous scarring in the absence of other retinal disorders. The current study included patients with typical exudative AMD and polypoidal choroidal vasculopathy (PCV). PCV was defined as a choroidal origin of polypoidal lesions, typically with branching choroidal vascular networks in the posterior poles on indocyanine green angiography and subretinal orange-reddish protrusions corresponding to the polypoidal lesions on indocyanine green angiography¹⁹⁾. However, patients with other macular abnormalities, i.e., pathologic myopia, idiopathic CNV, retinal angiomatous proliferation and other secondary types of CNV, were excluded. A total of 54 patients with typical exudative AMD and 34 patients with PCV were included in this study.

Measurement of the CAVI, Blood Pressure and Pulse Pressure

The measurements of the CAVI, blood pressure and heart rate were obtained using the program embedded in the VaSera VS-1000, a vascular screening system (Fukuda Denshi Co., Ltd., Tokyo, Japan). A detailed explanation of the methods used to measure the CAVI has been previously reported¹⁶⁾. Briefly, the brachial and ankle pulse waves were determined with inflatable cuffs with the pressure maintained between 30 to 50 mmHg to ensure that the cuff pressure had a minimal effect on the systemic hemodynamics. The blood pressure and pulse pressure were determined simultaneously¹⁶⁾. The measurements were obtained with the subject in the supine position. The CAVI was measured after the subject rested for 10 minutes in a quiet room. In addition, in the AMD group, the estimated CAVI values were determined using a linear regression equation²⁰⁾: Estimated CAVI = $5.43 + 0.053 \times \text{age}$, for men.

Measurement of the Carotid Intima-Media Thickness (IMT) and Plaque Score

High-resolution ultrasonographic imaging of the carotid artery with the B-scan mode was performed using the EUB-8500 (Hitachi Co., Ltd., Tokyo, Japan) with the probe frequency set to 7.5 MHz. The subjects were measured while in the supine position with their heads slightly turned away from the sonographer. The procedures involved scanning the near and far walls of the carotid artery every 1 cm proximal to the

carotid bulb in the longitudinal view. The IMT was defined as the average of the maximal IMT 1 cm proximal to and 1 cm distal to the carotid bulb^{15, 21, 22}. The IMT of the thickened side of the carotid artery was used for the data analyses. The plaque score was calculated as previously reported²³. Briefly, plaques (localized increases in IMT ≥ 1.1 mm) were detected using cross-sectional and longitudinal scanning of the bilateral common and internal carotid arteries. The plaque score was computed by adding the maximal thickness of each plaque in the bilateral carotid arteries.

Assessment of Laboratory Profiles

The laboratory profiles were assessed based on the serum total cholesterol (mg/dL), triglyceride (mg/dL), low-density lipoprotein-cholesterol (LDL-C mg/dL), high-density lipoprotein-cholesterol (HDL-C mg/dL), Hs-CRP (mg/L) and glycosylated hemoglobin (%HbA1c) levels. Fasting morning blood samples were collected and stored at -70°C until needed for the appropriate assays. The HbA1c level was expressed according to the scale of the Japan Diabetes Society.

Measurement of Other Parameters

The following parameters were determined in both groups: body mass index (BMI kg/m^2), hypertension, diabetes mellitus, coronary artery disease (CAD), the smoking status and the use of angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs) and lipid-lowering drugs. We diagnosed hypertension in patients with a blood pressure value of 140/90 mmHg or higher and those using antihypertensive drugs.

Statistical Analyses

The data are expressed as the mean $\pm$ standard deviation for continuous variables. Comparisons between the groups were made using the unpaired *t*-test, Mann-Whitney *U* test, 2×2 chi-square test, Yates 2×2 chi-square test and one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. A logistic regression analysis was used to evaluate whether the CAVI independently contributed to the development of AMD. Simple linear and multiple regression analyses were used to determine the relationships between the CAVI and other parameters. $P < 0.05$ was considered to be statistically significant. The StatView version 5.0 program (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

Results

The characteristics of the study groups are shown

in **Table 1**. The age-matched AMD and control groups comprised 88 and 40 subjects, respectively. The rate of use of lipid-lowering drugs in the AMD group was significantly lower than that observed in the control group ($p=0.02$). The frequency of CAD ($p=0.15$) and use of ACE-Is or ARBs ($p=0.07$) tended to be lower and the pulse pressure ($p=0.07$), frequency of smoking ($p=0.07$) and triglyceride levels ($p=0.10$) tended to be higher in the AMD group; however, none of these differences reached statistical significance.

The values of the IMT, plaque score and CAVI in the two groups are shown in **Table 2**. The IMT values and plaque scores in the AMD group did not differ significantly from those observed in the control group ($p=0.74$ and $p=0.20$, respectively). The CAVI values in the AMD group were significantly ($p=0.01$) higher than those observed in the control group.

The results of the logistic regression analyses of factors independently contributing to a diagnosis of AMD in the current study are shown in **Table 3**. The explanatory variables were the CAVI, frequency of smoking, triglyceride level, pulse pressure, LDL-C level, total cholesterol level and use of ACE-Is, ARBs or lipid-lowering drugs, which were significantly different or tended to be higher in the AMD group. The CAVI and use of lipid-lowering drugs were identified to be factors independently contributing to a diagnosis of AMD (CAVI, odds ratio [OR], 1.91; 95% confidence interval [CI], 1.20-3.04; $p=0.008$; lipid-lowering drugs, OR, 0.29; 95% CI, 0.10-0.86; $p=0.03$). The use of ACE-Is or ARBs tended to contribute to a diagnosis of AMD; however, the findings were not significant (OR, 0.42; 95% CI, 0.18-1.02; $p=0.06$).

The results of the simple linear and multiple regression analyses of factors independently contributing to the CAVI in all subjects are shown in **Table 4**. The CAVI was significantly correlated with age ($p < 0.0001$), systolic blood pressure ($p=0.002$), pulse pressure ($r=0.33$, $p=0.0001$), hypertension ($p=0.002$), total cholesterol ($p=0.02$), LDL-C ($p=0.03$), Hs-CRP ($p=0.006$) and the presence of AMD ($p=0.01$). The CAVI also tended to be correlated with diabetes mellitus ($p=0.10$), the use of ACE-Is or ARBs ($p=0.09$) and the plaque score ($p=0.11$); however, no analyses reached statistical significance. Age, the Hs-CRP level and the incidence of AMD were identified to be factors independently contributing to the CAVI (age, $p < 0.0001$; Hs-CRP, $p=0.03$; AMD, $p=0.003$).

The figure shows the CAVI values in the AMD and control groups and the estimated CAVI in the AMD group, which were calculated according to the following linear regression equation: $\text{CAVI} = 5.43 +$

Table 1. Characteristics of the AMD and control groups

	AMD Group (<i>n</i> =88)	Control Group (<i>n</i> =40)	<i>p</i>
Age (years)	71.5 ± 7.7	70.8 ± 4.5	0.61*
BMI (kg/m ²)	23.9 ± 3.1	23.7 ± 3.1	0.67*
Systolic BP (mmHg)	132.7 ± 16.7	130.7 ± 14.4	0.51*
Diastolic BP (mmHg)	79.1 ± 10.0	81.1 ± 9.8	0.32*
Pulse pressure (mmHg)	53.6 ± 11.6	49.7 ± 11.4	0.07*
History of:			
Hypertension no. (%)	45 (51.1)	25 (62.5)	0.23 [†]
Diabetes mellitus no. (%)	16 (18.2)	8 (20)	0.99 [‡]
Coronary artery disease no. (%)	8 (10)	8 (20)	0.15 [‡]
Smoking no. (%)	59 (67.1)	20 (50)	0.07 [†]
Medications:			
ACE-I or ARB no. (%)	31 (35.2)	21 (52.5)	0.07 [†]
Lipid-lowering drugs no. (%)	10 (11.4)	11 (27.5)	0.02 [†]
Laboratory profile :			
Hemoglobin A1c (%)	5.7 ± 0.9	5.7 ± 0.7	0.98*
Total cholesterol (mg/dL)	197.0 ± 35.6	191.2 ± 33.8	0.39*
Triglyceride (mg/dL)	153.6 ± 102.9	124.2 ± 69.2	0.10*
LDL-C (mg/dL)	114.9 ± 32.7	110.4 ± 25.5	0.44*
HDL-C (mg/dL)	54.2 ± 13.8	52.9 ± 16.6	0.63*
Hs-CRP (mg/L)	1.16 ± 1.59	1.44 ± 2.82	0.70 [§]

The data are expressed as the mean ± standard deviation.

*Unpaired *t*-test.

[†]2 × 2 chi-square test.

[‡]Yates 2 × 2 chi-square test.

[§]Mann-Whitney *U* test.

AMD: age-related macular degeneration; BMI: body mass index; BP: blood pressure; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein.

0.053 × age for men²⁰). The CAVI values in the AMD group were significantly higher than those observed in the control group and the estimated CAVI values in the AMD group (*p* = 0.01, *p* < 0.0001, respectively).

Discussion

The CAVI is a new index of the overall stiffness of an artery that branches from the aorta and runs to the ankle. In addition, the CAVI is independent of the blood pressure at the time of measurement²⁰). The CAVI is also correlated positively with age²⁰). In other words, the CAVI is speculated to represent the overall arterial age. Aging is a major risk factor for AMD^{2, 3}). To the best of our knowledge, the relationship between the CAVI and exudative AMD has not been evaluated; thus, we investigated this relationship in the current study. In addition, we used an age-matched control group, the members of which had some risk factors for atherosclerosis (Table 1) compared with the

Table 2. Values of the IMT, plaque score and CAVI in the AMD and control groups

	AMD Group	Control Group	<i>p</i> *
IMT (mm)	0.92 ± 0.15	0.93 ± 0.14	0.74
Plaque score	5.4 ± 3.6	6.4 ± 4.5	0.20
CAVI	9.9 ± 1.1	9.3 ± 0.9	0.01
Range	7.4 to 14.0	7.9 to 11.8	
Median	9.8	9.4	

The data are expressed as the mean ± standard deviation.

*Unpaired *t*-test.

AMD: age-related macular degeneration; IMT: intima-media thickness; CAVI: cardio-ankle vascular index.

AMD group. Our results showed that the CAVI values were significantly (*p* = 0.01) higher in the AMD group than in the control group, while there were no significant differences between the two groups in the IMT values or plaque scores obtained using high-reso-

Explanatory variables	odds ratio	95% CI	<i>p</i>
CAVI	1.91	1.20-3.04	0.007
Lipid-lowering drugs	0.29	0.10-0.86	0.03
ACE-I or ARB	0.42	0.18-1.02	0.06
Smoking yes = 1, no = 0	1.95	0.81-4.70	0.14
Triglycerides (mg/dL)	1.00	1.00-1.01	0.14
Pulse pressure (mmHg)	1.03	0.99-1.07	0.20
Total cholesterol (mg/dL)	1.00	0.98-1.03	0.85
LDL-C (mg/dL)	1.00	0.97-1.03	0.93

Objective variables   AMD group = 1   *n* = 88,
Control (without AMD) group = 0   *n* = 40

CI = confidence interval

lution B-mode ultrasonography. Furthermore, a logistic regression analysis performed in the current study showed that a high CAVI value was a contributing factor and the use of lipid-lowering drugs was a protective factor against a diagnosis of AMD. Specifically, the use of ACE-Is or ARBs tended to be protective against the development of exudative AMD, while smoking, which is a reported risk factor for AMD¹⁰⁾, exhibited a nonsignificant tendency (**Table 3**). Based on these results, we speculate that the IMT and presence of carotid plaque are not markers for exudative AMD, while the CAVI is a surrogate marker of exudative AMD in elderly individuals with some risk factors for atherosclerosis. In other words, the vascular stiffness indicated by the CAVI may strongly contribute to the pathogenesis of exudative AMD. The results of the current study are the first to show that a proper level of aortic stiffness is related to the development of exudative AMD. The pulse wave velocity (PWV) has also been reported to be a parameter of arterial stiffness^{24, 25)}, and a relationship between AMD and the PWV has been documented²⁶⁾. However, the PWV is dependent on the blood pressure at the time of measurement¹⁶⁾. The PWV may be overestimated in patients with hypertension. We previously reported that the CAVI significantly correlated with the optic nerve head circulation determined using a pulse wave analysis of laser speckle flowgraphy, which reflects the magnitude of the pulsation of the microvessels in the central retina and choroid²⁷⁾. A large degree of pulsation of the microvessels in the optic nerve head may be involved in the development of AMD. The precise mechanism underlying this phenomenon requires fur-

The current study found that the use of lipid-lowering drugs, such as ACE-Is or ARBs, tended to be protective against the development of exudative AMD. One study reported that lipid-lowering drugs are associated with a decreased rate of exudative AMD²⁸⁾. ARBs may also be useful as prophylaxis against exudative AMD, as observed in animal experiments²⁹⁾. We believe that the current results confirm these findings.

We subsequently investigated the factors independently correlated with the CAVI that were found to contribute to the development of exudative AMD in simple linear and multiple regression analyses of factors in all subjects. The results of the multiple regression analysis showed that age, the Hs-CRP level and the incidence of exudative AMD were independent contributors to the CAVI. A previous study reported no associations between the Hs-CRP level and AMD³⁰). In contrast, the data from the Age-Related Eye Disease Study showed that the Hs-CRP level is an independent risk factor for AMD³¹). In the current study, the Hs-CRP levels did not differ significantly between the AMD and control groups. Hs-CRP is a marker of systemic inflammation and an independent risk factor for and predictor of cardiovascular disease³²⁻³⁴). The current control group had some risk factors for atherosclerosis and tended to have a higher incidence of CAD than the AMD group. Therefore, the characteristics of the control group may have affected our Hs-CRP results. A previous study reported that the Hs-CRP level is significantly positively associated with the CAVI; however, no clear associations with the LDL-C level, a traditional risk

Table 4. Results of the simple linear and multiple regression analyses of factors independently contributing to the CAVI in all subjects

Explanatory variables	Simple linear regression analysis		Multiple regression analysis	
	<i>r</i>	<i>p</i>	Standard regression	<i>p</i>
Age (years)	0.52	<0.0001	0.43	<0.0001
BMI (kg/m ²)	0.11	0.24		
Systolic BP (mmHg)	0.28	0.002	0.22	0.06
Diastolic BP(mmHg)	0.05	0.55		
Pulse pressure (mmHg)	0.33	0.0001	−0.04	0.77
Hypertension	0.28	0.002	0.10	0.42
Diabetes mellitus	0.15	0.10	0.10	0.20
Coronary artery disease	0.09	0.32		
Smoking	0.05	0.61		
ACE-I or ARB	0.15	0.09	0.05	0.69
Lipid-lowering drugs	0.12	0.17	0.07	0.36
HbA1c (%)	0.07	0.49		
Total cholesterol (mg/dL)	−0.21	0.02	−0.18	0.24
Triglyceride (mg/dL)	0.01	0.88		
LDL-C (mg/dL)	−0.20	0.03	0.10	0.54
HDL-C (mg/dL)	−0.01	0.88		
Hs-CRP (mg/L)	0.24	0.006	0.16	0.03
IMT (mm)	−0.004	0.96		
Plaque score	0.14	0.11	−0.02	0.77
AMD	0.23	0.01	0.23	0.003

Objective variables CAVI *n* = 128 R = 0.66

BMI: body mass index; BP: blood pressure; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Hs-CRP: high-sensitivity C-reactive protein; IMT: intima-media thickness; AMD: age-related macular degeneration; CAVI: cardio-ankle vascular index.

factor for CAD, were reported³⁵). Statins, which are lipid-lowering drugs, have been reported to reduce the CRP level³⁶).

Finally, to confirm the validity of the findings of the current study, we calculated the estimated CAVI of the AMD group using a linear regression equation²⁰) and compared the results between the groups (**Fig. 1**). The CAVI values of the AMD group were significantly higher than those of the control group and the estimated CAVI values of the AMD group. Therefore, patients with exudative AMD may have high CAVI values.

The current study is associated with several limitations. First, the frequency of use of ACE-Is or ARBs and lipid-lowering drugs was higher in the control group than in the AMD group, which may have affected the current results. Second, only a small number of men were included. Therefore, our findings cannot be generalized to women. It is necessary to examine more subjects of both genders with and without

exudative AMD. Third, we did not evaluate the relationship between the CAVI and the severity of AMD. Furthermore, evaluating the efficacy of the CAVI in predicting the onset of exudative AMD may be more clinically important, since measuring the CAVI is a noninvasive procedure. More detailed studies are needed to clarify the correlation between the CAVI and the severity and onset of exudative AMD. Finally, the current study was cross-sectional, and treatment outcomes were not evaluated. Prospective studies are needed to evaluate whether the CAVI can be used to predict the prognosis of patients with exudative AMD.

In conclusion, the current study found that the CAVI, a novel index of overall arterial stiffness, is more significantly associated with exudative AMD than carotid arteriosclerosis parameters. The overall arterial stiffness may be correlated with the pathology of exudative AMD. Therefore, the CAVI may be a useful marker of exudative AMD in elderly individuals with some risk factors for arteriosclerosis. Further

Fig. 1. The box plot represents the cardio-ankle vascular index (CAVI) in the age-related macular degeneration (AMD) group and control group and the estimated CAVI in the AMD group, which were calculated according to the following formula: $5.43 + 0.053 \times \text{age}^{20}$. Statistical differences between groups were calculated using a one-way ANOVA followed by Dunnett's post hoc test.

studies are required to confirm our hypothesis and the involvement of an elevated level of aortic stiffness in the development of AMD.

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Conflicts of Interest

None.

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