Original Article

Relationship between Cardio-Ankle Vascular Index (CAVI) and Carotid Atherosclerosis in Patients with Essential Hypertension

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Aortic stiffness measured by aorta-iliac or carotid-femoral pulse wave velocity (PWV) predicts all-cause and cardiovascular mortality. Brachial-ankle PWV (baPWV) has been developed as a more convenient assessment of arterial stiffness. However, the problem with clinical use of baPWV is that the index itself is closely dependent on blood pressure. Recently, a new method, termed the cardio-ankle vascular index (CAVI), has been proposed in Japan to overcome the disadvantages associated with measuring PWV. However, its clinical usefulness has not yet been fully clarified. In the present study, we compared the usefulness of CAVI with that of ultrasound for evaluating atherosclerosis in patients with essential hypertension. CAVI was measured in 70 hypertensive patients. The intima-media thickness (IMT), cross-sectional distensibility coefficient (CSDC), stiffness parameter β, and mean diastolic (V_d) and systolic (V_s) flow velocities were evaluated by carotid ultrasound. The V_d/V_s ratio, an index of peripheral arterial resistance, was also calculated. CAVI was positively correlated with IMT ($r=0.360$, $p=0.0022$) and stiffness β ($r=0.270$, $p=0.0239$) and negatively correlated with V_d/V_s ($r=-0.471$, $p<0.0001$) and CSDC ($r=-0.315$, $p=0.0079$). Stepwise regression analysis revealed that age ($r=0.475$, $p<0.0001$) and pulse pressure ($r=0.492$, $r<0.0001$) were independent determinants of CAVI. These results suggest that CAVI is a useful clinical marker for evaluating atherosclerosis and arteriolosclerosis in patients with essential hypertension. (*Hypertens Res* 2007; 30: 335–340)

***Key Words*: cardio-ankle vascular index, pulse wave velocity, intima-media thickness, arterial stiffness, atherosclerosis**

Introduction

Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality, fatal and nonfatal coronary events, and fatal strokes in patients with essential hypertension (*1*, *2*). Arterial stiffness can be evaluated by measuring pulse wave velocity (PWV) between two sites in the arterial tree (*3*). However, aortic PWV measurement is technically difficult and has low reproducibility (*4*). Brachial-ankle PWV (baPWV), which provides a more convenient assessment of arterial stiffness, has been developed in Japan (*5*, *6*). BaPWV is also closely related to risk factors and organ damage associated with cardiovascular disease (*7–9*). However, the problem with the clinical use of baPWV is that the index itself is closely dependent on blood pressure levels (*10–12*). To overcome this disadvantage, a novel stiffness diagnostic parameter called the cardio-ankle vascular index (CAVI) has been developed in Japan. This stiffness parameter has been reported to be independent of blood pressure levels (*10*, *11*, *13*). CAVI is measured from an ECG, phonocardiogram (PCG), brachial artery waveform, and ankle artery waveform

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and calculated using a specific algorithm (*13*). However, its clinical usefulness has not yet been fully clarified in patients with essential hypertension.

An alternative method for evaluating arterial stiffness is the relative change in lumen diameter during the cardiac cycle adjusted for driving pulse pressure, expressed as arterial distensibility. Carotid distensibility is measured by ultrasound imaging. An ultrasound imaging of the common carotid artery (CCA) has been developed for *in vivo* evaluation of early atherosclerotic lesions (*14–16*). Hypertensive patients exhibit markedly increased intima-media thickness (IMT), a higher prevalence of plaques and increased peripheral vascular resistance in the CCA compared to normotensive individuals (*17*).

In the present study, we measured CAVI in hypertensive patients and noted a significant relationship between the index and morphological, functional and hemodynamic changes in the CCA.

Methods

Study Subjects

Seventy consecutive patients with essential hypertension were enrolled in this study. Hypertension was defined as the use of antihypertensive medications or a systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg. The SBP and DBP were the average of three measurements taken with a brachial sphygmomanometer with the patient in the seated position. Patients with congestive heart failure, previous myocardial infarction, angina pectoris, atrial fibrillation, diabetes mellitus (fasting glucose level >126 mg/dl), chronic renal failure (serum creatinine >1.5 mg/dl), history of stroke, malignant tumor or autoimmune diseases were excluded. The ethics committee of the Ehime University School of Medicine provided approval for this study. Informed consent was obtained from all patients prior to participation.

Blood Sampling

Serum creatinine, fasting glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and HbA1c were measured using a 200FR analyzer (Toshiba, Tokyo, Japan).

Ultrasound Evaluation

Ultrasound evaluation of the CCA was performed with a SONOS 5500 (PHILIPS Co., Tokyo, Japan) using a 7.5-MHz probe equipped with a Doppler system, as described previously (*17*). After the subjects had rested in the supine position for at least 10 min, their neck was placed in a slightly hyperextended position and then optimal bilateral visualization of the carotid artery was performed. Based on multiple visualizations, plaque formation was identified as the presence of wall thickening at least 50% greater than the thickness of the surrounding wall (*18*). To evaluate the distribution of atherosclerosis in the carotid arteries, we used a plaque scoring method, plaque score was calculated as the sum of the areas of bilateral thickness greater than 1.1 mm as described previously (*19*). The IMT of the far wall was measured in the CCA at sites 1 and 2 cm proximal to the bulb from the anterior, lateral, and posterior approaches, and the results were averaged in order to obtain the mean IMT values. No measurements were carried out at the level of discrete plaques.

Two-dimensional guide M-mode tracing of the right CCA 2 cm proximal to the bulb was recorded with simultaneous ECG and PCG. M-mode images were obtained in real time using a frame grabber. The axial resolution of the M-mode system was 0.1 mm. The internal diameters of the CCA at end-diastole (D_d) and peak-systole (D_s) were determined by continuous tracing of the intimal-luminal interface of the near and far wall of the CCA during three cycles, and the results were then averaged. The cross-sectional distensibility coefficient (CSDC) and carotid arterial stiffness index β were calculated by the following formulae:

$$\mathrm{CSDC} = (D_s^2 - D_d^2)/\{D_d^2 \times (\mathrm{SBP} - \mathrm{DBP})\}$$

$$\beta = \ln(\mathrm{SBP}/\mathrm{DBP}) \times \{D_d/(D_s - D_d)\}$$

SBP and DBP were measured at the brachial artery by an automated sphygmomanometer (BP-103 iII; Omlon-Colin Co., Ltd., Tokyo, Japan) immediately after the evaluation of carotid ultrasound.

Doppler evaluation was performed by scanning the right CCA in the anterior projection. Using color flow mapping, the sample volume was located at the center of the vessel. Flow velocity–time integrals of the systolic and diastolic phases were computed automatically by electronic integration of the instantaneous flow velocity curves, followed by calculation of the systolic (V_s) to diastolic flow velocity (V_d) ratios to assess hemodynamics in the CCA.

Measurement of CAVI

The patients were placed in the supine position for at least 10 min, and then ECG and PCG were monitored. PWV from the heart to the ankle was obtained by measuring the length from the aortic valve to the ankle (VaSera VS-1000; Fukuda Denshi, Tokyo, Japan) (*13*). The formula used to calculate CAVI was as follows:

$$\mathrm{CAVI} = a\{(2\rho/\Delta P) \times \ln(\mathrm{SBP}/\mathrm{DBP})\mathrm{PWV}^2\} + b,$$

where ΔP is SBP − DBP, ρ is blood density, and a and b are constants to match aortic PWV.

This equation was derived from Bramwell-Hill's equation and the stiffness parameter β. CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole, and is theoretically not affected by blood pressure (*13*). All these

Table 1. Characteristics of the Subjects

N (male/female)	70 (46/24)
Age (years)	61±12
BMI (kg/m^2)	25.3±3.7
Systolic blood pressure (mmHg)	137±17
Diastolic blood pressure (mmHg)	85±13
Pulse rate (/min)	66±12
Total cholesterol (mg/dl)	201±36
Triglyceride (mg/dl)	139±76
HDL-C (mg/dl)	55±17
Fasting plasma glucose (mg/dl)	102±15
HbA1c (%)	5.2±0.3
Serum creatinine (mg/dl)	0.80±0.22
CAVI	8.34±1.35
Mean IMT (mm)	0.78±0.17
Plaque score	2.28±3.17
CSDC ($\times 10^{-3}$/mmHg)	3.54±1.57
Stiffness β	7.41±5.17
V_d/V_s	0.53±0.08

BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CSDC, cross-sectional distensibility coefficient; V_s, systolic mean velocity; V_d, diastolic mean velocity; V_d/V_s, relative diastolic flow velocity.

measurements and calculation were made together and automatically in VaSera. The blood pressure was measured at the brachial artery. The average coefficient of variation for this measurement has been reported to be 3.8% (*13*).

Statistics

All values were expressed as the mean±standard deviation. Pearson's correlation coefficient was used to assess the association between continuous variables. Unpaired *t*-test was used to analyze the comparisons between means. We used stepwise multiple regression analysis to evaluate the independent determinants of CAVI. A p-value of <0.05 was considered to be statistically significant.

Results

Characteristics of the Study Participants

The mean age of the participants was 61±12 years. Forty-nine patients (70%) were treated with antihypertensive drugs, including calcium channel blockers (34 patients), angiotensin II receptor blockers/angiotensin converting enzymes (27 patients), β-blockers (6 patients), diuretics (2 patients) and α-blocker (1 patient). Eight (11.4%) patients were treated with statins and 8 (11.4%) were treated with anti-platelet drugs. The clinical characteristics and data of CAVI and carotid parameters of the study subjects are summarized in Table 1.

Table 2. Correlation between CAVI and Other Clinical Parameters (Pearson's Correlation Coefficients)

	r	*p* value
Age	0.609	<0.0001
Systolic blood pressure	0.279	0.0192
Diastolic blood pressure	0.175	0.1469
Pulse pressure	0.620	<0.0001
Total cholesterol	0.043	0.7241
Triglyceride	0.071	0.5608
HDL-C	0.101	0.4032
HbA1c	0.275	0.0022
Serum creatinine	0.133	0.2716

CAVI, cardio-ankle vascular index; HDL-C, high-density lipoprotein-cholesterol.

There were no differences in clinical characteristics, CAVI or carotid parameters between the antihypertensive drug–treated patients ($n=49$) and non-treated patients ($n=21$), with the exception of DBP (antihypertensive drug–treated patients: 84±11; non-treated patients: 92±11; $p<0.0085$).

Correlation between CAVI and Clinical Variables

We examined the relationships between CAVI and pro-atherosclerotic factors such as age, SBP and DBP, pulse pressure, serum creatinine, HbA1c, TC, TG and HDL-C. The univariate linear regression analysis showed that CAVI was strongly correlated with age ($r=0.609$, $p<0.0001$) and pulse pressure ($r=0.620$, $p<0.0001$), weakly correlated with SBP ($r=0.279$, $p=0.0192$) and HbA1c ($r=0.275$, $p=0.0022$), and not correlated at all with DBP ($r=0.175$, $p=0.1469$), serum creatinine ($r=0.133$, $p=0.2716$), TC ($r=0.043$, $p=0.7241$), TG ($r=0.071$, $p=0.5608$) or HDL-C ($r=0.101$, $p=0.4032$) (Table 2). There were no correlations between CAVI and TC, TG or HDL-C even in the 62 patients who did not take statins.

A stepwise multiple regression analysis was performed to evaluate the independent determinants of CAVI using age, SBP, pulse pressure and HbA1c as covariates. Pulse pressure and age were found to be independent determinants of CAVI (partial correlation coefficients: $\beta=0.492$ and $p<0.0001$ for pulse pressure, $\beta=0.475$ and $p<0.0001$ for age).

Correlation between CAVI and Carotid Ultrasound Parameters

There was a significant positive correlation between CAVI and IMT ($r=0.360$, $p=0.0022$) (Fig. 1a), but not between CAVI and plaque score ($r=0.116$, $p=0.3409$) (Fig. 1b). There was also a weak positive correlation between CAVI and stiffness β ($r=0.270$, $p=0.0239$) (Fig. 1c) and a weak negative correlation between CAVI and CSDC ($r=-0.315$, $p=0.0079$) or V_d/V_s ($r=-0.471$, $p<0.0001$) (Fig. 1d and e, respectively). The independent determinant factor of CAVI

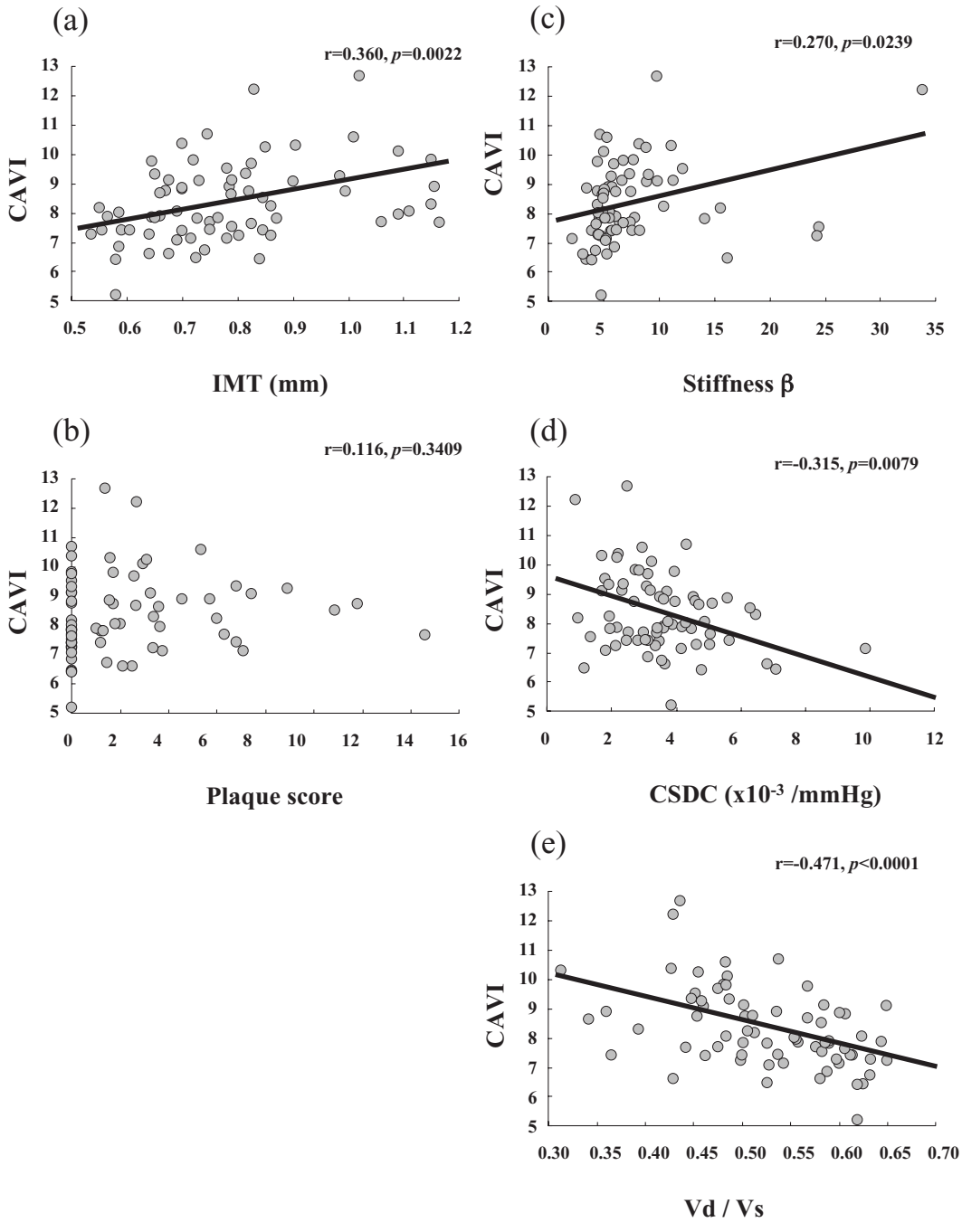

Fig. 1. *Relationship between CAVI and carotid parameters. CAVI was correlated significantly with IMT (a), stiffness* β *(c), CSDC (d) and* V_d/V_s *(e) but not with plaque score (b).*

was V_d/V_s (β=−0.471, p<0.0001) estimated by a stepwise regression analysis using IMT, PS, CSDC, β and V_d/V_s as covariates.

Discussion

Aortic PWV is an independent predictor of cardiovascular risk in the general population and an independent predictor of cardiovascular mortality in patients with essential hypertension (*1–3*). Recently a new index, baPWV, has been developed to provide a more convenient assessment of arterial stiffness (*5*, *6*). However, this method is influenced by both blood pressure and the autonomic nervous system (*12*). To overcome these disadvantages, CAVI, which is not influ-

enced by blood pressure, has been developed in Japan (*11–13*). Shirai *et al*. (*13*) and Wakabayashi *et al*. (*20*) reported that CAVI was associated with SBP but not with DBP in dialysis patients and type 2 diabetes patients, respectively. In the present study, CAVI was weakly related to SBP. It has previously been established that CAVI measurement is not affected by blood pressure levels, although CAVI may be affected by the presence of long-term hypertension. CAVI might be able to evaluate the risk of blood pressure during long term for arteriosclerosis properly (*13*).

The present study is the first report of the relationships between CAVI and carotid ultrasound parameters in patients with essential hypertension. The results showed that CAVI was related to carotid IMT, CSDC, stiffness β and V_d/V_s. Atherosclerosis involves a combination of fatty degeneration (atherosis) and vessel stiffening (sclerosis) of the arterial wall (*21*). Arterial stiffness is usually assessed in the aorta by measuring carotid-femoral PWV, but it can also be assessed in the CCA by measuring the distensibility coefficient. Atherosis is commonly assessed by IMT and the presence of plaques in the carotid artery (*22*). A significant relationship between PWV and IMT has been demonstrated, especially in the general population (*22*, *23*). However, these studies showed that the strength of the correlation between aortic and carotid stiffness became weaker as the number of cardiovascular risk factors increased (*23*). In the present study, CAVI was related to IMT but not to plaque score. Yambe *et al*. reported that baPWV was positively correlated with both IMT ($r=0.32$, $p<0.01$) and plaque score in hypertensive patients (*14*). However, the correlation between baPWV and plaque score was very weak ($r=0.24$, $p<0.01$). Tamaki *et al*. reported that baPWV was associated with the existence of plaque, but not with the severity of plaque in patients with cerebral thrombosis (*24*). In another study, plaque score was reported to be more closely related to serum CRP level than to IMT (*25*). CRP level has also been shown to be correlated with visceral fat accumulation and therefore linked to the metabolic syndrome and type 2 diabetes (*26*, *27*). Wakabayashi *et al*. reported that CRP was significantly associated with CAVI in patients with type 2 diabetes (*20*). These reports and our results suggest that the correlation between CAVI and plaque score may be stronger in patients with type 2 diabetes than in patients with hypertension. Indeed, Masugata *et al*. reported that baPWV was associated with plaque score in type 2 diabetes ($r=0.37$, $p=0.001$) (*28*). Another reason for the lack of a significant relationship between CAVI and plaque score may have been that about one-half of the patients 33 (47%) had a "zero" plaque score, which reduced the power of the statistical analysis to demonstrate a significant relationship.

The progression of arteriolosclerosis, as in the hyaline degeneration of arterioles, increases arterial stiffness and small arteriolar resistance leading to a decrease in diastolic flow velocity. We reported previously that relative diastolic blood flow, V_d/V_s, in the CCA of hypertensive patients was correlated with the intra-renal pulsatility index and resistive index evaluated by a Doppler flow method (*18*). This finding indicated that V_d/V_s is a useful index for evaluating peripheral resistance and arterial stiffness. It is interesting to note that, in the present study, the strongest and most independent association between CAVI and a carotid parameter was the association with V_d/V_s, a hemodynamic parameter ($r=0.471$, $p<0.0001$).

We have shown previously that there is a correlation between stiffness β, CSDC, V_d/V_s and hypertensive target organ damage. Hypertensive patients with left ventricular hypertrophy had a higher stiffness β and lower CSDC and V_d/V_s than normotensive subjects (*17*). We have also reported a negative correlation between V_d/V_s and the severity of asymptomatic cerebral deep gray matter lesions, "etat crible," estimated by brain MRI (*29*). In the present study, we found a significant correlation between CAVI and stiffness β, CSDC, and V_d/V_s, in addition to IMT, suggesting that CAVI may serve as a useful clinical marker of arteriosclerosis and atherosclerosis.

BaPWV has been reported to be associated with waist circumference, HDL-C, TG, uric acid, fasting glucose, fasting insulin and HbA1c, in addition to SBP and DBP (*30*). The present study in hypertensive patients showed that CAVI was associated with HbA1c but not with HDL-C and TG, despite the exclusion of diabetic patients from the study. CAVI may therefore be useful for evaluating the atherosclerotic state, especially in patients with impaired glucose tolerance and type 2 diabetes patients as well as hypertensive patients.

There were several limitations in our study, namely that the study population was relatively small and that we could not eliminate the effect of medications on CAVI level. Another limitation of this study is that brachial SBP and DBP were used to calculate the carotid CSDC and stiffness β instead of carotid SBP and DBP, respectively. Physiologically, mean blood pressure and DBP are nearly identical in the carotid and brachial arteries, whereas SBP and pulse pressure are significantly higher in the brachial arteries than the carotid arteries, although the differences are minimized with aging (*31*). This may be a reason that CAVI was associated with stiffness β and CSDC, although these associations were relative weak.

In conclusion, we demonstrated that CAVI was associated with carotid IMT, CSDC, strain β and V_d/V_s in patients with essential hypertension. CAVI may serve as a useful clinical marker for arteriolosclerosis and atherosclerosis in patients with essential hypertension.

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