Relationship of Cardio-Ankle Vascular Index (CAVI) to Carotid and Coronary Arteriosclerosis

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Background The cardio-ankle vascular index (CAVI) has been recently reported as a new index of aortic stiffness, which is less influenced by blood pressure than pulse wave velocity (PWV). The present study investigated the relationship between the levels of CAVI and carotid and coronary arteriosclerosis.

Methods and Results The 443 consecutive patients who underwent CAVI, carotid sonography, and coronary angiography in hospital were examined. Intima-media thickness (IMT) and carotid plaque were evaluated by ultrasonography. The severity of coronary artery disease (CAD) was evaluated by coronary angiography and the subjects were divided into 4 groups (0, no significant organic stenosis; 1, 1-vessel disease; 2, 2-vessel disease; 3, 3-vessel disease). Univariate analyses showed that both CAVI and brachial-ankle PWV (baPWV) were associated with IMT and the presence of carotid plaque. Multiple stepwise regression analyses revealed that CAVI (p=0.0427), but not baPWV, was associated with the IMT. Both CAVI (p<0.0001) and baPWV (p=0.0140) were significantly associated with the severity of CAD. Multiple logistic analyses revealed that CAVI (p<0.0001) and baPWV (p=0.0140) were independently associated with the risk factors and organ damage associated with cardiovascular diseases. However, a problem in clinical use is that baPWV itself essentially depends on blood pressure (BP).

Key Words: Aortic stiffness; Carotid arteriosclerosis; CAVI; Coronary artery disease

Cardiovascular and cerebrovascular diseases remain major causes of death in developed countries, and they are not entirely predicted by traditional risk factors such as aging, hypertension (HT), hyperlipidemia (HPL), smoking, and diabetes mellitus (DM). Aortic stiffness is a non-traditional risk factor, and increasing evidence has recently implied that arterial stiffness, evaluated by measuring pulse wave velocity (PWV), is a marker of all-cause and cardiovascular mortality, fatal and non-fatal coronary events, and fatal strokes in both patients with essential HT and in the general population. Aortic stiffness can be evaluated by measuring PWV between 2 sites in the arterial tree. Brachial-ankle PWV (baPWV) provides a more convenient assessment of arterial stiffness than aortic PWV, and is also closely associated with the risk factors and organ damage associated with cardiovascular diseases. However, a problem in clinical use is that baPWV itself essentially depends on blood pressure (BP).

Recently, a novel convenient arterial stiffness parameter, the cardio-ankle vascular index (CAVI), was developed by measuring PWV from the starting point of the aorta from the heart to the ankle, as well as BP, CAVI, which represents the stiffness of the aorta, femoral artery and tibial artery, is essentially independent of BP because of the adjustment of BP based on a stiffness parameter. Shirai et al demonstrated that CAVI in hemodialysis patients who have undergone percutaneous coronary intervention (PCI), or in patients with ischemic changes on electrocardiogram, was higher than in those without arteriosclerotic disease. CAVI was more useful for discriminating the probability of coronary atherosclerosis than the findings of carotid atherosclerosis by high-resolution B-mode ultrasonography. Okura et al reported that CAVI was associated with carotid arteriosclerosis in patients with HT, but only a relatively small number of patients were studied. Those findings prompted us to investigate the importance of CAVI for the development of carotid and coronary arteriosclerosis. In the present study, we examined the relationship between CAVI and carotid and coronary arteriosclerosis, and the superiority of CAVI in detecting the severity of carotid and coronary arteriosclerosis compared with baPWV.

Methods

Study Population To validate the baPWV level measured by VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan), we evaluated 26 outpatients who underwent both VaSera VS-1000 and folm PWV/ABI (Colin Co Ltd, Komaki, Japan) in hospital in April 2008.

To investigate the relationship between the level of CAVI and carotid and coronary arteriosclerosis, we evaluated 443 consecutive patients who underwent CAVI, carotid ultrasonography, and coronary angiography (CAG) for assessment of suspected coronary artery diseases (CAD) in hospital between October 2005 and August 2007. We enrolled patients without a low ankle-brachial index (ABI <0.9), systolic dysfunction (left ventricular ejection fraction <40%), atrial fibrillation/flutter, aortic disease,
second- or third-degree arterioventricular block, or valvular heart disease. The study was conducted in accordance with guidelines approved by the institutional ethics committee.

**Blood Analysis**

Blood samples were taken after the subjects had fasted overnight within 2 weeks before or after the CAVI measurement. In patients with acute myocardial infarction, serum concentrations of total cholesterol (TC) and high-density lipoprotein-cholesterol (HDL-C) were measured in the samples that were taken on admission.

**Definitions of Risk Factors**

DM was defined according to World Health Organization criteria, and/or as having received treatment for DM. HPL was defined as a TC concentration ≥220 mg/dl, a triglyceride (TG) concentration ≥150 mg/dl, and/or having received treatment for HPL. HT was defined as systolic BP (SBP) ≥140 mmHg, diastolic BP (DBP) ≥90 mmHg, or having received treatment for HT. Metabolic syndrome (MS) was defined according to National Cholesterol Education Program Adult Treatment Panel III Guidelines. Diagnosis of MS was made when 3 or more of the risk determinants (body mass index (BMI) ≥25, waist circumference measurements were not available in the present study), TG ≥150 mg/dl, HDL-C <40 mg/dl (male), <50 mg/dl (female), BP ≥130/85 mmHg, fasting blood glucose (FBS) ≥110 mg/dl) were present.

**CAG Procedure**

CAG was performed according to standard methods. After intracoronary injection of isosorbide dinitrate, angiograms were obtained in 2 or more views at baseline. Diseased artery was defined as significant (>50%) luminal diameter narrowing. An artery previously treated with PCI was defined as diseased. The coronary artery tree was divided into 3 components (left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery) for differential diagnosis among 1–3 CAD. If there was stenosis in the left main trunk artery, we diagnosed it as 2-vessel disease (both LAD and LCX were diseased).

**CAVI and BaPWV Procedures**

CAVI is a new index of arterial stiffness and is calculated as a[2/2ρΔP]×(ln SBP/DBP)×(PWV)2+a, (a,b constant; ρ, blood density; ΔP, difference in systolic and diastolic pressure). CAVI was calculated by VaSera VS-1000. Briefly, cuffs were applied to both upper arms and ankles, with the subject lying supine. After resting for 5 min, the examination was performed. To detect the brachial and ankle pulse waves with the cuffs, a low cuff pressure of 30–50 mmHg was used to ensure minimal effect of cuff pressure on hemodynamics. Next, BP was measured. Finally, scale conversion was performed for the convenience of comparison with the PWV. BP was obtained using a cuff on the upper arm. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to propagate from the aortic valve to the ankle. To be compatible with the aortic PWV method established by Hasegawa et al., scale conversion constants (a,b) were determined to match CAVI with the aortic PWV method. By using the scale conversion constants, massive previous data of PWV can be converted to CAVI. These measurements and calculation system were automatically done using the VaSera VS-1000.

For the assessment of the relationship between the level of CAVI and carotid and coronary arteriosclerosis, CAVI and baPWV were calculated by VaSera VS-1000. For the assessment of the validity of baPWV measured by VaSera VS-1000, baPWV was calculated by both VaSera VS-1000 and folm PWV/ABI.

**Ultrasound Evaluation**

The carotid arteries were evaluated with high-resolution ultrasonography (Toshiba Co, Tokyo, Japan) using a 7.5-MHz probe equipped with a Doppler system. After the subject had rested in the supine position, the neck was slightly hyperextended and optimal bilateral visualization of the carotid arteries was performed. Based on multiple visualizations, plaque formation was identified as the presence of wall thickness greater than 1.1 mm and wall thickening at least 50% greater than the thickness of the surrounding wall.

The intima–media thickness (IMT) was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. Three measurements of the IMT were made: at the thickest point by visual examination and at 2 other points (1 cm proximal and 1 cm distal to the thickest site). The average of these 3 measurements was calculated.

**Statistical Analysis**

Values are expressed as the mean±standard deviation. For TG values, logarithmic transformation was applied for the statistical tests, but untransformed values are shown in the Tables. All statistical analyses were performed using JMP (SAS Institute Inc, Cary, NC, USA). Differences in numerical data among the groups were analyzed by unpaired Student’s t-test or analysis of variance (ANOVA). Differences in frequencies among the groups were tested by contingency table analysis. Univariate linear regression analyses were performed. We used stepwise multiple regression analysis to evaluate the independent determinants of CAVI or IMT. Multiple logistic analyses were performed to evaluate the independent determinants of the presence of multi-vessel diseases. Estimated glomerular filtration fraction (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) Study equation.

**Results**

**Validity of BaPWV Measured by VaSera VS-1000**

Because folm PWV/ABI was used for the measurement of baPWV in previous studies, we investigated the correlation between baPWV levels measured by VaSera VS-1000 and those measured by folm PWV/ABI. Twenty-six outpatients were underwent baPWV measured by both VaSera VS-1000 and folm PWV/ABI. A good correlation (r=0.88, p<0.0001) was observed between the 2 measurements.

**Clinical and Procedural Characteristics**

The demographic and clinical characteristics of 443 patients are shown in Table 1. Of the 443 patients, 276 (188 men, 88 women) patients had CAVI ≥9.0, and 167 (116 men 51 women) had CAVI ≥9.0; 104 (23.5%) had acute coronary syndrome, 267 (60.2%) had stable ischemic heart
In 72 patients (16.3%), CAD was suspected before the CAG procedure, but no significant organic stenosis was observed. In addition, 18.4% of the study population had a past history of myocardial infarction. Before this study, 27.0% had a history of PCI. High CAVI (≥9.0) was associated with the presence of CAD, the severity of CAD, IMT, and the presence of carotid plaque.

Factors Associated With CAVI

In the univariate linear regression analyses, age, BMI, HT, DM, smoking habit, heart rate (HR), SBP, pulse pressure (PP), eGFR, hemoglobin (Hb) A1c, and TC correlated with CAVI (Table 2). Stepwise multiple regression analysis revealed that gender, age, BMI, DM, and HR were independently associated with CAVI (Table 2).
Factors Associated With Carotid Arteriosclerosis

In the univariate linear regression analyses, factors associated with IMT were baPWV, CAVI, age, HT, HPL, DM, smoking habit, SBP, PP, eGFR, and HbA1c (Table 3). Stepwise multiple regression analysis showed that CAVI (p=0.0427), but not baPWV, was independently associated with IMT (Table 3). The presence of carotid plaque was associated with CAVI [carotid plaque (–), CAVI \(7.9\pm1.4\); carotid plaque (+), CAVI \(8.7\pm1.8\), p=0.0005] and baPWV [carotid plaque (–), baPWV \(15.3\pm3.5\); carotid plaque (+), baPWV \(15.7\pm6.6\), p=0.0137]. However, multiple logistic analysis showed that neither CAVI nor baPWV was an independent factor.

Factors Associated With CAD

Of the 443 patients, 142 (79 men, 63 women) had no significant organic stenosis, 119 (91 men, 28 women) had 1-vessel disease, 108 (79 men, 29 women) had 2-vessel disease, and 74 (55 men, 19 women) had 3-vessel disease. BaPWV, CAVI, gender, age, HT, HPL, DM, eGFR, HbA1c, FBS and HDL-C were associated with the severity of CAD (Table 4). CAVI (p<0.0001) was more strongly associated with the severity of CAD than baPWV (p=0.0140, Table 4).

We next examined the correlation of CAVI with the presence of multivessel disease. Univariate analyses showed that patients with multivessel disease were more likely to be significant organic stenosis, 119 (91 men, 28 women) had 1-vessel disease, 108 (79 men, 29 women) had 2-vessel disease, and 74 (55 men, 19 women) had 3-vessel disease. BaPWV, CAVI, gender, age, HT, HPL, DM, eGFR, HbA1c, FBS and HDL-C were associated with the severity of CAD (Table 4). CAVI (p<0.0001) was more strongly associated with the severity of CAD than baPWV (p=0.0140, Table 4).

We next examined the correlation of CAVI with the presence of multivessel disease. Univariate analyses showed that patients with multivessel disease were more likely to be
male, with higher baPWV, CAVI, age, PP, Hba1c and FBS, higher prevalence of HPL and DM, and with lower eGFR and HDL-C (Table 5). Multiple logistic analyses including age and the foregoing parameters revealed that CAVI (p=0.0342), but not baPWV (p=0.8027), was independently correlated with the presence of multivessel disease (Table 5).

**Discussion**

The present study provides evidence that CAVI is (1) significantly associated with IMT and the presence of carotid plaques, (2) associated with the severity of CAD and the presence of multivessel disease, and (3) superior to baPWV in terms of the relationship to carotid and coronary arteriosclerosis. These results are partially consistent with previous reports. It has been reported that CAVI is independently associated with IMT in patients with essential HT, and CAVI is useful for discriminating the probability of coronary arteriosclerosis. To our knowledge, no studies have specially assessed the relationship of both CAVI and baPWV to both carotid and coronary arteriosclerosis. Furthermore, baPWV may be replaced by CAVI as a marker of the severity of arteriosclerotic vascular damage. CAVI may also be useful for evaluating aortic stiffness in drug intervention studies that evaluate drugs affecting BP.

PWV is an important diagnostic method; however, classic PWV is technically difficult and has low reproducibility. BaPWV is simple, reproducible, and independent of the examiner, but is influenced by BP. The novel stiffness parameter, CAVI, is not influenced by BP because CAVI is based on the stiffness parameter $\beta$, which is reported to be independent of BP. Recent studies show that this parameter is associated with arteriosclerotic risk factors and arteriosclerotic diseases. Moreover, CAVI may be useful in the diagnosis of arteriosclerosis in patients with heart transplantation or in those with long-term, well-controlled systemic lupus erythematosus. Otsuka et al reported that measuring CAVI may be useful, especially at high altitude, for the prevention of stroke and other adverse cardiovascular outcomes. Moreover, CAVI is independently associated with not only arterial stiffness but left ventricular diastolic stiffness in its early stages.

Many previous studies have reported that the PWV measurement predicts future cardiovascular events. In the present study, univariate analyses showed that both baPWV and CAVI were strongly associated with the severity of carotid and coronary arteriosclerosis. The correlation of the severity of carotid and coronary arteriosclerosis with aortic stiffness parameters, CAVI and baPWV, was weakened in the multivariate analyses because both the severity of carotid and coronary arteriosclerosis and the aortic stiffness parameters were significantly correlated with arteriosclerotic risk factors such as age, sex, HT and DM. Nonetheless, the stepwise multiple regression analysis revealed that CAVI, but not baPWV, was independently associated with IMT. In addition, multiple logistic analysis indicated that CAVI, but not baPWV, was independently associated with the presence of multivessel disease. Accordingly, CAVI was more useful for measuring aortic stiffness, which leads to carotid and coronary arteriosclerosis. Furthermore, baPWV may be replaced by CAVI as a marker of the severity of arteriosclerotic vascular damage. CAVI may also be useful for evaluating aortic stiffness in drug intervention studies that evaluate drugs affecting BP.

As described in the Methods, CAVI is calculated as $a[(2p/\Delta P) \times (\ln SBP/DBP) \times (PWV)^2] + b$; however, there are problems with the formula because it is based on the hypothesis that vascular diameter, BP and elastics from the aortic valve to the ankle are constant; but they are not constant. Second, BP is obtained by using a cuff on the upper arm in the CAVI measurement. Because BP and PP differ in the arterial tree, CAVI may not exactly reflect the severity of aortic stiffness between the aorta and ankle. The importance of central BP and wave reflections has been recently examined. It was reported that central PP was significantly associated with a post hoc-defined composite outcome of total cardiovascular events/procedures.

### Table 5 Characteristics of Patients With MVD

<table>
<thead>
<tr>
<th></th>
<th>MVD (–)</th>
<th>MVD (+)</th>
<th>p value</th>
<th>β</th>
<th>$\chi^2$</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>261</td>
<td>182</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BaPWV (mmHg)</td>
<td>14.7±6.0</td>
<td>16.5±7.0</td>
<td>0.0045</td>
<td>0.0004</td>
<td>0.06</td>
<td>0.8027</td>
</tr>
<tr>
<td>CAVI (mmHg)</td>
<td>8.3±1.6</td>
<td>9.0±1.9</td>
<td>&lt;0.0001</td>
<td>0.1631</td>
<td>4.49</td>
<td>0.0342</td>
</tr>
<tr>
<td>M/F</td>
<td>170/91</td>
<td>134/48</td>
<td>0.0567</td>
<td>0.2111</td>
<td>2.54</td>
<td>0.1109</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.2±11.7</td>
<td>67.4±11.0</td>
<td>0.0038</td>
<td>0.0018</td>
<td>2.08</td>
<td>0.1493</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0±3.5</td>
<td>23.8±3.5</td>
<td>0.4733</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HT (%)</td>
<td>53.6</td>
<td>59.8</td>
<td>0.1915</td>
<td></td>
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</tr>
<tr>
<td>HPL (%)</td>
<td>55.9</td>
<td>74.7</td>
<td>&lt;0.0001</td>
<td>0.5021</td>
<td>17.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>23.4</td>
<td>42.8</td>
<td>&lt;0.0001</td>
<td>0.2369</td>
<td>1.80</td>
<td>0.1794</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>39.1</td>
<td>34.0</td>
<td>0.2813</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MS (NCEP-ATP III)(yes/no, %)</td>
<td>30.5</td>
<td>36.7</td>
<td>0.1714</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67.8±13.9</td>
<td>68.9±15.4</td>
<td>0.5303</td>
<td></td>
<td></td>
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<tr>
<td>SBP (mmHg)</td>
<td>128.0±20.7</td>
<td>128.6±20.8</td>
<td>0.8099</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.0±11.9</td>
<td>74.7±10.3</td>
<td>0.0581</td>
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<tr>
<td>PP (mmHg)</td>
<td>51.1±13.7</td>
<td>53.8±16.0</td>
<td>0.0419</td>
<td>0.0029</td>
<td>0.13</td>
<td>0.7139</td>
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<tr>
<td>eGFR (ml·min⁻¹·1.73m⁻²)</td>
<td>67.7±17.7</td>
<td>60.7±16.8</td>
<td>&lt;0.0001</td>
<td>−0.0145</td>
<td>4.74</td>
<td>0.0295</td>
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<tr>
<td>HbA1c (%)</td>
<td>5.8±1.0</td>
<td>6.2±1.4</td>
<td>0.0002</td>
<td>0.0678</td>
<td>0.16</td>
<td>0.6928</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>107.3±38.5</td>
<td>120.7±50.3</td>
<td>0.0017</td>
<td>0.0027</td>
<td>0.45</td>
<td>0.5016</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>188.5±37.1</td>
<td>182.1±42.9</td>
<td>0.1004</td>
<td></td>
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<tr>
<td>HDL-C (mg/dl)</td>
<td>56.7±16.0</td>
<td>51.3±18.0</td>
<td>0.0010</td>
<td>−0.0168</td>
<td>5.89</td>
<td>0.0132</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>128.9±98.6</td>
<td>133.4±71.0</td>
<td>0.1730$^*$</td>
<td></td>
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</tr>
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</table>

In univariate analyses, differences in numerical data between the groups were analyzed by unpaired Student’s t-test and differences in frequencies between the groups were tested by contingency table analysis. Multiple logistic regression analysis was performed to evaluate the independent determinants of MVD. *Test performed on log-transformed values.

Abbreviations as in Tables 1,3.
and development of renal impairment in the Conduit Artery Function Evaluation (CAFE) cohort. A higher aortic augmentation index was associated with an increased risk of CAD in patients undergoing CAG. CAVI served as a useful clinical parameter associated with carotid and coronary arteriosclerosis in the present study, but further studies to investigate whether CAVI is a suitable parameter for aortic stiffness are required.

Study Limitations

CAVI cannot be accurately measured if the ABI <0.90. Accordingly, patients with ABI <0.90 were excluded in the present study. In addition, patients with systolic dysfunction, atrial fibrillation/flutter, aortic disease and/or valvular heart disease were also excluded because these conditions can affect arterial stiffness. The design of the present study (cross-sectional) meant that it was unable to address whether high CAVI values per se reflect progress of carotid and coronary arteriosclerosis to vascular events and mortality. Further studies using clinical long-term follow-up are required.

Conclusion

We demonstrated that CAVI is associated with carotid IMT and the presence of carotid plaques, and that it is associated with the severity of coronary arteriosclerosis and the presence of multivessel disease. CAVI may be a useful clinical marker for not only arterial stiffness but also the progression of carotid and coronary arteriosclerosis.

References