Clinical Significance and Reproducibility of New Arterial Distensibility Index

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Background  The brachial–ankle pulse wave velocity (baPWV) is used to evaluate the degree of atherosclerosis and arterial distensibility, but its major limitation is that it is affected by changes in blood pressure (BP) during measurement. Recently, a new atherosclerotic index, the cardio-ankle vascular index (CAVI), has been developed by measuring PWV and BP. CAVI is adjusted for BP based on the stiffness parameter and should measure arterial stiffness independent of BP. The purpose of this study was to evaluate the validity of CAVI compared with baPWV, the reproducibility of the measurement of CAVI, and the effect of BP changes on CAVI and baPWV.

Methods and Results  One thousand and thirty-three consecutive subjects undergoing health checkups were studied. CAVI was automatically calculated from the pulse volume record, BP, and the vascular length from heart to ankle. In this general population, both baPWV and CAVI demonstrated a positive correlation with age and systolic BP (SBP). CAVI showed a weaker correlation with SBP than baPWV. The measurement of CAVI demonstrated good reproducibility and was not affected by the increase in BP during measurement.

Conclusions  CAVI is a useful index of arterial distensibility and is not influenced by BP changes during measurement. (Circ J 2007; 71: 89–94)

Key Words: Blood pressure; Brachial–ankle pulse wave velocity; Cardio-ankle vascular index

Pulse wave velocity (PWV) has been used as a noninvasive clinical index of aortic stiffness. An elevated carotid–femoral PWV (cfPWV) has been reported to predict cardiovascular events and all-cause mortality in hypertensive patients and in the general population. Although conventional techniques for measuring cfPWV are noninvasive, a femoral artery transducer carefully adjusted to obtain an accurate pulse wave is required, which increases psychological stress. Also, such sophisticated and complex techniques are inconvenient, particularly in large clinical trials.

A simple, noninvasive, and automatic method of measuring the brachial–ankle PWV (baPWV) has been developed and a close correlation between baPWV and aortic PWV has been reported. BaPWV has also been shown to be a predictor for the presence of coronary artery disease and the diagnosis of acute coronary syndrome. Furthermore, baPWV correlates with abdominal aortic calcification and carotid intima–media thickness. We have previously reported that baPWV correlates with age in healthy subjects, suggesting that it reflects age-related changes in vascular stiffness. Along with age, blood pressure (BP) is a major determinant of baPWV. It is a problem that baPWV is affected by changes in BP during measurement. Recently, a new atherosclerotic index, the cardio-ankle vascular index (CAVI), was developed by measuring baPWV and BP. CAVI is adjusted for BP based on a stiffness parameter and is believed to measure arterial stiffness independent of BP.

We conducted this 3-part study to evaluate the validity of CAVI, comparing it with baPWV (Study 1), the reproducibility of the measurement of CAVI (Study 2), and the effect of BP changes on CAVI and baPWV (Study 3).

Methods  

Study 1: Comparison of CAVI and baPWV

The study group consisted of 1,033 consecutive subjects (567 men, 466 women, mean age: 50±15 years, range: 18–82) undergoing routine health checkups at JA Kagoshima Kouseiren Medical Health Care Center. On the basis of personal interviews, 114 subjects were receiving treatment for hypertension, 11 were receiving treatment for diabetes mellitus, and 37 were receiving treatment for hyperlipidemia; 14 subjects had a history of ischemic heart disease, and 10 had a history of stroke. Information on smoking history was obtained by means of a self-administered questionnaire. Blood samples were taken after the subjects had fasted overnight. Serum concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) were measured by standard laboratory procedures. Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedwald equation. Twelve subjects with a serum TG concentration of 400 mg/dl or higher were excluded from calculation of LDL-C.

CAVI and baPWV were measured using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan). Cuffs were applied to
the 4 extremities, and electrocardiographic electrodes were attached to the upper arm. A microphone was placed on the sternal angle for phonocardiography. The subjects rested in the supine position for 3 min. PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same wave was transmitted to the ankle, and the time difference between the 2nd heart sound on the phonocardiogram and the notch of the brachial pulse waves. To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with cuffs inflated to lower than the diastolic BP (DBP; 50 mmHg). Then, the extremity BP was measured by oscillography. Systolic BP (SBP), DBP and pulse pressure (PP) were obtained by measuring each pair of the BP at the right brachial artery. In this study, none of the patients had peripheral artery disease as evidenced by an ankle–brachial index of less than 0.9.

CAVI was obtained by substituting the stiffness parameter \( \Delta D \) in the following equation for determining vascular elasticity and PWV. The stiffness parameter indicates BP-dependent patient-specific vascular stiffness measured by arterial ultrasound. The stiffness parameter \( \Delta D \) is calculated by the following:

\[
\frac{\text{Stiffness parameter}}{\text{PWV}^2} = \frac{\ln(Ps/Pd) \times (D + \Delta D)}{AD} = CAVI.
\]

Where Ps and Pd are respectively the SBP and DBP in mmHg, D is the diameter of blood vessel and \( \Delta D \) is the change of D.

PWV can be estimated by the Bramwell-Hill equation as follows:

\[
(D + \Delta D)/\Delta D = 2 \pi \times 1/(Ps - Pd) \times \text{PWV}^2
\]

Where \( \pi \) is the density of blood.

If we substitute equation (2) for equation (1), we obtain:

\[
\frac{\text{Stiffness parameter}}{\text{PWV}^2} = 2 \pi \times 1/(Ps - Pd) \times \ln(Ps/Pd) \times \text{PWV}^2 = CAVI.
\]

The CAVI can therefore be obtained from measurement of BP and PWV.

Study 2: Reproducibility of Measurement of CAVI

CAVI was measured twice for each patient within an interval of 2 weeks between the 2 measurements in 21 consecutive patients at Kagoshima University Hospital. The reproducibility of CAVI was examined by linear regression analysis of the calculated values obtained from each pair of measurements.

Study 3: Influence of BP Changes on CAVI and baPWV

In order to analyze the effect of BP changes on CAVI and baPWV, we measured these 2 indices at the 2 time points in consecutive 62 patients taking antihypertensive medicine and selected 27 patients in whom there were changes in the SBP of more than 10 mmHg. For each index, differences between the mean values at the 2 time points of measurement were analyzed by paired t-test.

The protocol used for this study was approved by the Institutional Review Board of Kagoshima University. Informed consent was given by all volunteers and patients.

Statistical Analysis

Data are expressed as the mean±SD. Differences between mean values of 2 groups were analyzed by unpaired t-tests. In Study 3, differences between the mean values at the 2 time points of measurement were analyzed by paired t-test. The relationship between continuous variables was analyzed by linear regression analysis. The independence of the association between variables was tested with multiple regression analysis. Bland-Altman analysis was used to assess the reproducibility of CAVI measurement. Statistical analyses were performed with Stat View, version 5.0 or Prism, version 4.0, and p-values less than 0.05 were considered statistically significant.

Results

Study 1: Comparison of CAVI and baPWV

The clinical characteristics of the subjects are summarized in Table 1. There was no significant difference in age between men and women (men: 50±15 years, women: 49±15 years). The proportion of subjects with a history of smoking was significantly higher in men than in women. The differences in atherosclerotic risk factors between men and women in the general population were shown in the study subjects.

The relationships between baPWV or CAVI and age or SBP were analyzed. BaPWV and CAVI correlated positively with age in men (baPWV: r=0.752, CAVI: r=0.770, p<0.0001, respectively) (Figs 1A, B) and in women (baPWV: r=0.752, CAVI: r=0.750, p<0.0001, respectively) (Figs 2A, B).

Because the conventional measurement of PWV is dependent on BP, the relationships of baPWV and CAVI to SBP were analyzed. BaPWV strongly correlated with BP in both men and women (Figs 1C, 2C), whereas CAVI only correlated with SBP in women (Figs 1B, 2B).

In men, baPWV significantly correlated with TC, TG, fasting blood sugar (FBS), hemoglobin (Hb) A1c, blood urea nitrogen (BUN) and serum creatinine, and CAVI sig-

### Table 1 Characteristics of Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=567)</th>
<th>Women (n=466)</th>
<th>All subjects (n=1,033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50±15</td>
<td>49±15</td>
<td>50±15</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.5±3.2</td>
<td>21.8±3.2*</td>
<td>22.8±3.3*</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>204±33</td>
<td>207±33</td>
<td>205±32</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>128±82</td>
<td>88±54*</td>
<td>110±73</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>53±14</td>
<td>63±15*</td>
<td>58±15*</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>124±31</td>
<td>126±29</td>
<td>125±30</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>106±21</td>
<td>98±19*</td>
<td>103±21</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.3±0.7</td>
<td>5.2±0.5**</td>
<td>5.2±0.6</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>16.2±4.1</td>
<td>14.5±4.0*</td>
<td>15.4±4.2</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8±0.2</td>
<td>0.6±0.1*</td>
<td>0.7±0.2</td>
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<td>UA (mg/dl)</td>
<td>5.9±1.2</td>
<td>4.2±1.0*</td>
<td>5.2±1.4</td>
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<td>HR (beats/min)</td>
<td>70±12</td>
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<td>70±12</td>
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<td>SBP (mmHg)</td>
<td>129±15</td>
<td>122±18*</td>
<td>126±17</td>
</tr>
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<td>DBP (mmHg)</td>
<td>83±11</td>
<td>77±12*</td>
<td>81±12</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>100±14</td>
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<td>98±15</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>46±9</td>
<td>45±11</td>
<td>45±10</td>
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<td>Smoking history (%)</td>
<td>60</td>
<td>4*</td>
<td>36</td>
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<tr>
<td>baPWV (cm/s)</td>
<td>1.383±290</td>
<td>1.318±272*</td>
<td>1.354±284</td>
</tr>
<tr>
<td>CAVI</td>
<td>8.5±1.3</td>
<td>8.1±2.3*</td>
<td>8.3±1.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; UA, uric acid; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index.

*p<0.05 vs men; **p<0.0001 vs men.

\( \Delta D = \frac{2 \pi \times 1}{(Ps - Pd)} \times \text{PWV}^2 \)

\( \frac{\text{Stiffness parameter}}{\text{PWV}^2} = 2 \pi \times 1/(Ps - Pd) \times \ln(Ps/Pd) \times \text{PWV}^2 = CAVI. \)
Fig 1. Relationship between baPWV and age (A), CAVI and age (B), baPWV and SBP (C), and CAVI and SBP (D) in 567 men. baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure.

Fig 2. Relationship between baPWV and age (A), CAVI and age (B), baPWV and SBP (C), and CAVI and SBP (D) in 466 women. baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; SBP, systolic blood pressure.
significantly correlated with FBS, HbA1c, BUN, and serum creatinine (Table 2). In the multiple regression analysis of baPWV or CAVI and other clinical variables baPWV independently correlated with age, SBP, history of smoking, TG and FBS, and CAVI independently correlated with age, SBP, TG and history of smoking (Table 3).

In women, baPWV significantly correlated with TC, TG, HDL-C, LDL-C, FBS, HbA1c, BUN, serum creatinine and uric acid, and CAVI significantly correlated with TC, TG, HDL-C, LDL-C, FBS, HbA1c, BUN and uric acid (Table 2).

In the multiple regression analysis between baPWV or CAVI and other clinical variables baPWV independently correlated with age, SBP and PP, and CAVI independently correlated with age and serum creatinine (Table 3).

In all subjects, multiple regression analysis showed that baPWV independently correlated with age, FBS, SBP and smoking.
Study 2: Reproducibility of Measurement of CAVI

The reproducibility of CAVI measurements was analyzed in 21 consecutive patients at Kagoshima University Hospital. CAVI was measured twice for each patient with an interval of 2 weeks. There was no significant difference in BP between the 2 measurements. Linear regression analysis showed a very strong correlation between the 2 measurements of CAVI (r=0.93, p<0.0001). In Bland-Altman plots, the mean difference of 2 measurements was 0.2, and the 95% limits of agreement (mean ±1.96SD) was –1.2 and 1.7.

Study 3: Effect of BP Changes on CAVI and baPWV

To analyze the effect of BP changes on CAVI and baPWV, we measured that these 2 indices at the 2 time points in 27 patients who showed a change in SBP of more than 10 mmHg (13.3±3.2 mmHg, range 10–20 mmHg). Although baPWV increased in proportion to the increase in SBP, CAVI did not show a significant change between the 2 measurements (baPWV: 1,433±348 cm/s vs 1,489±381 cm/s, p<0.05; CAVI: 9.0±1.5 vs 9.1±1.5, not significant).

Discussion

In Study 1, both baPWV and CAVI demonstrated positive correlations with age and SBP, although CAVI showed a weaker correlation with SBP than did baPWV. In Study 2, good reproducibility of the CAVI measurements was demonstrated and in Study 3, we demonstrated that CAVI was not affected by changes in BP.

Aging causes degeneration of elastic fibers and is associated with stretching and remodeling of the arterial wall, which leads to increased collagen fibers and accumulation of smooth muscle cells. With aging, arteries progressively stiffen, dilate, and lengthen, and the arterial wall thickens. Increased arterial stiffness has been reported to lead to the age-related increase in PWV. Consistent with those previous reports, in the present study we demonstrated that CAVI, as with baPWV, significantly correlated with age.

Along with age, BP is a major determinant of PWV. PWV increases with increased stiffness of the vascular wall and increases in the internal pressure. CAVI is adjusted for BP based on the stiffness parameter and is hypothesized to measure arterial stiffness independent of BP. In the present study, CAVI demonstrated a weaker correlation with SBP than did baPWV. Furthermore, multiple regression analysis demonstrated that SBP was not an independent determinant of CAVI in women. Shirai et al recently reported that CAVI was correlated weakly with SBP and DBP compared with baPWV in 482 hemodialysis patients, which is the same tendency shown in our results, which were obtained in a general population.
It is problematic that baPWV increases with increases in the BP during measurement and patients have to rest prior to measurement in order to avoid the influence of changes in the BP. In this study, we demonstrated that CAVI is not influenced by an increase in BP during measurement. In Bland-Altman plots, the mean difference of 2 measurements should be 0 if there is perfect agreement. The reproducibility of measurement of CAVI was considered to be high, because the mean difference was 0.2 and the 95% limits of agreement was within the normal tolerance. Therefore, we suggest that CAVI may be useful for routine examination and large clinical trials. Although CAVI was not affected by a change of BP during measurement, as shown in this study, hypertension is an atherosclerotic risk factors, so CAVI may be influenced by the effect of hypertension on arterial stiffness.

Study Limitation

CAVI cannot be measured accurately in patients with aortic stenosis, peripheral arterial disease, or atrial fibrillation. An ankle–brachial pressure index (ABI) <0.95 has been reported to be the cut-off value for diminished baPWV accuracy20 and CAVI cannot be measured accurately if the ABI is less than 0.95. Further studies are needed to evaluate the clinical value of CAVI.

In summary, baPWV and CAVI increased with aging in a general population. CAVI demonstrated a weaker correlation with SBP compared with baPWV and was not affected by an increase in BP during measurement. We conclude that CAVI may be a new and useful index of arterial distensibility and is independent of BP changes.

References