A Novel Blood Pressure-independent Arterial Wall Stiffness Parameter; Cardio-Ankle Vascular Index (CAVI)

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To measure the stiffness of the aorta, femoral artery and tibial artery noninvasively, cardio-ankle vascular index (CAVI) which is independent of blood pressure was developed. The formula for measuring this index is:

\[ \text{CAVI} = a(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2 + b \]

where, Ps and Pd are systolic and diastolic blood pressures respectively, PWV is pulse wave velocity between the heart and ankle, \( \Delta P = Ps - Pd \), \( \rho \) is blood density, and a and b are constants. This equation was derived from Bramwell-Hill’s equation¹, and stiffness parameter².

To elucidate the clinical utility of CAVI, the reproducibility and dependence on blood pressure were studied using VaSera (Fukuda Denshi Co., Ltd.). Furthermore, CAVI in hemodialysis patients with or without atherosclerotic diseases was measured.

The average coefficient of variation for five measurements among 22 persons was 3.8%. In hemodialysis patients (n = 482), CAVI was correlated weakly with systolic and diastolic blood pressures (R = 0.175, 0.006), while brachial-ankle PWV was correlated strongly with systolic and diastolic blood pressures (R = 0.463, 0.335). CAVI in hemodialysis patients without signs of atherosclerotic diseases (NA) was 8.1 ± 0.3 (mean ± SD). That in patients receiving percutaneous transluminal coronary angioplasty was 8.8 ± 0.3 (p < 0.05 vs. NA). CAVI in patients with ischemic change in their electrocardiogram (ECG) was 8.5 ± 0.3 (p < 0.05 vs. NA). That in patients with diabetes mellitus was 8.5 ± 0.3 (p < 0.002 vs. NA). CAVI in the patients with all three complications was 8.9 ± 0.35 (p < 0.001 vs. NA). These results suggested that CAVI could reflect arteriosclerosis of the aorta, femoral artery and tibial artery quantitatively.


Key words; Arteriosclerosis, PWV, CAVI, Hemodialysis, Stiffness parameter, Vascular function

Introduction

Arteriosclerosis is a major contributor to cardiovascular-and cerebrovascular diseases accounting for much of the mortality and morbidity.³,⁴ The increase in cases of metabolic syndrome which raises multiple risks is becoming a serious problem throughout the world, because the probability of arteriosclerotic diseases such as cardio-and cerebro-vascular diseases developing in young, middle-aged as well as elderly persons with this syndrome is high.⁵,⁷ The situation requires a simple and quantitative diagnostic index of arteriosclerosis.

For the evaluation of arteriosclerosis or vascular function, several parameters such as pulse wave velocity (PWV) and the change in diameter of the vessel wall have been used.¹,²,⁸,⁹ That is contraction of the left ventricular myocardium and the ejection of blood into the ascending aorta enlarge the diameter of the
aorta, and generate a pulse wave, which is propagated throughout the arterial tree at a speed determined by the elastic and geometric properties of the arterial wall and blood density. Actually, the structure of the arterial wall is complicated. The wall is composed of an endothelial cell layer, an intimal layer, a medial layer, and adventitia. The components are smooth muscle cells, various fibers such as collagen, elastin and glycoprotein \(^{10-12}\). Furthermore, muscular arteries are under the control of nerves. The blood vessel is not a Hookean substance.

In spite of the many factors affecting the stiffness of the arterial wall, PWV could be calculated using the formula: Velocity = D/T, where D represents the distance traveled by the pulse between two recording sites, proximal and distal, and T represents the time needed by the front wave to travel from one site to the other. In the case of Hasegawa’s method of calculating PWV\(^8\), D is \(1.3 \times (\text{length from aortic valve to inguinal portion of the femoral artery})\). T is a summation of the time interval between the feet of the carotid wave and of the inguinal wave, and the time interval between heart sound II (aortic valve closure sound) and the notch of the carotid pulse wave. A problem in clinical use is that PWV itself is essentially dependent on blood pressure. Then, Hasegawa and coworkers\(^8\) obtained PWV variability depending on diastolic pressure from studies using human aorta, and made a nomogram compensating PWV by diastolic pressure. Using this nomogram, they established the aortic PWV method (aPWV, Hasegawa’s method)\(^2\). Using this method, several researchers have reported valuable results\(^13-16\). Shoji et al.\(^15\) reported that intermediate density lipoprotein is most closely associated with aortic PWV in hemodialysis patients. Saito et al.\(^16\) reported that serum calcium \& inorganic phosphate (Pi) value was significantly correlated with the degree of increase in PWV. These results suggested that measuring vascular stiffness could provide information useful for controlling arteriosclerotic diseases.

However, the detection of carotid and femoral pulse waves had several difficulties in finding the notch of the pulse wave, and required some technical skill. Thus, it has not been widely used for routine study.

Hayashi et al.\(^2\) proposed the stiffness parameter \(\beta\), which represents the local stiffness of a blood vessel. The parameter is based on a change in vascular diameter corresponding to arterial pressure variance and does not depend on blood pressure. Using systolic pressure and diastolic pressure, Kawasaki et al.\(^17\) defined \(\beta\) as \(\ln (\mathrm{Ps/Pd}) \cdot D/\Delta D\) which enabled the measurement of \(\beta\) with an echo phase tracking system. However, there were also some problems: \(\beta\) reflected the property of local segments of the arteries, and special ultrasonic equipment was required for detecting D/\(\Delta D\).

Thus, a new index which reflects the properties of the whole artery has long been desired.

Here, a cardio-ankle vascular index (CAVI), which essentially represents the stiffness of the aorta, femoral artery and tibial artery, was developed. CAVI is essentially independent of blood pressure.

In this paper, we described the theory behind CAVI, and clarified the clinical utility in determining arteriosclerosis quantitatively among patients on hemodialysis.

### Subjects and Methods

1. **Principle of CAVI and method of measurement**

Bramwell-Hill’s formula\(^1\) expresses the relationship between volume elastic modulus and pulse wave velocity (PWV) as follows;

\[
\text{PWV}^2 = \Delta P / \rho \cdot V / \Delta V
\]

\(\Delta P\): pulse pressure, \(V\): volume of blood vessel, \(\Delta V\): change of \(V\), \(\rho\): blood density

From equation 1, the following formula is derived.

\[
V / V = D / D / 2 = 2 \rho / \Delta P \cdot \text{PWV}^2
\]

\(D\): Diameter of blood vessel, \(\Delta D\): change of \(D\)

Equation 2 is derived from equation 1 as follows:

Supposing that a blood vessel is a cylindrical model of length \(L\) and diameter \(D\), the volume \(V\) is:

\[
V = \rho L (D / 2)^2
\]

Accordingly, a volumetric change, \(\Delta V / V\) is:

\[
\Delta V / V = [\pi L ((D + \Delta D) / 2)^2 - \pi L (D / 2)^2] / \pi L (D / 2)^2
\]

\(= (D + 2 \Delta D + D^2 - D^2) / (D^2)
\]

\(= (2 \Delta D + D^2) / D^2\)

\(= (2 \Delta D) / (D + (D / D))^2\)

Since \((\Delta D / D)^2\) is very small compared with \((2 \Delta D) / D\), it may be ignored. Then, \(\Delta V / V = (2 \Delta D) / D\). Namely, \(V / V = D / 2 \Delta D\)

Thus, equation 2 can be obtained by replacing \(V / V\) of equation 1 with \(D / 2 \Delta D\)

Next, equation 2 is changed to the following equation of the stiffness parameter: \(\beta = \ln (\mathrm{Ps/Pd}) \cdot (D / \Delta D)\)

Then, \(\beta’ = \ln (\mathrm{Ps/Pd}) \times 2 \rho / \Delta P \times \text{PWV}^2\) is obtained. This equation means that a new index can be determined, when PWV is measured between the aortic valve and the ankle. This new index is named the cardio-ankle vascular index (CAVIo).

That is, \(\text{CAVIo} = \ln (\mathrm{Ps/Pd}) \times 2 \rho / \Delta P \times \text{PWV}^2\)

Thus, CAVIo reflects stiffness of the aorta and femoral artery and tibial artery as a whole, and is not affected
Patients were placed supine. Electrocardiogram and heart sound were monitored. PWV from the heart to the ankle was obtained by measuring the length from the aortic valve to the ankle, and by \( T = \text{tb} + \text{tba} \). The blood pressure was measured at the brachial artery. \( \text{Ps} \): systolic blood pressure, \( \text{Pd} \): diastolic blood pressure, \( \text{PWV} \): pulse wave velocity, \( \Delta \text{P} \): \( \text{Ps} - \text{Pd} \), \( \rho \): blood density, \( L \): length from Aortic Valve to Ankle, \( T \): time taken for the pulse wave to propagate from the aortic valve to the ankle, \( \text{tba} \): time between the rise of brachial pulse wave and the rise of ankle pulse wave, \( \text{tb} \): time between aortic valve's closing sound and the notch of brachial pulse wave, \( \text{t'}b \): time between aortic valve's opening sound and the rise of brachial pulse wave.

To detect the brachial and ankle pulse waves with cuffs, the pressure of the cuffs is kept low at 30 mmHg to 50 mmHg to ensure a minimal effect of cuff pressure on the hemodynamics. Furthermore, blood pressure is measured thereafter.

Finally, for the convenience of comparison with the PWV, scale conversion is performed:

\[
\text{CAVI} = a \left( 2 \rho / \Delta \text{P} \right) \times \ln (\text{Ps}/\text{Pd}) \times \text{PWV}^2 + b
\]

\( \text{Ps} \): systolic blood pressure, \( \text{Pd} \): diastolic blood pressure, \( \text{PWV} \): pulse wave velocity, \( \Delta \text{P} \): \( \text{Ps} - \text{Pd} \), \( \rho \): blood density, \( a \) and \( b \): constants.

Scale conversion constants are determined so as to match CAVI with PWV (Hasegawa's method). All these measurements and calculations were made together and automatically in VaSera (Fukuda Denshi Co. LTD, Tokyo).

Brachial-ankle pulse wave velocity (baPWV) was measured according to a previous report\(^{(18)}\), also using VaSera.

### 3. Subjects

For determination of the reproducibility of CAVI,
the index was measured 5 times on different days in twenty two healthy volunteers. The coefficient of variation (CV) of each person was obtained as was the mean CV.

For the study on the clinical usage of CAVI, the index was measured in hemodialysis patients (n = 482). Measurements were performed at 30 min to 60 min during hemodialysis. At that time, the hemodynamics of the patients was most stable. Among the patients, arteriosclerotic patients were those receiving percutaneous trans-luminal coronary angioplasty (PTCA), because stenosis of the coronary arteries was found. Furthermore, patients with ischemic changes in their electrocardiogram such as ST depression and negative T, and patients with diabetes mellitus were included. Patients without arteriosclerotic signs were those who had no clinical signs and no history of ischemic arterial disease.

Statistical analysis
The relation between blood pressure and baPWV or CAVI was investigated by simple regression analysis. Data on the CAVI of groups with or without arteriosclerotic diseases were presented as the mean ± SD and subjected to one-way ANOVA with Dunnett’s multiple comparison of means test. A value of $P<0.05$ was regarded as significant.

Results

1. Reproducibility
Twenty two testees were subjected to CAVI measurements, five times each, on different days, but at the same time of day. The results are shown in Table 1. The average coefficient of variation for the five measurements in all testees was 3.8%. This value was less than 5%, and small enough for clinical usage, indicating that CAVI had good reproducibility.

2. The relationship between blood pressure and CAVI or baPWV
To examine the relationship between blood pressure and CAVI or baPWV, CAVI and baPWV were measured in hemodialysis patients (n = 482) using VaSera (Fukuda Denshi, Co. LTD). Fig. 2 shows the relationships. The upper row shows the relationship between baPWV and blood pressure. As systolic and diastolic pressures were becoming high, baPWV became high significantly (r = 0.463, $p < 0.0001$, r = 0.3353, $p < 0.0001$, respectively) indicating that baPWV is affected greatly by blood pressure.

The lower row in Fig. 2 shows the relationship between CAVI and blood pressure. When systolic pressure was becoming high, CAVI increased significantly but slightly (r = 0.1750, $p < 0.001$), indicating that CAVI is dependent on systolic blood pressure, but less so than baPWV.

When diastolic pressure was becoming high, CAVI scarcely increased (r = 0.0063, $p = 0.8903$). These results indicated that CAVI was correlated weakly with blood pressure, compared with baPWV.

3. CAVI in patients with arteriosclerotic diseases
The usefulness of CAVI for the diagnosis of arteriosclerosis was examined in dialysis patients with or without arteriosclerotic diseases. The background of the patients is shown in Table 2. In a preliminary study, CAVI was apparently low in patients with a low ankle-brachial pressure index (less than 0.9), which is the ratio of ankle blood pressure to brachial blood pressure (data not shown). Then, the patients with a low ABI ($<0.9$) were excluded. Ages were from 40 to 79 years, and the mean age of each of the groups was 63 years.

Fig. 3 shows the CAVI in various arteriosclerotic

<table>
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<tr>
<th>Volunteer</th>
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<th>CAVI (mean)</th>
<th>%CV</th>
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<td>0.18</td>
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</table>

Mean is the mean of 5 measurements for each person on different days.
patients on hemodialysis. CAVI in patients (n = 229) without signs of atherosclerotic diseases was 8.1 ± 0.3 (mean ± SD). That in patients receiving percutaneous transluminal coronary angioplasty (PTCA) (n = 18) was 8.8 ± 0.3. CAVI in patients with ischemic change in their electrocardiogram (ECG) (n = 49) was 8.5 ± 0.3. That in patients with diabetes mellitus (n = 66) was 8.5 ± 0.3. CAVI in the diabetic patients with PTCA and/or ischemic change in ECG (n = 28) was 8.9 ± 0.35. CAVI in the latter four groups was significantly higher than that in the patients without signs of atherosclerotic disease (p < 0.05, p < 0.05, p = 0.002, p = 0.001). The mean ages of the above 5 groups were not significantly different.

These results suggested that CAVI could reflect arteriosclerosis of the aorta, femoral artery and tibial artery quantitatively.

**Discussion**

The theory of CAVI, which reflects stiffness of the aorta, femoral artery and tibial artery as a whole, was described. CAVI is essentially the stiffness parameter of a long segment of arterial wall and can be determined by measuring PWV and blood pressure.

The reproducibility of CAVI was 3.8%. This value is within a satisfactory range, because it is generally accepted that 5% is the limit for clinical laboratory testing. Measurement is easy and does not need special techniques. Thus, it can be used in routine studies.

CAVI was correlated weakly with systolic and diastolic blood pressures, compared with baPWV (Fig. 2). The reason for this is that baPWV is theoretically affected by the blood pressure at the time of measurement, whereas CAVI might not be affected by the blood pressure when it is measured, but is probably affected by a hypertensive state long term. This is an important merit of CAVI, because the effect of blood pressure on CAVI is relatively weak.

**Table 2. Subjects on hemodialysis (0.9 ≤ ABI < 1.3)**

<table>
<thead>
<tr>
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<th>Total</th>
<th>male</th>
<th>female</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>390</td>
<td>263</td>
<td>127</td>
</tr>
<tr>
<td>age</td>
<td>59.8 ± 10.8</td>
<td>59.7 ± 10.7</td>
<td>60.1 ± 11.1</td>
</tr>
<tr>
<td>Hemodialysis year</td>
<td>7.6 ± 7.0</td>
<td>7.3 ± 6.7</td>
<td>8.3 ± 7.5</td>
</tr>
</tbody>
</table>

mean ± SD
pressure control with antihypertensive drugs or other means on proper vascular stiffness could be evaluated. Namely, the risk of blood pressure during long term for arteriosclerosis could be evaluated properly. CAVI in hemodialysis patients without signs of atherosclerotic disease was 8.1 ± 0.3. That in arteriosclerotic patients receiving percutaneous transluminal coronary angioplasty (PTCA) or in patients having ischemic change in their electrocardiogram (ECG) was higher than the values for those without arteriosclerotic diseases. Patients with diabetes mellitus also had a significantly higher CAVI. Patients having diabetes mellitus, and PTCA or ECG abnormality showed the highest CAVI. These results suggested that CAVI might quantitatively reflect the degree of arteriosclerosis. However, it is worth noting that CAVI measures the properties of the aorta, femoral artery and tibial artery as a whole. The aorta is an elastic vessel, while the femoral artery and tibial artery are muscular vessels under the control of nerves. Accordingly, CAVI could be affected by vasospasms of the arteries. To avoid such effect, vascular stress should be minimized. For this purpose, patients should be kept resting on a bed for a while before the test, so that their hemodynamics are stabilized. And, the brachial and ankle pulse waves are detected with the cuff pressure as low as possible such as 30 mmHg to 50 mmHg, before measuring blood pressure requiring much more high cuff pressure.

In patients with a severe arteriosclerotic femoral artery (ABI <0.9), CAVI was apparently low (data not shown). Thus, CAVI in such cases should be regarded as a false value.

In summary, new concept of measuring the stiffness of the aorta, femoral artery, and tibial artery as a whole was proposed. A device for measuring it was also developed. From studies on hemodialysis patients, this new index, CAVI, is considered to reflect arteriosclerosis. The usefulness of CAVI will have to be verified further by accumulating clinical data.

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**References**

5. Friedrich MJ: Epidemic of obesity expands its spread to
developing countries. JAMA, 2002; 287:1382-1386.