Aim: The Cardio-Ankle Vascular Index (CAVI) is a stiffness index of the arterial tree from the origin of the aorta to the ankle, independent of blood pressure at the time of measurement. The CAVI equation includes the coefficients “a” and “b” to adjust it to the value of Hasegawa’s pulse wave velocity, which is compensated for at 80 mmHg of diastolic pressure. To verify this adjustment with the coefficients, the clinical significance of CAVI and CAVI without the coefficients (ha К b) were compared in both an epidemiological study and an acute clinical study.

Methods: In the epidemiological study, the significances of CAVI and ha К b among people with or without coronary risks such as hypertension, dyslipidemia, hyperglycemia, and abnormal electrocardiography change, were compared. In the acute clinical study, nitroglycerin was administered to subjects in a control group and to coronary artery disease patients, observing CAVI and ha К b values over a 20-min period.

Results: There was no discrepancy in terms of statistically significant differences between CAVI and ha К b among subjects with or without risk factors. Furthermore, there was also no discrepancy in terms of statistically significant differences between CAVI and ha К b during the changes of those values following nitroglycerin administration over a 20-min period.

Conclusion: In both the epidemiologic and clinical studies, there was no discrepancy in terms of significant differences between CAVI and ha К b. These results suggest that both are valid as indices of stiffness of the arterial tree from the origin of the aorta to the ankle.

Key words: Hasegawa’s pulse wave velocity, Stiffness Parameter β, CAVI, ha К b

Introduction

Arterial stiffness is a surrogate marker of arteriosclerosis and is established as a good predictor of cardiovascular events. Several methods have been designed to assess arterial stiffness, including pulse wave velocity (PWV), and plenty of valuable data have been reported using PWV. However, theoretically, PWV is known to depend directly on blood pressure at the time of measurement. Therefore, the validity of PWV is limited especially in studies on hypertension. Hasegawa intended to overcome this limitation of PWV and obtained a nomogram to adjust the PWV value at 80 mmHg of diastolic pressure. This adjusted PWV was called Hasegawa’s PWV (H-PWV), and it represented PWV from the origin of the aorta to the inguinal artery. H-PWV has been used since 1987, and sufficient data have been accumulated in...
Aim

The values of the coefficients “a” and “b” have not been disclosed before. To stimulate research in the field of arterial stiffness, and in the spirit of sharing scientific information, we intend to disclose key elements of the CAVI formula, including the coefficients “a” and “b” in this article.

One major concern following this disclosure is the change in the interpretation of CAVI in various studies. To investigate this possibility, a comparison of CAVI with and without the coefficients “a” and “b” (which will hereafter be named heart-to-ankle Beta= haβ) in an epidemiological and a clinical study was performed. The epidemiological study (n=32,627) assesses the significance of CAVI and haβ among people with or without coronary risk factors. In this study, the statistical significance of CAVI and haβ was assessed in people with coronary risk factors, such as hypertension, dyslipidemia, hyperglycemia, and abnormal electrocardiography (ECG), by comparing values with those of healthy people.

Simple regression analysis and multiple regression analysis were performed with related parameters to compare CAVI and haβ.

Furthermore, this clinical study compares the effect of nitroglycerin on CAVI and haβ and the statistical significance of any changes in stiffness.

Methods

1. Establishment of the Equation of haβ and CAVI From Stiffness Parameter β

CAVI is derived from Stiffness Parameter β, and Bramwell-Hill formula was used to apply this theory to a certain length of the artery.

Bramwell-Hill’s formula indicates the relationship between volume elastic modulus and PWV as follows:

$$\epsilon P = \frac{V}{\rho} \cdot \frac{\Delta V}{\Delta P}$$

Where P is pulse pressure, V is volume of the blood vessel, ΔV is the change of V, and ρ is the blood density.

From eq.1, the following equation is derived, when ΔD/D is small:

$$\text{PWV}^2 = \frac{\Delta P}{\rho} \cdot \frac{D}{2\Delta D}$$

Where D is the diameter of the blood vessel and ΔD is the change of D.

Next, the stiffness parameter β represents the following equation:
Comparison between CAVI and haβ

\[
\beta = \ln \left( \frac{P_s}{P_d} \right) \cdot \frac{D}{DA} \tag{eq.3}
\]

Where \( P_s \) is systolic blood pressure and \( P_d \) is diastolic blood pressure.

When \( D/DA \) of the eq.2 is substituted for that in eq.3, the following equation arises:

\[
\beta = \ln \left( \frac{P_s}{P_d} \right) \times \frac{2D}{\Delta P} \times \text{PWV}^2 \tag{eq.4}
\]

Thus, Stiffness Parameter \( \beta \) can be combined with PWV and \( \rho \). When PWV is measured between the origin of the aorta to the ankle, the new stiffness index is presented as \( \text{haβ} \).

\[
\text{haβ} = \ln \left( \frac{P_s}{P_d} \right) \times \frac{2D}{\Delta P} \times \text{haPWV}^2 \tag{eq.5}
\]

Where \( \text{haPWV} \) is heart-ankle PWV.

Finally, CAVI is defined by applying the coefficients “a” and “b” to eq.5, as follows:

\[
\text{CAVI} = a \times \ln \left( \frac{P_s}{P_d} \right) \times \frac{2 \rho}{\Delta P} \times \text{haPWV}^2 + b \tag{eq.6}
\]

2. Elements in the CAVI Equation

a. The Blood Pressure Value Used in the CAVI Equation

There are blood pressure variations between the heart and the ankle. CAVI uses the right upper arm blood pressure as a representative pressure for the whole pathway. When it is difficult to measure blood pressure at the right upper arm, for instance in patients receiving hemodialysis, the left upper arm blood pressure is used.

b. The haPWV Used in the CAVI Equation

CAVI applies haPWV from the origin of aorta to the ankle. The pulse propagation time from the heart to the ankle is measured by adding \( tb \), the time difference between the second heart sound (II) and the dicrotic notch detected in the pulse wave at the upper right arm cuff, and \( tba \), the time difference between the arrival of the pulse wave at the upper arm cuff and that at the ankle cuff. Thus, by dividing the length of artery by the propagation time, haPWV is calculated by following equation:

\[
\text{haPWV} = \frac{L}{tb + tba} \tag{eq.7}
\]

Where \( L \) is the length of artery, \( tb \) is the duration from heart sound II to the dicrotic notch at the upper arm cuff, and \( tba \) is the time between the pulse wave arrival point at the upper arm cuff and at the ankle cuff.

Similar to blood pressure measurement, \( tb \), and \( tba \) are preferentially measured at the right side. Namely, \( tb \) is measured from heart sound II to the dicrotic notch at the cuff of the right upper arm, and “R-tba” is measured with the cuff of the right upper arm and right ankle, “L-tba” is measured at the right upper arm and left ankle. Then, “R-CAVI” and “L-CAVI” are calculated with \( tb + “R-tba” \) and \( tb + “L-tba” \), respectively.

When only the left upper arm is available because of physical difficulties on the right side, \( tb \) is measured with the left upper arm, and “R-CAVI” and “L-CAVI” are calculated in the same manner.

c. The Length of Arterial Tree From the Origin of the Aorta to the Ankle

The length of the artery is defined as follows: \( L_1 \): from the aortic valve to the femoral artery, \( L_2 \): from the femoral to the popliteal artery, and \( L_3 \): from the popliteal artery to the ankle. \( L_1 \) is calculated as \( L_1 = 1.3 \times \text{AF} \) (Aorta to Femoral) using Nye’s method \(^{(22)} \), where \( \text{AF} \) is the direct distance from the sternum at the second intercostal space to the femoral artery at the groin. Then, the total length of the artery from the heart to the ankle is calculated as \( L = L_1 + L_2 + L_3 \).

When using the VaSera device’s automatic measurement mode, \( L \) is calculated from the subject’s body height using the following equation:

\[
L = 7.7685 \times \text{body height} - 17.536 \tag{eq.8}
\]

This formula was obtained from the correlation equation between \( L \) and the body height of the 813 subjects at Mihama Hospital.

d. Blood Density \( \rho \)

Because the blood density in individuals is generally between 1.045 and 1.055 \(^{(23)} \), the fixed value of 1.05 is used in the CAVI equation.

3. Hasegawa’s PWV

To overcome the limitation of PWV’s dependency on blood pressure, Hasegawa et al. created a nomogram of diastolic pressure and PWV by carefully observing their relationship and developed H-PWV using a PWV value corresponding to 80 mmHg of diastolic pressure\(^{(7)} \). Previous PWV methods had the additional problem of ambiguity in the segment of measurement. H-PWV enabled an accurate measurement by specifying the segment from the origin of the aorta to the femoral artery using a phonocardiogram\(^{(7)} \).

This method was implemented in the PWV-100 (Fukuda Denshi) equipment, which was launched in 1987 as the world’s first dedicated apparatus for the measurement of arterial stiffness.

H-PWV was measured in 169 subjects and
results were analyzed to investigate the relationship with cerebral hemorrhage, cerebral infarction, and coronary artery disease. The following results were observed: coronary artery disease: 0% with no more than 7 m/s of PWV, 3.7% with 8 m/s, and 24.2% with 9 m/s and over; cerebral artery diseases: 0% with no more than 7 m/s, 7.7% with 8 m/s, and 39.3% with 9 m/s and over; either coronary or cerebral artery disease: 0% with no more than 7 m/s, 15.4% with 8 m/s, and 53.6% with 9 m/s and over. Thus, H-PWV showed a high sensitivity and a capability to appropriately diagnose arteriosclerotic diseases.

Until CAVI was introduced, H-PWV was considered to be the gold standard in Japan, because of its independency of blood pressure\(^7\), and because significant data had been accumulated using this method. Therefore, to establish the compatibility between H-PWV and CAVI, we adjusted the CAVI values to H-PWV values with a linear transformation.

For the adjustment, coefficient values “a” and “b” in the CAVI equation were obtained to coincide with the age-dependency of H-PWV, because the age-relationship of H-PWV had already been established.

4. Adjustment of haβ to H-PWV Using Coefficients “a” and “b” in the CAVI Equation

Arterial stiffness is known to increase with aging. Therefore, “a” and “b” can be determined to correspond to age-based change. The averaged haβ at each age of the 7,540 subjects who underwent a physical check at Osaka Hospital Anti-Tuberculosis Association was obtained and is shown in Fig. 1 using solid squares.

As for H-PWV, the average values of 106,559 subjects who underwent a physical check at the Japan Health Promotion Foundation are as shown in Fig. 1, using an open circle\(^7\). Both values increased with age, but the average haβ increased much more than H-PWV in the elderly group (more than 60 years).

We decided to perform a linear transformation to adjust haβ at the Osaka Hospital Anti-Tuberculosis Association to H-PWV at the Japan Health Promotion Foundation.

Because haβ is based on PWV squared, whereas H-PWV is based solely on PWV, it is difficult to maintain a high correlation in a wide range of values with one approximate adjustment. For this reason, the portion that coincides with the correlation equation of haβ and H-PWV was defined as the middle range. For the upper and lower ranges that were outside the middle range, the coefficients were adjusted so that the difference between H-PWV and CAVI was small throughout the clinical range.

As a result, we divided the data into three sections (low: haβ < 7.34875, middle, and high: 10.30372 ≤ haβ), so that the haβ could be adjusted
Comparison between CAVI and haβ

Table 1. Coefficients “a” and “b” in CAVI

<table>
<thead>
<tr>
<th>haβ before transformation</th>
<th>Low Range</th>
<th>Middle Range</th>
<th>High Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7.34875</td>
<td>0.85</td>
<td>0.658</td>
<td>0.432</td>
</tr>
<tr>
<td>≥ 10.30372</td>
<td>0.695</td>
<td>2.103</td>
<td>4.441</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coefficient a</th>
<th>Coefficient b</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85</td>
<td>0.695</td>
</tr>
<tr>
<td>0.658</td>
<td>2.103</td>
</tr>
<tr>
<td>0.432</td>
<td>4.441</td>
</tr>
</tbody>
</table>

Abbreviations: haβ, heart-ankle BETA

Fig. 2. Comparison of Average Data Between CAVI of Healthy Subjects, 2,239 Men and 3,730 Women, Total 5,969 among 32,627 who Underwent a Physical Check and the Previous H-PWV at the Japan Health Promotion Foundation Versus Age (5 years each)

5. Comparison of the Significant Differences of CAVI and haβ Between People With and Without Coronary Risk Factors in the Epidemiological Study

In an epidemiological study, significant differences in the CAVI and haβ values between people with and without coronary risk factors such as hypertension, dyslipidemia, hyperglycemia, and ischemic ECG change were investigated. Subjects were selected from the 32,627 patients who underwent a physical check at the Japan Health Promotion Foundation. The flow diagram of this study population is shown in Fig. 3. The criteria are mentioned below:

Healthy group: 2,239 men and 3,730 women with the following criteria: Ps ≤ 139 mmHg and Pd ≤ 89 mmHg; lipid: TC ≤ 219 mg/dL and 40 ≤ HDL-C ≤ 99 mg/dL and TG ≤ 149 mg/dL; blood Sugar: glucose ≤ 105 mg or HbA1c ≤ 5.8%; renal: creatinine (men) ≤ 1.10 mg/dL, creatinine (women) ≤ 0.80 mg/dL, uric Acid ≤ 7.0 mg/dL; white blood cell: 3.2–8.5 × 103/µL; fundus: S findings = 0 and H findings = 0, and ECG: exclude...
Healthy people and those with risk factors, and the following parameters’ results were compared: Sex, Age, BMI, Ps, Pd, HDL-C, TG, Creatinine, and Glucose. Dummy variables were set in Sex (men: 1, women: 2).

6. Comparison of Significant Differences in the Changes of CAVI and haβ during Nitroglycerin Administration in Normal Control Subjects and Coronary Artery Disease (CAD) Patients

Arterial stiffness consists of structural stiffness and functional stiffness. To investigate whether there is a difference between CAVI and haβ with the transient change of functional stiffness, the difference between CAVI and haβ was analyzed following the administration of nitroglycerin.

We reported a significant decrease of CAVI after administration of nitroglycerin in normal control subjects (n = 31) and CAD patients (n = 25). The haβ values obtained in this study, and the statistical significance of the changes of haβ values were calculated and compared with those of CAVI.

7. Statistical Analysis

Unpaired Welch’s t-test was used to evaluate comparisons of each parameter among the different healthy people and those with risk factors, and the following parameters’ results were compared: Sex, Age, BMI, Ps, Pd, HDL-C, TG, Creatinine, and Glucose. Dummy variables were set in Sex (men: 1, women: 2).
coronary risk factor groups in the epidemiological study. Regression analysis was used to compare CAVI and haβ in the R of simple regression and the β of multiple regression with each related parameter. Comparisons of each parameter before and after taking nitroglycerin were analyzed using Student t-test. We performed post hoc power analysis using the G*Power 3 software (Dusseldorf, Germany) in the nitroglycerin administration study. The detection power was 77% (p<0.05, two tails) in the normal controls (n=31), and 67% in the CAD patients (n=25). In both t-tests, results were expressed as the mean ± standard deviation.

All statistical analyses were double-sided, and p<0.05 was considered significant. Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, IL, USA).

Results

Comparison of the Significant Differences of CAVI and haβ between People with or without Coronary Risk Factors in the Epidemiological Study

The statistically significant differences of CAVI and haβ between people with or without coronary risk factors in the epidemiological study are shown in Fig. 4 (men) and Fig. 5 (women).

As for hypertension, CAVI and haβ were significantly higher in 30-39 year-old men, but not women. And, both indices were significantly higher in 40-79 year-old men and women. The age groups with a significant difference (p<0.05) were identical between CAVI and haβ.

Concerning dyslipidemia, CAVI and haβ were not significantly higher in 30-39 year-old women. Both indices were significantly higher in 40-69 year-old men and women as well as in 70-79 year-old women, however they were not significantly higher in 70-79 year-old men. The age groups with a significant difference (p<0.05) were identical between CAVI and haβ.

For hyperglycemia, CAVI and haβ were significantly higher in 50-79 year-old men and women. The age groups with a significant difference (p<0.05) were identical between CAVI and haβ.

As for ischemic ECG abnormality, CAVI and
et al.\textsuperscript{21}). The CAVI and ha\(\beta\) values were obtained from this study and those values at 5, 10, 15, and 20 min. were compared with baseline values and these are shown in Fig. 6 (normal controls) and Fig. 7 (CAD patients).

The \(p\) values in each group were less than 0.05, and no discrepancy in terms of statistically significant differences was found between CAVI and ha\(\beta\) in the change of values from baseline.

**Discussion**

CAVI was developed to overcome the problem of the blood pressure dependency of PWV\textsuperscript{8}. The idea was to create an index reflecting the proper arterial stiffness of the arterial tree from the origin of the aorta to the ankle. When CAVI was developed, plenty of data on H-PWV had already been collected and analyzed. To compare the values of CAVI with the existing data of H-PWV, CAVI values were adjusted to H-PWV at different ages by including coefficients “a”

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**Fig. 5.** CAVI and ha\(\beta\) in the Healthy Group (open circles) and Each Risk Group (solid circles) in Women

Notes: Data are presented as mean \(\pm\) standard deviation; Unpaired Welch’s \(t\)-test was used to compare healthy groups and each risk group. Abbreviations: CAVI, Cardio-Ankle Vascular Index; ha\(\beta\), heart-ankle BETA

ha\(\beta\) were not significantly higher in the 30-39 year-old women. And, both indices were significantly higher in 40-79 year-old men and women. Again, the age groups with a significant difference \((p < 0.05)\) were identical between CAVI and ha\(\beta\).

In summary, the statistical significance of higher CAVI and ha\(\beta\) values in people with hypertension, dyslipidemia, hyperglycemia and abnormal ECG compared with those in the healthy people matched at each age in men and women.

Regression analysis was performed, and no substantial discrepancy was found between CAVI and ha\(\beta\) in the R of simple regression and the \(\beta\) of multiple regression analysis (Table 2).

**Comparison of the Significant Differences of the Changes of CAVI and ha\(\beta\) during Nitroglycerin Administration in Normal Control Subjects and CAD Patients**

Nitroglycerin administration decreased CAVI values over a period of 20 min. as reported by Shimizu et al.\textsuperscript{21}. The CAVI and ha\(\beta\) values were obtained from this study and those values at 5, 10, 15, and 20 min. were compared with baseline values and these are shown in Fig. 6 (normal controls) and Fig. 7 (CAD patients).

The \(p\) values in each group were less than 0.05, and no discrepancy in terms of statistically significant differences was found between CAVI and ha\(\beta\) in the change of values from baseline.
and “b” in the CAVI equation. As a result, CAVI succeeded in largely matching H-PWV in age-dependency. Originally, arterial stiffness measurements were not limited to indices of vascular aging alone, but also used as indices to measure the functional stiffness of the arterial wall. We have disclosed the coefficients “a” and “b” to stimulate research in the field of arterial stiffness.

One concern, that the significance or interpretations of CAVI with and without coefficients “a” and “b” (haβ) might cause differences in epidemiological studies and clinical studies, was raised.

To assuage this concern two studies were performed.

In the epidemiological study (n=32,627), the statistical significance between CAVI and haβ were essentially the same in people with higher coronary risks such as hypertension, dyslipidemia, hyperglycemia, and abnormal ECG compared with those of healthy men and women in each age group. Also, no
substantial discrepancy was found in the simple regression and multiple regression analysis with related parameters. These results suggest that the CAVI and haβ are essentially the same in people with those risk factors.

In the clinical study, changes in CAVI and haβ values were compared after the administration of nitroglycerin in normal controls and CAD patients. There was no discrepancy between the statistical significances of the changes in CAVI and haβ in normal controls and in CAD patients.

In conclusion, there is no concern that the significance or interpretation of CAVI and haβ would be different in either epidemiological studies or clinical studies.

With this publication, all of the previously undisclosed information of CAVI has been revealed including coefficients “a” and “b”, and the calculation method of the arterial length based upon a subject’s height.

Studies using haβ are also now possible.

We sincerely hope this publication contributes to the progress of clinical research in the field of both organic and functional arterial stiffness.

Disclosures
Koji Takahashi, Tomoyuki Yamamoto, and Shin-ichi Tsuda belong to Fukuda Denshi Co. Ltd and are involved in the development of CAVI.

Fumio Okabe, Tadashi Shimose, Yoshinori Tsuji, Kenji Suzuki, Kuniaki Otsuka, Masanobu Takata, Kazuhiro Shimizu, Junji Uchino, and Kohji Shirai have no conflict of interest concerning this paper.

Acknowledgments
We thank the late Motoharu Hasegawa for providing valuable suggestions during the development of CAVI.

References


10) Bramwell JC, Hill AV. Velocity of transmission of the pulse and elasticity of arteries. Lancet, 1922; 199: 891-892


