Cardio-Ankle Vascular Index is a New Noninvasive Parameter of Arterial Stiffness

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Background  Beta is an index of arterial stiffness independent of blood pressure. Beta of the thoracic descending aorta (TDA) has been obtained by transesophageal echocardiography (TEE) and the cardio-ankle vascular index (CAVI) is a new noninvasive estimation of β.

Methods and Results  The purpose of this study was to evaluate the accuracy and usefulness of CAVI and to compare it with other parameters of arteriosclerosis by carotid ultrasound (CU). The instantaneous dimensional change of the TDA on TEE was measured simultaneously with systemic pressure of the brachial artery in 70 patients in sinus rhythm. There were significant correlations between CAVI and age (r=0.65, p<0.01), and CAVI and the β from TEE (AoD) (r=0.67, p<0.01). Next, 110 patients with chest pain syndrome underwent CU and measurement of CAVI, intima–media thickness (IMT), plaque score and β. There were significant relationships between CAVI and IMT (r=0.42, p<0.01), and between CAVI and β (r=0.39, p<0.01). CAVI of the group diagnosed with plaque was significant higher than that of the normal group (9.872±1.464 vs 9.038±1.377, p=0.0039).

Conclusions  CAVI is measured easily and noninvasively and is a new index of arterial stiffness that is independent of blood pressure. (Circ J 2007; 71: 1710–1714)

Key Words: Atherosclerosis; Cardio-ankle vascular index; Carotid ultrasound; Pulse wave velocity; Transesophageal echocardiography

Stiffness of large arteries has been related to cardiovascular mortality, but the mechanisms underlying this relationship have not been established. Methods are used to estimate this stiffness include carotid ultrasound (CU) and pulse-wave-velocity (PWV). Carotid artery stiffness detected by CU is known to represent of systemic arteriosclerosis. The measurement of PWV is very useful for diagnosing arteriosclerosis in any part of the body and a new method for measuring PWV has been proposed in Japan. Brachial–ankle PWV (baPWV) measures the PWV in the arm and leg by applying air pressure using the volume plethysmographic method. However, baPWV is reportedly influenced by several factors such as blood pressure (BP), autonomic nerve function etc and therefore does not reflect arteriosclerosis in some cases.

The stiffness parameter β is reported to be independent of BP. Beta of the thoracic descending aorta (TDA) has been obtained previously only by transesophageal echocardiography (TEE), but recently this problem has been solved with the advent of the cardio-ankle vascular index (CAVI). CAVI is a new parameter that is also independent of BP10–12 and in the present study, we examined the accuracy and usefulness of CAVI and compared it with other parameters of arteriosclerosis, using CU and serum lipids measurement in patients with chest pain syndrome.

Methods

Principle of CAVI and Method of Measurement  CAVI was obtained by substituting the stiffness parameter β in the following equation for determining vascular elasticity and PWV. The stiffness parameter indicates BP-independent patient-specific vascular stiffness measured by arterial US. The stiffness parameter β is calculated as:

$$\beta = \ln(\frac{Ps}{Pd}) \times D \Delta D$$  \hspace{1cm} (1)

where Ps and Pd are respectively the systolic and diastolic BP in mmHg, D is the diameter of the blood vessel and ΔD is the change of D.

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

$$PWV^2 = \Delta P / \beta \times V / \Delta V$$ \hspace{1cm} (2)

where ΔP is pulse pressure, β is blood density, V is the volume of the blood vessel and ΔV is the change of V.

From equation (2), the following formula is derived:

$$V = \Delta V = D / \Delta D / 2 \times 2 \beta \Delta P \cdot PWV^2$$ \hspace{1cm} (3)

where D is the diameter of the blood vessel and ΔD is the change of D. If we substitute equation (3) for equation (1), we obtain the stiffness parameter:

$$\beta = \text{CAVI} = \ln(\frac{Ps}{Pd}) \times 2 \beta \Delta P \times PWV^2$$

CAVI is measured as follows. PWV is obtained by dividing vascular length (L) by the time (T) taken for the pulse wave to propagate from the aortic valve to the ankle.
Cardio-Ankle Vascular Index and Arterial Stiffness

It is difficult to obtain, because the starting time of the blood stream from the aortic valve is difficult to identify from the valve’s opening sound. T is obtained by summing the time between the aortic valve’s closing sound and the notch of the brachial pulse wave ($t_b$) and the time between the rise of the brachial pulse wave and rise of the ankle pulse wave ($t_{ba}$) instead of the time between the aortic valve’s opening sound and rise of the ankle pulse wave ($t’b$) and $t_{ba}$, because $t’b$ and $t_b$ are theoretically equal.

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

The present study consisted of 2 steps.

**First Study**

We examined the instantaneous dimensional change of the TDA with TEE, simultaneously with the systemic pressure ($P_s$ and $P_d$) of the brachial artery (Cuff method) in 70 patients in sinus rhythm (47 men, 23 women; age range 35–85 years; mean age 67±11; 60 patients with paroxysmal atrial fibrillation, 1 with angina pectoris (AP), 9 without heart disease) to estimate the accuracy of CAVI. A commercially available echocardiography machine (Aplio 80, Toshiba) with a multi-plane probe (PET-510MA) equipped with 5-MHz transducer (64 elements) was used in this study. We measured the minimum dimension ($D_s$) and maximum dimension ($D_d$) of the TDA and calculated the stiffness parameter $\beta = \ln\left(\frac{P_s}{P_d}\right) \times \frac{D_d - D_s}{L}$.

### Table 1 Anthropometric Data of All Participants

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>Men: 47, Women: 23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67±11</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136±22</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78±12</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>197±40</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>146±133</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>54±20</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>112±41</td>
</tr>
<tr>
<td>Treated hypertension (n)</td>
<td>29</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>12</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>19</td>
</tr>
<tr>
<td>Stroke (n)</td>
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</tr>
<tr>
<td>PAF (n)</td>
<td>60</td>
</tr>
<tr>
<td>AP (n)</td>
<td>1</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PAF, paroxysmal atrial fibrillation; AP, angina pectoris.
and we calculated the $\theta$ of TDA (Ao\$). CAVI was measured noninvasively by VaSera VS-1000 (Fukuda Denshi) and adjusted for BP based on the stiffness parameter $\theta$. We compared CAVI with Ao\$.

**Second Study**

We examined the usefulness of CAVI and compared it with other arteriosclerotic parameters on the CU images. This study group consisted of 110 patients (71 men, 39 women; age range 35–88 years, mean age 68±11) with chest pain syndrome who underwent coronary angiography (CAG). The left ventricular ejection fraction (LVEF) of all patients was normal (LVEF $\geq 60\%$). Significant coronary artery stenosis was defined as $>75\%$ stenosis on CAG. We performed CU and measured CAVI before CAG. IMT, plaque score (PS) calculated by the sum of IMT $\geq 1.1$ mm and $\theta$ at the carotid artery were obtained by CU. US was performed using an SSD 4000 ultrasound machine (Aloka Co Ltd, Tokyo, Japan) with 7.5-MHz transducer. The IMT was evaluated as the distance between the lumen–intimal interface and the medial–adventitial interface, and was measured using 2 calipers on the frozen frame of a suitable longitudinal image. We used average $\theta$ and max IMT of both common carotid arteries in this study. The leading edge of near and far gain in the carotid artery was inside the IMT. The measurement of $\theta$ in the carotid artery was done at the site without plaque. The upper limit of normal for the IMT was defined as 1.0 mm, and lesions with an IMT $\geq 1.1$ mm were defined as atheromatous plaque. To assess the severity of atherosclerosis, we used the PS, which was calculated by summing all plaque thickness in both carotid systems$^{13,14}$ The stiffness parameter $\theta$ was used to express the stiffness of the carotid arterial wall. Beta was calculated from the relationship between systemic BP and the diameter of the carotid artery, as for Ao\$.

All participants gave informed consent for participation in the 2 studies, which were approved by the Ethics Committee of Tokuyama Central Hospital and conducted in accordance with the Declaration of Helsinki (2000) of the World Medical Association.

Fig. 3. There is a good relationship between cardio-ankle vascular index (CAVI) and age.

Fig. 4. There is a good relationship between cardio-ankle vascular index (CAVI) and Ao\$.

Fig. 5. There is a significant relation between cardio-ankle vascular index (CAVI) and intima-media thickness (IMT).

Fig. 6. There is a significant relation between cardio-ankle vascular index (CAVI) and $\theta$. 
Statistical Analysis

Statistical analysis was performed using StatView version 5.0 (Abacus Concepts, Calabasus, CA, USA). Quantitative data are expressed as the mean value ± SD. Multivariate analysis of the associations was performed using standard linear regression technique. Significance was established at p<0.05.

Results

First Study

Relationship Between Ao and CAVI in Patients in Sinus Rhythm  The average of examination time for CAVI was approximately 4 min and the average CAVI was 9.6±1.4. Fig 3 depicts the relationship. There was a good correlation between CAVI and age (r=0.65, p<0.01; Fig 3). Fig 4 shows the relationship between CAVI and Ao (r=0.67, p<0.01).

Second Study

Relationship Between CAVI and Coronary Artery Disease With Chest Pain Syndrome  Eighty patients (80/110×100=73%: AP group) with chest pain syndromes underwent CAG and significant coronary arterial stenosis was detected. The CAVI of the AP group was significant higher than that of the normal group (9.614±1.502 vs 9.068±1.374, p=0.0363). Age was not significantly different between the AP and normal groups (68±12 vs 69±13 years). CAVI was not significantly different in those with 1-vessel or multi-vessel disease (9.568±1.934 vs 9.784±2.896, p=0.10).

Relationship Between CAVI and Other Parameters on CU in Patients With Chest Pain Syndrome  There were significant relationships between CAVI and IMT (r=0.42, p<0.01) and between CAVI and [r(r=0.39, p<0.01) (Figs 5,6). CAVI of the group with plaque (group A) was significant higher than that of the normal group (group N) (9.872±1.464 vs 9.038±1.377, p=0.0039). Age was not significantly different between group A and group N (69±9 vs 67±13 years).

Relationship Between CAVI and Other Parameters According to Lipid Measurements in Patients With Chest Pain Syndrome  Total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels were associated with CAVI (Fig 7), although CAVI did not have significant correlations with triglycerides (TG) or high-density lipoprotein-cholesterol (HDL-C).

Discussion

BaPWV enabled a simple measurement of atherosclerosis to be carried out and it has been reported that baPWV is a predictor of the prognosis of the patients with cardiovascular disease and a marker of the severity of atherosclerotic vascular damage. It increases proportionally with age.15,16 In the present study CAVI also showed good correlation with age (r=0.65, p<0.01). PWV is strongly influenced by BP compared with CAVI, whereas CAVI, a new index of arterial stiffness, is independent of BP and compatible with conventional baPWV, a known independent risk factor for cardiovascular disease.17,18 However, it is important to note that CAVI measures the properties of the aorta, femoral artery and tibial artery as a whole. The aorta is an elastic artery, whereas the femoral and tibial arteries are muscular vessels. Therefore, we first assessed the accuracy of CAVI according to Ao calculated from TEE. Tomochika et al reported that there were good correlations between Ao and age (r=0.67, p<0.01) and serum TC levels (r=0.62, p<0.01) in patients with familial hypercholesterolemia (FH) and that Ao was significantly higher in FH patients than in normal subjects.9 TEE is used for accurate evaluation of the morphology and physiology of atherosclerotic lesions of the thoracic aorta in patients with atherogenic factors. This method thus seems capable of providing a diagnosis of the early stage of atherosclerotic lesions. In the present study, a good correlation was observed between CAVI and Ao (r=0.70, p<0.01), which suggested that CAVI was an accurate tool for detecting arterial stiffness and a reasonably good parameter of it. CAVI in patients undergoing percutaneous transluminal coronary angioplasty or in those showing ischemic changes on ECG was higher than the values in patients without arteriosclerotic disease.12 Similarly, our data suggested that 80 patients with significant coronary arterial disease had a higher value for CAVI than the normal group (9.614±1.502 vs 9.068±1.374, p=0.0363). However, it was impossible to distinguish significant coronary stenosis caused by 1-vessel disease from that of multivessel disease by CAVI. Muti- or single-vessel disease of the coronary artery is influenced by many factors, such as age, lipids, diabetes mellitus, hypertension, smoking etc. Moreover, arteriosclerosis of the coronary artery is influenced by antihypertensive drugs and statins, etc. Therefore, it will be difficult to distinguish between multivessel and 1-vessel disease of the coronary
Carotid artery arteriosclerosis detected by CU is known to be representative of the whole body. Moreover, arteriosclerosis of the carotid artery is also known to be a useful indicator of ischemic heart disease. In particular, it has been reported that the carotid IMT is a marker of the presence of severe symptomatic coronary artery disease. Other previous studies have proposed that the PS is related to progression of coronary artery disease. The stiffness index, which represents the mechanical properties of the arterial wall, is calculated from the relationship between systemic BP and the diameter of the artery. Hirai et al reported the importance of carotid aortic distensibility (I) as a prognostic indicator of extent of the coronary artery disease, so in the present study we compared CAVI with parameters such as IMT, PS and I in the carotid artery. There were significant relationships between CAVI and IMT (r=0.42, p<0.01) and between CAVI and I (r=0.39, p<0.01). There were some differences between CAVI and AoI and I because CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole. Moreover, CAVI of the group with plaque was significantly higher than that of the normal group. These results suggest that CAVI is a good, simple index of arteriosclerosis and may be a useful marker predicting clinical coronary events in the future.

Previous studies have reported that levels of elevated LDL-C may predict progression of carotid stenosis. LDL-C is also a major risk factor for coronary artery disease, and the National Cholesterol Education Program (NCEP) recommends LDL-C lowering by drug therapy for patients with ischemic heart disease. In our study, 33 patients (30%) of all subjects had been prescribed statins. The clinical benefit of statins in the primary and secondary prevention of cardiovascular complications of advanced arteriosclerosis, especially coronary artery disease, is being tested in several large clinical trials.

CAVI had a poor relationship with TC and LDL-C levels in patients with chest pain syndrome; however, there were not correlations among CAVI and the TG and HDL-C levels.

In summary, CAVI is considered to reflect arteriosclerosis of the aorta and is a novel parameter of arterial distensibility.

References