Review

The Role of a Novel Arterial Stiffness Parameter, Cardio-Ankle Vascular Index (CAVI), as a Surrogate Marker for Cardiovascular Diseases

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Measurement of arterial stiffness in routine medical practice is important to assess the progression of arteriosclerosis. So far, many parameters have been proposed to quantitatively represent arterial stiffness. Among these, pulse wave velocity (PWV) has been most frequently applied to clinical medicine because those could be measured simply and non-invasively. PWV had established the usefulness of measuring arterial wall stiffness. However, PWV essentially depends on blood pressure at the time of measurement. Therefore, PWV is not appropriate as a parameter for the evaluation of arterial stiffness, particularly for the studies involving blood pressure changes.

On the other hand, stiffness parameter \( \beta \) is an index reflecting arterial stiffness without the influence of blood pressure. Recently, this parameter has been applied to develop a new arterial stiffness index called cardio-ankle vascular index (CAVI). Therefore, CAVI does not depend on blood pressure changes during the measurements; CAVI could represent the stiffness of the arterial tree from the origin of the aorta to the ankle.

Many clinical studies obtained from CAVI are being accumulated. CAVI showed high value in arteriosclerotic diseases, such as coronary artery diseases, cerebral infarction, and chronic kidney diseases, and also in majority of people with various coronary risk factors. The improvement of those risk factors decreased CAVI. Furthermore, the role of CAVI as a predictor of cardio-vascular events was reported recently.

We review the clinical studies on CAVI and discuss the clinical usefulness of CAVI as a candidate surrogate end-point marker for cardiovascular disease.


**Key words:** Cardio-ankle vascular index, Arterial stiffness, Stiffness parameter \( \beta \), Coronary artery disease, Surrogate marker

Introduction

Arteriosclerosis is difficult to diagnose in routine medical practice. Arterial wall stiffness is one of the properties accompanying the progression of arteriosclerosis. Then, many parameters have been proposed to quantitatively represent arterial stiffness\(^\text{1, 2}\). Among these, pulse wave velocity (PWV)\(^3\) has been most frequently applied to clinical medicine because those could be measured simply and non-invasively. Many studies using carotid-femoral PWV (cfPWV)\(^4\) and brachial-ankle PWV (baPWV)\(^5\) had almost established the meaning of measuring arterial wall stiffness. However, PWV essentially depends on the blood pressure at the time of measurement\(^6\). Therefore, PWV is
improvement in most of those risk factors decreased CAVI. The role of CAVI as a predictor of cardio-vascular events was reported recently.

In this study, we review the clinical studies on CAVI and discuss the clinical usefulness of CAVI as a candidate surrogate end-point marker for cardiovascular disease.

The Principle of CAVI and Measuring Method

CAVI was originally derived from the stiffness parameter $\beta$ proposed by Hayashi and Kawasaki and was expanded to some length of the artery with the application of the modified Bramwell-Hill equation. CAVI adopted PWV from the origin of the aorta to the ankle (heart-ankle PWV; haPWV).

$$\text{CAVI} = a[(2\rho/\Delta P) \times \ln(P_s/P_d) \times \text{haPWV}^2] + b$$ (Equation 1)
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Factors Affecting CAVI

Because measuring conditions, room temperature, food intake, smoking, and rigorous exercise affected CAVI value, it is recommended that room temperature should be kept at 24-26°C during the measurement of CAVI. Moreover, rigorous exercise, smoking, and diet should be avoided 3-4 h prior to the measurement. CAVI is invalid when ankle brachial index (ABI), which is the ratio of mean blood pressure in the tibial artery to that in the brachial artery, is <0.9.

1. Aging and Gender

CAVI of healthy people without cardiovascular risk factors gradually increases with age from 20 to 70 years (Fig. 4). CAVI values in men are higher than those in women at all ages by 0.2 on average. Choi et al. reported that CAVI is a sensitive marker of the arterial aging process, above and beyond conventional arm blood pressure in Korean people (CAVI = 5.0 + 0.048 \times \text{age in men}, 4.8 + 0.045 \times \text{age in women}).

2. Arteriosclerotic Diseases

(a) CAD

As for CAD, CAVI increases as the number of coronary vessels with stenosis increases, as shown in Fig. 5. Nakamura et al. reported that the cutoff point of CAVI for the presence of coronary stenosis was 8.91 among the patients with a suspicion of ischemic CAD. Izuhara et al. reported the multiple logistic analysis revealing that CAVI, but not baPWV,
was associated with the presence of carotid and coronary arteriosclerosis. Several researchers reported that CAVI was high in patients with CAD\textsuperscript{20, 22, 23}. Yingchoncharoen et al.\textsuperscript{24} reported that the traditional risk score (RAMA-EGAT) has been shown to be an accurate scoring system for predicting CAD. In this study, adding CAVI to the RAMA-EGAT score improved the prediction of CAD incidence, increasing

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig3.png}
\caption{Effects of blood pressure on CAVI values in healthy individuals administered (a) $\beta$1 blocker and (b) $\alpha$1 blocker\textsuperscript{16}.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{fig4.png}
\caption{Effects of age on CAVI. CAVI was measured in Japanese workers and their families. CAVI increased with age, and the values of CAVI were higher in men than in women at any age. CAVI\textsuperscript{0.5} by 10 years; men > women by 0.2 (\#difference of 5 years)\textsuperscript{17}.}
\end{figure}
Cerebral Infarction

CAVI values are high in patients with cerebral infarction\(^27\). Choi et al.\(^28\) reported that CAVI reflects cerebral small-vessel diseases in healthy young and middle-aged individuals. On the other hand, cerebral atherosclerosis associated with cognitive impairment in old age is controversial. Otsuka et al.\(^29\) reported that a high CAVI value in community-dwelling elderly people was a greater risk of cognitive impairment.

C-statistics from 0.72 to 0.85 and resulting in a net reclassification improvement (NRI) of 27.7\%\((p < 0.0001)\) (Fig. 6). Park et al.\(^25\) reported that the addition of CAVI > 8 to traditional risk factors improved the predictive value of coronary stenosis. Park et al.\(^26\) reported that CAVI was related to coronary artery calcification or stenosis in asymptomatic subjects in Korea. These results suggested that CAVI is well correlated with the progression of coronary arteriosclerosis.

(b) Cerebral Infarction

CAVI values are high in patients with cerebral infarction\(^27\). Choi et al.\(^28\) reported that CAVI reflects cerebral small-vessel diseases in healthy young and middle-aged individuals. On the other hand, cerebral atherosclerosis associated with cognitive impairment in old age is controversial. Otsuka et al.\(^29\) reported that a high CAVI value in community-dwelling elderly people was a greater risk of cognitive impairment.
(c) Chronic Kidney Diseases and Maintenance Hemodialysis

Several studies about chronic kidney diseases described that CAVI correlated with estimated glomerular filtration rate and cystatin C and that CAVI is high in patients undergoing hemodialysis therapy.

(d) Carotid Arteriosclerosis

There are several studies reporting the relationship between CAVI and carotid arteriosclerosis observed using ultrasonography.

In summary, the abovementioned results indicated that CAVI could be a good maker of the progression of arteriosclerosis.

3. Coronary Risk Factors

(a) Hypertension

CAVI is essentially independent of blood pressure at the measuring time. However, arterial stiffness is influenced by the chronic exposure of arterial wall to increased blood pressure. Then, there are many reports that CAVI showed high values in hypertension. Most of those reports showed that the correlation coefficients between CAVI and blood pressure were lower than those between PWV and blood pressure. In hemodialysis patients, CAVI was correlated weakly with systolic and diastolic blood pressures, whereas baPWV was correlated significantly with systolic and diastolic blood pressures.

(b) Diabetes Mellitus

CAVI is reported to be high in patients with diabetes mellitus. Kim et al. reported that diabetic peripheral neuropathy was associated with increased CAVI without changes in carotid IMT in type 2 diabetes. Kim et al. found that increased CAVI in type 2 diabetes was associated with the presence of arterial plaque, increased IMT, and microvascular complication. Furthermore, Tsuboi et al. reported that the 1-h postprandial glucose levels are associated with increased CAVI values in non-diabetic subjects.

(c) Dyslipidemia

Soska et al. showed that CAVI was not high in heterozygous familial hypercholesterolemic patients. On the other hand, some reports showed that CAVI is related to low-density lipoprotein (LDL) cholesterol level and also to the cholesterol / high-density lipoprotein (HDL) cholesterol ratio. CAVI may increase when complicated lesions occur.

(d) Obesity and metabolic syndrome

In the studies dealing with healthy people, CAVI is negatively related with body mass index. However, Park et al. reported that visceral fat, especially epicardial fat, showed positive association with CAVI, but not subcutaneous fat. These results suggested that CAVI could differentiate between the visceral and subcutaneous obesity. Satoh et al. reported that CAVI is high in metabolic syndrome in which visceral fat is thought to be the main cause of risk factors, such as hypertension, glucose intolerance, and hypertriglyceridemia.

(e) Uric Acid

Uric acid as a risk factor for arteriosclerosis is controversial because uric acid is known to have both antioxidant and pro-oxidative action in the process of production. Recently, Nagayama et al. reported that CAVI increased progressively with increasing serum uric acid tertile after adjusting for age, BMI, and systolic blood pressure in multiple regression analysis. Li et al. also documented that uric acid increased arterial stiffness measured by CAVI.

(f) Smoking

The harmful effects of smoking are not only respiratory and digestive systems but also cardiovascular organs. CAVI is high in people who smoke.

(g) Sleep Apnea Syndrome

Sleep apnea syndrome is one of the important risk factors of atherosclerosis. CAVI is also high in the patients with sleep apnea syndrome.

(h) Mental Stress

Shimizu et al. reported that people who experienced a severe earthquake had hardened arterial stiffness, indicating that mental stress also increases CAVI. These results indicated that CAVI is correlated with the severities of most of the coronary risk factors (Table 1). These results also suggested that the so-called coronary risk factors were working to stiffen the arterial tree composing the aorta, femoral artery, and tibial artery.

The Role of CAVI as a Predictor of Cardiovascular Events

Several studies dealing with the relationship between mortality or morbidity and CAVI are being accumulated. Kubota et al. reported that the group with CAVI > 10 showed a high incidence...
of cardiovascular disease and stroke in 3 years. A multivariate analysis showed that the hazard ratio of cardiovascular diseases was significantly higher in this group (hazard ratio, 2.2) (Fig. 7).

Kato et al.\textsuperscript{53} reported that baPWV is superior to CAVI as a predictor of cardiovascular outcomes in patients on chronic hemodialysis ($n = 135$).

Laucevičius et al.\textsuperscript{54} reported the association between CAVI and cardiovascular events in middle-aged metabolic syndrome patients. CAVI was associ-
events, increasing C-statistics from 0.712 to 0.736, and NRI was 16.4% \( (p = 0.066) \).

Sato et al.\(^{56}\) reported that CAVI was an independent predictor of future cardiovascular events in 1080 subjects with metabolic disorders, such as diabetes mellitus, hypertension, and dyslipidemia. In Cox proportional hazards regression analysis, every 1.0 increment of CAVI was one of the factors independently associated with the higher risk of future cardiovascular events (hazard ratio, 1.126, \( p = 0.039 \)).

Furthermore, Otsuka et al.\(^{57}\) reported that persistently impaired CAVI was an independent predictor of future cardiovascular events \( (p = 0.01) \), and cardiovascular outcomes were worse in patients with persistently impaired CAVI than in those with improved CAVI \( (p < 0.001) \). This report suggests that the change in CAVI is also a predictor of future cardiovascular events.

The role of CAVI as a surrogate endpoint of various risks management

1. Treatment of Hypertension

CAVI is independent of blood pressure at the measuring time, and CAVI showed high values in the patients with hypertension. Therefore, CAVI may be a good marker of arterial stiffness, reflecting coronary risks control including hypertension treatment.

(a) Calcium Channel Blockers

There are several calcium channel blockers (CCBs), such as L-channel blocker type, T-channel blocker type, and N-channel blocker type. Kurata et
CAVI is interesting. Further studies on the comparison between the prognosis of various antihypertensive drugs and their effects on CAVI are needed. In summary, the abovementioned reports suggest that CAVI could discriminate the effects of antihypertensive agents on proper arterial stiffness in addition to blood pressure control itself.

2. Treatment of Diabetes Mellitus

CAVI is high in patients with diabetes mellitus and postprandial hyperglycemia as mentioned before. The values of CAVI are sometimes influenced by the glucose-lowering treatment; there are some glucose-lowering treatments that lower CAVI and others that do not. Alpha-glucosidase inhibitor, acarbose, reduces CAVI mediated by an improvement of postprandial hyperglycemia. Ohira et al. reported that switching biphasic insulin from human insulin 30/70 to insulin aspart 30/70 improved CAVI together with the marker of postprandial hyperglycemia. Ohira et al. reported that an insulin-sensitizer pioglitazone decreased CAVI accompanied with adiponectin-increasing effect. Nagayama et al. reported that Glimepiride, a third generation sulfonylurea, improved CAVI and the marker of insulin resistance and oxidative stress, but not glibenclamide, a conventional sulfonylurea.

These reports suggest that the improvement of postprandial hyperglycemia and insulin resistance has favorable effect on CAVI in diabetes mellitus treatment.

![Fig. 8. Change in CAVI before and after administration of ARB (olmesartan) and CCBs (amlodipine).](image1)

![Fig. 9. After pitavastatin treatment for 12 months, significant decreases in CAVI were observed in type 2 diabetic patients.](image2)
3. Treatment of Dyslipidemia

It is controversial whether CAVI in the patients with hypercholesterolemia is high as mentioned before. On the other hand, cholesterol-lowering agents, such as pitavastatin, (Fig. 9) and the triglyceride-lowering agent, eicosapentaenoic acid, have been reported to decrease CAVI.

4. Treatment of Obesity and Metabolic Syndrome

Metabolic syndrome is the accumulation of diabetes mellitus, hypertension, and hypertriglyceridemia based on obesity, and now this is one of the most important risk factors for CADs. CAVI is high in metabolic syndrome as mentioned before. The reduction of body weight improves CAVI in addition to many risk factors in the patients with metabolic syndrome. Nagayama et al. reported that weight reduction using a calorie restriction diet decreased CAVI in obese patients with type 2 diabetes. The change in VFA was a significant independent predictor of the change in CAVI.

5. Smoking Cessation

CAVI is high in people who smoke and is decreased by stopping smoking.

6. Treatment of Sleep Apnea Syndrome

CAVI is elevated in the patients with sleep apnea syndrome and is decreased by continuous positive airway pressure treatments.

The abovementioned results indicated that CAVI could be a good maker of arteriosclerosis and is also a marker of arterial stiffness raised by several coronary risk factors. Therefore, CAVI is a candidate of surrogate endpoint marker for cardiovascular event; however, there is no intervention study investigating the association of CAVI with cardiovascular event and mortality, by various interventions.

### Conclusions

CAVI, reflecting the arterial stiffness from the origin of the aorta to the tibial artery at the ankle, has been developed in Japan. It was based on the theory of stiffness parameter \( \beta \). CAVI reflects the degree of arteriosclerosis. Moreover, CAVI shows high values in

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**Table 3. Effects of various treatments on CAVI**

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<thead>
<tr>
<th>Treatments</th>
<th>CAVI value</th>
<th>References</th>
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<tr>
<td>Body weight reduction</td>
<td>↓ ( \rightarrow )</td>
<td>Satoh N. Hypertens Res 2008&lt;sup&gt;49&lt;/sup&gt;</td>
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<td></td>
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<td>Nagayama D. Obes Res Clin Pract 2011&lt;sup&gt;73&lt;/sup&gt;</td>
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<tr>
<td>Glucose control</td>
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<td>Insulin</td>
<td>↓ or ( \rightarrow )</td>
<td>Ohira M. Metabolism 2011&lt;sup&gt;67&lt;/sup&gt;</td>
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<tr>
<td>Sulfonlurea</td>
<td>↓ or ( \rightarrow )</td>
<td>Nagayama D. Int J Clin Pract 2010&lt;sup&gt;69&lt;/sup&gt;</td>
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<td>Pioglitazone</td>
<td>↓</td>
<td>Ohira M. Diabetes Metab Syndr Obes 2014&lt;sup&gt;68&lt;/sup&gt;</td>
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<td>( \alpha )-glucosidase inhibitor</td>
<td>↓</td>
<td>Uzui H. J Diabetes Investig 2011&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>Blood pressure control</td>
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<td>Ca blocker (Amlodipine)</td>
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<td>Kurata M. Curr Ther Res Clin Exp 2008&lt;sup&gt;58&lt;/sup&gt;</td>
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<td>( \rightarrow )</td>
<td>Sasaki H. J Atheroscler Thromb 2009&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>( \rightarrow )</td>
<td>Miyashita Y. J Atheroscler Tromb 2009&lt;sup&gt;59&lt;/sup&gt;</td>
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<td>Ca blocker (T-channel blocker type)</td>
<td>↓</td>
<td>Sasaki H. J Atheroscler Thromb 2009&lt;sup&gt;60&lt;/sup&gt;</td>
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<td>angiotensin II receptor antagonists</td>
<td>↓</td>
<td>Kinouchi K. Kidney Blood Press Res 2010&lt;sup&gt;41&lt;/sup&gt;</td>
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<td>Uehara G. J Int Med Res 2008&lt;sup&gt;62&lt;/sup&gt;</td>
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<td>Bokuda K. Vasc Health Risk Manag 2010&lt;sup&gt;63&lt;/sup&gt;</td>
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<td>Lipid control</td>
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<td>Statins</td>
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<td>Miyashita Y. J Atheroscler Thromb 2009&lt;sup&gt;70&lt;/sup&gt;</td>
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<td>Eicosapentaenoic acid</td>
<td>↓</td>
<td>Satoh N. Hypertens Res 2009&lt;sup&gt;71&lt;/sup&gt;</td>
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<td>Smoking cessation</td>
<td>↓</td>
<td>Noike H. J Atheroscler Thromb 2010&lt;sup&gt;74&lt;/sup&gt;</td>
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<tr>
<td>Continuous positive airway pressure</td>
<td>↓</td>
<td>Kasai T. Am J Hypertens 2011&lt;sup&gt;71&lt;/sup&gt;</td>
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patients with coronary risk factors, and the control of the risks improves CAVI. The latter fact indicates that CAVI reflects not only the organic stiffness of the arterial wall but also the functional stiffness composed of smooth muscle cell contracture. Furthermore, several prognostic studies of cardiovascular events using CAVI have emerged, and CAVI is reported as a prognostic factor for cardiovascular disease. CAVI has an additional diagnostic value of cardiovascular events in several studies. CAVI could be useful for the cardiovascular risk stratification in future guideline of patients with coronary risk factors, although further studies are required to confirm these.

Moreover, CAVI has relationships with the left ventricular function and retinal artery pulsation. These results suggest that CAVI is an adequate marker of vascular function as Windkessel. CAVI may open a new field for the studies on vascular functions.

In summary, CAVI could be a marker for the diagnosis of arteriosclerotic diseases and also for the evaluation of the pathophysiology of systemic circulation relating to the left ventricular function and blood flow in the peripheral organs. Routine measurement of CAVI is recommended in clinical practice, in addition to various coronary risk factors.

**Conflict of Interest**

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