Review

Cardio-Ankle Vascular Index (CAVI) as a Novel Indicator of Arterial Stiffness: Theory, Evidence and Perspectives

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The cardio-ankle vascular index (CAVI) is a new index of the overall stiffness of the artery from the origin of the aorta to the ankle. The most conspicuous feature of CAVI is its independence of blood pressure at the time of measurement.
CAVI increases with age and in many arteriosclerotic diseases, such as coronary artery disease, carotid arteriosclerosis, chronic kidney disease and cerebrovascular disease, and is related to many coronary risk factors, such as hypertension, diabetes mellitus, dyslipidemia and smoking. Furthermore, CAVI decreases by controlling diabetes mellitus and hypertension, and also by abstaining from smoking. This suggests that CAVI is a physiological surrogate marker of athero- or arteriosclerosis, and also might be an indicator of lifestyle modification.
Recently, it has been reported that CAVI and several left ventricular functions are co-related, suggesting a connection between the heart muscle and vascular function.
This review covers the principles of CAVI and our current knowledge about CAVI, focusing on its roles and future outlook.

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Introduction

Many previous studies have demonstrated the significance of arterial stiffness as a surrogate marker for determining the prognosis of cardiovascular disease[1-3]. Aortic stiffness is based on the structural changes occurring prior to plaque or thrombus formation in muscular and elastic vessels. Increased arterial stiffness is seen in patients with coronary risk factors such as hypertension[4], diabetes mellitus[5] and hyperlipidemia[6]; therefore, it is meaningful to estimate the degree of arteriosclerosis by examining arterial stiffness in order to prevent cardio- and cerebrovascular events[7].

Many methods have been designed to assess arterial stiffness. Among them, pulse wave velocity (PWV)[1-7], augmentation index[8], stiffness parameter β[9, 10], and carotid-femoral PWV (cfPWV)[11] have been proposed as markers of arterial stiffness. In 2002, brachial-ankle pulse wave velocity (baPWV) was proposed as a marker of vascular damage[12], and was reported to be a predictive factor of coronary artery disease[13]; however, PWV is known to depend on blood pressure at the time of measurement[14]. Hence, the validity of PWV in reflecting actual arterial stiff-

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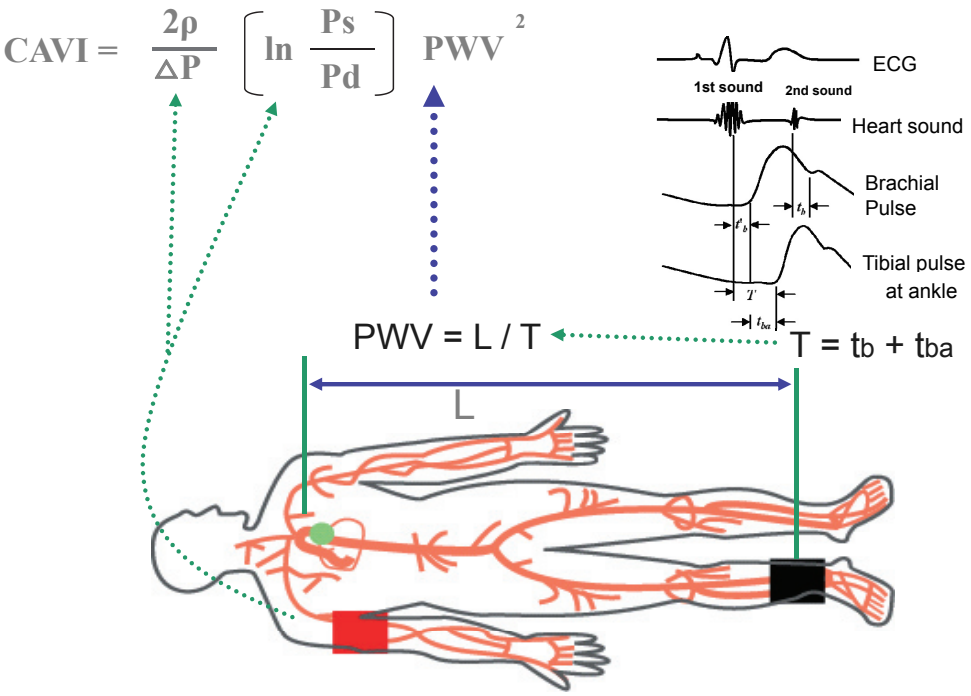

Fig. 1. CAVI and its measurement.

With the patient lying supine, an electrocardiogram and heart sounds are monitored. PWV from the heart to the ankle is obtained by measuring the length from the origin of the aorta to the ankle, and by calculating $T = t_b + t_{ba}$. Blood pressure is measured at the brachial artery.
Ps: systolic blood pressure, Pd: diastolic blood pressure, PWV: pulse wave velocity, ΔP: Ps − Pd, ρ: blood density, ΔP: pulse pressure, L: length from the origin of the aorta to the ankle, T: time taken for the pulse wave to propagate from the aortic valve to the ankle, t_{ba}: time between the rise of brachial pulse wave and the rise of ankle pulse wave, t_b: time between aortic valve closing sound and the notch of brachial pulse wave, t'_b: time between aortic valve opening sound and the rise of brachial pulse wave[18].

ness is questionable, and this parameter is unsuitable to evaluate the role of hypertension control with drugs in the arterial wall.

In 1970, Hasegawa[15] established a method of measuring heart-femoral PWV (hfPWV) corrected for blood pressure. In this method, hfPWV is corrected by adjusting diastolic pressure to 80 mmHg. The usefulness of corrected hfPWV has been reported in several studies[16, 17]; however, this examination can be difficult to conduct, especially in women, because the inguinal region has to be palpated to detect the pulse.

In 1980, Hayashi *et al.*[9] developed a calculation for stiffness parameter $\beta = 1n(Ps/Pd) \cdot D/\Delta D$, where Ps is systolic, Pd is diastolic blood pressure, D is the diameter of the artery, and ΔD is the change in arterial diameter according to blood pressure difference. In simple terms, stiffness parameter β represents the blood pressure change required to expand the diameter of the artery; therefore, this value does not depend on blood pressure. Kawasaki *et al.*[10] succeeded in measuring β in the cervical artery using an echo-phase tracking system. A limitation of stiffness parameter β is that it is applicable only to a local segment of the artery.

The cardio-ankle vascular index (CAVI) was developed with the objective of obtaining an arterial stiffness index that is not affected by blood pressure at the time of measurement, and which reflects the stiffness of a considerable length of the artery[18].

Theory and Principle of CAVI

CAVI reflects the stiffness of the whole arterial segment composed of the aorta, femoral artery and tibial artery (**Fig. 1**, from ref. 18). CAVI can be calculated from PWV at the origin of the aorta to the ankle portion of the tibial artery, and systolic and diastolic blood pressures measured at the upper brachial artery. This index was originally derived from stiffness parameter β proposed by Hayashi[9] and Kawasaki *et*

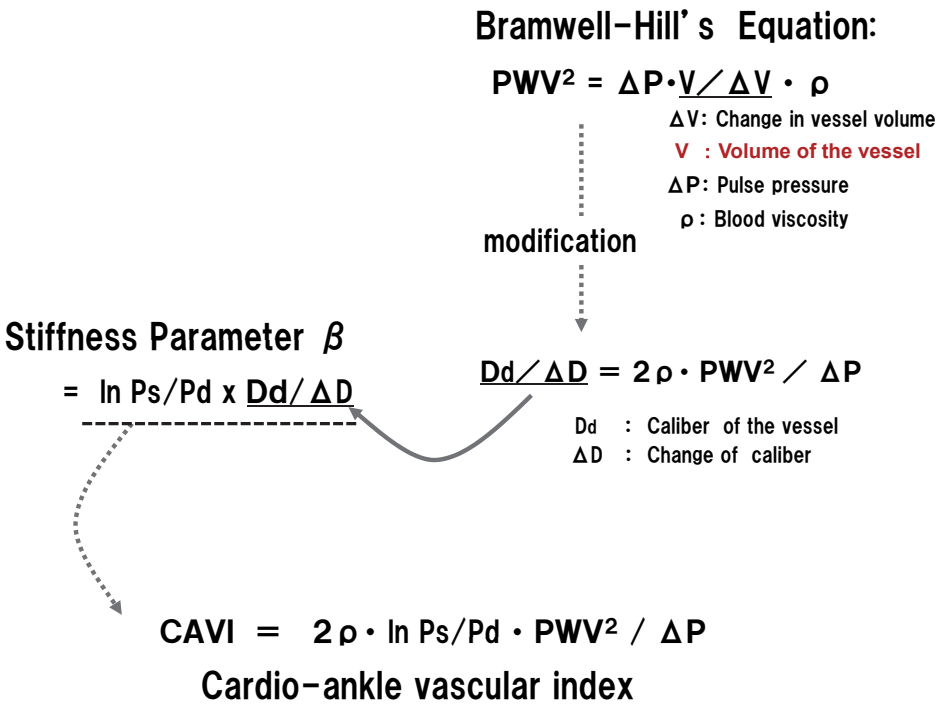

Fig. 2. Deduction of CAVI from the stiffness parameter β by applying Bramwell-Hill's equation.

The CAVI equation originated from stiffness parameter $\beta = 1n\ (Ps/Pd) \cdot D/\Delta D)$[9, 10]. $D/\Delta D$, derived from a modification of Bramwell-Hills equation[19], was substituted in the equation of stiffness parameter β. CAVI was ther deduced.

al.[10], with application of Bramwell-Hill's equation[19].

Here, the principle of the CAVI formula is described briefly (**Fig. 2**):

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

---------- CAVI formula

where, Ps is systolic diastolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity from the origin of the aorta to tibial artery at the ankle through the femoral artery, ΔP is Ps − Pd, ρ is blood density, and a and b are constants.

The above equation is derived as follows:

CAVI is essentially β, and $\beta = \ln (Ps/Pd) \cdot D/\Delta D$

where D is the diameter of the artery, ΔD is the change in the diameter of the artery according to pressure change[9, 10].

$D/\Delta D$ can be obtained from a modification of the Bramwell-Hill's equation[19]:

$$PWV^2 = \Delta P/\rho \cdot V/\Delta V$$ ------ equation 1

where ΔP is pulse pressure, V is blood vessel volume, ΔV is the change in V, and ρ is blood density

$V/\Delta V$ can be expressed in terms of D and ΔD as follows:

$$V/\Delta V = (\pi L(D/2)^2)/[\pi L((D+\Delta D)/2)^2 - \pi L(D/2)^2]$$
$$= D^2/[D2 + 2D\ \Delta D + \Delta D^2 - D^2]$$
$$= D^2/(2D\Delta D + \Delta D^2)$$

Since ΔD^2 is negligibly small compared with $2D\Delta D$, it is ignored. The equation becomes:

$$V/\Delta V = D^2/2D\Delta D = D/2\Delta D$$ --------- equation 2

Thus, $V/\Delta V$ in equation 1 can be replaced by $D/2\Delta D$. Equation 1 becomes:

$PWV^2 = \Delta P/\rho \cdot V/\Delta V = \Delta P/\rho \cdot D/2\Delta D$, and
$D/\Delta D = 2\rho/\Delta P \cdot PWV^2$ ---------- equation 3

Next, equation 3 is substituted into the equation of stiffness parameter β to obtain the new β (β').

$$\beta'(=CAVI) = \ln(Ps/Pd) \cdot (D/\Delta D)$$
$$= \ln(Ps/Pd) \cdot 2\rho/\Delta P \cdot PWV^2$$

This new index was named the cardio-ankle vascular index (CAVI), which reflects the overall stiffness of the aorta, femoral artery and tibial artery, and is theoretically not affected by blood pressure.

Thus, CAVI originated from stiffness parameter

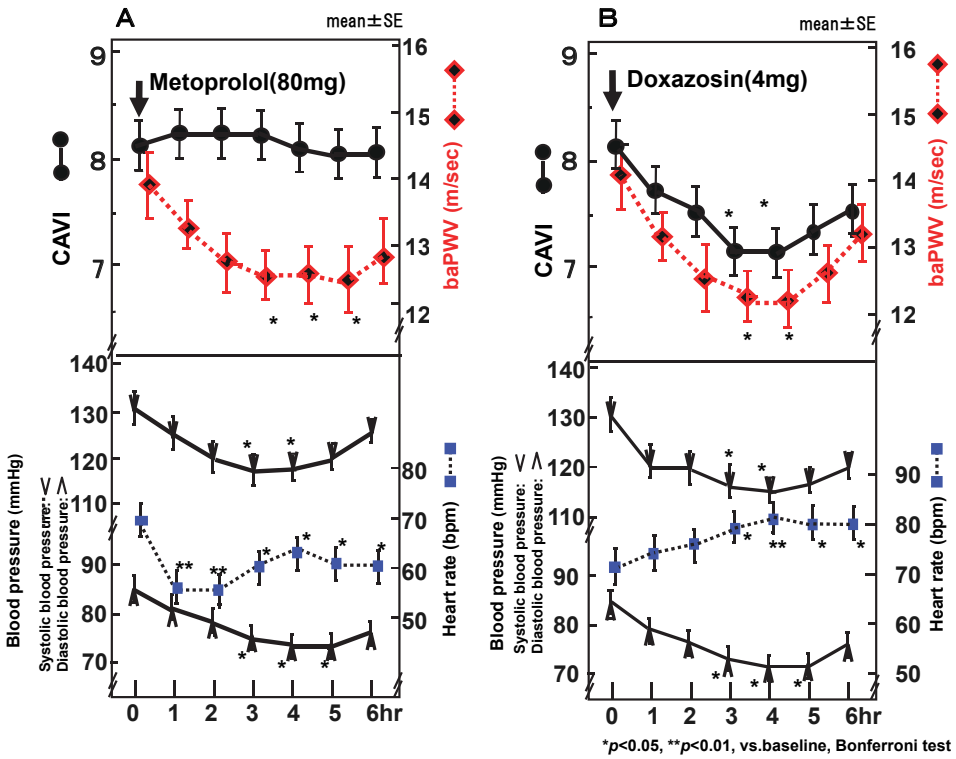

Fig. 3. Effects of the β1 blocker, metoprolol and α1-blocker, doxazosin, on CAVI and baPWV.

With the administration of a selective β1 adrenergic blocker, metoprolol (80 mg), both systolic and diastolic blood pressures decrease and baPWV also decreases, but CAVI does not change[23] (Fig. 3A). This study indicates that CAVI is independent of blood pressure at the time of measurement. Furthermore, with the administration of a selective α1-aderenergic receptor blocker, doxazosin, both systolic and diastolic blood pressures decreased and CAVI decreased as well as baPWV (Fig. 3B), indicating that CAVI decreased with relaxation of the smooth muscles induced by α1-aderenergic receptor blocker.

$\beta = \ln(Ps/Pd) \cdot (D/\Delta D)$, and is calculated from PWV for a given length of the artery and ΔP, instead of diameter change ($D/\Delta D$).

The Rationale for CAVI and Independence on Blood Pressure

There remains a question of whether it is valid to apply Bramwell-Hill's equation to the equation of stiffness parameter β, which is essentially applied to a portion of the aorta. Takaki *et al.*[20] provided evidence for the validity of CAVI by showing a positive correlation between stiffness parameter β of the aorta and CAVI. They measured β of the thoracic descending aorta using transesophageal echocardiography, and reported a positive correlation between aortic stiffness parameter β and CAVI ($r = 0.67$, $p < 0.01$), suggesting that the application of Bramwell-Hill's equation to stiffness parameter β equation is appropriate.

Next, the most conspicuous feature of CAVI is its theoretical independence on the blood pressure at the time of measurement; however, this theory has not been proven experimentally. Several reports[18, 20-22] showed that CAVI is less dependent on blood pressure than PWV, but these results do not necessarily mean that CAVI is independent on blood pressure at the time of measurement. We studied this point using a selective β1 receptor blocker[23]. Metoprolol is a selective β1 blocker and is known to reduce the contraction of the heart muscle and decrease blood pressure without affecting the tone of the arterial wall. When metoprolol was administered to 12 men, baPWV decreased over 6 hours, but CAVI did not change (**Fig. 3A**). This result clearly demonstrates that CAVI is not influenced by blood pressure at the time of measurement.

Thus, CAVI can be used to compare the properties of the artery, even though blood pressure may

Table 1. CAVI in arteriosclerotic diseases and in coronary risks

	CAVI value	Reference
Coronary artery diseases [Acute coronary disease]	↑↑	Nakamura[24], Izuhara[25], Miyoshi[26], Horinaka[27] [Sairaku[29]]
Intima media thickness of cervical artery	↑	Nakamura[24], Ibata[22], Takaki[20, 28], Izuhara[25], Miyoshi[26], Okura[36], Sairaku[29], Horinaka[27], Hayashi[38]
Chronic kidney disease [Mortality rate in patients with hemodialysis]	↑↑	Izuhara[25], Kobuzono[30], Takenaka[31], Nakamura[32], Ueyama[33], Satoh-Asahara[36] [Kato[40]]
Cerebral infarction, Dementia	↑	Yamamoto[39]
Metabolic syndrome	↑	Satoh[55]
Diabetes mellitus	↑	Ibata[22], Izuhara[25], Okura[37]
Hypertension	↑	Kubozono[21], Okura[37], Takaki[42], Kadota[43]
Dyslipidemia	↑	Takaki[28]
Smoking	↑	Kubozono[21], Noike[62]
Obstructive sleep apnea syndrome	↑	Kumagai[60]

change. CAVI permits, for the first time, analysis of the effect of antihypertensive treatments on arterial stiffness.

Factors Affecting CAVI (Table 1)

(1) Aging and Sex

The effects of age and sex on CAVI in healthy persons living in major cities throughout Japan were studied. Among the subjects, 32,627 persons who were receiving an annual health check, healthy persons without risk factors were selected. Their ages ranged from 20 to 79 years. The results are shown in **Fig. 4**. The VaSera VS-1500 (Fukuda Denshi Co., Tokyo) was used to measure CAVI. CAVI of healthy men without cardiovascular risk factors increased almost linearly with age from 20 to 70 years. CAVI of men is higher than that of women in almost all age groups by 0.2. The linear regression equation is CAVI = 5.43 + 0.053 × age for men, and CAVI = 5.34 + 0.049 × age for women. The rate of increase was nearly 0.5 per 10 years in men and women.

(2) Arteriosclerotic Diseases

Confirming that CAVI is an indicator of arteriosclerosis is no easy task, because quantitative measurement of arteriosclerosis is difficult *in vivo*. To confirm that CAVI reflects the degree of arteriosclerosis, the gross appearance of the aorta at postmortem was compared with CAVI, which was measured when the subjects were alive. **Fig. 5** shows some typical examples.

The aorta of a 50-year-old woman showed almost no atheroma, and the CAVI was 7.0. The aortas of 74-and 76-year-old men showed advanced stages of arteriosclerosis. The CAVI was 11.0 in both. As described below, the cutoff point of CAVI is 9.0. Post-mortem gross appearance of aortas thus supports the notion that CAVI reflects the progression of arteriosclerosis. CAVI in various arteriosclerotic diseases is described in the next section.

A. Coronary Artery Disease

Nakamura *et al.*[24] reported that CAVI increases as the number of vessels with stenosis (>75%) increases. Stepwise ordinal logistic regression analysis using mean intimal-media thickness (IMT), maximum IMT, plaque score and CAVI as independent variables identified only CAVI as positively related to the severity of coronary atherosclerosis. Receiver operating characteristic curve analysis (ROC analysis) of mean IMT, max IMT, plaque score and CAVI showed that the area under the ROC defined by CAVI was the greatest among the 3 scores[24]. CAVI might be more useful for discriminating the probability of coronary atherosclerosis by high-resolution B-mode ultrasonography. The cutoff point of CAVI for the presence of coronary stenosis was 8.91.

Izuhara *et al.*[25] reported that CAVI is indepen-

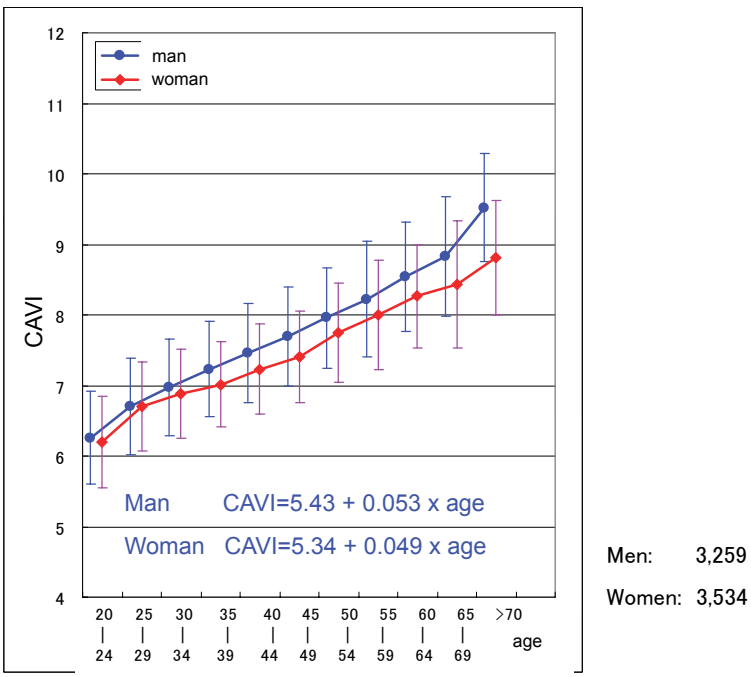

Fig. 4. CAVI in aging and sex.

The effects of age and sex on CAVI were studied in 32,627 residents of major cities throughout Japan, who received an annual health check. They were healthy and had no coronary risk factors. CAVI increases with age almost linearly from 20 to 70 years in males and females by almost 0.5 over 10 years. CAVI of men is higher than that of women in almost all age groups by 0.2.

dently associated with the severity of coronary atherosclerosis. Recently, Miyoshi *et al.*[26] also supported a correlation between CAVI and coronary atherosclerosis. Horinaka *et al.*[27] reported that CAVI is superior to baPWV in predicting coronary artery disease. Takaki *et al.*[28] confirmed that CAVI is better than baPWV for predicting the presence of coronary and cervical arteriosclerosis. Sairaku *et al.*[29] reported that CAVI is significantly and independently higher in patients with acute coronary disease than in those with stable angina pectoris.

B. Chronic Kidney Disease and Hemodialysis Patients

Several studies examined the relationship between CAVI and renal disease. Kubozono *et al.*[30] reported that CAVI correlates independently with the estimated glomerular filtration rate in the Japanese general population. Takenaka *et al.*[31] found that CAVI is high in end-stage renal diseases. Nakamura *et al.*[32] reported that CAVI is closely associated with cystatin C levels, suggesting a significant role of arterial stiffness in renal insufficiency. Ueyama *et al.*[33] also reported that CAVI is high in hemodialysis patients.

Ichihara *et al.*[34] showed that CAVI was higher in patients with kidney failure and reported a correlation between the severity of arterial fibrosis and CAVI. Shen *et al.*[35] used CAVI to predict the risk of *de novo* arterial stiffness in patients on chronic dialysis.

Recently, Satoh-Asahara *et al.* reported that CAVI was higher in metabolic syndrome, and negatively correlated with eGFR and S-CysC, and body weight reduction reduced CAVI in obese patients with metabolic syndrome[36].

The positive correlation between chronic kidney disease and CAVI may be explained by the fact that arteriosclerosis is a systemic disease involving the renal and central arteries simultaneously. Another possible reason is that the kidney of a person with arteriosclerosis secretes many factors such as renin, which promotes systemic arteriosclerosis.

C. Intimal Thickness of Carotid Artery

Nakamura *et al.*[24] reported that CAVI correlates positively with maximum IMT and the plaque score in the carotid arteries. Okura *et al.*[37] reported that CAVI correlated positively with IMT ($r=0.360$, $p=0.0022$) and the stiffness parameter β ($r=0.270$, $p=0.0239$) in 70 hypertensive patients. Similarly,

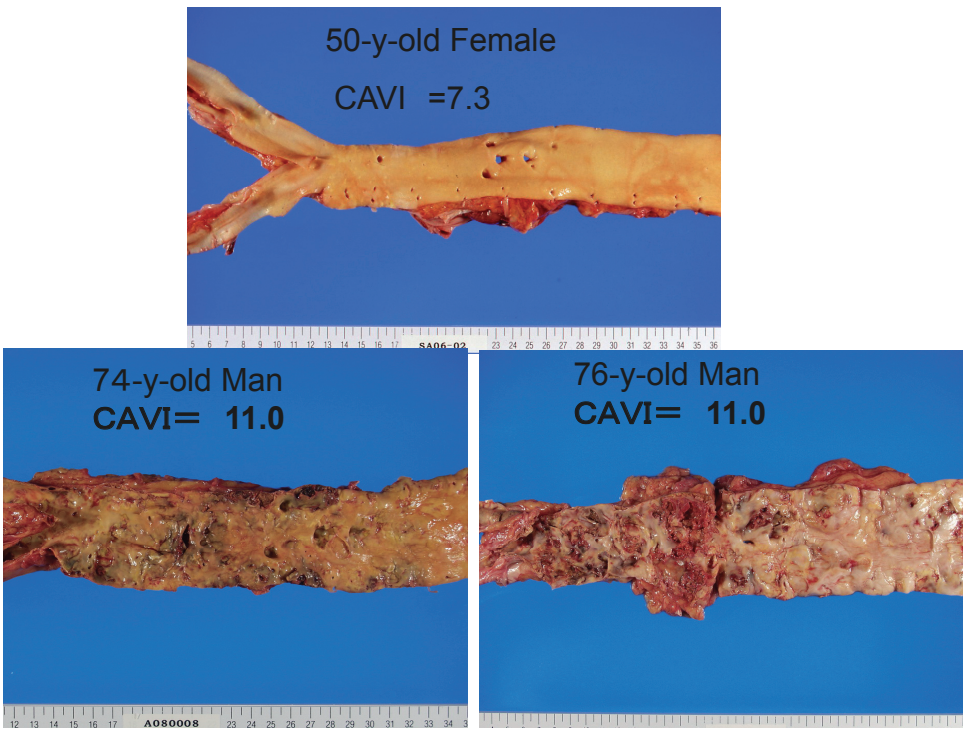

Fig. 5. Appearance of the abdominal aorta at postmortem study and CAVI.

Top: The aorta was from a 50-year-old woman who died of pancreatic cancer. The surface of the abdominal aorta is smooth and atheroma is scarcely observed.
Bottom: The abdominal aortae were obtained from a 74-year-old man and a 76-year-old man. Both aortae show an advanced stage of atherosclerosis. CAVI of both individuals is 11.0. Nakamura *et al.*[24] reported that CAVI=9.0 was the cut-off value for the presence of coronary artery stenosis.

Takaki *et al.*[20] reported a significant correlation between CAVI and IMT ($r=0.48$, $p<0.01$). Izuhara *et al.*[25] concluded that high CAVI implies the progression of carotid arteriosclerosis, and that CAVI may be more closely linked with arteriosclerosis than baPWV. Hayashi[38] reported that D-dimer is significantly higher in the arteriosclerotic group (CAVI >8.0 and IMT >1.1 mm). The combination of CAVI and IMT could be a more significant predictor of thrombosis in highly atherosclerotic patients.

D. Cerebrovascular Events and Dementia

In a four-year follow-up study, Yamamoto *et al.* reported[39] that community-dwelling elderly people with a high CAVI value are at a greater risk of cognitive decline. Preliminary study on the relationship between CAVI and cerebrovascular events has been conducted, but not yet published.

E. Survival Prognosis

Kato *et al.*[40] conducted a 39-month follow-up study on the mortality rate of 194 hemodialysis patients. They found that a small reduction in the ankle-brachial index is associated with increased mortality in patients on chronic hemodialysis, while CAVI and baPWV are not associated with mortality.

An on-going study of CAVI in predicting survival prognosis in patients on chronic hemodialysis has started to report preliminary findings, but full papers have not yet been published. Time is required to reach a conclusion.

CAVI and Coronary Risk Factors

A. Hypertension

CAVI is not affected by blood pressure at the time of measurement[18, 23]; therefore, the effect of blood pressure on the properties of the arterial wall can be evaluated by CAVI. Okura *et al.*[37], Takaki *et al.*[41], and Kadota *et al.*[42] reported that CAVI correlates with blood pressure. These reports were the first to demonstrate the real correlation between blood pressure itself and arterial wall stiffness.

Interestingly, when sunitinib maleate was administered to a patient, CAVI startedto increase before

Table 2. Improving factors or treatment for CAVI

Treatments	CAVI value change	Reference
Weight reduction	↓	Satoh[55]
Blood glucose control	↓	Nagayama[51], Ohira[52]
Hypertension control		
Angiotensin Ⅱ receptor blocker	↓	Uehara[44], Kinouchi[45], Bokuda[46]
Calcium channel antagonist	↓	Sasaki[47]
Lipid-lowering agents		
Statin	↓	Miyashita[54]
Ezetimib	↓	Miyashita[56]
Eichosapentanoic acid	↓	Satoh[55]
Stop smoking	↓	Noike[62]
Continuous pulmonary assistance	↓	Lü[61]

blood pressure increased[43]. This finding suggests that CAVI may reflect the stress on the artery induced by sunitinib maleate before hypertension occurs. CAVI may be useful to predict the occurrence of hypertension. but more detailed studies are required.

Several blood pressure-lowering agents have been reported to decrease CAVI (**Table 2**). CAVI was decreased by angiotensin Ⅱ receptor antagonists[44-46]. Among calcium channel blockers, efonidipine decreased CAVI in diabetic patients[47]. When the calcium channel blocker amlodipine and the angiotensin Ⅱ receptor blocker (ARB) olmesartan were compared, olmesartan decreased CAVI to a greater extent even though both agents effected blood pressure to a similar decrease[48]. Bokuda *et al.*[46] reported that candesartan decreased CAVI much more than calcium channel blockers.

Diuretics are known to decrease blood pressure, but may exacerbate insulin resistance. Ishimitsu *et al.*[49] reported that the combination of olmesartan and azelnidipine has advantages over the combination of olmesartan and a thiazide with respect to avoiding increased arterial stiffness in patients with moderate hypertension. A tablet combining losartan and hydrochlorothiazide has been found to decrease CAVI[50]. These clinical data suggest that CAVI might discriminate the causes of hypertension and also the mechanism of blood pressure-lowering agents. For example, the causes of hypertension might be divided into 3 categories: increased heart muscle contraction; increased resistance of the peripheral artery; increased circulatory blood volume. CAVI is supposed to reflect the second effect; therefore, monitoring CAVI would contribute to clarifying or identifying the cause of hypertension. Moreover, monitoring CAVI during the administration of different antihypertensive drugs may contribute to elucidating the patho-physiology during various treatments for hypertension. To confirm this hypothesis, further studies are required.

B. Diabetes Mellitus

CAVI is reported to be high in patients with diabetes mellitus[22]. Most studies found that diabetes mellitus is a potent factor that increases CAVI in aged persons.

Recent studies have shown that insulin therapy decreases CAVI while lowering the blood glucose level (**Table 2**). Nagayama *et al.*[51] reported that glimepiride decreases CAVI accompanied by an improved glucose level. Ohira *et al.*[52] reported that insulin injection also decreases CAVI concomitant with a decrease in the blood glucose level. These clinical observations may suggest that CAVI is a sensitive physiological index for monitoring the stress on the arterial wall by high blood glucose, probably due to glucose toxication. A high glucose level may modulate the arterial wall to increase stiffness within a relatively short time, resulting in an increase in CAVI. This increase may be reversible, because blood glucose control decreases CAVI in a rather short period. Further studies are required to clarify the mechanism by which high glucose or glucose toxication modulates arterial wall stiffness.

C. Dyslipidemia

CAVI and dyslipidemia are not closely connected; however, Takaki[53] reported that CAVI is related to the LDL-cholesterol level and also the total

cholesterol/HDL-cholesterol ratio. Hyperlipidemia per se does not immediately increase arterial wall stiffness. After accumulation of cholesterol in the lipid pool, oxidative stress generates oxysterol, which is highly toxic and enhances inflammation, followed by the onset of atherosclerosis; therefore, CAVI may increase under certain conditions in dyslipidemia.

The effects of lipid-lowering agents have been reported (**Table 2**). Miyashita *et al.*[54] reported that pitavastatin treatment decreased CAVI after one year. Eicosapentaenoic acid reduces CAVI in association with decreased serum amyloid A-LDL in metabolic syndrome[55]. Ezetimibe monotherapy decreases CAVI in type 2 diabetic patients[56]. The arterial stiffness-improving effect of lipid-lowering agents might be due to some functional modulation in addition to organic pathologic changes.

D. Metabolic Syndrome, Obesity and Weight Reduction

Metabolic syndrome prevails worldwide. Visceral fat accumulation has been suggested to induce glucose intolerance, hypertension, and dyslipidemia, such as low HDL-cholesterol and hypertriglyceridemia[57]. These conditions are believed to be due to insulin resistance. High CAVI is associated with obesity and metabolic syndrome[58]. Adiponectin, which is implicated in insulin sensitivity and considered to be a biomarker of metabolic syndrome, is related negatively to CAVI[59]. The above findings indicate that CAVI could be a good marker of macroangiopathy in metabolic syndrome, for which there are few initial signs and symptoms.

Weight reduction is known to improve metabolic syndrome, and Satoh *et al.*[58] reported that weight reduction through diet and exercise therapy over a 3-month period significantly decreased CAVI values in parallel with increasing adiponectin. CAVI may be useful for evaluating and managing the cardiovascular risks of patients with metabolic syndrome.

E. Sleep Apnea Syndrome

CAVI has been reported to be high in sleep apnea syndrome[60] and to decrease with continuous positive airway pressure (CPAP)[61]. The mechanism by which CAVI increases in sleep apnea syndrome may be due to the activation of sympathetic nerves by sleep apnea, which consequently increases arterial wall stiffness.

Interestingly, since CAVI decreases after CPAP therapy in patients with sleep apnea syndrome, CAVI could be used as an efficient marker for CPAP therapy.

F. Smoking

Kubozono *et al.*[21] reported that CAVI was high in smoking subjects. Noike *et al.*[62] reported that smoking increases CAVI but, interestingly, CAVI decreases after stopping smoking. This reversible change of CAVI might imply that smoking contracts the arterial wall of smooth muscle cells. CAVI may be a good indicator to enhance the motivation of persons who are trying to stop smoking.

G. CAVI in Inflammatory Vascular Disease

Inflammatory diseases of the arterial wall are known to be associated with accelerated atherosclerosis. Detection of increased arterial stiffness in patients in the early stage of large vessel vasculitis may be possible by measuring CAVI. Recent case reports showed that CAVI was high in patients with systemic lupus erythematosis[63] and aortitis syndrome[64, 65], and the augmented CAVI was decreased by immunosuppressive therapy[65]. These results indicate that CAVI reflects the presence of an inflammatory reaction of arteries in the whole body. The mechanism by which CAVI increases in such conditions is not known. Inflammatory cytokines generated in the arterial wall might induce the contraction of smooth muscle cells or induce remodeling of the arterial wall, but detailed studies on these issues are required. Wakabayashi *et al.*[66] reported that CAVI is associated with acute phase reactants, such as C-reactive protein, amyloid A protein, sialic acid, fibrinogen and white blood cells in type 2 diabetes mellitus.

H. Miscellaneous Diseases and/or Conditions

Besides arteriosclerosis-related disorders, CAVI is changed in many diseases and/or conditions. Torisu *et al.*[67] reported that CAVI was significantly higher in atrophic gastritis-positive patients than in atrophic gastritis-negative patients, even after adjusting for possible confounding factors (8.59 ± 1.20 vs. 8.27 ± 1.19 $p = 0.022$).

Wu *et al.*[68] reported that personal exposure to ozone was associated with a 4.8% increase in CAVI, suggesting that vascular function may be more sensitive to air pollutants. Those reports may indicate that many unidentified factors involved in the development of arteriosclerosis could be evaluated using CAVI in the future.

Relationship between CAVI and Cardiac Functions

Mizuguchi[69] reported that arterial stiffness is associated with left ventricular diastolic function in

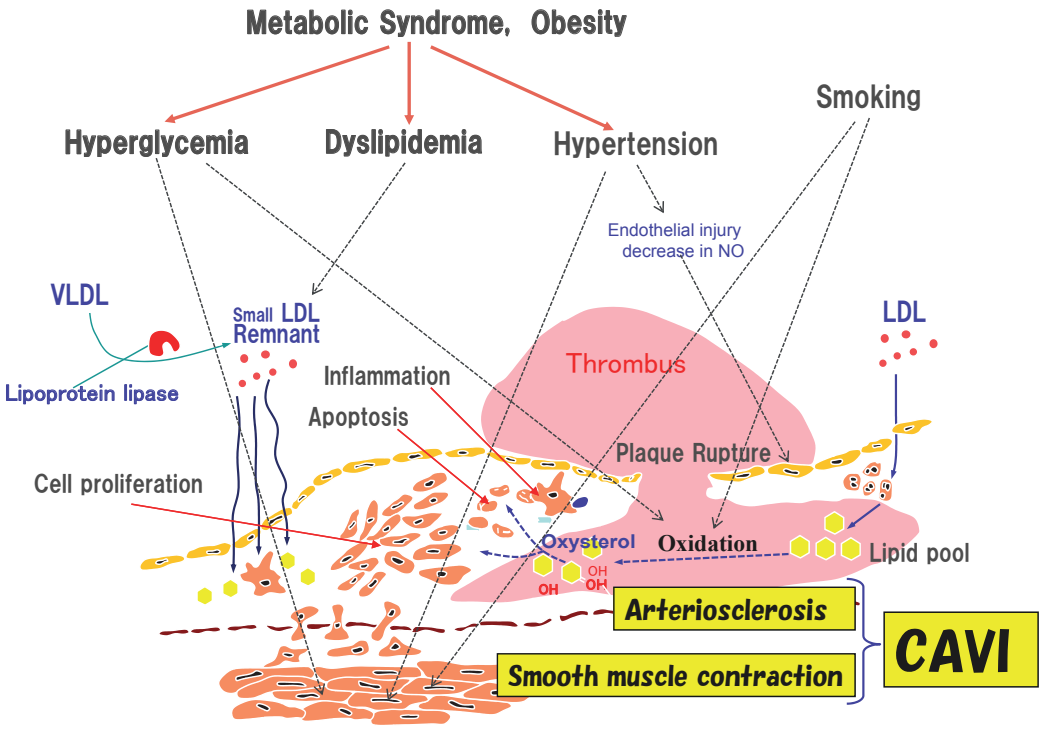

Fig. 6. Atheroma formation with coronary risk factors and CAVI.

The process of athero- and arteriosclerosis is supposed as follows. A lipid pool is formed with infiltration of LDL, small dense LDL and remnants. Oxidation of lipids provokes inflammation. Then, smooth muscle cells proliferate to form intimal thickening. Inflammatory reaction gathers macrophages, which degrade the matrix, and also induce smooth cell apoptosis. Then, plaque rupture occurs and thrombus is formed.
Risk factors are involved in various steps. Some target the endothelial cells and produce injuries. Some promote oxidation stress in the arterial wall. Others target medial smooth muscle cells, increasing contraction or provoking cell proliferation. Interestingly, all these injurious reactions seem to be integrated in CAVI.

patients with cardiovascular risk factors. They demonstrated that CAVI correlated positively with peak early diastolic trans-mitral flow velocity, E/A, and the deceleration time of early diastolic transmitral flow velocity (E-DT). Sakane *et al.*[70] showed that CAVI was significantly higher in patients with reduced left ventricular (LV) diastolic function than in those with normal LV diastolic function (9.0±1.1 versus 8.5±1.1, $p=0.009$), and concluded that increased CAVI is independently associated with LV diastolic dysfunction in patients with preserved systolic function. Masugata *et al.*[71] measured the peak early diastolic mitral annular velocity (E') as an index of LV diastolic function using tissue Doppler echocardiography, and demonstrated that E' correlates with CAVI ($r=-0.518$, $p<0.001$). They also reported that aortic annular velocity assessed by tissue Doppler echocardiography is a potential parameter of arterial stiffness[72]. These results indicate that left ventricular diastolic function correlates with vascular elasticity indicated by CAVI. In other words, the state of high CAVI of the elastic and muscular arterial wall might worsen left ventricle diastolic function; therefore, measuring CAVI may be important when considering diagnostic and therapeutic strategies aiming at cardiac protection[69, 70]. Further investigations are needed to confirm a causal relationship.

Summary

What is CAVI? What is the Outlook of CAVI a Marker of Arteriosclerosis?

A high CAVI is observed in many arteriosclerotic diseases, such as coronary artery disease, carotid arteriosclerosis, chronic kidney disease and cerebrovascular disease, and is related to many coronary risk factors, such as hypertension, diabetes mellitus, dyslipidemia and smoking, as shown in **Table 1**. These clinical data indicate that CAVI can be a surrogate marker of athero- or arteriosclerosis. Furthermore, CAVI decreases in a relatively short period by various treatments, as shown in **Table 2**. Furthermore, vasodilators such as doxazosin and α1- aderenergic receptor

Table 3. Cardiac Function and CAVI

Left ventricular diastolic function	CAVI value	Reference
Left ventricular ejection fraction	→	Sakane[70], Mizuguchi[69]
Left atrial dimension	↑	Sakane[70], Mizuguchi[69]
Peak early diastolic velocity (E)	↑	Sakane[70], Mizuguchi[69], Masugata[71]
Peak atrial diastolic velocity (A)	↑	Sakane[70]
E/A	↑	Sakane[70], Mizuguchi[69]
Deceleration time of E velocity (DcT)	→	Sakane[70], Mizuguchi[69]

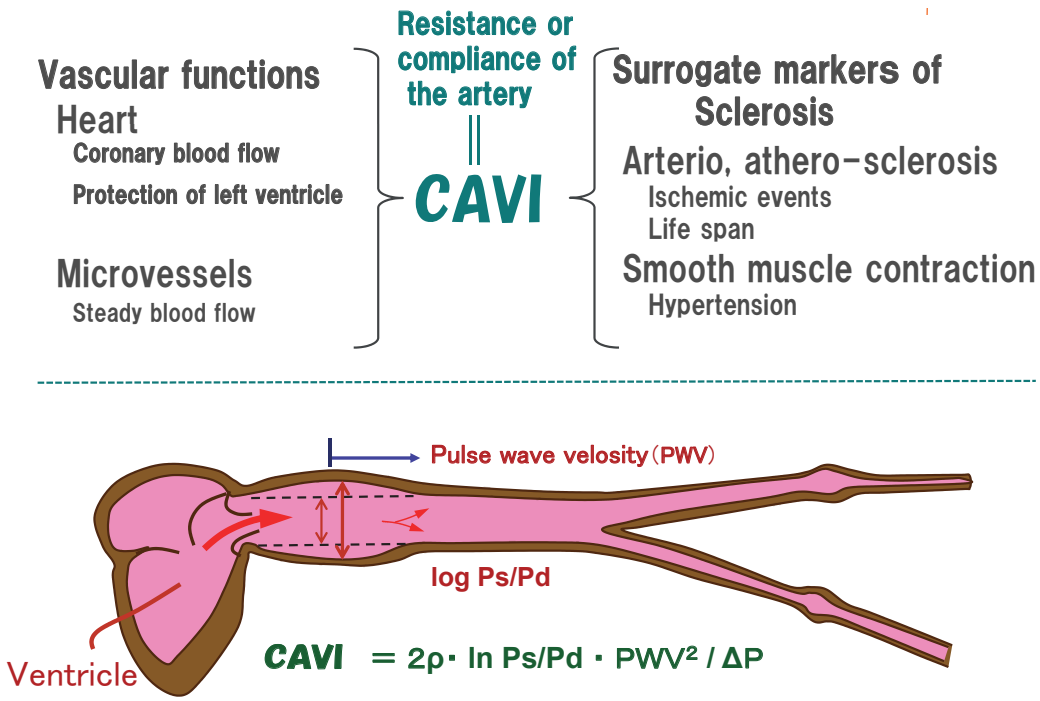

Fig. 7. Roles of CAVI in resistance or compliance of the artery as a surrogate marker of arteriosclerosis and also vascular function.

CAVI reflects the resistance or compliance of the artery; therefore, CAVI indicates the degree of sclerosis of the artery, and also reflects vascular function which keeps the heart functioning and maintains peripheral steady blood flow as a Windkessel. The former is a surrogate marker of arteriosclerosis and smooth muscle contraction. The latter might protect or improve left ventricular function, and maintain steady blood flow. To confirm this, many more basic and clinical studies are required.

blocker decrease CAVI in 1 to 5 hours, concomitant with a decrease in blood pressure (**Fig. 3B**, Ref. 23), indicating that smooth muscle cell contraction is an important determinant of CAVI, in addition to the organic components of the arterial wall, summarized in **Fig. 6**.

Many risk factors, such as hyperglycemia, hypertension, dyslipidemia (small dense LDL, remnants, LDL) and smoking, act injuriously on the arterial wall in their own ways, including endothelial dysfunction, oxidative stress and provoking inflammation. One method is by promoting organic sclerosing process and an other is by promoting the contraction of smooth muscle cells. Both processes might be integrated into CAVI.

In the future, CAVI might be useful to compare the severity of arteriosclerosis in people in different districts or countries, and might be useful to find risk

factors in each[73, 74]. CAVI might also be a good physiological surrogate marker of lifestyle change, such as ceasing smoking, control of blood pressure and glucose level, and resultantly might be expected to contribute to the prevention of arteriosclerotic diseases.

As a Marker of Vascular Function

The circulation system is composed of the heart, large- and medium-sized arteries and microvessels. Pulsatile movement of the heart efficiently transports the blood to peripheral organs with the aid of vascular function; that is, the arteries dilate in the systolic phase and contract during the diastolic phase. While this windkessel action is ascribed to vascular compliance or resistance[1], an index to reflect this function has not been available. Several reports have confirmed that CAVI and left ventricular functions are related, as shown in **Table 3**[69-71]. Furthermore, the α1-aderenergic receptor blocker doxazosin, which dilates the peripheral arteries by decreasing resistance, decreases CAVI as described above[23]. These results indicate that CAVI reflects the compliance or resistance of the artery, and may have a protective effect on the left ventricle, as shown in **Fig. 7** (lower panel).

The possibility that CAVI plays a role in the analysis of systemic circulation as a marker of peripheral resistance or compliance deserves to be evaluated. In this context, CAVI may open a new field in the study of systemic circulation.

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