

Evaluation of Arteriosclerotic Vascular Disease with a New Noble Stiffness Indicator, Cardio-Ankle Vascular Index (CAVI)

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Abstract

Arterial stiffness is a well-known predictor of arteriosclerotic vascular disease. One index of arterial stiffness was the pulse wave velocity (PWV). But, it is known that PWV depends on the blood pressure at measuring time. Cardio-ankle vascular index (CAVI) is derived from stiffness parameter beta, and reflects the stiffness of the artery from the origin of the aorta to the ankle as a whole. Conspicuous feature is independency from the blood pressure at measuring time.

An administration of alfa-1 blocker, doxazosin decreased CAVI transiently. Prostacyclin analogue, beraprost also decreased CAVI. These results suggest that CAVI might reflect the smooth muscle cell contracture.

CAVI showed high value with aging, and in patients with cerebral infarction, coronary stenosis, and chronic hemodialysis, suggesting that CAVI is reflecting systemic vascular arteriosclerosis.

As for the risks of coronary artery disease, CAVI showed high value in hypertension, diabetes mellitus, dyslipidemia, smoking and metabolic syndrome. Improvement of those risk factors reduced CAVI. CAVI seems to be a useful indicator for the management of the risk factors. Arterial inflammatory diseases also showed high CAVI value. Furthermore, various associations between CAVI and cardiac functions such as left ventricular diastolic function were reported. Above results suggested that CAVI reflect the degrees of arteriosclerosis and of ages, and also reflect the contracture of arterial smooth muscle cells. CAVI might be useful to investigate a new insight of vascular function.

Keywords: Pulse wave velocity; Cardio-ankle vascular index; Arteriosclerotic vascular disease

Introduction

Many studies have demonstrated the significance of arterial stiffness as a surrogate marker for determining the prognosis of cardiovascular diseases [1-4]. Aortic stiffness is based on the structural changes occurring prior to plaque or thrombus formation in muscular and elastic vessels. Many methods have been designed to assess arterial stiffness including pulse wave velocity (PWV) [1-7] and augmentation index [8]. As for PWV, there were many methods such as carotid-femoral PWV (cfPWV) [9], heart to femoral PWV (hfPWV) [10] and brachial-ankle pulse wave velocity (baPWV) [11]. And, many valuable data as a surrogate marker of arteriosclerosis had been reported [3-5,12-15].

However, PWV is known to depend on blood pressure at the time of measurement, theoretically [16]. Hence, the validity of PWV is limited especially for the studies on the role of hypertension.

The cardio-ankle vascular index (CAVI) was recently developed to measure proper arterial stiffness, which is not affected by blood pressure at the time of measurement [17]. CAVI was originally derived from the stiffness parameter beta proposed by Hayashi et al. [18]. Modified Bramwell-Hill's equation [19] was introduced into the equation of stiffness parameter beta, then CAVI is born as a new stiffness index, reflecting the stiffness of the artery from the origin of the aorta to the ankles as shown in Figure 1 [18]. Independency from blood pressure was supported theoretically, and also by the pharmacological study using beta 1 selective adrenoceptor blocker, metoprolol [20].

CAVI shows high value with aging [21]. Recently, many studies on CAVI in various arteriosclerotic diseases have been published, and the outline of CAVI became clearer year by year. In many arteriosclerotic

diseases such as coronary artery disease [22], carotid arteriosclerosis [23], chronic kidney disease [24] and cerebrovascular disease [25], and is also related with many coronary risk factors such as diabetes mellitus, dyslipidemia and smoking [26,27]. In addition, the role of CAVI as a factor predicting the occurrence of cardiovascular events has also been reported recently [28].

Furthermore, an association between CAVI and cardiac functions such as left ventricular diastolic function was reported [29].

This review described the principle of CAVI and provided an overview of the properties, the role of surrogate marker of arteriosclerosis and an association with cardiac functions. Then, the utilities of CAVI were discussed.

The Principle of CAVI and Its Independency from Blood Pressure at a Measuring Time

The theory of CAVI

The CAVI reflects the stiffness of the whole arterial segment

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Received June 23, 2012; Accepted August 27, 2012; Published August 27, 2012

Citation: Shirai K, Utino J, Saiki A, Tatsuno I, Shimizu K, et al. (2012) Evaluation of Arteriosclerotic Vascular Disease with a New Noble Stiffness Indicator, Cardio-Ankle Vascular Index (CAVI). J Clin Exp Cardiol S1:004. doi:10.4172/2155-9880.S1-004

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comprising the aorta, femoral artery and tibial artery (Figure 1) [20]. This index was originally derived from the stiffness parameter β proposed by Hayashi et al. [18] and Kawasaki et al. [30], with application of Bramwell-Hill's equation [19].

Here, the principle of the CAVI formula is described briefly:

$$\text{CAVI} = a\{(2\rho/\Delta P) \times \ln(P_s/P_d) \text{PWV}^2\} + b \quad \text{----- CAVI formula}$$

where, P_s is systolic diastolic blood pressure, P_d 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 $P_s - P_d$, ρ is blood density, and a and b are constants.

The above equation is derived as follows:

CAVI is essentially β .

$$\beta = \ln(P_s/P_d) \cdot D/\Delta D$$

where D is diameter of the artery, ΔD is change in diameter of artery according to pressure change.

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

$$\text{PWV}^2 = \Delta P/\rho \cdot V/\Delta V \approx \Delta P/\rho \cdot D/2\Delta D, \quad \text{equation 1}$$

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

$$\beta' (= \text{CAVI}) = \ln(P_s/P_d) \cdot (D/\Delta D)$$

$$\approx a\{\ln(P_s/P_d) \cdot 2\rho/\Delta P \cdot \text{PWV}^2 + b\}$$

This new index has been named cardio-ankle vascular index (CAVI), which reflects the stiffness of the aorta, femoral artery and tibial artery as a whole. a and b were adopted to adjusted to the value of $c\text{PWV}$.

The independence of CAVI from blood pressure at a measuring time

As for the validity of applying Bramwell-Hill's equation to the equation of the stiffness parameter β , which is essentially applied to some segment of the artery, Takaki et al. [31] provided evidence that CAVI was positively correlated with the stiffness parameter β of the aorta ($r = 0.67$, $P < 0.01$).

The most conspicuous feature of CAVI is independence of the blood pressure at the time of measurement. Several reports [18,23,31,32] 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 tried to solve this question using a selective β_1 adrenoceptor blocker, metoprolol as shown in Figure 2A [20]. Metoprolol is known to decrease blood pressure by decreasing cardiac contraction, but not by influencing arterial wall. When metoprolol was administered to 12 men, systolic and diastolic blood pressure decreased for 6 hours. baPWV decreased accompanying with a decrease in blood pressure as expected, but CAVI did not change. This result suggested that CAVI was not influenced by blood pressure at the time of measurement. Then, CAVI could be used to evaluate the real effect of blood pressure on the proper stiffness of arterial wall.

The Properties of CAVI

Aging and gender

Among healthy Japanese people (men=3259, women=3534, age

20-79 years old), CAVI increased with aging. CAVI increased 0.5 / 10years in both men and women [21].

Gender difference was observed in CAVI. CAVI of men was significantly higher than that of women by 0.2, in almost all ages [21].

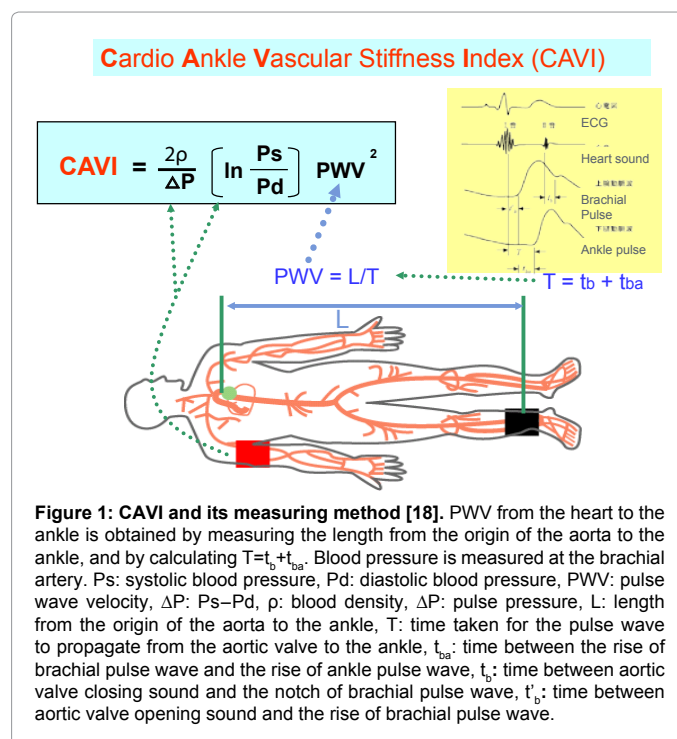


Figure 1: CAVI and its measuring method [18]. PWV from the heart to the ankle is obtained by measuring the length from the origin of the aorta to the ankle, and by calculating $T = t_b + t_{ba}$. Blood pressure is measured at the brachial artery. P_s : systolic blood pressure, P_d : diastolic blood pressure, PWV: pulse wave velocity, ΔP : $P_s - P_d$, 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_b : time between the rise of brachial pulse wave and the rise of ankle pulse wave, t_{ba} : 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.

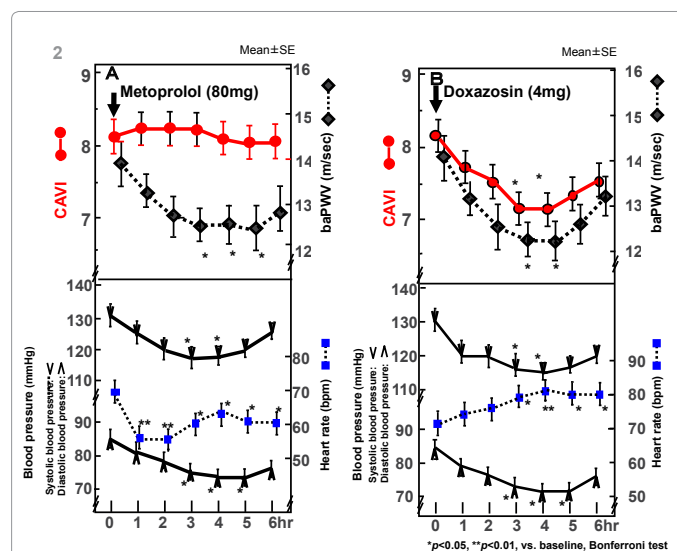


Figure 2: Effects of the β_1 blocker, metoprolol and α_1 - blocker, doxazosin on CAVI and baPWV [20]. When selective β_1 adrenergic blocker metoprolol (80 mg) was administered, both systolic and diastolic blood pressures decrease and baPWV also decreases, but CAVI does not change [20] (Figure 2A). This study indicates that CAVI is independent of blood pressure at the time of measurement. Furthermore, with the administration of selective α_1 -adrenergic receptor blocker, doxazosin, both systolic and diastolic blood pressures decreased and CAVI decreased as well as baPWV (Figure 2B), indicating that CAVI decreased with a relaxation of smooth muscles induced by α_1 -adrenergic receptor blocker.

Generally, the incidence of cardiovascular diseases is higher in men than in women in Japan. And, interestingly, life span of men was shorter than that of women by 5 years in Japanese, which term was corresponding to CAVI difference 0.2.

Effect of physical conditions

CAVI is changed transiently by anesthesia [33]. CAVI is reported to decrease just after taking a meal as same as baPWV and augmentation index [34]. Probably, in order to obtain stable values of CAVI, the conditions such as smoking, exercise and meal at measuring time, must be same as those of the other pulse wave indices. Precise studies were required in the future.

Effect of vasodilators

When vasodilator drugs were administered, CAVI would be expected to decrease, because the contraction of arterial wall smooth muscle cell would be released. Actually, administration of alfa-1 selective adrenoceptor blocker, doxazosin decreased CAVI for 2-4 hour transiently, accompanying with a decrease in systolic and diastolic blood pressure (Figure 2B) [20].

A prostacyclin analogue, beraprost also decreased CAVI, transiently, in spite of no changes in blood pressure [35].

These results suggest that CAVI might reflect the smooth muscle cell contracture in addition to organic stiffness such as collagen or elastin.

It is interesting that vasomotor nerve function influencing the stiffness of arterial wall could be monitored with CAVI.

Endo et al. reported that CAVI was correlated with flow-mediated dilatation of the artery [36]. These results also support that CAVI was monitoring contracture of smooth muscle cells, as well as organic stiffness.

The Role of CAVI in an Indicator of Arteriosclerosis - Various Arteriosclerotic Diseases and CAVI -

Arteriosclerotic disease

Cerebro-vascular disease: The patients with cerebral infarction showed high CAVI [25] as baPWV [37]. It is also reported that high CAVI value might be a predictor of cognitive impairment [38]. CAVI does not directly reflect the artery in the brain, but the aorta mainly. The above data showing a relationship between cerebral infarction and the degree of aortic sclerosis measured by CAVI might indicate that the arteriosclerosis of the cerebral artery and of the aorta may have common pathogenesis (Figure 5).

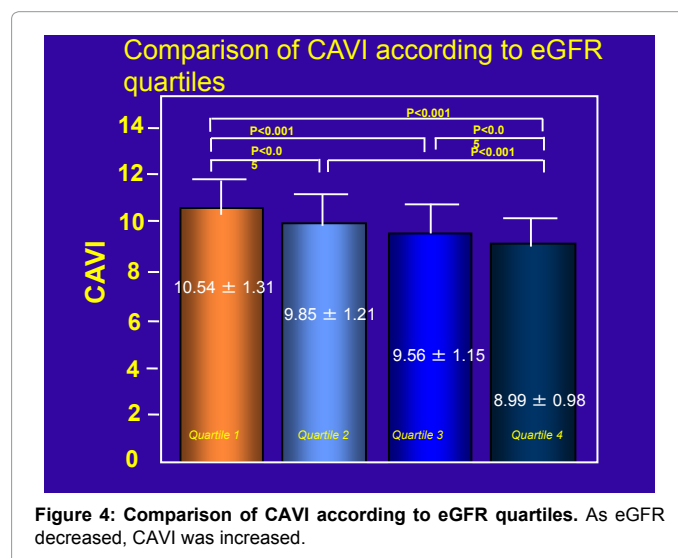
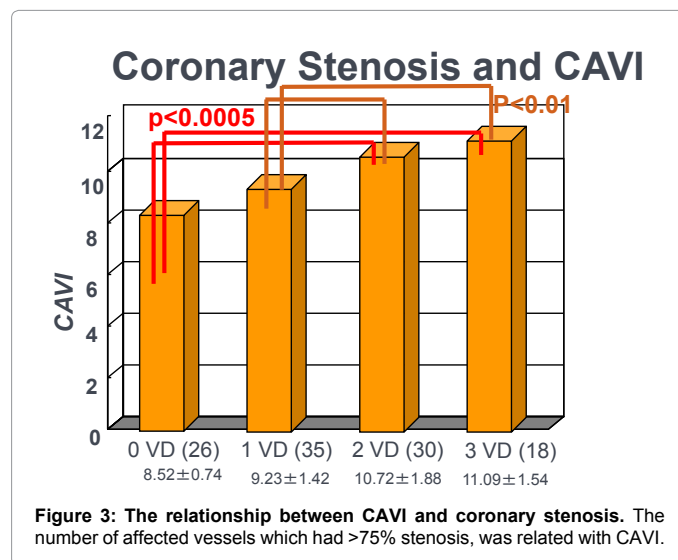
Cardiovascular disorder: Nakamura et al. [22] reported that the number of coronary stenosis vessels is correlated with CAVI among the patients who took a coronary angiography with a suspicion of ischemic coronary disease (Figure 3). Miyoshi et al. [39] and Horinaka et al. [40] have reported nearly identical results, and concluded that CAVI correlated with the degree of coronary arteriosclerosis.

Carotid artery atherosclerosis: As for intima-media thickness (IMT) of carotid artery, several workers showed strong correlation between CAVI and IMT, but, plaque score showed much more stronger correlation with CAVI [31,40-42].

The combination of CAVI and IMT might be a much significant predictor of cerebral thrombosis in highly atherosclerotic patients.

Renal sclerosis: The increase in the number of patients taking chronic hemodialysis is social problem, now. Nakamura et al. [24] reported that CAVI is correlated with a decrease in kidney function (Figure 4). Patients taking hemodialysis therapy showed high CAVI values [43,44].

Arterial inflammatory diseases: CAVI value was high in patients with Systemic Lupus Erythematosus (SLE) [45]. And, it is reported that administration of steroids reduced CAVI in SLE. These observations confirmed that SLE was associated with inflammation of the large artery. CAVI value is also reported to be high in patients with aortitis syndrome [46,47]. Kume et al. [48] reported that CAVI was high in patients with rheumatoid arthritis, and administration of ocilizumab monotherapy reduced CAVI as same as etanercept or adalimumab monotherapy. This finding suggested that rheumatoid arthritis is essentially associated with systemic arterial inflammation. CAVI might become a clinical marker of the treatment in arterial inflammatory diseases.



Risk Factors of Coronary Artery Disease and CAVI

And management of CAVI

The accelerating factor of CAVI including coronary risk factors and improvement factors of CAVI are shown in Figure 5 (Table 1).

High blood pressure: Hypertension was a strong risk factor raising CAVI. CAVI does not depend on the blood pressure at the time of measurement. Then, CAVI can demonstrate the real effects of blood pressure on the properties of arterial wall [18,20,26,49,50]. Numerous studies of antihypertensive agents on CAVI have already been done. CAVI is reported to decline with candesartan [51,52], telmisartan [53], olmesartan [54] among the angiotensin II receptor blockers (ARBs). In comparison between ARB and calcium channel blockers, olmesartan improved CAVI much more than amlodipine, in despite of equivalent decrease in blood pressure [52]. Efonidipine [55] reportedly improves CAVI. Further study will be required to conclude ARB is superior to calcium channel blocker (CCB).

Recently, thiazides have been used in addition to CCB or ARB. Its effect on CAVI is currently under investigation. Available data showed that an addition of thiazide to angiotensinogen converting enzyme (ACE) did not improve CAVI, even though blood pressure decreased [56]. The implications of this trend will be examined from now on.

Diabetes mellitus: Diabetes mellitus is an important factor promoting arteriosclerosis. CAVI shows a high value in patients with diabetes mellitus [49,57]. In addition to a high value of CAVI in the chronic phase, CAVI showed a high value at acute phase of high glucose level [57]. High glucose level seems to be toxic to the artery, and might work injuriously to smooth muscle cells and promote their contracture, resulting in elevating CAVI in a short period.

A decline in HbA1c due to weight loss causes improvement of CAVI [58]. By controlling HbA1c using drugs such as insulin and glimepiride, CAVI decreased [59,60]. CAVI might be a good marker of blood glucose control in routine clinical practice.

Dyslipidemia: LDL cholesterol has been mentioned as atherogenic factor. CAVI showed high in mass study [49,61]. But, CAVI is not necessarily high in heterogeneous familial hypercholesterolemia (LDL-receptor deficiency) [62]. In the initial stage of arteriosclerosis in hypercholesterolemia, fatty streak is observed. At this stage, the artery does not stiffen and CAVI might not be elevated. When inflammatory reaction occurs, the blood vessels stiffen.

Administration of pitavastatin reduces CAVI [63]. One of the reasons, by which, CAVI decreased by pitavastatin might be due to enhancement of NO synthesis by pitavastatin in the endothelial cells.

Obesity, Metabolic syndrome: So-called metabolic syndrome is now thought to be a major risk factor for coronary artery disease. Sato-Asahara showed [26] that CAVI was high in metabolic syndrome and was improved by body weight reduction. CAVI might be a good marker of arteriosclerosis provoked by metabolic syndrome.

Smoking: Smoking is the high risk factor for arteriosclerosis. CAVI value was high in smokers, and ceasing smoking reduced CAVI in a few months, and also in acute phase [27,64].

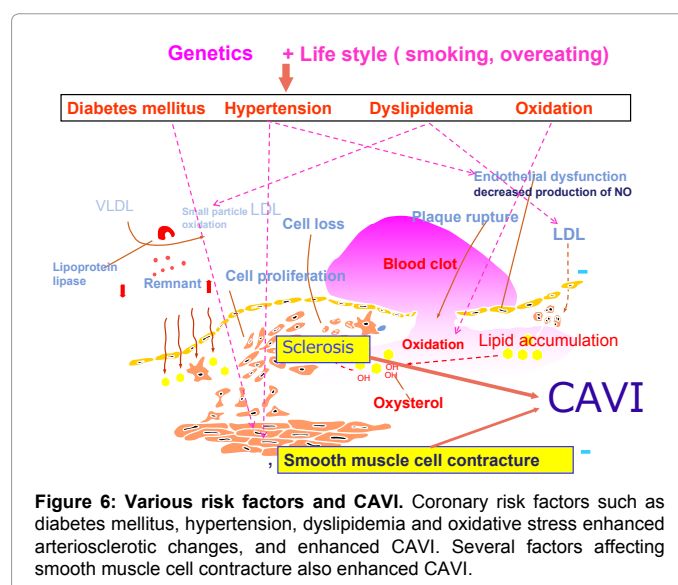
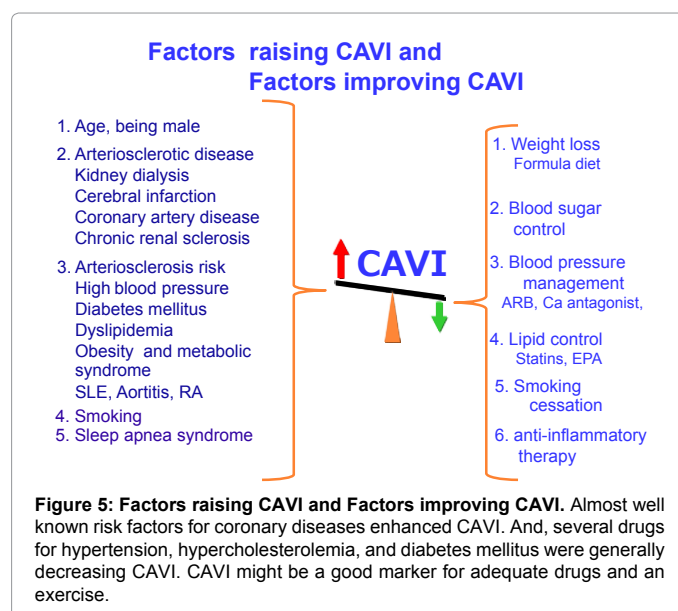
Measuring CAVI might contribute to provoke a motivation, when the person tried to stop smoking.

Sleep apnea syndrome: Sleep apnea is thought to impose a substantial burden on blood vessels due to the repetition of low oxygen

and high oxygen levels. CAVI value is reported to be high in patients with sleep apnea [65]. And, CAVI was decreased by continuous positive pressure assisting therapy [66].

A summary of the above is illustrated in Figure 6. Some genetics and life style disturbance provoked diabetes mellitus, hypertension, dyslipidemia and oxidation stress. Those might influence the arterial wall by their own ways. And, it might be said that organic sclerosis and smooth muscle cell contracture in the artery wall, elevated CAVI.

As an availability of CAVI as a surrogate marker of arterial stiffness, comparing with baPWV, several workers reported that CAVI is superior to baPWV. Takaki et al. [31] reported that only CAVI was correlated with the parameters of left ventricular diastolic indices. Additionally, LDL-C and T-C/HDL-C were associated with only CAVI, but not baPWV. Horinaka et al. [40] reported that CAVI was correlated high-sensitivity C-reactive protein, but not baPWV. The receiver operating characteristic curve for coronary stenosis showed that the diagnostic



	CAVI value		Reference
	Untreated	Treated	
Aging, man> woman	↑		Namekata (21)
Coronary artery diseases [Acute coronary disease]	↑		Nakamura (22), Izuhara (23), Miyoshi (37), Horinaka (38) [Sairaku (39)]
Intima-media thickness of cervical artery	↑		Nakamura (22), Izuhara (23), Miyoshi (37), Horinaka (38)
Chronic kidney disease Hemodialysis	↑		Nakamura (24), Satoh-Asahara (26) Ueyama (41), Ichihara (42)
Cerebral infarction	↑		Suzuki (25)
Metabolic syndrome	↑	↓	Satoh (26)
Diabetes mellitus	↑	↓	Namekata (46), Ibata (54), Izuhara(23)
Dyslipidemia	↑	↓	Takaki (58)
Smoking	↑	↓	Noike (27), Kubozono (64)
Obstructive sleep apnea syndrome	↑	↓	Kumagai (61), Kasai (62)
Hypertension	↑	↓	Satoh-Asahara (26), Namekata (46), Okura (47), Kubozono (32), Ibata (54), Takaki (31), Horinaki (38), Mizuguchi (28)
SLE, Aortitis, Reumatic Arthritis	↑	↓	Sato (43), Masugata (44,45), Kume (67)

Table 1: CAVI in arteriosclerotic diseases and in coronary risks.

accuracy of coronary artery disease was significantly higher in CAVI than in baPWV. Ibata et al. [57] showed that significant risk factors of high CAVI were age and hemoglobinA1c, while systolic blood pressure was not relevant. He described that CAVI is independent of blood pressure, and useful as an indicator of early arteriosclerosis in diabetic subjects.

Prospective Studies on the Occurrence of Coronary Disease Events

It has been reported that an increase in stiffness of arterial wall is a strong prognostic factor for the occurrence of cardiovascular events. As for CAVI, Kubota et al. [28] have reported a significant difference in the occurrence of cardiovascular events and cerebrovascular events with a CAVI value over 10 as the boundary in positive studies of 400 patients for 3 years. Now, massive prospective studies were going.

Cardiac Function and CAVI

Arteries have the role to transport the blood ejected from the heart to the peripheral organs. To do this role efficiently, the artery used the elasticity of the arterial wall. High elasticity of the blood vessel facilitates the heart function by reducing the burden on the cardiac muscles. Namely, the linkage between the heart and arteries exist. Takaki et al. [61] and Mizoguchi et al. [29] investigated the heart functions in angina pectoris patients, and in particular, the relationship between left ventricular diastolic function and CAVI. They examined CAVI and the peak velocity of early (E) and late (A) mitral inflow, and presented that the E/A ratio was inversely correlated to CAVI and that the deceleration time of the E wave (EDCT) was positively correlated with

CAVI. Their results suggested the association between CAVI and left ventricular diastolic function. There is a possibility that CAVI reflects the phenomenon that has conventionally been called “afterload.”

On the other hand, the relationship between CAVI and the peripheral circulation dynamics has yet to be adequately examined. The aortic system has the role of changing the pulsating flow from the heart to a steady flow in the peripheral organs. CAVI may be able to play a role in this field as a marker of the compliance of the artery.

Summary: The Future of CAVI

CAVI showed stable value in healthy person for years. So, the quick enhancement of CAVI is suspected to have some meaning. Usually, enhanced CAVI is associated with poor control of diabetes mellitus, body weight and hypertension.

Six or seven years have passed since CAVI was born. The data were still poor in volume. To establish the CAVI, further strenuous effort to confirm those data is required. But, the analysis of vascular functions using CAVI will develop a new field in the research of arteriosclerotic vascular diseases.

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This article was originally published in a special issue, [Arteriosclerotic Vascular Disease](#) handled by Editor(s). Dr. Weibin Shi, University of California Los Angeles, USA