Comparison of Predictive Ability of Arterial Stiffness Parameters Including Cardio-Ankle Vascular Index, Pulse Wave Velocity and Cardio-Ankle Vascular Index$_0$

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Abstract: Cardio-ankle vascular index (CAVI) was developed to reflect the stiffness of the arterial tree from the aortic origin to the ankle. This arterial stiffness parameter is useful for assessing the severity of cardiovascular disease (CVD) and its risk. However, compared to pulse wave velocity (PWV), the conventional gold standard of arterial stiffness parameter, there has been a concern regarding CAVI that there are fewer longitudinal studies for CVD. Furthermore, the accuracy of CAVI for atherosclerotic diseases compared to other parameters has not been well validated. This review article aims to summarize recent findings to clarify the predictive ability of CAVI in longitudinal studies. First, several large longitudinal studies have found that not only baseline CAVI but also CAVI changes during the observation period predict cardiovascular events. Second, CAVI may have superior discriminatory power for all-cause mortality and major adverse cardiovascular endpoints compared to PWV. Furthermore, one large longitudinal study found CAVI to be a stronger predictor for renal function decline compared to PWV as well as CAVI$_0$, a variant of CAVI that mathematically excludes BP dependence. Additionally, CAVI shows the properties that allow the elucidation of specific hemodynamics in aortic valve disease or hypovolemia. In conclusion, CAVI may be a modifiable arterial stiffness parameter not only for predicting and preventing atherosclerotic diseases but also for elucidating specific hemodynamic pathophysiology.

Keywords: cardio-ankle vascular index, pulse wave velocity, CAVI$_0$, longitudinal study, cardiovascular disease, renal function decline

Plain Language Summary
- Cardio-ankle vascular index (CAVI) is an arterial stiffness parameter in which the blood pressure dependence observed in pulse wave velocity (PWV) is eliminated.
- Many longitudinal studies revealed the independent contribution of CAVI for cardiovascular events.
- CAVI$_0$ is a variant of CAVI that theoretically corrects even more strongly for the dependence on blood pressure.
- CAVI may predict the development of atherosclerotic diseases more effectively than PWV and CAVI$_0$.

Preface
Arterial stiffness reflects the ageing and loss of elasticity in blood vessels, and is used as a predictor of cardiovascular disease (CVD). The most commonly used arterial stiffness parameter is pulse wave velocity (PWV). However, this parameter is inherently influenced by blood pressure (BP) at the time of measurement, and may underestimate the degree of vascular dysfunction due to CVD risks other than hypertension. The cardio-ankle vascular index (CAVI) has been established to address this issue. CAVI reflects the stiffness of the whole arterial tree comprising the aorta, femoral artery and tibial artery. The BP independence of CAVI has been confirmed both theoretically and...
CAVI can therefore clarify the intrinsic impact of BP on atherogenesis, and has been reported to be associated positively with a number of CVD risk factors, severity of CVD and future cardiovascular (CV) events. Additionally, appropriate therapeutic interventions to reduce CAVI are expected to contribute to the prevention of future CV events. However, there has been a concern regarding CAVI that there are fewer longitudinal studies for CV events compared to PWV. Moreover, a warning was issued that CAVI may lead to erroneous conclusions because it does not fully correct for BP dependence. Spronck et al have proposed CAVI₀ as a variant of CAVI that theoretically corrects even more strongly for the BP dependence. The accuracy of these aforementioned arterial stiffness parameters has not yet been fully compared. Based on these backgrounds, this review article aims to summarize recent findings about CAVI in longitudinal studies for predicting atherosclerotic diseases. In addition, the predictive ability of the three arterial stiffness parameters (CAVI, PWV and CAVI₀) was compared.

**CAVI as a Predictor of Cardiovascular Events**

Table 1 shows large-scale longitudinal studies examining the predictive ability of CAVI in which there were more than 200 participants. In most studies, baseline CAVI was a predictor of future cardiovascular (CV) events or mortality, and was also associated with new-appearance of atrial fibrillation. Especially, some reports showed that the change in CAVI was also associated with CVD outcomes. Otsuka et al demonstrated that persistent impairment of arterial stiffness was an independent risk for future CV events in 211 subjects with coronary artery disease. The study revealed that the incidence of CV events for 2.9 years was lower in the group with improved CAVI at 6 months compared to those without (Figure 1). Additionally, Saiki et al also reported that the change in CAVI during the first year was associated with 3 point-major adverse cardiac events (MACE) in the 5-year prospective cohort trial enrolling 254 dyslipidemic patients. Furthermore, the annual change in CAVI throughout the observation period was significantly higher in subjects with CV events compared to those without (Figure 2). In other words, appropriate therapeutic interventions to reduce CAVI are expected to contribute to the prevention of future CVD events.

**Measurement of the Three Arterial Stiffness Parameters**

The methods for measuring arterial stiffness parameters cited in this review article are described.

CAVI and CAVI₀ are based on the stiffness index β and a wave equation derived from Newton’s second law. CAVI is calculated by the following formula:

\[
\text{CAVI} = a \left\{ 2 \rho \times \ln(P_s/P_d)/\Delta P \times PWV^2 \right\} + b
\]

where \(P_s\) is systolic blood pressure (SBP); \(P_d\) is diastolic blood pressure (DBP); \(\Delta P\) is \(P_s - P_d\); \(\rho\) is blood density; \(PWV\) is pulse wave velocity, and \(a\) and \(b\) are constants. On the other hand, CAVI₀ is calculated by the following formula:

\[
\text{CAVI}_0 = 2 \rho \times PWV^2/P_d - \ln(P_d/P_{\text{ref}})
\]

where \(P_{\text{ref}}\) is reference pressure (ie, 100 mmHg).

There are several variants of PWV with different ranges of targeted vessels. Heart-ankle PWV (haPWV) and brachial-ankle PWV (baPWV) mainly cited in this article were calculated by the following formulas:

\[
\text{haPWV} = L_{ha}/(T_{hb} + T_{ba})
\]

\[
\text{baPWV} = (L_{ha} - L_{hb})/T_{ba}
\]

where \(L_{ha}\) is the arterial path length from the aortic annulus to the midpoint of the right ankle cuff estimated by the subjects height, \(T_{hb}\) is the time interval between the commencement of the second heart sound and the dicrotic notch on the right brachial arterial pressure wave, \(T_{ba}\) is the “foot-to-foot” time interval between brachial and posterior-tibial arterial pressure waves, respectively, and \(L_{hb}\) is the arterial path length from the aortic annulus to the midpoint of right brachial cuff estimated by the subjects height.
Table 1 Summary on Association of CAVI with Cardiovascular Outcomes in Prospective Studies

| References                  | Country   | Population Characteristics | Mean Age (Years) | Baseline CAVI | Duration of Follow-Up | Outcomes                                                                 | Incidence (%) (1000 Person-Years) | Prognostic Value                                                                 |
|-----------------------------|-----------|-----------------------------|------------------|---------------|----------------------|---------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Kubota et al, 2011<sup>9</sup> | Japan     | 400 patients with CV risk or CAD history | 63.2–73.9        | Not described | 27.2 months          | CAD, stroke and death                                                    | 54.0                              | HR of CVD was significantly higher in CAVI ≥ 10.0 group (HR: 2.25).            |
| Otsuka et al, 2014<sup>10</sup> | Japan     | 211 CAD patients            | 65               | 9.87–10.05    | 2.9 years            | Cardiac death, non-fatal MI, unstable AP, recurrent AP requiring coronary revascularization or stroke | 45.8                              | Persistently impaired CAVI was a significant independent predictor of CV events compared with improved CAVI at 6 months (HR: 3.3). |
| Laucevičius et al, 2015<sup>11</sup> | Lithuania | 2106 MetS patients          | 53.83            | 7.92          | 3.8 years            | MI, stroke or transient ischemic attack, and sudden cardiac death        | 11.6                              | CAVI was significantly associated with the occurrence of total CV events and MI. |
| Satoh-Asahara et al, 2015<sup>12</sup> | Japan     | 425 obese patients          | 51.5             | 7.6           | 5 years              | AP, MI, stroke and arteriosclerosis obliterans                            | 15.8                              | CAVI was a significant predictor of CV events (HR: 1.44 per 1 unit increase). |
| Sato et al, 2015<sup>13</sup>   | Japan     | 1003 subjects with CV risk  | 62.5             | 9.25          | 6.7 years            | MI and stable/unstable AP                                                | 13.4                              | CAVI was independently associated with future CV event risk (HR: 1.126 per 1 unit increase). |
| Chung et al, 2015<sup>14</sup>  | Taiwan    | 626 type 2 diabetic patients | 64               | 8.8           | 4.1 years            | Death, ACS, ischemic stroke and any coronary, revascularization for CAD   | 38.2                              | Patients with CAVI ≥ 9.0 had greater CV events than those with CAVI <9.0 (OR: 1.23). |
| Gohbara et al, 2016<sup>15</sup> | Japan     | 288 patients with ACS       | 58–71            | Not described | 1.25 years           | CV death, non-fatal MI, non-fatal ischemic stroke                        | 52.8                              | Patients with CAVI ≥8.325 was an independent predictor of CV events (HR: 18.0) and nonfatal ischemic stroke (HR: 9.37). |
| Hitsumoto et al, 2018<sup>16</sup> | Japan     | 460 patients with CKD       | 74               | 9.7           | 60.1 months          | Cardiovascular death, nonfatal MI, nonfatal ischemic stroke and heart failure hospitalization | 39.5                              | A MACE was significantly higher in group CAVI ≥ 10 than in non-group CAVI < 10 (HR: 2.04). |

(Continued)
| References                  | Country               | Population Characteristics | Mean Age (Years) | Baseline CAVI | Duration of Follow-Up | Outcomes                                                                 | Incidence (%) (1000 Person-Years) | Prognostic Value                                                                 |
|-----------------------------|-----------------------|----------------------------|------------------|---------------|-----------------------|---------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Kirigaya et al, 2019        | Japan                 | 387 patients with ACS      | 64               | 8.4–9.0       | 62 months            | CV death, ACS recurrence, heart failure hospitalization, or stroke         | 31.0                              | CAVI was an independent predictor of MACE (HR: 1.496) and CV death (HR: 2.204), but baPWV was not. The addition of CAVI to GRACE score enhanced NRI (0.337). |
| Miyoshi et al, 2021         | Japan                 | 2932 patients with CV risk | 63               | Not described | 4.9 years            | CV death, nonfatal stroke, or nonfatal MI                                  | 5.7                               | CAVI predicted the primary outcome (HR: 1.38). The addition of CAVI to known CV risks enhanced NRI (0.254). |
| Murakami et al, 2021        | Japan                 | 242 hemodialysis patients  | 60               | 8.64–9.64     | 6 years              | All-cause mortality                                                       | 26.2                              | CAVI was a significant predictor of mortality (HR:1.595 per 1 SD increase). |
| Saiki et al, 2021           | Japan                 | 254 subjects with CV risk  | 64.8             | 9.56          | 5 years              | CV death, nonfatal stroke or nonfatal MI                                   | 7.9                               | Change in CAVI during the first year tended to be an independent predictor of 3P-MACE (HR: 1.736, p = 0.079). Not described |
| Nagayama et al, 2021        | Japan                 | 5418 subjects receiving health screening | 48            | 7.6–8.7       | 4 years              | New-appearance of AF                                                      | 1.0                               | CAVI ≥ 8.0 was an independent predictor of new-appearance of AF. |
| Sumin AN et al, 2021        | Russia                | 238 patients after elective CABG | 56.5–62.0     | Not described | 5 years              | CV mortality, MI, Stroke or transient ischemic attack, percutaneous coronary intervention, carotid endarterectomy, pulmonary embolism, hospitalizations for CVD | 79.8                              | CAVI ≥ 9.0 was an independent factor associated with the combined endpoint (OR: 1.78) |
| Watanabe et al, 2021        | Japan                 | 223 heart failure patients | 58.0–69.0       | 7.31–9.62     | Median 1623 days      | Cardiac death or unplanned re-hospitalization for HF treatment, ischemic coronary events and all-cause mortality | 58.5                              | CAVI ≥ 8.9 was an independent predictor of cardiac events (HR: 1.845). |
| Authors               | Location | Sample Size | Age (mean) | Sex | Follow-up | Event(s)                                                                 | CAVI (95% CI) | CAVI ≥ 9.64 as independent predictor |
|-----------------------|----------|-------------|------------|-----|-----------|---------------------------------------------------------------------------|--------------|-------------------------------------|
| Sato et al, 202124    | Japan    | 557 patients | 65.6–73.0  | Not described | Median 1415 days | Ischemic or hemorrhagic stroke                                              | 11.6         | CAVI ≥ 9.64 was an independent predictor of stroke (HR: 3.599) compared to CAVI < 9.64. |
| Tabara et al, 202125  | Japan    | 7249 urban residents | 59.8 | 7.91 | Median 8.53 years | First-ever MI, coronary artery bypass grafting or angioplasty, Ischemic or hemorrhagic stroke | 3.5          | CAVI was significant predictor of incident CVD (HR: 1.23 per 1 unit). |
| Aiumtrakul et al, 202226 | Thailand | 4898 subjects with CV risk | 60.2–70.0 | 7.05–10.06 | 60 months | eGFR decline over 40%, eGFR less than 15 mL/min/1.73 m², doubling of serum creatinine, initiation of dialysis and death related to renal causes | 15.7         | Subjects with CAVI ≥ 9 had a 1.45-fold significant risk for the primary composite outcome and 1.72-fold risk for all-cause mortality, compared with subjects with CAVI < 8. |
| Rerkasem et al, 202227 | Thailand | 347 adults with HIV | Aged ≥50 | Not described | 5 years | A composite of total deaths and hospitalizations due to myocardial infarction, coronary revascularization, stroke, and heart failure | 25.9         | Subjects with CAVI ≥ 8.0 was a independent predictor of MACE (HR = 2.11, 95% CI 1.06–4.20). |

**Abbreviations:** CAVI, cardio-ankle vascular index; CV, cardiovascular; CAD, coronary artery disease; CVD, cardiovascular disease; HR, hazard ratio; AP, angina pectoris; MI, myocardial infarction; MetS, metabolic syndrome; ACS, acute coronary syndrome; NRI, net reclassification improvement; ACS, acute coronary syndrome; CKD, chronic kidney disease; OR, odds ratio; SD, standard deviation; MACE, major adverse cardiovascular events; GRACE, global registry for acute coronary events; baPWV, brachial-ankle pulse wave velocity; AF, atrial fibrillation; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.
Figure 1 Kaplan–Meier curves of event-free survival according to CAVI. 211 patients with coronary artery disease (age 65±10 years, 118 men). (A) Comparison of Kaplan–Meier curves of event-free survival between patients above the median and below the median CAVI value in the first CAVI test. (B) Comparison of Kaplan–Meier curves of event-free survival between patients with persistently impaired CAVI and improved CAVI. Reprinted with permission from Otsuka T, Fukuda S, Shimada K et al. Serial assessment of arterial stiffness by cardio-ankle vascular index for prediction of future cardiovascular events in patients with coronary artery disease. Hypertens Res. 2014;37(11):1014–1020.

Abbreviation: CAVI, cardio-ankle vascular index.

Figure 2 Differences in the annual CAVI changes in patients with or without CV events. 254 patients with CVD risk (age 64.8 ± 9.3 years, 118 men). (A) Primary end points and (B) 3P-MACE. Mean ± SD, Mann–Whitney U-test. Annual CAVI change was defined as the annual change in CAVI until the occurrence of any CV event or the end of 5-year study period. Primary end point: composite of cardiovascular death, sudden death of unknown origin, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, and heart failure requiring hospitalization. 3P-MACE: three-point major cardiac adverse events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke). Reprinted with permission from Saiki A, Watanabe Y, Yamaguchi T et al. CAVI-Lowering Effect of Pitavastatin May Be Involved in the Prevention of Cardiovascular Disease: Subgroup Analysis of the TOHO-LIP. J Atheroscler Thromb. 2021;28(10):1083–1094. Creative Common.

Abbreviations: CAVI, cardio-ankle vascular index; CV, cardiovascular.
Comparison of the Predictive Ability of CAVI with Other Arterial Stiffness Parameters

This section lists longitudinal studies comparing the arterial stiffness parameters.

Comparison of CAVI and PWV

The Nagahama study,\(^{25}\) a five-year longitudinal study of 8850 Japanese community residents, showed that baPWV and CAVI were similarly associated with future CVD events. However, it was concluded that the association was clearer for baPWV. On the other hand, several longitudinal studies have been reported showing the superiority of CAVI.

We have previously conducted a longitudinal study comparing CAVI with haPWV, an index incorporated into the CAVI structural equation including central and peripheral arteries.\(^{19}\) Of the 209 hemodialysis patients, 38 died for 6 years. Resultantly, in the Cox-proportional hazards analyses, 1 SD increase in both parameters contributed almost equally to all-cause mortality [CAVI: hazards ratio (HR) 1.595, haPWV: HR 1.695]. On the other hand, receiver operating characteristic analysis showed that CAVI had better discriminatory power for all-cause mortality compared to haPWV (Figure 3).

Kirigaya et al\(^{17}\) also compared the predictive ability of CAVI and baPWV in 387 consecutive patients with history of acute coronary syndrome (ACS) in a longitudinal study. Resultantly, MACE (CV death, recurrence of ACS, heart failure requiring hospitalization or stroke) occurred in 62 patients (16.0%) during a median follow-up of 62 months. Multivariate analysis suggested that mean CAVI was a significant predictor of MACE (HR = 1.494) and CV death (HR = 2.217), but baPWV was not.

Comparison of CAVI, PWV and CAVI\(_0\) (Part 1)

Spronck et al\(^{28}\) compared the three arterial stiffness parameters including haPWV, CAVI and CAVI\(_0\) in 154 outpatients during an average of 2.53 years of observation, and the predictive ability of each parameter for the composite endpoint

![Discriminatory powers of arterial stiffness parameters for the prediction of all-cause mortality. Of the 209 hemodialysis patients (mean age 60 years, 129 men), 38 patients died during the 6-year period. Curves represent receiver-operating-characteristics analyses for discriminating the probability of all-cause mortality. The Youden's J statistic was used to select the optimum cutoff point of each arterial stiffness parameter. \(^*P < 0.05\), \(†P < 0.001\) between haPWV and CAVI. Reprinted with permission from Dove Medical Press. Murakami K, Inayama E, Itoh Y et al. The Role of Cardio-Ankle Vascular Index as a Predictor of Mortality in Patients on Maintenance Hemodialysis. Vasc Health Risk Manag. 2021;17:791–798.\(^{19}\)

**Abbreviations:** AUC, area under curve; NRI, net reclassification index; IDI, integrated discrimination improvement; 95% CI, 95% confidence interval; haPWV, heart-ankle pulse wave velocity; CAVI, cardio-ankle vascular index.
[death (n = 21) and heart failure requiring hospitalization (n = 18)] was examined. Resultantly, after adjustment for baseline heart failure status assessed by Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and systolic BP, only right sided haPWV (HR = 1.58) and right sided CAVI (HR = 1.44) remained predictive, whereas only CAVI₀ was not a significant factor.

**Comparison of CAVI, PWV and CAVI₀ (Part 2)**

Most renal impairment is attributable to renal atherosclerosis, and renal function can be quantified using estimated glomerular filtration rate (eGFR). The predictive ability of three arterial stiffness parameters for renal function decline was therefore validated.²⁹ A total of 27,864 Japanese urban residents without renal impairment at baseline who participated in two to eight consecutive (mean 3.5 ± 1.7 times) annual health examinations were studied, and 6.6% of them developed renal function decline (eGFR < 60 mL/min/1.73m²).

The discriminatory power for renal function decline showed a decreasing trend of CAVI to haPWV to CAVI₀ (C-statistic: 0.740 vs 0.734 vs 0.726). The cutoffs defined using Youden’s J statistic were CAVI 8.0, haPWV 7.23, and CAVI₀ 11.6 (Table 2A). The results of the analyses showed that CAVI was most strongly associated with renal function decline, followed by haPWV and CAVI₀, in that order (Table 2B). Furthermore, the contribution of each parameter (increase above cutoff or by 1 SD) to renal function decline was assessed using Cox-proportional hazards analysis (Table 3). If the arterial stiffness parameter is not significant in Model 1 [confounders: age, sex, BMI, proteinuria, systolic BP, fasting plasma glucose and high-density lipoprotein cholesterol (HDL-C)], it implies a lack of predictive ability beyond any metabolic parameters including BP, for renal function decline. Alternatively, if the arterial stiffness parameter is significant in Model 1 but not in Model 2 (confounders: treatments for hypertension, diabetes and dyslipidemia replaced by systolic BP, FPG and HDL-C in Model 1), it implies that the parameter depends on any metabolic abnormality. In other words, if the arterial stiffness parameter is not extracted as a significant factor in both Model 1 and 2, the parameter can be considered as having no value as a new risk factor. The results confirmed that only CAVI significantly contributed to the renal function decline in both models. On the other hand, haPWV and CAVI₀ were not necessarily significant contributors.

The cutoff is defined by the intersection point in the frequency distribution curves of arterial stiffness parameter in each of the two groups with and without renal function decline. Since arterial stiffness is strongly age-dependent, the cutoffs vary widely across age groups. In other words, the cutoff for predicting renal function decline is higher when restricted to older

| Table 2 Comparison of Associations of Arterial Stiffness Parameters with Renal Function Decline |
|-----------------------------------------------|----------------------|------------------|-----------------|-----------------|
| (A)                                           | **C-statistics (95% CI)** | **p value**     | **Cutoff**      | **Sensitivity** | **Specificity** |
| CAVI                                          | 0.740 (0.729–0.751)     | <0.001          | 8.0             | 0.672           | 0.690           |
| haPWV                                         | 0.734 (0.722–0.775)     | <0.001          | 7.23            | 0.726           | 0.632           |
| CAVI₀                                         | 0.726 (0.714–0.738)     | <0.001          | 11.6            | 0.657           | 0.688           |
| (B)                                           | **p value for C-statistics** | **NRI (95% CI)** | **p value for NRI** | **IDI (95% CI)** | **p value for IDI** |
| CAVI vs haPWV                                 | 0.038                  | 0.159 (0.112–0.206) | <0.001          | 0.004 (0.002–0.006) | <0.001          |
| CAVI vs CAVI₀                                 | <0.001                 | 0.477 (0.430–0.523) | <0.001          | 0.007 (0.006–0.009) | <0.001          |
| haPWV vs CAVI₀                                | 0.095                  | 0.201 (0.154–0.248) | <0.001          | 0.003 (0.004–0.006) | 0.023           |

**Notes:** 27,864 Japanese urban residents (median age 46.0 years) without renal impairment at baseline who participated in 2 to 8 consecutive (mean 3.5±1.7 times) annual health examinations. (A) Discriminatory powers and cutoff values of arterial stiffness parameters for renal function decline. Youden’s J statistic was used to select the optimum cutoff point for each arterial stiffness parameter. (B) Comparisons of discriminatory power between arterial stiffness parameters for renal function decline. Adopted from reference.²⁹

**Abbreviations:** CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval.
people. Therefore, when the cutoff of arterial stiffness parameter estimated in this study is treated for predicting renal function decline, the interpretation should only be targeted to the middle aged general Japanese population.

In summary, haPWV, a remarkable BP dependent arterial stiffness parameter, was more predictive for renal function decline than CA VI\textsuperscript{0}, which has been proposed to theoretically eliminate BP dependence. However, CA VI was most strongly associated with renal function decline compared with haPWV and CA VI\textsuperscript{0}. The major difference between CA VI and CA VI\textsuperscript{0} is that CA VI employs $\beta$ over a range of diastolic to systolic pressures, whereas CA VI\textsuperscript{0} employs $\beta$ at only diastolic pressure. This difference in structural formula might cause the divergence of predictive ability between CA VI and CA VI\textsuperscript{0}.

### Comparison of the Predictive Ability for Hemodynamic Changes

Finally, the predictive ability of arterial stiffness parameters for the specific hemodynamic is discussed.

Mestanik et al\textsuperscript{30} reported that cold pressor test caused a transient increase in CA VI, but not in CA VI\textsuperscript{0}. Since the cold pressor test inherently induces vascular smooth muscle contraction through sympathetic activation,\textsuperscript{31} this result therefore means that CA VI, not CA VI\textsuperscript{0}, is influenced by short-term arterial smooth muscle contraction. This finding is consistent with our previous report revealing that CA VI can be reduced by $\alpha_1$-adrenergic receptor blocker, but not by $\beta_1$ blocker.\textsuperscript{3}

In other words, CA VI accurately reflects not only organic stiffness (ie, arteriosclerosis) but also functional stiffness (ie, vascular smooth muscle contraction).

Plunde et al\textsuperscript{32} reported that aortic valve replacement (AVR) for aortic valve disease increased CA VI. The prolonged pulse wave caused by preoperative aortic valve disease leads to an extended and larger arterial dilatation to comply with the systolic flow and consequently resulting in a modified measurement of arterial stiffness. Relief of obstruction by AVR therefore leads to true arterial stiffness can be measured by CA VI.\textsuperscript{33} However, carotid-femoral PWV, which essentially lacks information on the aortic valve and ascending aorta, remained unchanged after AVR in the same population.

Nagasawa et al\textsuperscript{34} used a rabbit model to assess the effect of changes in intra-aortic blood volume on arterial stiffness. When blood was removed, BP and blood flow in the common carotid artery gradually decreased. At that point, CA VI increased during blood removal, whereas haPWV conversely decreased slightly as the decreased BP. The finding suggests that CA VI, not haPWV, accurately reflects the acute response of conduit artery elasticity to changes in intra-aortic blood volume.

### Conclusions

As discussed in this chapter, CA VI may predict the development of atherosclerotic diseases more effectively compared to PWV and CA VI\textsuperscript{0}, and is also useful for assessing the pathophysiology of hemodynamics in relation to left ventricular function and peripheral organ blood flow. This index is a suitable arterial stiffness parameter reflecting the Windkessel effect, and may therefore open up a new horizons of vascular function research.

| Table 3 Adjusted Hazard Ratios of Arterial Stiffness Parameters for Renal Function Decline |
|---------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
|                                | CAVI          | haPWV         | CAVI\textsuperscript{0} |
|                                | ≥ 8.0         | 1 SD Increase | ≥ 7.23        | 1 SD Increase | ≥ 11.6        | 1 SD Increase |
| Model 1                        |               |               |               |               |               |               |
|                                | 1.182         | 1.115         | 1.120         | 1.144         | 1.147         | 1.023         |
|                                | (1.010–1.383)$^*$ | (0.946–1.325)$^*$ | (0.985–1.336) | (0.985–1.336) | (0.968–1.080) |
| Model 2                        | 1.188         | 1.108         | 1.238         | 1.115         | 1.151         | 1.023         |
|                                | (1.043–1.353)$^*$ | (1.041–1.179)$^*$ | (1.054–1.179)$^*$ | (1.054–1.179)$^*$ | (1.014–1.306)$^*$ | (0.974–1.074)$^*$ |

Notes: 27,864 Japanese urban residents (median age 46.0 years) without renal impairment at baseline who participated in 2 to 8 consecutive (mean 3.5 ± 1.7 times) annual health examinations. $^*$p < 0.05. Hazards ratios (95% confidence interval) estimated using Cox-proportional hazards analyses are shown. Renal function decline is defined as eGFR < 60 mL/min/1.73m$^2$ during the study period. Cutoff of each parameter was defined using Youden's J statistic. Model 1: Confounders include age, sex, BMI, proteinuria, systolic blood pressure, fasting plasma glucose and HDL-C. Model 2: Confounders include age, sex, BMI, proteinuria, and treatments for hypertension, diabetes and dyslipidemia. Adopted from reference.\textsuperscript{29}

Abbreviations: CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity; SD, standard deviation; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

Abbreviations: CAVI, cardio-ankle vascular index; haPWV, heart-ankle pulse wave velocity; SD, standard deviation; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.
Disclosure
The authors report no conflicts of interest in this work.

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