Successful prediction of clinical outcomes using arterial velocity pulse index, a new non-invasive vascular index, in Japan

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Abstract:

Objectives: Earlier detection of vascular stiffness and endothelial dysfunction will be useful in preventing atherosclerotic catastrophic conditions. Individuals with high risks for future cardiovascular (CV) events should be recognized by physicians to strengthen preventive therapeutic procedures, such as antihypertensive therapy, antidiabetic therapy, and anti-dyslipidemic therapy. As such, various non-invasive devices have been developed and are currently applied in clinical settings. Among them, we previously reported arterial velocity pulse index (AVI) and arterial pressure volume index (API) measured using a cuff-oscillometric-based medical electronic blood pressure monitor. These are significantly correlated with arterial stiffness and cardiac overload; therefore, these indexes might be useful in predicting future CV events.

Materials and methods: We performed survival and CV event analyses in a total of 180 subjects with various clinical implications who visited Yokohama City University Hospital between May 2013 and March 2015 and followed them up until March 2016. The mean age was 66±13 years, and 101 subjects (56.1%) were men. A total of 116 subjects (64.4%) had hypertension, 87 subjects (48.3%) had dyslipidemia, and 39 subjects (21.7%) had diabetes mellitus. The mean AVI and API were 23.3±7.7 and 31.8±8.4, respectively.

Results: The mean follow-up duration was 769±275 days. A total of 13 major adverse cardiac events (MACEs) occurred during the observational period, which consisted of 1 cardiac death, 8 CV events, and 4 hospitalizations owing to heart failure. After we performed Kaplan-Meier analysis, univariate Cox proportional hazard regression analysis, and multivariate Cox proportional hazard regression analysis, we found that AVI is significantly correlated with the risk of MACE. Therefore, we successfully revealed the clinical implications of the new non-invasive indexes for CV mortality and morbidity. Conclusion: The new non-invasive vascular index, AVI, was significantly correlated with the CV outcomes in our Japanese cohort.

Key words: Arterial stiffness, Cuff-oscillometric methods, Cardiovascular event, Arterial velocity pulse index (AVI)

Introduction

Cumulative evidence shows that the cardiovascular (CV) mortality and morbidity from systemic atherosclerosis are increasing and becoming major obstacles to a healthy life expectancy, especially in developed countries.²-⁴ Currently, lifestyle-related diseases, such as hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HL), are considered common risk factors for CV complications. Vascular inflammation with immunological background²⁻⁴ has also been recently recognized as a basic pathological condition in CV diseases, which remains to be elucidated in terms of unknown treatable risks, i.e., “residual risks.” However, there are only limited procedures available for the diagnosis and recognition of earlier atherosclerotic changes; therefore, the symptomatic complications of CV diseases are still catastrophic, which lead to substantial socioeconomic burden on both the affected individual and the society.

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community. Considerable efforts, along with both medical and social resources, for unexpected CV catastrophic conditions are required to prevent CV mortality and morbidity. Therefore, appropriate earlier diagnoses and recognition of atherosclerosis with effective treatment are one of the major unmet medical needs in the current clinical cardiology settings. Various procedures, such as flow-mediated dilatation (FMD), pulse wave velocity (PWV), and arterio-brachial index, have been used to date to evaluate atherosclerosis by assessing arterial stiffness and impaired endothelial function for these purposes, which develop before clinical manifestations\(^5\). However, the currently available diagnostic procedures are insufficient because of variability among investigators and time-consuming manual methods. The AVE-1500 (Shisei Datum, Tokyo, Japan) is a newly developed device that can non-invasively evaluate arterial stiffness and endothelial dysfunction of the central arteries (arterial velocity pulse index [AVI]) and peripheral arteries (arterial pressure volume index [API]) using a cuff-oscillometric technique in a single blood pressure measurement. We previously reported that the AVI and API are significantly correlated but showed different CV implications\(^6,7\); conversely, other studies have reported various implications of these indexes for CV risks\(^8-11\). Additionally, both the severity of coronary heart disease and complexity of the coronary artery in affected patients are significantly correlated with API\(^7\). Our examinations revealed that API and AVI are differently associated with their own characteristic implications; however, these indexes are evaluated using only one common procedure - with AVE-1500 using cuff-oscillometric technique.

To elucidate the detailed potential utilities of AVI and API in relation to CV outcomes, we performed survival and CV event analyses in subjects with various clinical implications and successfully revealed the clinical implications of these two new non-invasive indexes for CV mortality and morbidity.

**Materials and methods**

**Subjects**

We performed a cross-sectional, retrospective, observational cohort study at Yokohama City University Hospital in Japan. The study protocol was registered and approved by the ethical committee of Yokohama City University Hospital in 2015 with notification for guaranteed withdrawal of participants on the website providing means of “opt-out.” Because of the non-invasive observational study design, we did not obtain additional informed consent from the participants. We assessed major adverse cardiac events (MACEs) in a total of 180 outpatients who underwent AVI and API measurements using a multifunctional blood pressure monitoring device (AVE-1500) between May 2013 and March 2015 and followed them up until March 2016. Patients who were receiving hemodialysis or had atrial fibrillation were excluded. Data on each patient’s general status, medical history, results of blood tests, concomitant medications, and outcomes were obtained retrospectively from their electronic medical records. HT was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of anti-hypertensive drugs. Dyslipidemia (DL) was defined as LDL (low density lipo-protein) cholesterol level ≥140 mg/dL, HDL cholesterol level ≤40 mg/dL, triglyceride level ≥150 mg/dL, or use of lipid-lowering drugs. DM was defined as blood glucose level ≥200 mg/dL, hemoglobin A1c level ≥6.5%, or use of antidiabetic drugs. Congestive heart failure (CHF) was defined as B-type natriuretic peptide (BNP) level ≥40 pg/mL caused by a CV disease. Valvular heart disease was defined as moderate to severe valve regurgitation/stenosis. Both plasma glucose and triglyceride levels were measured using random blood sampling (without overnight fasting).

**AVI and API**

Both AVI and API were measured using AVE-1500, with the subjects in the sitting position. Measurements were obtained in a quiet, temperature-controlled room (24-26°C). The initial measurements for both AVI and API at the time of enrollment of the participants were used for subsequent analyses. The measurement principles for AVI and API have been previously described elsewhere\(^5,9\).

**End point**

The study end point was defined as the first occurrence of any of the following MACEs: cardiac death, non-fatal myocardial infarction (MI), unstable angina pectoris (UAP), hospitalization due to stroke, hospitalization due to angina pectoris, and hospitalization due to heart failure (HF). Non-fatal MI, UAP, hospitalization due to stroke, and hospitalization due to angina pectoris were collectively considered CV events.

**Statistical analyses**

P-values <0.05 indicated statistical significance. Data are expressed as means±standard deviations for continuous variables or as numbers (%) for categorical variables. The patients were divided into two groups according to the presence of MACE, hospitalization due to HF, or a CV event. An unpaired t-test was used to evaluate the differences between the two groups. A receiver operating characteristic (ROC) curve analysis was performed, and the cutoff value, sensitivity, and specificity were determined. An event-free survival analysis was performed using the Kaplan-Meier method, with the AVI cutoff value set at 27 or the API cutoff value set at 32 based on the ROC curve analysis findings. The predictors for MACE were assessed using both univariate and multivariate Cox hazard proportional analyses. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 22.0; SPSS, Inc., Chicago, IL, USA).
### Table 1. Baseline Characteristics

|                      | MACE (+) (n=13) | MACE (-) (n=167) | p     |
|----------------------|-----------------|------------------|-------|
| Age (years)          | 76±8            | 65±13            | 0.007 |
| Male (%)             | 92 (55.1)       | 9 (69.2)         | n.s.  |
| HT (%)               | 107 (64.1)      | 9 (69.2)         | n.s.  |
| DL (%)               | 79 (47.3)       | 8 (61.5)         | n.s.  |
| DM (%)               | 35 (21.0)       | 4 (30.8)         | n.s.  |
| Smoking              |                 |                  |       |
| Current (%)          | 22 (13.2)       | 1 (7.7)          | n.s.  |
| Previous (%)         | 45 (26.9)       | 4 (30.7)         |       |
| Never (%)            | 100 (59.9)      | 8 (61.5)         |       |
| IHD (%)              | 27 (16.2)       | 3 (23.1)         | n.s.  |
| ASO (%)              | 8 (4.8)         | 0 (0.0)          | n.s.  |
| VHD (%)              | 12 (7.2)        | 3 (23.1)         | n.s.  |
| OMI (%)              | 10 (6.0)        | 1 (7.7)          | n.s.  |
| CHF (%)              | 13 (7.8)        | 1 (7.7)          | n.s.  |
| Cardiomyopathy (%)   | 9 (5.4)         | 0 (0.0)          | n.s.  |
| Medication           |                 |                  |       |
| RAS inhibitors (%)   | 8 (61.5)        | 91 (54.5)        | n.s.  |
| Ca antagonists (%)   | 6 (46.2)        | 80 (47.9)        | n.s.  |
| β-blockers (%)       | 4 (30.4)        | 46 (27.5)        | n.s.  |
| Diuretics (%)        | 2 (8.7)         | 30 (19.1)        | n.s.  |
| Nitrites (%)         | 0 (0.0)         | 18 (11.5)        | n.s.  |
| Statins (%)          | 11 (47.8)       | 67 (42.7)        | n.s.  |
| Aspirin (%)          | 7 (30.4)        | 43 (27.4)        | n.s.  |
| Laboratory data      |                 |                  |       |
| LDL-C (mg/dl)        | 115±36          | 109±36           | n.s.  |
| HDL-C (mg/dl)        | 63±16           | 60±18            | n.s.  |
| TG (mg/dl)           | 118±91          | 159±95           | n.s.  |
| Plasma glucose (mg/dl)| 124±32       | 130±44           | n.s.  |
| HbA1c (%)            | 6.1±0.4         | 6.1±1.1          | n.s.  |
| CRP (mg/dl)          | 0.47±0.63       | 0.36±0.90        | n.s.  |
| Creatinine (mg/dl)   | 0.90±0.58       | 0.80±0.33        | n.s.  |
| eGFR (ml/min/1.73m²) | 67.8±24.1       | 74.7±25.4        | n.s.  |
| BNP (pg/ml)          | 108.2±112.1     | 47.7±92.9        | n.s.  |
| SBP (mmHg)           | 144±23          | 133±21           | 0.025 |
| DBP (mmHg)           | 73±14           | 74±14            | n.s.  |
| Heart rate (/min)    | 74±13           | 75±13            | n.s.  |
| AVI                  | 29.0±7.9        | 22.5±7.4         | <0.001|
| API                  | 35.6±8.4        | 31.3±8.3         | 0.020 |

Data are mean±standard deviation or n (%). n.s., not significant; HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus; IHD, ischemic heart disease; ASO, arteriosclerosis obliterans; VHD, vulvular heart disease; OMI, old myocardial infarction; CHF, chronic heart disease; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, Triglyceride; RAS inhibitors, renin-angiotensin system; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AVI, arterial velocity pulse index; API, arterial pressure volume index.

### Results

#### Baseline characteristics

The baseline characteristics of the subjects are shown in **Table 1**. The mean age was 66±13 years, and 101 subjects (56.1%) were men. A total of 116 subjects (64.4%) had HT, 87 subjects (48.3%) had DL, and 39 subjects (21.7%) had DM. The mean AVI and API were 23.3±7.7 and 31.8±8.4, respectively.

#### Relationship between the new vascular indexes and clinical outcomes

The mean follow-up duration was 769±275 days. **Table 2** shows the frequency of the MACEs observed. MACEs were observed in 13 subjects (7.2%). AVI was significantly higher in the subjects with MACEs and those hospitalized due to HF than in those without MACEs (29.1±8.3 vs. 22.8±7.5, p =0.004) (**Figure 1-1**) and those hospitalized due to HF (33.3±3.9 vs. 23.1±7.6, p=0.009) (**Figure 1-2**). In contrast, API was significantly higher in the subjects with CV events than in those without CV events (38.9±10.0 vs. 31.5±7.6, p=0.005) (**Figure 1-3**).
Table 2. Frequency of MACEs

| Number of subjects (%) | MACE | Cardiac death | CV event | Nonfatal myocardial infarction | Unstable angina pectoris | Hospitalization due to stroke | Hospitalization due to angina pectoris | Hospitalization due to heart failure |
|------------------------|------|--------------|----------|-------------------------------|-------------------------|-------------------------------|--------------------------------------|-----------------------------------|
| MACE                   | 13 (7.2) | 1 (0.6)     | 8 (4.4)  | 1 (0.6)                       | 1 (0.6)                 | 3 (1.7)                       | 3 (1.7)                             | 4 (2.2)                           |

Data are presented as n (%). MACE, major adverse cardiac event; CV, cardiovascular.

AVI

| p=0.009 | 33.25 |
|---------|-------|
| 27      | 23.09 |

API

| ns      | 32.25 |
|---------|-------|
| 32      | 31.81 |

Figure 1-1. Difference in AVI and API between the subjects with and without MACEs. The AVI was significantly higher in the subjects with MACEs than in those without MACEs (p=0.004).

Efficacy of the new vascular indexes in predicting clinical outcomes

Based on the ROC curve analysis, we assessed the efficacy of AVI and API as predictors of clinical outcomes. The area under the curve (AUC) for MACE prediction by AVI was 0.717 (95% confidence interval [CI], 0.566-0.868; p=0.009) with “27” as the proposed cutoff value, and the AUC for hospitalization due to HF was 0.877 (95% CI, 0.813-0.941; p=0.01) with “28” as the proposed cutoff value (Figures 2-1 and 2-2). Additionally, the AUC for CV event prediction by API was 0.749 (95% CI, 0.622-0.875; p=0.017) with “32” as the proposed cutoff value (Figure 2-3).

In the log-rank test, the subjects with higher AVI (defined as AVI ≥27) had a significantly higher frequency of MACEs (log rank, p<0.001) and hospitalization due to HF (log rank, p=0.004). Furthermore, the subjects with higher API (defined as API ≥32) had a marginally and significantly higher frequency of MACEs (log rank, p=0.055) and a significantly higher frequency of CV events (log rank, p=0.016) (Figure 3).

In the univariate Cox proportional hazard regression...
Figure 2-1. ROC curve for AVI in predicting MACEs. AVI, arterial velocity pulse index; MACE, major adverse cardiovascular event.

Figure 2-2. ROC curve for AVI in predicting hospitalization due to HF. AVI, arterial velocity pulse index; HF, heart failure.

Figure 2-3. ROC curve for API in predicting CV events

Discussion

Our current analyses showed that both the AVI and API effectively predicted clinical outcomes, such as MACEs, hospitalization due to HF, and CV events, at certain cutoff values (Figure 1-3 and Table 3); however, the multivariate Cox proportional hazard regression analyses revealed an AVI ≥27 as a significant predictor of MACEs (Table 4). Additionally, as described previously, both indexes are correlated with each other, but our present results showed that each index is differently correlated with characteristic clinical outcomes. As analyzed and reported previously, the API represented peripheral arterial stiffness, CV risks such as the Framingham CV and Suita scores, and complexity of the coronary arteries and severity of the associated conditions.

Multiple regression analyses failed to show API as a significant predictor of CV events, which might be representative of the degree and extent of atherosclerosis of the end arteries of vital organs such as the brain and the heart.

In contrast, the AVI was significantly correlated with the total MACEs, including CV death and hospitalization due to CHFs, which might be related to an impaired cardiac function as shown previously. Because AVI is calculated from the pulse wave pattern of the brachial artery under suprasystolic pressure, it reflects central arterial stiffness and cardiac afterload. Our previous analyses revealed that AVI is significantly correlated with the augmentation index but not with FMD in the same individuals. Moreover, our multivariate analyses previously showed that the plasma BNP levels and a history of CHF were independently associated with AVI, suggesting enhanced central arterial pressure and cardiac afterload. These differences indicated that although API and AVI are correlated, the CV pathophysiological implications of these two indexes are different; therefore, both indexes may be used for risk evaluations and stratifications independently.

These characteristic features will enable us to differentiate among the divergent types of CV risks using single cuff-
oscillometric techniques simultaneously. Resolution of the 
detailed characteristics of both indexes will help improve an 
individual’s mortality and morbidity with sophisticated 
therapeutic procedures for both conditions. In the future, us-
ing quantified CV risks estimated by both API and AVI, bet-
ter prevention of CV diseases in subjects with HT, DM, and 
HL are expected in actual clinical settings. AVE-1500 is use-
ful because it can measure conventional blood pressure and 
the two new indexes in a single procedure without any com-
plicated steps. Currently, there are various procedures for 
evaluating vascular stiffness and endothelial dysfunction, 
such as FMD, PWV, and reactive hyperemia peripheral arte-
rial tonometry. Each procedure showed significant prognos-
tic values for subjects with CV risks. The current study 
revealed that AVI might have significant prognostic values 
with easier measurement procedures using cuff-
oscillometric-based technology, which will enable physicians and researchers to perform clinical trials easier than ever. This might be one of the advantages of these indexes in terms of future clinical use.

The current study has several limitations. Although we successfully revealed the prognostic significance of both indexes using Kaplan-Meier methods and both univariate and multivariate Cox proportional hazard regression analyses, our population was recruited from a single institution, and the study design had a retrospective and cross-sectional nature. Initially, a total of 252 subjects were enrolled in previous analyses, and currently, a total of 180 subjects were analyzed. Therefore, re-evaluation of precise prognostic values in a prospective manner is recommended. To our knowledge, the significant roles of both indexes for the future prediction of CV events have not been reported previously. Therefore, we decided to perform the current analyses. Further studies are also needed to establish the optimal clinical use of AVE-1500 and the two new CV indexes.

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Conflicts of Interest

AVE-1500 was kindly lent to us by Shisei Datum, Tokyo.

Kouichi Tamura and Kazuo Kimura contributed equally to this work.

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### Table 3-1. Univariate Cox proportional hazard regression analysis of the risk of MACEs

|               | HR    | 95% CI          | p-value |
|---------------|-------|-----------------|---------|
| Age           | 1.086 | 1.018-1.159     | 0.013   |
| SBP           | 1.031 | 1.010-1.051     | 0.003   |
| AVI           | 1.091 | 1.024-1.164     | 0.008   |
| Suita score   | 1.163 | 1.062-1.273     | 0.001   |

MACE, major adverse cardiac event; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; AVI, arterial velocity pulse index

### Table 3-2. Univariate Cox proportional hazard regression analysis of the risk of hospitalization due to HF

|               | HR    | 95% CI          | p-value |
|---------------|-------|-----------------|---------|
| Age           | 1.274 | 1.040-1.561     | 0.019   |
| VHD           | 0.127 | 0.017-0.064     | 0.046   |
| Cre           | 4.976 | 1.695-14.604    | 0.003   |
| AVI           | 1.160 | 1.013-1.328     | 0.032   |

HF, heart failure; HR, hazard ratio; CI, confidence interval; VHD, valvular heart disease; Cre, creatinine; AVI, arterial velocity pulse index

### Table 3-3. Univariate Cox proportional hazard regression analysis of the risk of hospitalization due to CV events

|               | HR    | 95% CI          | p-value |
|---------------|-------|-----------------|---------|
| SBP           | 1.044 | 1.021-1.068     | <0.001  |
| API           | 1.074 | 1.011-1.140     | 0.020   |
| Suita score   | 1.161 | 1.035-1.303     | 0.011   |

CV, cardiovascular; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; API, arterial pressure volume index

### Table 4. Multivariate Cox proportional hazard regression analysis for the risk of MACE

|               | HR    | 95% CI          | p   |
|---------------|-------|-----------------|-----|
| Age           | 1.062 | 1.008-1.118     | 0.024 |
| Gender        | 0.880 | 0.334-1.797     | n.s.|
| SBP           | 1.010 | 0.987-1.033     | n.s.|
| High AVI (≥27)| 3.380 | 1.197-9.546     | 0.021 |

MACE, major adverse cardiovascular event; HR, hazard ratio; CI, confidence intervals; n.s., not significant; SBP, systolic blood pressure; AVI, arterial velocity pulse index.

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