

# Arterial Stiffness Measured with the Cuff Oscillometric Method Is Predictive of Exercise Capacity in Patients with Cardiac Diseases

Yasushi Tazawa,<sup>1</sup> Nobuyoshi Mori,<sup>1</sup> Yoshiko Ogawa,<sup>1</sup> Osamu Ito<sup>1</sup> and Masahiro Kohzuki<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Arterial stiffness is widely used in assessing arteriosclerosis in the background of increased cardiovascular events. Arteriosclerosis also causes reduction in exercise capacity, which is a most important prognostic factor in patients with cardiovascular disease; however, data on the association between arterial stiffness and exercise capacity are limited. Therefore, a simple and noninvasive measurement of arterial stiffness that reflects the central circulation and exercise capacity is needed. The arterial velocity pulse index (AVI) is a parameter of arterial stiffness measurable with the cuff oscillometric method; however, the clinical utility of this method is unclear. We aimed to evaluate the trend of AVI in patients with coronary artery disease (CAD), and the association between AVI and exercise capacity. A cross-sectional study of 116 patients with cardiac disease (34 CAD and 82 non-CAD patients) was performed. Non-CAD patients were those with any cardiac diseases who did not have proven CAD. The results showed that the AVI was significantly higher in CAD patients than non-CAD patients ( $P < 0.05$ , analysis of covariance). The AVI was inversely correlated with peakVO<sub>2</sub> ( $r = -0.239$ ,  $P < 0.05$ ) and was a significant explanatory variable for peakVO<sub>2</sub> in stepwise regression analysis ( $\beta = -14.62$ ,  $t = -2.5$ ,  $P < 0.05$ ). These results indicate that the AVI is strongly associated with CAD and predictive of the exercise capacity in patients with cardiac diseases. We, therefore, propose that the cuff oscillometric method is clinically useful in evaluating arterial stiffness in patients with cardiac diseases, especially CAD.

**Keywords:** arterial stiffness; coronary artery disease; cuff oscillometric method; exercise capacity; noninvasive measurement

Tohoku J. Exp. Med., 2016 June, 239 (2), 127-134. © 2016 Tohoku University Medical Press

## Introduction

Arteriosclerosis is a major cause of cardiovascular disease (CVD) (Perk et al. 2012; Goff et al. 2014). The previously reported risk factors for arteriosclerosis include hypertension, dyslipidemia, and diabetes (D'Agostino et al. 2008). As the prevalence of CVD due to arteriosclerosis is increasing, a simple and easy assessment of arteriosclerosis is needed.

To assess arteriosclerosis, arterial stiffness is used as a surrogate marker for cardiovascular risk (Laurent et al. 2006). The pulse wave velocity (PWV) (Bramwell and Hill 1922; van Popele et al. 2001) and cardio-ankle vascular index (CAVI) (Shirai et al. 2006) are commonly used to assess arterial stiffness, and these parameters are predictive of the presence of coronary artery disease (CAD) in the general population (Imanishi et al. 2004; Koji et al. 2004). However, to measure these parameters, a certain amount of

time for winding cuffs around the extremities and a procedure for detecting heart sound are required (Yamashina et al. 2002; Shirai et al. 2006).

Aortic pulse wave comprises the initial pulse wave from the left ventricle and a later reflected wave (Karamanoglu et al. 1993). The reflected wave represents the central blood pressure (CBP) (London and Guerin 1999), which is known to predict cardiovascular events (Pini et al. 2008; Roman et al. 2009); however, its measurement by using a catheter is invasive. Brachial pressure provides inaccurate CBP information, whereas the secondary peak of the brachial pulse waveform includes the reflected wave (Vlachopoulos and O'Rourke 2000). On the basis of this theory, the tonometric method and the cuff oscillometric method are being used for the noninvasive estimation of the CBP (e.g., augmentation index) with radial or brachial pulse waveforms. However, tonometric estimation is well correlated with directly measured CBP ( $r > 0.9$ ) (Ding et al.

Received March 1, 2016; revised and accepted May 10, 2016. Published online June 2, 2016; doi: 10.1620/tjem.239.127.

Correspondence: Masahiro Kohzuki, Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.  
e-mail: kohzuki@med.tohoku.ac.jp

2011); a two-step procedure that precisely detects radial pulse waveforms and measures the brachial pressure at the same time is required to complete the measurement, and it is sometimes dependent on an operator (Wilkinson et al. 1998).

On the other hand, the cuff oscillometric method is widely and routinely used in the (noninvasive and automatic) measurement of upper arm blood pressure, and the later waves in cuff oscillation indicate the reflected waves (El Aklouk et al. 2008). The arterial velocity pulse index (AVI) is one of arterial stiffness parameters measured with the cuff oscillometric method. This measurement requires only one upper arm, and also provides information on the central circulation (Liang et al. 2013); however its clinical utility is still unclear. Sueta et al. (2015) reported that the AVI predicted CBP in combination with brachial blood pressure. Horváth et al. (2010) reported that the oscillometric estimation of the aortic augmentation index measured from the brachial artery was well correlated with directly measured aortic systolic blood pressure (SBP) and aortic augmentation index. These studies revealed the mathematical interaction of the parameters; however, the relationship of these parameters to CVD is still unknown.

Arteriosclerosis causes not only acute cardiovascular events but also a reduction in exercise capacity, which is one of most important prognostic factors in patients with CVD (Pilote et al. 1989; Guazzi et al. 2012). Resting cardiac function is insensitive in assessing exercise capacity in patients with cardiac diseases (Franciosa et al. 1981), whereas arterial stiffness, which represents the elastic properties of large arteries and wave reflection, at least partly provides information about exercise capacity (Edwards et al. 2004; Pfoh et al. 2014). In fact, increase in arterial stiffness reduces coronary blood flow and increases cardiac workload, which causes functional limitations in patients with CVD because of coronary perfusion insufficiency to increased oxygen demand in the myocardium during exercise loading (Kingwell et al. 2002). Previous studies have reported the association between arterial stiffness and exercise capacity in particular populations. Vaitkevicius et al. (1993) reported that the aortic PWV and the carotid arterial pressure pulse augmentation index were inversely associated with maximal oxygen uptake in a healthy cohort. Binder et al. (2006) reported that the augmentation index measured from the radial artery was inversely associated with maximal oxygen uptake in men without known CAD. Jae et al. (2010) reported that the brachial-ankle PWV (baPWV) was inversely associated with maximal oxygen uptake in patients with metabolic syndrome. Tanisawa et al. (2015) reported that CAVI was inversely associated with peak oxygen uptake (peakVO<sub>2</sub>) in hypertensive middle-aged and elderly Japanese men. However, few studies have focused on arterial stiffness and exercise capacity in patients with cardiac diseases such as CAD (Enko et al. 2008) and hypertrophic cardiomyopathy (Austin et al. 2010). Thus, data suggesting that arterial stiffness predicts

exercise capacity in patients with cardiac disease are limited.

As described previously, central arterial stiffness and exercise capacity are implicated in cardiovascular risk; however, the association between exercise capacity and arterial stiffness measured by using the oscillometric method in patients with cardiac disease including CAD has not been fully determined.

Therefore, the first aim of this study was to elucidate the relationship between arterial stiffness measured with the cuff oscillometric method from the peripheral artery and CAD. The second aim of this study was to test the interaction between exercise capacity and the thus measured arterial stiffness in patients with cardiac disease.

## Methods

This was a cross-sectional study, and patients with cardiac disease who visited Tohoku University Hospital from February in 2014 to January in 2015 for cardiac rehabilitation (to assess exercise capacity) were considered eligible for inclusion. The inclusion criteria for this study were as follows: patients with cardiac disease in whom blood pressure can be measured from the brachial artery and New York Heart Association (NYHA) class I-III. The exclusion criteria were as follows: patients with non-cardiac disease, disturbance of consciousness, and NYHA class IV. Cardiac disease included CAD, atrial fibrillation, cardiomyopathy, valvular disease, pulmonary hypertension, and congenital heart disease. Patient profiles, medical history, medication use, and laboratory data were obtained from the medical records. Body mass index (BMI) was calculated by using the patient's height and weight (in kg/m<sup>2</sup>), and defined as weight (kg) divided by the square of height (m). CAD was defined as ≥ 50% stenosis in at least one major coronary artery determined by using coronary angiography. Hypertension was defined as a resting blood pressure of ≥ 140/90 mmHg or the use of antihypertensive drugs. Dyslipidemia was defined as a low-density lipoprotein level of ≥ 140 mg/dL, high-density lipoprotein level of ≤ 40 mg/dL, triglyceride level of ≥ 150 mg/dL, or the use of lipid-lowering drugs. Diabetes was defined as a fasting blood glucose level of ≥ 126 mg/dL, hemoglobin A1c of ≥ 6.5%, or the use of antidiabetic drugs. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min. Informed consent was obtained from all patients in accordance with the regulation of the institutional review board (Tohoku University Ethics Committee, Sendai, Miyagi, Japan). This study was conducted according to the principles of the Declaration of Helsinki and with institutional review board approval.

### Measurement of AVI

The AVI was measured by using an oscillometric blood pressure measurement device (AVE-1500; Shisei Datum, Tokyo, Japan). The patient was placed in the supine position, and the cuff was wound around the right upper arm after a 5-min rest. At the same time, blood pressure was measured by sensing the cuff oscillation waves. The AVI was calculated by using the following formula (Sueta et al. 2015).

$$AVI = (|Vr|/|Vf|) \times 20,$$

where Vf is the first peak of the time differentiated value of the pulse

waveform and  $V_r$  is the nadir of the time differentiated value of the pulse waveform.

The pulse waveform is composed of the forward wave and the reflected wave (Vlachopoulos and O'Rourke 2000).  $V_f$ , which is the first peak of the time differentiated value of the suprasystolic cuff oscillation wave, mainly represents the strength of the forward wave, which is not influenced by the reflected wave. On the other hand,  $V_r$ , which is the nadir of the brachial pulse wave speed change, mainly represents the steepness of the pressure decline after the second peak of the cuff oscillation wave (Liang et al. 2013). Increase in aortic stiffness causes reflected wave to arrive at the brachial artery early in systole, and pressure declines more steeply in late systole because of the attenuated pressure augmentation effect. Therefore, the ratio  $|V_r|/|V_f|$  indicates the tendency of the increase in aortic stiffness.

The measurement was performed two times, and the second measurement was performed immediately after the first measurement. We adopted the value of the second measurement.

In our preliminary study, the error in two measurements each SBP, DBP, and AVI was 0.2 mmHg, 1 mmHg and 0.14, respectively, in seven healthy volunteers.

#### Assessment of exercise capacity

All patients underwent symptom-limited cardiopulmonary exercise testing (CPET) on a bicycle ergometer (Q STRESS; Nihonkoden, Tokyo, Japan) according to a ramp protocol with a workload increment of 15 W/min. The 12-lead electrocardiogram was continuously recorded; blood pressure was measured every 2 min; continuous expired gas analysis was performed during CPET; and peak oxygen consumption was calculated after CPET. PeakVO<sub>2</sub> was defined as the highest VO<sub>2</sub> value recorded during exercise testing.

Resting blood pressure, heart rate (HR), blood pressure change, and HR change were also recorded during CPET.

#### Assessment of arterial stiffness

The CAVI was measured to assess arterial stiffness by using a PWV measurement apparatus (VS-1500A; Fukudadenshi, Tokyo, Japan). During the measurement, the patient was at rest and in the supine position. The electrocardiogram and heart sound were monitored. Cuffs were wound around both upper arms and both ankles. Then, the CAVI was automatically calculated by using the following formula (Shirai et al. 2006):

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

where Ps: systolic blood pressure, Pd: diastolic blood pressure, PWV: pulse wave velocity,  $\Delta P$ : Ps–Pd,  $\rho$ : blood density, and a and b: constants.

The PWV was calculated by using the length from the aortic valve to the ankle divided by the time taken for the pulse wave to propagate from the aortic valve to the ankle. The CAVI represented arterial stiffness as well as the baPWV (Takaki et al. 2008). The CAVI was not influenced by blood pressure in comparison with the baPWV (Yambe et al. 2004).

#### Echocardiography

Echocardiography was performed to assess the left ventricular ejection fraction (LVEF) according to the guidelines of the American Society of Echocardiography (Schiller et al. 1989). LVEF was measured by using the long-axis area-length method. The standard oper-

ating procedure was used in the measurement (Schiller et al. 1989). LVEF was calculated as  $[\text{end diastolic volume} - \text{end systolic volume}]/\text{end diastolic volume} \times 100\%$ .

#### Biomarker

Blood samples were taken in standard conditions. B-type natriuretic peptide (BNP) was analyzed by means of an immunochromatographic method by using an immunochromatography device (Rapidchip BNP; Sekisui Medical, Tokyo, Japan).

#### Statistical analysis

Data are presented as mean  $\pm$  standard deviation for normally distributed variables and proportions for categorical variables. Nonnormally distributed variables are presented as median  $\pm$  interquartile range. Several variables were log transformed to obtain a normal distribution. The patients were divided into two groups according the presence or absence of CAD. Unpaired t test (for normally distributed variables), Fisher's exact test (for categorical variables), and Mann-Whitney U test (for nonnormally distributed variables) were used to evaluate the differences between the two groups. Analysis of covariance (ANCOVA) with age as the covariate was used to compare the AVI between the two groups. Pearson's correlation was performed to determine the association among peakVO<sub>2</sub>, AVI, and other variables. Stepwise multiple linear regression analysis with backward elimination was used to determine the predictive variables for peakVO<sub>2</sub>. Statistical significance was considered at  $P < 0.05$  (two-tailed). Missing data were excluded from the analysis. Data were analyzed with EZR version 1.24 for Windows (Kanda 2013).

## Results

A total of 116 patients were enrolled in this study. The baseline characteristics of patients are summarized in Table 1. The average age of all patients was  $61.8 \pm 14.5$  years. A total of 34 patients were included in the CAD group, and 82 patients were included in the non-CAD group. The average age of the CAD group was higher than that of the non-CAD group ( $71.2 \pm 10.7$  years vs.  $58.0 \pm 14.2$  years,  $P < 0.001$ ). The CAVI in the CAD group was higher than that in the non-CAD group ( $9.0 \pm 1.5$  vs.  $7.8 \pm 1.5$ ,  $P < 0.001$ ). The eGFR in the CAD group was lower than that in the non-CAD group ( $57.4 \pm 20.1$  vs.  $73.8 \pm 23.2$ ,  $P < 0.001$ ).

The AVI in the CAD group was higher than that in the non-CAD group ( $P < 0.05$ , ANCOVA; Fig. 1).

Table 2 shows the correlation between the AVI and other variables. The AVI was positively correlated with age, SBP, pulse pressure (PP), and BNP, whereas it was inversely correlated with BMI, HR, eGFR, and peakVO<sub>2</sub>. Fig. 2 shows the correlation between the AVI and CAVI. The AVI was positively correlated with the CAVI.

To determine the association between AVI and peakVO<sub>2</sub>, a stepwise multiple linear regression analysis was performed. Age, BMI, SBP, HR, eGFR, LVEF, BNP, and AVI were selected as explanatory variables, and there was no multicollinearity among the variables as the variance inflation factor was sufficiently small. PP was excluded because of the presence of multicollinearity

Table 1. Baseline characteristics.

	All patients (n = 116)	CAD group (n = 34)	Non-CAD group (n = 82)	P-value <sup>¶</sup>
Age (years)	61.8 ± 14.5	71.2 ± 10.7	58.0 ± 14.2	< 0.001
Sex (m/f %)	75.9/24.1	76.5/23.5	75.6/24.4	0.264 <sup>†</sup>
BMI (kg/m <sup>2</sup> )	24.0 ± 3.9	23.9 ± 3.7	24.0 ± 4.0	0.893
NYHA-class (%)				0.03 <sup>†</sup>
1	44.0	32.3	48.8	
2	37.0	55.9	29.2	
3	19.0	11.8	22.0	
SBP (mmHg)	115.0 ± 18.4	119.5 ± 19.8	113.1 ± 17.5	0.11
DBP (mmHg)	68.9 ± 12.4	65.1 ± 13.0	70.5 ± 11.9	0.035
Heart rate (bpm)	73.6 ± 17.5	68.2 ± 11.2	75.4 ± 18.8	0.069
<b>Laboratory data</b>				
eGFR (mL/min/1.73m <sup>2</sup> )	69.0 ± 23.5	57.4 ± 20.1	73.8 ± 23.2	< 0.001
BNP (pg/mL)	38.8 (18.2-90.45)	60.5 (23.7-153.9)	31.4 (17.8-81.4)	0.08 <sup>‡</sup>
<b>Echocardiography</b>				
LVEF (%)	59.0 ± 15.5	56.1 ± 15.3	60.1 ± 15.5	0.219
<b>Arterial stiffness</b>				
CAVI	8.2 ± 1.6	9.0 ± 1.5	7.8 ± 1.5	< 0.001
<b>Cardiac disease</b>				
Atrial fibrillation (%)	54.3	20.6	68.3	< 0.001 <sup>†</sup>
Cardiomyopathy (%)	11.2	2.9	17.1	0.104 <sup>†</sup>
Valvular disease (%)	5.2	11.7	3.0	0.06 <sup>†</sup>
Pulmonary hypertension (%)	6.0	3.0	7.3	0.672 <sup>†</sup>
Congenital heart disease (%)	6.0	0.0	8.5	0.104
<b>Comorbidity</b>				
Hypertension (%)	53.4	85.3	40.2	< 0.001 <sup>†</sup>
Dyslipidemia (%)	48.3	91.2	30.5	< 0.001 <sup>†</sup>
Diabetes mellitus (%)	19.0	35.3	12.2	0.008 <sup>†</sup>
<b>Medication</b>				
ACE-I/ARB (%)	57.8	79.4	48.8	0.003 <sup>†</sup>
Ca antagonist (%)	36.2	55.9	28.0	0.006 <sup>†</sup>
Diuretics (%)	32.8	47.1	26.8	0.05 <sup>†</sup>
Beta blocker (%)	52.6	64.7	47.6	0.106 <sup>†</sup>
<b>Exercise capacity</b>				
PeakVO2 (mL/kg/min)	19.2 ± 6.9	17.5 ± 7.7	19.7 ± 6.5	0.147
% predicted peakVO2 (%)	74.8 ± 23.4	74.9 ± 21.3	74.2 ± 29.3	0.883

The data are presented as mean ± standard deviation, median (interquartile range), or percentage.

<sup>¶</sup>The CAD group vs. the non-CAD group.

<sup>†</sup>Fisher's exact test.

<sup>‡</sup>Mann-Whitney U test.

BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B type natriuretic peptide; LVEF, left ventricular ejection fraction; CAVI, cardio-ankle vascular index; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

between PP and SBP. As a result, AVI was a significant explanatory variable for peakVO2 ( $\beta = -14.62$ ,  $P = 0.014$ ; Table 3). Age, BMI, SBP, and BNP were also significant explanatory variables for peakVO2 (SBP:  $\beta = 0.14$ ,  $P < 0.001$ ; age:  $\beta = -0.17$ ,  $P < 0.001$ ; BNP:  $\beta = -1.48$ ,  $P =$

$0.007$ ; BMI:  $\beta = -0.39$ ,  $P = 0.015$ ; Table 3).

## Discussion

The present study is the first to demonstrate that the AVI measured with the cuff oscillometric method from the

brachial artery is higher in CAD patients than in non-CAD patients. Moreover, this study is also the first to demonstrate that AVI is a significant explanatory variable for exercise capacity in patients with cardiac disease.

Previous studies have demonstrated the relationship between arterial stiffness and CAD. Imanishi et al. (2004) reported that the baPWV was an independent predictor for the presence of CAD in men who underwent coronary angiography. Nakamura et al. (2008) reported that the CAVI

was positively correlated with the severity of coronary atherosclerosis in patients who underwent coronary angiography. On the other hand, no previous study has reported on the relationship between CAD and arterial stiffness measured with the cuff oscillometric method, which is a more easily measured parameter than the baPWV or CAVI.

A few studies reported on the correlation between arterial stiffness measured with the oscillometric method and the augmentation index or CBP, which is strongly associated with wave reflection. Liang et al. (2015) reported that the estimated CBP measured by using an oscillometric method from the brachial artery was well correlated ( $r > 0.9$ ) with directly measured CBP from a catheter, which indicated the reliability of the oscillometric method for estimating the CBP. Horváth et al. (2010) also reported that the estimated CBP measured by using the cuff oscillometric

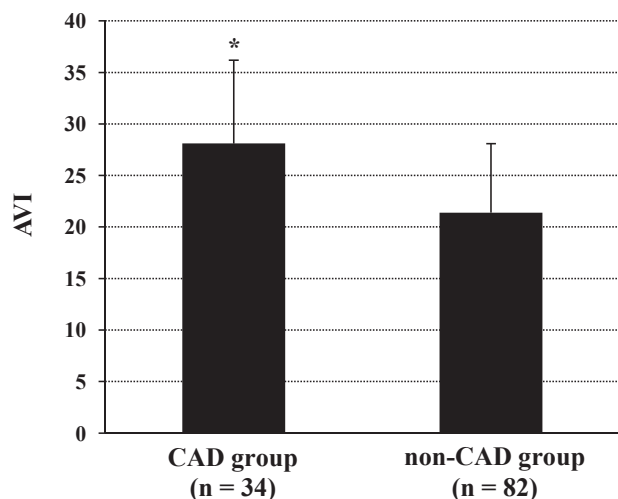


Fig. 1. Difference in AVI between the CAD group and the non-CAD group.

Bars indicate the mean values of AVI, and the ends of the vertical lines show the standard deviations. The data were compared between the two groups by analysis of covariance with age as the covariate. Statistical significance was considered at  $P < 0.05$  (two-tailed).

\* $P < 0.05$  compared with non-CAD group.

AVI, arterial velocity pulse index; CAD, coronary artery disease.

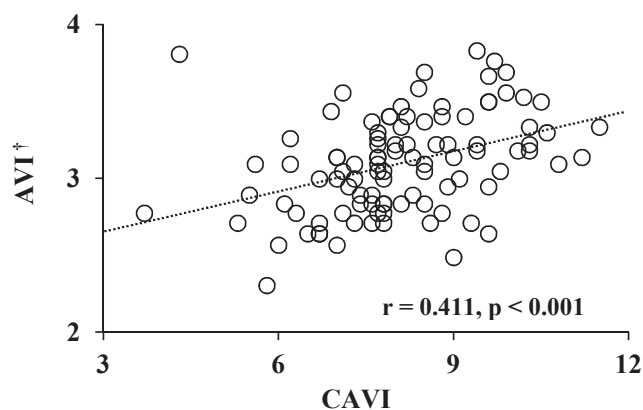


Fig. 2. Correlation between the AVI and CAVI.

The AVI was significantly correlated with the CAVI.

†Log transformed.

AVI, arterial velocity pulse index; CAVI, cardio-ankle vascular index.

Table 2. Correlations between the AVI and other variables.

	AVI †	
	r	P
Age (years)	0.529	< 0.001
BMI (kg/m <sup>2</sup> )	- 0.327	< 0.001
SBP (mmHg)	0.431	< 0.001
PP (mmHg)	0.45	< 0.001
Heart rate (bpm)	- 0.208	0.032
BNP (pg/mL) †	0.275	0.003
eGFR (mL/min/1.73m <sup>2</sup> )	- 0.204	0.029
LVEF (%)	NS	NS
PeakVO2 (mL/kg/min)	- 0.239	0.014

†Log transformed.

BMI, body mass index; SBP, systolic blood pressure; PP, pulse pressure (systolic blood pressure-diastolic blood pressure); eGFR, estimated glomerular filtration rate; BNP, B type natriuretic peptide; LVEF, left ventricular ejection fraction; AVI, arterial velocity pulse index; NS, not significant.



Table 3. Stepwise regression analysis of peakVO<sub>2</sub> and significantly associated variables.

Independent variables	$\beta$	t	P
SBP (mmHg)	0.14	3.76	< 0.001
Age (years)	- 0.17	- 3.51	< 0.001
BNP (pg/mL) <sup>†</sup>	- 1.48	- 2.76	0.007
AVI <sup>†</sup>	- 14.62	- 2.5	0.014
BMI (kg/m <sup>2</sup> )	- 0.39	- 2.48	0.015

<sup>†</sup>Log transformed.

Adjusted R-squared = 0.3601, P < 0.001.

SBP, systolic blood pressure; BNP, B type natriuretic peptide; AVI, arterial velocity pulse index; BMI, body mass index.

method was well correlated ( $r > 0.9$ ) with directly measured CBP from a catheter. Sueta et al. (2015) reported that an estimated regression formula that included AVI measured with the cuff oscillometric method as the dependent variable was well correlated ( $r > 0.9$ ) with directly measured CBP from a catheter in patients who underwent coronary angiography. Therefore, it was considered that AVI strongly represents the wave reflection, the magnitude of which is an independent predictor of cardiovascular events (Chirinos et al. 2012).

The present study revealed that the AVI is inversely correlated with exercise capacity. However, although exercise capacity is an important prognostic factor in patients with cardiac disease (especially CADs) (Mark et al. 1991; Vanhees et al. 1994), few studies have reported on the relationship between arterial stiffness and exercise capacity in these patients. Enko et al. (2008) reported that the baPWV was correlated with peakVO<sub>2</sub> in patients with CAD. Austin et al. (2010) reported that the PWV measured by using cardiac magnetic resonance imaging was correlated with peakVO<sub>2</sub> in patients with hypertrophic cardio myopathy. These studies focused on the PWV but not on wave reflection.

Few studies have reported on the correlation between exercise capacity and the index representing wave reflection in patients with cardiac disease. Müller et al. (2015) reported that peakVO<sub>2</sub> was a negative predictor of the augmentation index in patients with congenital heart disease. Chrysohoou et al. (2015) reported that a 12-week training intervention increased maximal oxygen consumption but also increased the augmentation index despite decreasing the PWV in patients with chronic heart failure. Most of the patients in that study had ischemic heart failure and their LVEFs were lower than those in the patients of the present study. It was assumed that the reflected waves did not increase the SBP in patients with heart failure with reduced ejection fraction because of the incapability to overcome the increased ventricular load due to the reflected waves. Therefore, wave reflection might not be predictive of exercise capacity especially in patients with cardiac disease with reduced ejection fraction; however, it is reasonable to hypothesize that wave reflection, represented by AVI in our

results, is correlated with exercise capacity in patients with preserved ejection fraction as well as in a population without known cardiac diseases (Vaitkevicius et al. 1993; Jung et al. 2014). Increased arterial stiffness causes decreased diastolic pressure and increased systolic pressure, which results in PP elevation (Mitchell et al. 1997; Torjesen et al. 2014). Increased PP causes decreased coronary perfusion because the coronary circulation is regulated by diastolic pressure (Anrep et al. 1931). Decreased coronary perfusion diminishes exercise capacity in patients with CAD. A higher AVI is implicated in increased reflected waves, which cause increased left ventricular afterload because of the reflected waves generated at the peripheral artery from diastole to systole (Laskey and Kussmaul 1987). During exercise, coronary perfusion is insufficient to maintain myocardial performance especially in patients with CAD because of their low ischemic threshold (Kingwell et al. 2002), which leads to a reduction in exercise capacity.

The cuff oscillometric method with the use of a simple upper arm cuff is less time consuming than the measurement of baPWV and CAVI. This method requires only 1-2 min to finish, and does not require a professional or a complicated procedure that can cause measurement errors. Therefore, the cuff oscillometric method might be suitable particularly in the primary care and ambulatory care settings; however, the reproducibility and validity of AVI measurement in a specific population, such as the elderly, is still unclear. The cuff oscillometric method tended to be as reliable in the assessment of the stiffness of central arteries as the tonometric method (Baulmann et al. 2008); however, the cuff oscillometric method was found to be superior to the tonometric method in terms of the measurement procedures.

This study has some limitations. First, the patients in the present study had a heterogeneous background, and the population was small because of its being a single-center study. Second, the causal relationship is unknown because the present study was a cross-sectional study. The predictive value of the AVI in CVD is still unclear, unlike that for PWV or CAVI. Further study is needed to determine the predictive value of the AVI in CVD and the disease-specific trend of the AVI.

In conclusion, the AVI measured by using the cuff oscillometric method is higher in patients with CAD, and is associated with exercise capacity in patients with cardiac disease. If the relationship between arterial stiffness measured with the cuff oscillometric method and the specific cardiac disease could be clarified, then this simple and easy assessment of arterial stiffness would be useful in the primary care setting. Further studies, especially multi-center intervention studies, are needed to confirm the usefulness of an upper-arm cuff oscillometric method in assessing arterial stiffness.

### Conflict of Interest

The authors declare no conflict of interest.

### References

- Anrep, G.V., Davis, J.C. & Volhard, E. (1931) The effect of pulse pressure upon the coronary blood flow. *J. Physiol.*, **73**, 405-426.
- Austin, B.A., Popovic, Z.B., Kwon, D.H., Thamilarasan, M., Boonyasirinant, T., Flamm, S.D., Lever, H.M. & Desai, M.Y. (2010) Aortic stiffness independently predicts exercise capacity in hypertrophic cardiomyopathy: a multimodality imaging study. *Heart*, **96**, 1303-1310.
- Baulmann, J., Schillings, U., Rickert, S., Uen, S., Düsing, R., Illyes, M., Cziraki, A., Nickering, G. & Mengden, T. (2008) A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. *J. Hypertens.*, **26**, 523-528.
- Binder, J., Bailey, K.R., Seward, J.B., Squires, R.W., Kunihiro, T., Hensrud, D.D. & Kullo, I.J. (2006) Aortic augmentation index is inversely associated with cardiorespiratory fitness in men without known coronary heart disease. *Am. J. Hypertens.*, **19**, 1019-1024.
- Bramwell, J.C. & Hill, A.V. (1922) The Velocity of the Pulse Wave in Man. *Proc. Roy. Soc. B*, **93**, 298-306.
- Chirinos, J.A., Kips, J.G., Jacobs, D.R. Jr., Brumback, L., Duprez, D.A., Kronmal, R., Bluemke, D.A., Townsend, R.R., Vermeersch, S. & Segers, P. (2012) Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J. Am. Coll. Cardiol.*, **60**, 2170-2177.
- Chrysohoou, C., Angelis, A., Tsitsinakis, G., Spetsioti, S., Nasis, I., Tsiachris, D., Rapakoulis, P., Pitsavos, C., Koulouris, N.G., Vogiatzis, I. & Dimitris, T. (2015) Cardiovascular effects of high-intensity interval aerobic training combined with strength exercise in patients with chronic heart failure. A randomized phase III clinical trial. *Int. J. Cardiol.*, **179**, 269-274.
- D'Agostino, R.B. Sr., Vasan, R.S., Pencina, M.J., Wolf, P.A., Cobain, M., Massaro, J.M. & Kannel, W.B. (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, **117**, 743-753.
- Ding, F.H., Fan, W.X., Zhang, R.Y., Zhang, Q., Li, Y. & Wang, J.G. (2011) Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. *Am. J. Hypertens.*, **24**, 1306-1311.
- Edwards, D.G., Schofield, R.S., Magyari, P.M., Nichols, W.W. & Braith, R.W. (2004) Effect of exercise training on central aortic pressure wave reflection in coronary artery disease. *Am. J. Hypertens.*, **17**, 540-543.
- El Aklouk, E., Al Jumaily, A.M. & Lowe, A. (2008) Pressure Waves as a Noninvasive Tool for Artery Stiffness Estimation. *J. Med. Devices*, **2**, 021001-021008.
- Enko, K., Sakuragi, S., Kakishita, M., Ohkawa, K., Nagase, S., Nakamura, K., Fukushima-Kusano, K. & Ohe, T. (2008) Arterial stiffening is associated with exercise intolerance and hyperventilatory response in patients with coronary artery disease. *Clin. Med. Cardiol.*, **2**, 41-48.
- Franciosa, J.A., Park, M. & Levine, T.B. (1981) Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am. J. Cardiol.*, **47**, 33-39.
- Goff, D.C. Jr., Lloyd-Jones, D.M., Bennett, G., Coady, S., D'Agostino, R.B., Gibbons, R., Greenland, P., Lackland, D.T., Levy, D., O'Donnell, C.J., Robinson, J.G., Schwartz, J.S., Shero, S.T., Smith, S.C. Jr., Sorlie, P., et al. (2014) 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, **129**, S49-S73.
- Guazzi, M., Adams, V., Conraads, V., Halle, M., Mezzani, A., Vanhees, L., Arena, R., Fletcher, G.F., Forman, D.E., Kitzman, D.W., Lavie, C.J. & Myers, J. (2012) EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*, **126**, 2261-2274.
- Horváth, I.G., Németh, A., Lenkey, Z., Alessandri, N., Tufano, F., Kis, P., Gaszner, B. & Cziráki, A. (2010) Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *J. Hypertens.*, **28**, 2068-2075.
- Imanishi, R., Seto, S., Toda, G., Yoshida, M., Ohtsuru, A., Koide, Y., Baba, T. & Yano, K. (2004) High brachial-ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. *Hypertens. Res.*, **27**, 71-78.
- Jae, S.Y., Heffernan, K.S., Fernhall, B., Oh, Y.S., Park, W.H., Lee, M.K. & Choi, Y.H. (2010) Association between cardiorespiratory fitness and arterial stiffness in men with the metabolic syndrome. *Diabetes. Res. Clin. Pract.*, **90**, 326-332.
- Jung, J.Y., Min, K.W., Ahn, H.J., Kwon, H.R., Lee, J.H., Park, K.S. & Han, K.A. (2014) Arterial stiffness by aerobic exercise is related with aerobic capacity, physical activity energy expenditure and total fat but not with insulin sensitivity in obese female patients with type 2 diabetes. *Diabetes Metab. J.*, **38**, 439-448.
- Kanda, Y. (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*, **48**, 452-458.
- Karamanoglu, M., O'Rourke, M.F., Avolio, A.P. & Kelly, R.P. (1993) An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur. Heart J.*, **14**, 160-167.
- Kingwell, B.A., Waddell, T.K., Medley, T.L., Cameron, J.D. & Dart, A.M. (2002) Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J. Am. Coll. Cardiol.*, **40**, 773-779.
- Koji, Y., Tomiyama, H., Ichihashi, H., Nagae, T., Tanaka, N., Takazawa, K., Ishimaru, S. & Yamashina, A. (2004) Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am. J. Cardiol.*, **94**, 868-872.
- Laskey, W.K. & Kussmaul, W.G. (1987) Arterial wave reflection in heart failure. *Circulation*, **75**, 711-722.
- Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I. & Struijker-Boudier, H. (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur. Heart J.*, **27**, 2588-2605.
- Liang, F., Takagi, S., Himeno, R. & Liu, H. (2013) A computational model of the cardiovascular system coupled with an upper-arm oscillometric cuff and its application to studying the suprasystolic cuff oscillation wave, concerning its value in

- assessing arterial stiffness. *Comput. Methods Biomech. Biomed. Engin.*, **16**, 141-157.
- Liang, F., Yin, Z., Fan, Y., Chen, K. & Wang, C. (2015) In vivo validation of an oscillometric method for estimating central aortic pressure. *Int. J. Cardiol.*, **199**, 439-441.
- London, G.M. & Guerin, A.P. (1999) Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am. Heart J.*, **138**, 220-224.
- Mark, D.B., Shaw, L., Harrell, F.E. Jr., Hlatky, M.A., Lee, K.L., Bengtson, J.R., McCants, C.B., Califf, R.M. & Pryor, D.B. (1991) Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N. Engl. J. Med.*, **325**, 849-853.
- Mitchell, G.F., Moyé, L.A., Braunwald, E., Rouleau, J.L., Bernstein, V., Geltman, E.M., Flaker, G.C. & Pfeffer, M.A. (1997) Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation*, **96**, 4254-4260.
- Müller, J., Ewert, P. & Hager, A. (2015) Increased aortic blood pressure augmentation in patients with congenital heart defects—A cross-sectional study in 1125 patients and 322 controls. *Int. J. Cardiol.*, **184**, 225-229.
- Nakamura, K., Tomaru, T., Yamamura, S., Miyashita, Y., Shirai, K. & Noike, H. (2008) Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. *Circ. J.*, **72**, 598-604.
- Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verschuren, M., Albus, C., Benlian, P., Boysen, G., Cifkova, R., Deaton, C., Ebrahim, S., Fisher, M., Germano, G., Hobbs, R., et al. (2012) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur. Heart J.*, **33**, 1635-1701.
- Pfob, M., Mürzl, N., Müller, E., Eber, B. & Weber, T. (2014) Ambulatory cardiac rehabilitation improves pulsatile arterial hemodynamics: a pilot trial. *Wien. Med. Wochenschr.*, **164**, 220-227.
- Pilote, L., Silberberg, J., Lisbona, R. & Sniderman, A. (1989) Prognosis in patients with low left ventricular ejection fraction after myocardial infarction. Importance of exercise capacity. *Circulation*, **80**, 1636-1641.
- Pini, R., Cavallini, M.C., Palmieri, V., Marchionni, N., Di Bari, M., Devereux, R.B., Masotti, G. & Roman, M.J. (2008) Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomano Study. *J. Am. Coll. Cardiol.*, **51**, 2432-2439.
- Roman, M.J., Devereux, R.B., Kizer, J.R., Okin, P.M., Lee, E.T., Wang, W., Umans, J.G., Calhoun, D. & Howard, B.V. (2009) High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J. Am. Coll. Cardiol.*, **54**, 1730-1734.
- Schiller, N.B., Shah, P.M., Crawford, M., DeMaria, A., Devereux, R., Feigenbaum, H., Gutgesell, H., Reichek, N., Sahn, D., Schnitger, I., Silverman, N.H. & Tajik, A.J. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J. Am. Soc. Echocardiogr.*, **2**, 358-367.
- Shirai, K., Utino, J., Otsuka, K. & Takata, M. (2006) A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J. Atheroscler. Thromb.*, **13**, 101-107.
- Sueta, D., Yamamoto, E., Tanaka, T., Hirata, Y., Sakamoto, K., Tsujita, K., Kojima, S., Nishiyama, K., Kaikita, K., Hokimoto, S., Jinnouchi, H. & Ogawa, H. (2015) The accuracy of central blood pressure waveform by novel mathematical transformation of non-invasive measurement. *Int. J. Cardiol.*, **189**, 244-246.
- Takaki, A., Ogawa, H., Wakeyama, T., Iwami, T., Kimura, M., Hadano, Y., Matsuda, S., Miyazaki, Y., Hiratsuka, A. & Matsuzaki, M. (2008) Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. *Hypertens. Res.*, **31**, 1347-1355.
- Tanisawa, K., Ito, T., Sun, X., Kawakami, R., Oshima, S., Gando, Y., Cao, Z.B., Sakamoto, S. & Higuchi, M. (2015) Cardiorespiratory fitness is a strong predictor of the cardio-ankle vascular index in hypertensive middle-aged and elderly Japanese men. *J. Atheroscler. Thromb.*, **22**, 379-389.
- Torjesen, A.A., Sigurðsson, S., Westenberg, J.J., Gotal, J.D., Bell, V., Aspelund, T., Launer, L.J., de Roos, A., Gudnason, V., Harris, T.B. & Mitchell, G.F. (2014) Pulse pressure relation to aortic and left ventricular structure in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. *Hypertension*, **64**, 756-761.
- Vaitkevicius, P.V., Fleg, J.L., Engel, J.H., O'Connor, F.C., Wright, J.G., Lakatta, L.E., Yin, F.C. & Lakatta, E.G. (1993) Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*, **88**, 1456-1462.
- Vanhees, L., Fagard, R., Thijs, L., Staessen, J. & Amery, A. (1994) Prognostic significance of peak exercise capacity in patients with coronary artery disease. *J. Am. Coll. Cardiol.*, **23**, 358-363.
- van Popele, N.M., Grobbee, D.E., Bots, M.L., Asmar, R., Topouchian, J., Reneman, R.S., Hoeks, A.P., van der Kuip, D.A., Hofman, A. & Witteman, J.C. (2001) Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*, **32**, 454-460.
- Vlachopoulos, C. & O'Rourke, M.F. (2000) Genesis of the normal and abnormal arterial pulse. *Curr. Probl. Cardiol.*, **5**, 303-367.
- Wilkinson, I.B., Fuchs, S.A., Jansen, I.M., Spratt, J.C., Murray, G.D., Cockcroft, J.R. & Webb, D.J. (1998) Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J. Hypertens.*, **16**, 2079-2084.
- Yamashina, A., Tomiyama, H., Takeda, K., Tsuda, H., Arai, T., Hirose, K., Koji, Y., Hori, S. & Yamamoto, Y. (2002) Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens. Res.*, **25**, 359-364.
- Yambe, T., Yoshizawa, M., Saijo, Y., Yamaguchi, T., Shibata, M., Konno, S., Nitta, S. & Kuwayama, T. (2004) Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed. Pharmacother.*, **58**, S95-S98.