Original Article

Cardio-Ankle Vascular Index is Independently Associated with the Severity of Coronary Atherosclerosis and Left Ventricular Function in Patients with Ischemic Heart Disease

Toru Miyoshi[1], Masayuki Doi[2], Satoshi Hirohata[1], Kosuke Sakane[2], Shigeshi Kamikawa[1], Tomoki Kitawaki[3], Youko Kaji[2], Kengo Fukushima Kusano[4], Yoshifumi Ninomiya[1], and Shozo Kusachi[3]

[1]Department of Molecular Biology and Biochemistry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[2]Division of Cardiology, Sumitomo Besshi Hospital, Niihama, Japan
[3]Department of Medical Technology, Okayama University Graduate School of Health Sciences, Okayama, Japan
[4]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

***Aim*: The cardio-ankle vascular index (CAVI) has been proposed as a new noninvasive marker of arterial stiffness independent of blood pressure. We investigated the association of the CAVI with coronary atherosclerosis and left ventricular (LV) systolic and diastolic function in patients with ischemic heart disease (IHD).**

***Methods*: A total of 206 consecutive subjects undergoing coronary angiography were enrolled. CAVI measurement and echocardiography were performed simultaneously. Patients having significant coronary stenosis were classified into the IHD group.**

***Results*: CAVI in the IHD group ($n=133$) was significantly higher than in the non-IHD group ($n=73$) (9.1 ± 1.3 vs. 8.7 ± 1.2, $p=0.02$). In all IHD patients, CAVI was negatively correlated with LV ejection fraction (LVEF) ($r=-0.31$, $p<0.01$), LV mass index ($r=0.24$, $p<0.01$) and angiographic scores of coronary atherosclerosis. Stepwise regression analysis revealed that CAVI was independently associated with LVEF, along with a history of myocardial infarction, LV mass index, and left atrial diameter in all IHD patients ($p<0.01$). In the sub-analysis of IHD patients with preserved LVEF, CAVI was correlated with echocardiographic parameters regarding LV diastolic function. Multivariate analysis demonstrated that the increased CAVI was significantly associated with LV diastolic dysfunction in patients with preserved LVEF.**

***Conclusion*: CAVI, a new parameter of aortic stiffness, was independently associated with LV systolic and diastolic function as well as coronary artery disease in IHD patients.**

J Atheroscler Thromb, 2010; 17:249-258.

Key words; Cardio-ankle vascular index, Arterial stiffness, Ischemic heart disease, Left ventricular function

Introduction

Many studies have examined the effect of cardiovascular risk factors on vessels[1-3]. It is recognized that these factors lead to increased aortic stiffness, which has been reported to predict cardiovascular morbidity and mortality in patients with hypertension[4], diabetes[5], and chronic renal failure[6]. In patients with coronary artery disease, aortic stiffness was shown to be increased compared to patients without coronary artery disease and was related to the severity of coronary atherosclerosis[7, 8]. Increased aortic stiffness was also associated with the recurrence of cardiovascular events[9]. On the other hand, the association of aortic stiffness

Address for correspondence: Toru Miyoshi, Department of Molecular Biology and Biochemistry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Okayama, Okayama 700-8558, Japan
E-mail: miyoshit@cc.okayama-u.ac.jp
Received: January 25, 2009
Accepted for publication: September 9, 2009

with left ventricular (LV) structure and LV function, particularly diastolic dysfunction, has been evaluated in patients with hypertension and diabetes[10, 11]. Although LV ejection fraction (LVEF) has been shown to be a significant predictor of adverse cardiac events in patients with ischemic heart disease (IHD)[12], only a few studies have reported the effect of aortic stiffness on LV systolic function in IHD patients[13].

Stiffness parameter β is based on the change in vascular diameter corresponding to arterial pressure variance, and the value does not depend on blood pressure[14]. Recently, an arterial stiffness parameter, termed the cardio-ankle vascular index (CAVI), has been developed as a marker of vascular properties, including the aorta, femoral artery and tibial artery[15] by combining two indices: stiffness parameter β[16] and Bramwell-Hill's formula[17]. Previous studies showed that CAVI was weakly correlated with systolic blood pressure and the measurement does not require special techniques[15, 18, 19]. Emerging data indicate that CAVI is useful to detect carotid and coronary atherosclerosis[20-23].

In the present study, we measured CAVI in patients with suspected coronary artery disease who underwent coronary angiography. Accordingly, the relationship of CAVI to coronary atherosclerosis, LV systolic function, and LV diastolic function determined by echocardiography was evaluated in IHD patients.

Methods

Study Population

We enrolled 206 consecutive subjects (159 men and 47 women; mean age: 67 ± 12 years) undergoing coronary angiography (CAG) for the assessment of suspected coronary artery disease at Sumitomo Besshi Hospital (Niihama, Japan) from January 2007 to October 2008. All subjects were examined by CAVI measurement and echocardiography before CAG. The subjects were divided into two groups on the basis of the CAG findings: patients with significant coronary stenosis defined as 50% or greater luminal diameter narrowing (n=133) and without significant coronary stenosis (n=73).

Exclusion criteria were as follows: (1) patients with restrictive cardiomyopathy and hypertrophic cardiomyopathy on echocardiography (2) patients with clinically significant valvular disease and a prosthetic valve; (3) renal insufficiency (serum creatinine, more than 1.5 mg/dL); (4) patients with acute coronary syndrome or cor pulmonale; (5) patients with atrial fibrillation; and (6) peripheral arterial disease as evidenced by an ankle-brachial index of less than 0.9. Hypertension was diagnosed in accordance with the 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension[24]. Diabetes was defined as a fasting blood glucose level >126 mg/dL or requiring anti-diabetic medication. Dyslipidemia was diagnosed according to the 2007 Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases[25]. This study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Sumitomo Besshi Hospital. Informed consent was obtained from all patients before the study.

Coronary Angiography

Coronary angiography was performed according to standard methods. After intracoronary injection of isosorbide dinitrate, angiograms were obtained in two or more views. The coronary angiogram was scored by two independent investigators and according to three techniques. (1) Vessel score: The number of vessels with significant stenosis, defined as 50% or greater luminal diameter narrowing[26]. (2) Stenosis score: A modified Gensisni score, which has been previously reported[27, 28]. Briefly, the most severe stenosis in each of eight segments was graded according to severity, from 1 to 4. The scores in each of the eight segments were added to give a total score out of 32. (3) Extent score: According to the proportional length of each vessel segment in the coronary artery tree, segments were graded with different maximum numbers of points, as previously reported. The scores of each vessel were added to give a total score out of 100[29].

Cardio-Ankle Vascular Index

After a 5-min rest and with the subject seated, brachial blood pressure was measured using an automatic cuff oscillometric device, and the average of two readings was used to determine systolic pressure, diastolic pressure, and pulse pressure. CAVI was measured automatically using a VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan), as previously described[15, 30]. Briefly, cuffs were applied to bilateral upper arms and ankles, with the subjects lying supine and the head held in the midline position. After resting for 10 min, the examination was performed. Pulse wave velocity (PWV) was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the time between the aortic valve closing sound and the notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and rise of the ankle pulse wave. CAVI was determined using the following equation:

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

where Ps and Pd are systolic and diastolic blood pressures, respectively, PWV is the pulse wave velocity between the heart and ankle, ΔP is Ps − Pd, ρ is blood density, and a and b are constants. The average of right and left CAVI was used for analysis.

Transthoracic Echocardiography

Comprehensive examinations were performed, including M-mode, two-dimensional conventional Doppler, and color Doppler echocardiography[31]. Measurements were made according to the guidelines laid down by the American Society of Echocardiography[32]. The left atrial dimension (LAD) was measured from M-mode images according to standard criteria. The LV mass index was calculated as left ventricular mass divided by the body surface area[33]. Using pulsed Doppler echocardiography, the LV diastolic filling pattern was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. Peak early diastolic velocity (E velocity) and peak atrial diastolic velocity (A velocity) were recorded, and the ratio of E to A (E/A) was calculated. The deceleration time of E velocity (DcT) was measured as the time interval from the E-wave peak to the decline of velocity to baseline values. The LV isovolumetric relaxation time (IVRT) was taken as the time in milliseconds from the end of ejection fraction to the onset of LV filling. Experienced cardiologists blinded to CAVI interpreted all echocardiograms.

Echo Classifications of Diastolic Function

The subjects with preserved LV systolic function with ejection fraction ≥55% were divided into two groups according to LV diastolic function determined by the LV filling pattern. Impaired LV diastolic function was defined as impaired relaxation, and a pseudonormal and restrictive pattern based on the mitral inflow profile, including the E/A ratio and DcT, as described by Redfield *et al.*[34]: 1) impaired relaxation: in patients <55 years of age, E/A ratio <1 or DcT >240 ms. In patients ≥55 years of age, E/A ratio <0.8 and DcT >240 ms. Additional confirming evidence was IVRT >90 ms. 2) Pseudonormal: E/A ratio of 1 to 1.5 and DcT >240 ms. 3) Restrictive: E/A >1.5 and DT <160 ms.

Statistical Analysis

Data are shown as the mean ± standard deviation. Categorical variables were compared between groups by chi-square analysis. The unpaired Student's test was used for continuous variables between groups. The difference in CAVI between groups was evaluated by analysis of covariance using confounding factors (ANCOVA). Differences in characteristics among groups were compared by one-way analysis of variance (ANOVA), followed by the Bonferroni post-hoc test for continuous variables. Relationships between variables were tested by Pearson and Spearman correlations. Factors independently associated with CAVI were assessed using univariate and multivariate liner regression analysis. Multivariate logistic analysis was performed to evaluate the relationship between the presence of LV diastolic dysfunction and CAVI, and the following factors were included: age, diabetes, use of calcium channel blockers and statins, systolic blood pressure, vessel score, and CAVI. A value of $p<0.05$ was considered significant. Data were analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL).

Table 1. Clinical characteristics in patients with and without IHD

	Ischemic heart disease		p
	absence (n=73)	presence (n=133)	
Age (years)	66 ± 12	68 ± 11	0.11
Male, n (%)	57 (75)	102 (77)	0.88
BMI (kg/m^2)	23.4 ± 3.5	23.9 ± 3.2	0.21
Hypertension, n (%)	39 (52)	79 (59)	0.30
Dyslipidemia, n (%)	32 (41)	87 (65)	<0.01
Diabetes, n (%)	17 (25)	57 (43)	<0.01
Smoking, n (%)	21 (28)	41 (31)	0.88
Prior MI, n (%)	0 (0)	55 (41)	<0.01
SBP (mmHg)	137 ± 19	136 ± 20	0.48
DBP (mmHg)	81 ± 13	80 ± 10	0.42
LAD (mm)	36 ± 6	38 ± 5	0.13
LVEF (%)	67.4 ± 9.9	61.5 ± 11.8	<0.01
LVMI (g/m^2)	118 ± 29	124 ± 38	0.27
E/A	0.79 ± 0.30	0.76 ± 0.2	0.51
DcT (ms)	201 ± 48	208 ± 49	0.39
CAVI	8.7 ± 1.2	9.1 ± 1.3	0.02

Values are expressed as numbers with percentages in parentheses or as the mean ± SD. p, probability value; BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; E/A, ratio of peak early transmitral velocity and peak transmitral atrial velocity; DcT, deceleration time of E velocity; CAVI, cardio-ankle vascular index

Results

Comparison of CAVI and Characteristics in Patients with and without IHD

Table 1 shows the clinical characteristics and echocardiographic parameters in patients with and

Table 2. Association between CAVI and clinical characteristics in all patients ($n=133$), patients with preserved LVEF ($n=96$), and patients with reduced LVEF ($n=37$)

Dependent variable: CAVI	All IHD patients		IHD Patients with preserved LVEF		IHD Patients with reduced LVEF	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.47	<0.01	0.53	<0.01	0.29	0.08
Male	0.26	0.28	0.06	0.59	0.11	0.51
BMI	−0.17	0.05	−0.13	0.21	−0.12	0.47
SBP	0.16	0.07	0.22	0.04	0.16	0.35
DBP	0.07	0.40	0.05	0.65	0.18	0.29
Pulse pressure	0.16	0.07	0.24	0.02	0.08	0.64
Creatinine	0.13	0.15	0.15	0.15	0.17	0.33
LDL-C	0.19	0.03	0.18	0.08	0.19	0.27
HDL-C	0.01	0.90	−0.03	0.77	0.09	0.61
HbA1c	0.08	0.38	0.17	0.10	−0.18	0.30
LVMI	0.24	<0.01	0.31	<0.01	0.05	0.76
LVEF	−0.31	<0.01	−0.16	0.12	−0.20	0.23
LAD	0.08	0.38	−0.01	0.92	0.04	0.81
E/A	−0.25	<0.01	−0.43	<0.01	0.08	0.64
DcT	0.09	0.32	0.22	0.03	0.01	0.94
Vessel score	0.25	<0.01	0.17	0.09	0.35	0.03
Stenosis score	0.32	<0.01	0.22	0.03	0.40	0.01
Extent score	0.34	<0.01	0.21	0.04	0.50	<0.01

Preserved LVEF, LVEF ≥55%; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. Other abbreviations are shown in Table 1.

without IHD. Dyslipidemia and diabetes were more prevalent in IHD patients, while systolic and diastolic blood pressures were comparable between groups. Patients with prior myocardial infarction were included in 41% of subjects with IHD. Echocardiographic findings showed that the LVEF in patients with IHD was significantly lower than in patients without IHD, while there were no significant differences in LAD, LV mass index, E/A, and DcT between groups. CAVI in patients with IHD was significantly higher than in patients without IHD, and this difference remained significant after adjustment for the presence of dyslipidemia, diabetes, prior myocardial infarction, and LVEF (9.2 ± 0.1 vs. 8.7 ± 0.2, as expressed mean ± SE, $p=0.03$, respectively).

Relationship between CAVI and Clinical Characteristics in IHD Patients

Table 2 shows univariate analysis regarding the association of CAVI with other parameters in all IHD patients and in sub-groups classified by LVEF, respectively. In all IHD patients, CAVI was significantly correlated with age, LDL-cholesterol, LV mass index, E/A, and angiographic scores of coronary atherosclerosis, besides LVEF. **Fig. 1A** also demonstrated the negative correlation between CAVI and LVEF. In the sub-group of IHD patients with preserved LVEF (LVEF ≥55%), univariate analysis demonstrated that CAVI was associated with echocardiographic parameters regarding LV diastolic function, such as E/A, DcT, and LV mass index, along with age, systolic blood pressure, pulse pressure, and angiographic scores of coronary atherosclerosis. In the sub-group of IHD patients with reduced LVEF (LVEF <55%), univariate analysis showed that CAVI was correlated with only angiographic scores of coronary atherosclerosis. The association between CAVI and LVEF did not reach statistical significance in analyses of sub-groups according to LVEF.

Furthermore, in all IHD patients, multivariate analysis was performed and CAVI was shown to be independently associated with age ($\beta=0.37$, $p<0.01$), LDL-cholesterol ($\beta=0.15$, $p=0.04$), LV mass index ($\beta=0.21$, $p=0.01$), LVEF ($\beta=-0.56$, $p<0.01$), and extent score as a parameter of coronary atherosclerosis ($\beta=0.19$, $p=0.02$) (data not shown). The relationships of CAVI with systolic blood pressure and diastolic blood pressure in all IHD patients did not

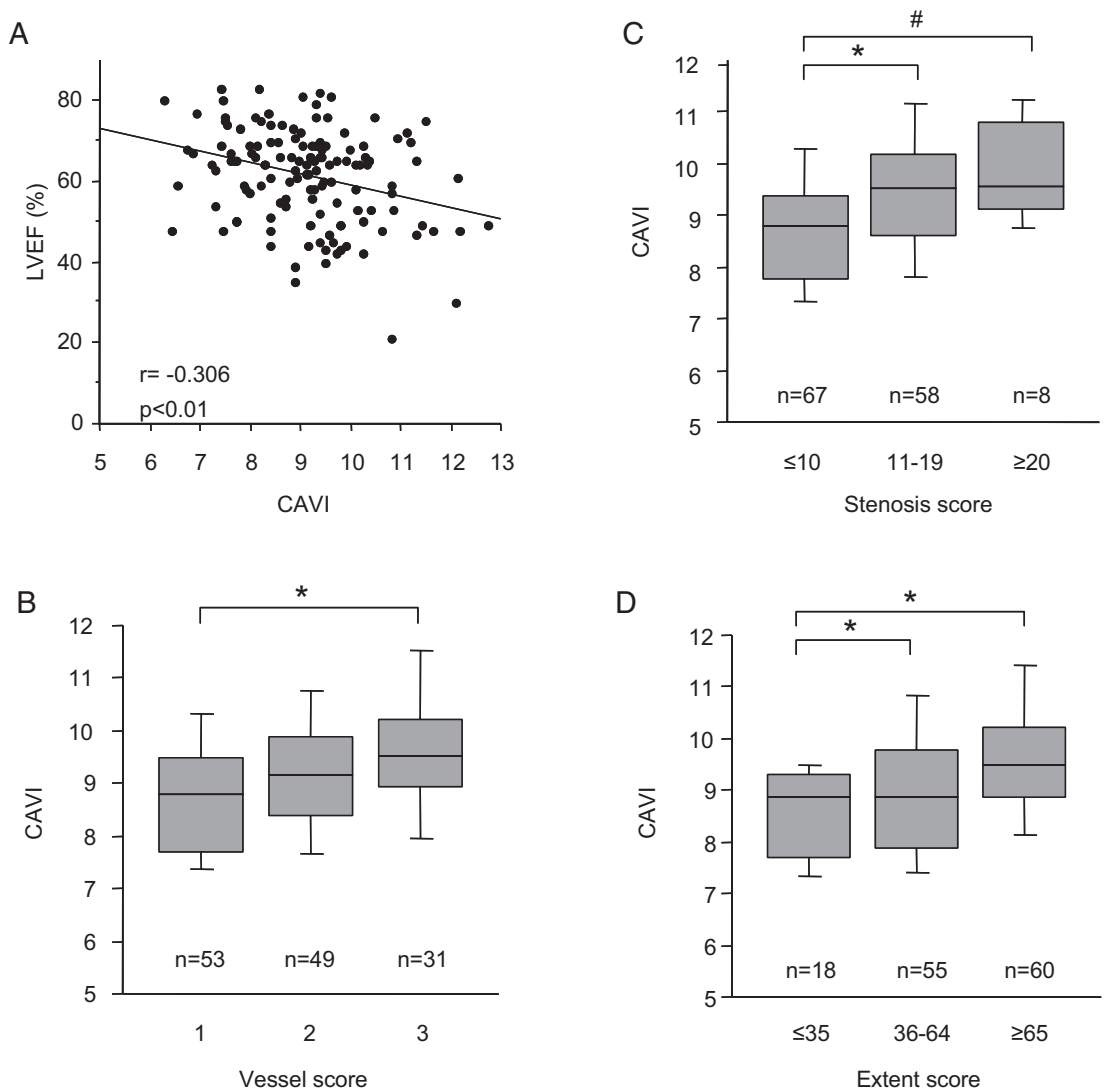

Fig. 1. (A) Scatter plot of the association between CAVI and LVEF. (B) Box plots showing the associations of CAVI with vessel score, (C) stenosis score, and (D) extent score.

Lower and upper boundaries of boxes indicate 25th and 75th percentiles, and bars. $^{*}p<0.01$; $^{\#}p<0.05$.

remain significant in multivariate analysis.

Fig. 1B, **1C** and **1D** demonstrate the association between CAVI and the development of coronary atherosclerosis determined with coronary angiography. CAVI gradually increased with the vessel, stenosis, and extent scores in all IHD patients, respectively.

Clinical Parameters in IHD Patients According to EF Tertiles

To assess factors associated with LV systolic function, patients with IHD were classified into tertiles on the basis of LVEF (**Table 3**). Patients in the lowest LVEF tertile (the most reduced LVEF) had smaller BMI, a lower prevalence of dyslipidemia, and a higher presence of prior myocardial infarction, larger LAD, and greater LV mass index than those in the highest LVEF tertile. CAVI in the lowest LVEF tertile was shown to be significantly greater than in the highest EF tertile. **Table 4** shows the results of stepwise analysis. CAVI, as well as prior myocardial infarction, the LV mass index, and LAD were selected as independent factors associated with LVEF in patients with IHD.

LV Diastolic Dysfunction and CAVI in Patients with Preserved LVEF

To evaluate the relationship between LV diastolic

Table 3. Clinical characteristics among LVEF tertiles in IHD patients

	LVEF (%)			*p*
	T1 (*n*=44) (21.2–58.4)	T2 (*n*=45) (58.8–67.6)	T3 (*n*=44) (67.9–83.2)	
Age (years)	71±11	66±12	68±11	0.15
Male, n (%)	36 (82)	37 (82)	29 (66)	0.12
BMI (kg/m^2)	22.9±3.0	24.3±2.9	24.8±3.4	0.01
Hypertension, n (%)	22 (50)	27 (60)	30 (68)	0.22
Dyslipidemia, n (%)	21 (48)	32 (71)	34 (77)	0.01
Diabetes, n (%)	18 (41)	20 (44)	19 (43)	0.94
Prior MI, n (%)	30 (68)	18 (40)	7 (16)	<0.01
Smoking, n (%)	11 (25)	18 (41)	12 (27)	0.21
Medications n (%)				
ACEI/ARBs	20 (53)	25 (57)	24 (56)	0.93
CCBs	15 (35)	16 (36)	17 (39)	0.93
β blockers	17 (43)	10 (23)	12 (28)	0.13
Digitalis	5 (14)	2 (4)	1 (2)	0.08
Diuretics	8 (18)	3 (7)	4 (9)	0.20
Statins	22 (50)	20 (44)	27 (61)	0.27
SBP (mmHg)	134±17	133±17	140±25	0.23
DBP (mmHg)	80±10	80±10	81±10	0.89
Pulse pressure (mmHg)	54±11	53±13	59±20	0.13
LAD (mm)	39±5	36±4	37±5	0.02
LVMI (g/m^2)	133±43	127±37	110±30	0.02
E/A	0.74±0.26	0.79±0.24	0.74±0.18	0.59
DcT (ms)	206±71	208±47	209±56	0.98
Vessel score	2.0±0.9	1.8±0.7	1.8±0.8	0.55
CAVI	9.5±1.4	9.0±1.2	8.8±1.2	0.02

Values are expressed as numbers with percentages in parentheses or as the mean±SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCBs, calcium channel blockers. Other abbreviations are seen in Table 1.

Table 4. Stepwise multiple regression analysis of variables associated with LVEF

Dependent variable	Selected factors	Standardized Regression Coefficient	*t*	*p*
LVEF	Prior myocardial infarction	−0.43	−5.76	<0.01
	CAVI	−0.21	−2.72	<0.01
	LV mass index	−0.18	−2.21	<0.01
	Left atrial diameter	−0.17	−2.22	0.03
	Multiple regression coefficient $r=0.59$, $p<0.01$			

For analysis, the following variables were included: age, gender, body mass index, history of smoking and prior MI, use of digitalis, LDL-cholesterol, systolic blood pressure, pulse pressure, LAD, LV mass index, vessel score, and CAVI.

dysfunction and CAVI, patients with preserved LVEF (*n*=96) were divided into two groups on the basis of the manifestation of normal (*n*=66) or impaired (*n*=30) LV diastolic function by echocardiography. As shown in **Table 5**, there was a difference in the prevalence of diabetes, the use of calcium channel blockers, the use of statins, systolic blood pressure, pulse pressure, vessel score, and CAVI between groups. CAVI in patients with impaired LV diastolic function was significantly higher than in subjects with normal LV diastolic function, and this difference remained significant after adjustment for confounding factors (9.3±

Table 5. Comparison of clinical characteristics in IHD patients with LVEF ≥55% according to LV diastolic function

	LV diastolic function		*p*
	normal (*n*=66)	impaired (*n*=30)	
Age (years)	66±11	71±12	0.05
Male, n (%)	47 (71)	24 (80)	0.36
BMI (kg/m^2)	24.3±3.3	24.6±3.3	0.69
Hypertension, n (%)	38 (58)	22 (73)	0.14
Dyslipidemia, n (%)	48 (73)	22 (73)	0.95
Diabetes, n (%)	22 (33)	19 (63)	<0.01
Prior MI, n (%)	20 (30)	8 (27)	0.72
Smoking, n (%)	22 (33)	10 (35)	0.91
Medications, n (%)			
ACEI/ARBs	35 (55)	18 (60)	0.63
CCBs	19 (29)	16 (53)	0.02
β blockers	15 (27)	5 (17)	0.29
Digitalis	1 (2)	2 (7)	0.18
Diuretics	4 (6)	3 (10)	0.49
Statins	39 (59)	11 (37)	0.04
Creatinine (mg/dL)	0.9±0.3	1.0±0.5	0.11
SBP (mmHg)	133±21	145±19	0.01
DBP (mmHg)	80±9	83±11	0.14
Pulse pressure (mmHg)	54±17	62±15	0.02
LAD (mm)	37±4	37±4	0.88
LVMI (g/m^2)	117±29	123±46	0.46
Vessel score	1.7±0.7	2.1±0.8	<0.01
CAVI	8.6±1.0	9.5±1.1	<0.01

0.2 vs. 8.7±0.1, expressed as the mean±SE, $p=0.02$, respectively). Furthermore, multiple logistic analysis, including age, diabetes, use of calcium channel blockers and statins, systolic blood pressure, vessel score, and CAVI, revealed that an increase in CAVI was independently related with LV diastolic dysfunction. The adjusted odds ratio of LV diastolic dysfunction was 1.67 (95% confidential interval: 1.07 to 3.26) for each index of CAVI increase ($p=0.03$) (data not shown).

Discussion

The present study demonstrated that CAVI, a new parameter of arterial stiffness, was higher in patients with IHD than in patients without IHD. In addition, CAVI was independently associated with not only LV systolic dysfunction in all IHD patients, but also LV diastolic dysfunction, as assessed by echocardiography in IHD patients with preserved LVEF.

Among several markers of arterial stiffness, CAVI has been theoretically proposed as a new noninvasive estimation of β, which is independent of blood pressure[15]. Previous studies showed that the contribution of blood pressure to CAVI was weaker than brachial-ankle PWV[15, 18, 23]. Our finding also supported the weak correlation between CAVI and systolic, diastolic, and pulse pressure in suspected IHD patients undergoing coronary angiography. In addition, recent studies showed that CAVI was associated with carotid and coronary atherosclerosis. Thus, emerging data suggest that CAVI would be promising tool for atherosclerosis screening in the clinical setting. On the other hand, CAVI essentially represents stiffness of the aorta, femoral artery and tibial artery as a whole[15]. Although a study demonstrated that β of the thoracic descending aorta obtained by transesophageal echocardiography was closely correlated with CAVI[35], evidence for theoretical rationale for CAVI in determining vascular function has not been fully elucidated. Further study is needed to enhance the value of CAVI in the clinical setting.

Aortic stiffness in IHD patients has been reported to be higher than in patients without IHD[8], and was associated with the severity of coronary atherosclerosis[7]. Previous studies reported that CAVI increased with the number of diseased coronary arteries[21, 22]. In this study, coronary atherosclerosis was evaluated with three different angiographic scores. We found that CAVI was associated with not only the severity of stenosis, but also the extent of coronary atherosclerosis. Arterial stiffness was shown to be associated with the incidence of cardiovascular events[3, 36] and an important predictor of the recurrence of adverse events in post-myocardial infarction patients with impaired left ventricular function[9]. Thus, the determination of arterial stiffness is useful for risk stratification.

The relationship between arterial stiffness and left ventricular structures, such as hypertrophy, has been reported previously[8]; however, the relation between arterial stiffness and LV systolic function has not been fully elucidated. Only one study has shown that brachial-ankle PWV and pulse pressure in patients with coronary artery stenosis was involved in LVEF[13], which is in line with our finding of the significant association between increased CAVI and reduced LV systolic dysfunction in IHD patients. Regarding LV diastolic function, several studies have shown a relationship between preclinical LV diastolic dysfunction and CAVI in patients with cardiovascular risk factors[11, 30], but this has not been evaluated only in patients with IHD. LV systolic and diastolic dysfunction are closely linked, as it was previously reported that LV dysfunction develops before LV systolic dys-

function in patients with cardiovascular risk factors[37, 38]. Increased arterial stiffness shifts pressure wave reflections from diastole to systole, and thus augments systolic pressure and decreases diastolic pressure[9]. The elevation of systolic pressure caused LV pulsatile load and led to LV hypertrophy, which is one of the major determinants of LV diastolic dysfunction[39]. In addition, the coronary blood supply may be reduced because of decreased diastolic pressure, and this reduction is more severe in IHD patients, leading to enhanced cardiac fibrosis. In an animal model, it was reported that cardiac dysfunction after acute coronary occlusion is adversely influenced when the heart ejects into a stiff arterial system[40]. Thus, these factors may, at least in part, predispose consecutive LV systolic dysfunction in IHD patients with increased arterial stiffness, independent of other influential factors, such as prior myocardial infarction.

Although we found a negative correlation between CAVI and LVEF in all IHD patients, this relationship in patients with advanced systolic dysfunction sould be interpreted with case, because the formula for measuring CAVI includes PWV, which was affected by LV contractility. A previous study showed a positive correlation between PWV and LVEF in patients with cardiomyopathy (LVEF $<40\%$)[41]; however, they also showed no significant difference in mean PWV between patients with cardiomyopathy and control patients with preserved LVEF. An explanation for this contradictory finding might lie in the different populations of the studies. The present study evaluated patients with definite coronary artery disease, whose arterial stiffness was expected to be increased. In addition, our finding revealed that LVEF and coronary atherosclerosis were independently associated with CAVI in patients with IHD. Taken together, an explanation for the negative correlation between CAVI and LVEF is that the contribution of increased arterial stiffness in patients with IHD might overwhelm the impact of reduced LV contractility on PWV. Given the relatively small sample size in this study, further research with a large number of patients is needed to confirm the relationship.

There were several limitations of our study. First, based on its cross-sectional study design, the present findings are inherently limited in their ability to eliminate causal relationships between coronary atherosclerosis, LV function, and CAVI. Second, it is well known that antihypertensive agents influence arterial stiffness and LV systolic and diastolic function. In this study, we evaluated the relationship between CAVI and LV systolic and diastolic functions receiving medicines. The possibility that pharmacological therapy has different effects on its relationship cannot be excluded. Third, in the present study, subjects with ABI <0.9 were excluded, because CAVI in these subjects may be inaccurate; however, IHD is closely associated with peripheral artery disease so ABI may be included to evaluate these data in subjects with ABI <0.9. Fourth, with regard to LV diastolic function, although Doppler echocardiography is the best noninvasive tool to confirm diagnosis[42], cardiac catheterization remains the preferred method to obtain precise data.

In conclusion, the present study demonstrated that, in patients with IHD, CAVI, a new parameter of arterial stiffness, was correlated with the severity of coronary atherosclerosis, and was associated with LV systolic and diastolic function independent of the severity of coronary atherosclerosis. Thus, the determination of arterial stiffness, such as CAVI, may be useful for risk stratification and secondary prevention in patients with IHD.

Acknowledgments

The authors thank the members of the SKY research group (Sumitomo Besshi Hospital, Kagawa Prefectural Central Hospital, and Yashima General Hospital) for stimulating discussions.

References

1) Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Kamp O, Westerhof N, Bouter LM, Stehouwer CD: Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation, 2003; 107: 2089-2095
2) Blacher J, Asmar R, Djane S, London GM, Safar ME: Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension, 1999; 33: 1111-1117
3) Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, Guize L: Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension, 1997; 30: 1410-1415
4) Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M: Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation, 2006; 113: 1213-1225
5) Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation, 2002; 106: 2085-2090
6) Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-

stage renal disease. Circulation, 1999; 99: 2434-2439
7) Hirai T, Sasayama S, Kawasaki T, Yagi S: Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation, 1989; 80: 78-86
8) Gatzka CD, Cameron JD, Kingwell BA, Dart AM: Relation between coronary artery disease, aortic stiffness, and left ventricular structure in a population sample. Hypertension, 1998; 32: 575-578
9) Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, Flaker GC, Pfeffer MA: 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, 1997; 96: 4254-4260
10) Mottram PM, Haluska BA, Leano R, Carlier S, Case C, Marwick TH: Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. Heart, 2005; 91: 1551-1556
11) Eren M, Gorgulu S, Uslu N, Celik S, Dagdeviren B, Tezel T: Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. Heart, 2004; 90: 37-43
12) Schulman SP, Achuff SC, Griffith LS, Humphries JO, Taylor GJ, Mellits ED, Kennedy M, Baumgartner R, Weisfeldt ML, Baughman KL: Prognostic cardiac catheterization variables in survivors of acute myocardial infarction: a five year prospective study. J Am Coll Cardiol, 1988; 11: 1164-1172
13) Sakuragi S, Iwasaki J, Tokunaga N, Hiramatsu S, Ohe T: Aortic stiffness is an independent predictor of left ventricular function in patients with coronary heart disease. Cardiology, 2005; 103: 107-112
14) Buntin CM, Silver FH: Noninvasive assessment of mechanical properties of peripheral arteries. Ann Biomed Eng, 1990; 18: 549-566
15) Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2006; 13: 101-107
16) Kawasaki T, Sasayama S, Yagi S, Asakawa T, Hirai T: Noninvasive assessment of the age related changes in stiffness of major branches of the human arteries. Cardiovasc Res, 1987; 21: 678-687
17) Bramwell JC, Hill AV: Velocity of the Pulse wave in Man. Proc Roy Soc, 1922; B:298-306
18) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tei C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94
19) Yambe T, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Konno S, Nitta S, Kuwayama T: Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). Biomed Pharmacother, 2004; 58 Suppl 1: S95-98
20) Izuhara M, Shioji K, Kadota S, Baba O, Takeuchi Y, Uegaito T, Mutsuo S, Matsuda M: Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary arteriosclerosis. Circ J, 2008; 72: 1762-1767
21) Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H: Cardio-Ankle Vascular Index is a Candidate Predictor of Coronary Atherosclerosis. Circ J, 2008; 72: 598-604
22) Takenaka T, Hoshi H, Kato N, Kobayashi K, Takane H, Shoda J, Suzuki H: Cardio-ankle vascular index to screen cardiovascular diseases in patients with end-stage renal diseases. J Atheroscler Thromb, 2008; 15: 339-344
23) Yambe M, Tomiyama H, Hirayama Y, Gulniza Z, Takata Y, Koji Y, Motobe K, Yamashina A: Arterial stiffening as a possible risk factor for both atherosclerosis and diastolic heart failure. Hypertens Res, 2004; 27: 625-631
24) Chalmers J: The 1999 WHO-ISH Guidelines for the Management of Hypertension. Med J Aust, 1999; 171: 458-459
25) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M: Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb, 2007; 14: 45-50
26) Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK: Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation, 2003; 108: 2206-2211
27) Gensini GG: A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol, 1983; 51: 606
28) Reardon MF, Nestel PJ, Craig IH, Harper RW: Lipoprotein predictors of the severity of coronary artery disease in men and women. Circulation, 1985; 71: 881-888
29) Sullivan DR, Marwick TH, Freedman SB: A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. Am Heart J, 1990; 119: 1262-1267
30) Sakane K, Miyoshi T, Doi M, Hirohata S, Kaji Y, Kamikawa S, Ogawa H, Hatanaka K, Kitawaki T, Kusachi S, Yamamoto K: Association of new arterial stiffness parameter, the cardio-ankle vascular index, with left ventricular diastolic function. J Atheroscler Thromb, 2008; 15: 261-268
31) Matsuura H, Murakami T, Hina K, Yamamoto K, Kawamura H, Sogo T, Shinohata R, Usui S, Ninomiya Y, Kusachi S: Association of elevated plasma B-type natriuretic peptide levels with paroxysmal atrial fibrillation in patients with nonobstructive hypertrophic cardiomyopathy. Clin Biochem, 2007
32) Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO: ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr, 2003; 16: 1091-1110

33) Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman NH, Brundage B, Botvinick EH, Boswell R, Carlsson E, Parmley WW: Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation, 1979; 60: 547-555
34) Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. Jama, 2003; 289: 194-202
35) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Matsuda T, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J, 2007; 71: 1710-1714
36) van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC: Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke, 2001; 32: 454-460
37) Ahmed SS, Jaferi GA, Narang RM, Regan TJ: Preclinical abnormality of left ventricular function in diabetes mellitus. Am Heart J, 1975; 89: 153-158
38) Fouad FM, Slominski JM, Tarazi RC: Left ventricular diastolic function in hypertension: relation to left ventricular mass and systolic function. J Am Coll Cardiol, 1984; 3: 1500-1506
39) Watabe D, Hashimoto J, Hatanaka R, Hanazawa T, Ohba H, Ohkubo T, Kikuya M, Totsune K, Imai Y: Electrocardiographic left ventricular hypertrophy and arterial stiffness: the Ohasama study. Am J Hypertens, 2006; 19: 1199-1205
40) Kass DA, Saeki A, Tunin RS, Recchia FA: Adverse influence of systemic vascular stiffening on cardiac dysfunction and adaptation to acute coronary occlusion. Circulation, 1996; 93: 1533-1541
41) Weber T, Auer J, Lamm G, O'Rourke MF, Eber B: Arterial stiffness, central blood pressures, and wave reflections in cardiomyopathy-implications for risk stratification. J Card Fail, 2007; 13: 353-359
42) Nishimura RA, Tajik AJ: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol, 1997; 30: 8-18