

ORIGINAL ARTICLE

Head-to-head comparison of the cardio-ankle vascular index between patients with acute coronary syndrome and stable angina pectoris

Akinori Sairaku¹, Shin Eno¹, Tatsuya Hondo¹, Hiroki Teragawa², Yukiko Nakano³, Keiji Matsuda¹, Tomohiko Kisaka¹ and Yasuki Kihara³

We aimed to evaluate whether there was a difference in the arterial stiffness assessed by the cardio-ankle vascular index (CAVI) between patients with acute coronary syndrome (ACS) and those with stable angina pectoris (SAP). A total of 199 consecutive patients, 79 with ACS and 120 with SAP, who underwent emergency or elective coronary revascularization were enrolled. The CAVI was measured within 2 days after the procedures, and was compared between the ACS and SAP patients. As parameters related to arteriosclerosis, carotid intima-media thickness (IMT) and number of stenotic coronary vessels were also evaluated. Although IMT was significantly greater in SAP patients (2.1 ± 1.1 vs. 2.4 ± 0.9 ; $P=0.022$), CAVI was significantly higher in ACS patients (10.0 ± 1.7 vs. 9.3 ± 1.3 ; $P=0.0012$). After an adjustment for the clinical parameters with a significant difference between the two patient groups, CAVI remained significantly higher in ACS patients than in SAP patients (odds ratio 1.92, 95% confidence interval 1.30–3.02; $P=0.0023$). A multiple linear regression analysis revealed that age ($\beta=0.44$; $P<0.0001$) and ACS ($\beta=0.3$; $P<0.0001$) were the independent determinants of CAVI. A significant decrease in CAVI was observed at 6 months of follow-up as compared with the acute phase in 18 patients with ACS (10.9 ± 1.6 vs. 10.0 ± 1.5 ; $P=0.019$). In conclusion, CAVI was significantly and independently higher in patients with ACS than in those with SAP, which might result from a transient increase in the CAVI caused by acute myocardial ischemia.

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INTRODUCTION

Recently, a novel arterial stiffness parameter called the cardio-ankle vascular index (CAVI) has been developed that is independent of blood pressure and differs from pulse wave velocity.^{1,2} The CAVI is significantly associated with the parameters related to atherosclerosis;^{3–7} furthermore, it is positively correlated with the severity of coronary artery disease.^{5,6} However, there are few reports on CAVI in patients with acute coronary syndrome (ACS) requiring emergency revascularization.

Increased arterial stiffness has been shown to be an independent predictor of cardiovascular events and mortality in high-risk populations.^{8–11} In addition, the aortic stiffness assessed by invasive methods is also a powerful and independent risk factor for recurrent acute coronary events in patients with coronary artery disease (CAD), including stable angina pectoris (SAP).¹² Hence, we hypothesized that the arterial stiffness assessed by CAVI in ACS patients would be significantly higher than that in SAP patients. The aim of our study was to evaluate whether there was a difference in CAVI between patients with ACS and those with SAP.

METHODS

Study population

Between July 2007 and March 2009, a total of 199 consecutive patients (age 71 ± 11 years, 138 men) with ACS ($n=79$), defined as an acute ST- or non-ST-segment elevation myocardial infarction or Braunwald's class IIIIB unstable angina pectoris, and SAP ($n=120$) were enrolled. An emergency percutaneous coronary intervention or coronary artery bypass grafting was performed in patients with ACS and an elective percutaneous coronary intervention or coronary artery bypass grafting was performed in those with SAP.

Patients with hypotension, systolic blood pressure (SBP) ≤ 90 mm Hg, cardiac decompensation, a previous myocardial infarction, a history of coronary revascularization and peripheral arterial disease with an ankle-brachial pressure index of <0.9 were excluded.

The study was approved by the local ethics committees, and all subjects gave their written informed consent.

CAVI measurement

CAVI was measured according to the methods described previously.^{1,2} Briefly, patients were placed in the supine position and their electrocardiogram and heart sounds were monitored. Pulse wave velocity was obtained by dividing

¹Department of Cardiology, Chugoku Workers Compensation Hospital, Kure, Japan; ²Department of Cardiovascular Medicine, Hiroshima General Hospital of West Japan Railway Company, Hiroshima, Japan and ³Department of Cardiovascular Medicine, Hiroshima University Hospital, Hiroshima, Japan
Correspondence: Dr A Sairaku, Department of Cardiovascular Medicine, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail: rjrgw059@ybb.ne.jp

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vascular length by the time taken for the pulse wave to propagate from the aortic valve to the ankle. Thereafter, blood pressure was measured at the brachial artery. CAVI was calculated by the following equation: $CAVI = a \{ (2\rho \times 1 / (SBP - DBP)) \times \{ \ln(SBP / DBP) \times PWV^2 \} \} + b$, where SBP is the systolic blood pressure, DBP is the diastolic blood pressure, ρ is the density of blood and a and b are constants. All measurements and calculations were made automatically using a VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan). CAVI was measured within 2 days after coronary revascularization in all patients, and at a 6-month follow-up in 18 patients with ACS and in 21 with SAP. A preliminary evaluation of CAVI without CAD was conducted in 30 patients who had an intact coronary artery demonstrated by coronary angiography.

Carotid IMT measurement

The carotid arteries were evaluated with high-resolution B-mode ultrasonography (HD11XE, PHILIPS, Tokyo, Japan).¹³ One longitudinal image of the common carotid artery and three longitudinal images of the internal carotid artery were acquired. The carotid intima-media thickness (IMT) was measured as the distance between the lumen-intima interface and the media-*adventitia* interface on the B-mode. Atherosclerotic lesions were defined as plaques when the thickness of the intima-media complex was ≥ 1.1 mm. The maximal IMT was used for analysis.

Echocardiography

Echocardiography was performed using B- and M-mode ultrasonography (SEQUOIA C256, SIEMENS, Tokyo, Japan). The left ventricular (LV) end-diastolic diameter, maximal left atrial diameter and end-diastolic thickness of the ventricular septum were measured. The LV end-diastolic and end-systolic volumes (EDV and ESV) were calculated from the apical two- and four-chamber views using a modified Simpson's method. Thereafter, the LV ejection fraction (LVEF) was calculated as $LVEF = (EDV - ESV) / EDV \times 100$.

Assessment of the severity of CAD

Coronary angiography was performed according to the standard methods before percutaneous coronary intervention or coronary artery bypass grafting. Significant stenosis was defined as narrowing of $\geq 75\%$ in any of the three major coronary branches or $\geq 50\%$ in the left main trunk artery. The severity of CAD was assessed on the basis of the number of stenotic coronary vessels. If there was stenosis in the left main trunk artery, we diagnosed it as two-vessel disease.

Coronary risk factors and laboratory parameters

We recorded the following traditional coronary risk factors: (1) diabetes mellitus (a fasting plasma glucose level ≥ 126 mg dl⁻¹ and hemoglobin A1c $\geq 6.5\%$, or the use of oral antidiabetic agents or insulin); (2) dyslipidemia (low-density lipoprotein-cholesterol ≥ 140 mg dl⁻¹ or high-density lipoprotein-cholesterol < 40 mg dl⁻¹ or triglyceride ≥ 150 mg dl⁻¹ or the use of lipid-lowering drugs); (3) hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or the use of antihypertensive agents); and (4) smoking history (previous or current cigarette smoking).

At baseline, the following measurements related to arteriosclerosis risk were evaluated: body mass index, estimated glomerular filtration rate,¹⁴ lipid profile, fasting plasma glucose level and hemoglobin A1c. In addition, C-reactive protein was measured on the day after the procedures. In ACS patients, the peak serum creatine kinase level was determined by measurements taken every 3 h after the procedures.

Statistical analysis

Statistical analyses were performed using JMP software version 5.1 (SAS Institute Japan, Tokyo). The clinical characteristics of the study subjects were presented using frequencies for categorical variables and means with s.d.'s for continuous variables. The differences between the two patient groups were examined using Pearson's χ^2 -tests for categorical variables or *t*-tests for continuous variables. Correlations between CAVI and other clinical parameters were assessed by Pearson's correlation test. Subsequently, significantly correlated variables were further analyzed using a multiple linear regression analysis to assess their independent relationship with CAVI. A multiple logistic regression

analysis was performed using the variables found to be significant in the univariate comparisons and age to assess whether there was a significant difference in CAVI between the two patient groups. For all analyses, a *P*-value of < 0.05 was considered statistically significant.

RESULTS

In ACS patients ($n=79$), there were 67 patients who had an ST-segment elevation myocardial infarction, four who had a non-ST segment elevation myocardial infarction and eight who had an unstable angina pectoris. The number of patients who underwent a coronary artery bypass grafting was 4 in ACS patients and 11 in SAP patients ($n=120$).

The prevalence of hypertension (54 vs. 83%; $P < 0.0001$), SBP (123 ± 19 vs. 134 ± 17 ; $P < 0.0001$), LVEF (55 ± 10 vs. 63 ± 13 ; $P < 0.0001$), IMT (2.1 ± 1.1 vs. 2.4 ± 0.9 ; $P = 0.022$) and triglyceride (110 ± 58 vs. 150 ± 99 ; $P = 0.0018$), as well as the frequency of the use

Table 1 Clinical characteristics of the subjects with ACS and SAP

	ACS	SAP	<i>P</i> -value
<i>n</i>	79	120	
Age (years)	69 \pm 1.2	72 \pm 1.0	0.13
Male	57 (72%)	81 (68%)	0.49
Systolic blood pressure (mm Hg)	123 \pm 19	134 \pm 17	< 0.0001
Diastolic blood pressure (mm Hg)	75 \pm 12	78 \pm 11	0.11
Body mass index (kg m ⁻²)	23.5 \pm 3.9	24.5 \pm 3.7	0.08
<i>Traditional coronary risk factors</i>			
Diabetes mellitus	33 (42%)	54 (45%)	0.41
Hypertension	43 (54%)	100 (83%)	< 0.0001
Dyslipidemia	42 (53%)	79 (66%)	0.063
Smoking	37 (47%)	56 (47%)	0.98
No. of coronary risk factors	1.8 \pm 0.9	2.1 \pm 1.0	0.056
No. of stenotic coronary vessels	1.4 \pm 0.7	1.6 \pm 0.7	0.067
Left ventricular ejection fraction (%)	55 \pm 10	63 \pm 13	< 0.0001
Inter ventricular septum thickness (mm)	10.4 \pm 2.1	10.7 \pm 1.7	0.24
Left atrium diameter (mm)	37.2 \pm 5.7	38.7 \pm 6.8	0.13
Intima media thickness (mm)	2.1 \pm 1.1	2.4 \pm 0.9	0.022
Cardio-ankle vascular index	10.0 \pm 1.7	9.3 \pm 1.3	0.0012
<i>Laboratory measurement</i>			
Triglyceride (mg dl ⁻¹)	110 \pm 58	150 \pm 99	0.0018
LDL-cholesterol (mg dl ⁻¹)	103 \pm 30	112 \pm 36	0.07
HDL-cholesterol (mg dl ⁻¹)	50 \pm 15	53 \pm 15	0.1
Fasting plasma glucose (mg dl ⁻¹)	134 \pm 45	125 \pm 45	0.17
Hemoglobin A1c (%)	6.2 \pm 1.5	6.2 \pm 1.4	0.86
Estimated glomerular filtration rate (mg dl ⁻¹ per min)	65 \pm 16	64 \pm 18	0.64
C-reactive protein (mg dl ⁻¹)	3.1 \pm 4.5	0.6 \pm 1.2	< 0.0001
Peak creatine kinase	2647 \pm 2261		
<i>Medications</i>			
Antihypertensive agents	36 (46%)	90 (75%)	< 0.0001
ACE inhibitors/ARBs	25 (32%)	47 (39%)	0.28
Calcium channel blockers	21 (27%)	58 (48%)	0.0019
Diuretics	5 (6%)	28 (23%)	0.0016
α/β blockers	6 (8%)	17 (14%)	0.16
Statins	8 (10%)	47 (39%)	< 0.0001
Oral antidiabetic agents/insulin	14 (18%)	24 (20%)	0.69

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAP, stable angina pectoris.

of antihypertensive agents (46 vs.75%; $P < 0.0001$) and that of statins (10 vs.39%; $P < 0.0001$), was significantly lower in ACS patients than in SAP patients. Meanwhile, CAVI (10.0 ± 1.7 vs. 9.3 ± 1.3 ; $P = 0.0012$) and C-reactive protein (3.1 ± 4.5 vs. 0.6 ± 1.2 ; $P < 0.0001$) were significantly higher in ACS patients as compared with SAP patients (Table 1).

According to the preliminary evaluation of CAVI in the 30 subjects without CAD (age 67 ± 11 years, 20 men, 12 (40%) had hypertension, 5 (17%) diabetes, 4 (13%) dyslipidemia and 6 (20%) were current smokers), CAVI was significantly lower than that in patients with ACS or SAP (8.6 ± 1.8 vs. ACS; $P < 0.0001$ vs. SAP; $P = 0.0002$).

In the univariate analysis, hypertension ($r = 0.36$; $P = 0.0016$), smoking ($r = 0.23$; $P = 0.048$), IMT ($r = 0.36$; $P = 0.0031$), estimated glomerular filtration rate ($r = 0.45$; $P < 0.0001$) and antihypertensive agents ($r = 0.29$; $P = 0.012$) were significantly correlated with CAVI in ACS patients, and body mass index ($r = 0.3$; $P = 0.0014$) was a significant correlate in SAP patients. Age was the only factor that was significantly related to CAVI in the univariate and multivariate linear regression analyses in both patient groups ($r = 0.66$; $P < 0.0001$, $\beta = 0.56$; $P < 0.0001$ in ACS patients, $r = 0.31$; $P = 0.0007$, $\beta = 0.23$; $P = 0.013$ in SAP patients). In all patients, ACS emerged as an independent determinant of CAVI ($\beta = 0.3$; $P < 0.0001$), as well as

age ($\beta = 0.44$; $P < 0.0001$). In ACS patients, there was no significant correlation between CAVI and LVEF ($r = 0.12$; $P = 0.32$) or peak serum creatine kinase level ($r = 0.13$; $P = 0.26$) (Table 2).

A multiple regression analysis revealed that ACS patients had a significantly higher CAVI as compared with SAP patients (odds ratio 1.92, 95% confidence interval 1.30–3.02; $P = 0.0023$) after an adjustment for age, hypertension, SBP, IMT, LVEF, triglyceride, C-reactive protein, antihypertensive agents and statins (Figure 1).

The CAVI measured at the 6-month follow-up was significantly decreased compared with that measured within 2 days after coronary revascularization in 18 patients with ACS (10.9 ± 1.6 vs. 10.0 ± 1.5 ; $P = 0.019$; mean follow-up period 200 ± 33 days), although their hemodynamic status and medications prescribed remained unchanged. In contrast, in 21 patients with SAP who were followed up, CAVI was significantly increased in the chronic phase as compared with the acute phase (9.2 ± 1.4 vs. 9.9 ± 1.3 ; $P = 0.022$; mean follow-up period 220 ± 44 days).

DISCUSSION

This study demonstrated that CAVI was significantly higher in patients with ACS as compared with those with SAP. We also found that the CAVI of patients with ACS in the acute phase significantly decreased in

Table 2 Correlations between the CAVI and clinical parameters

	ACS (n=79)				SAP (n=120)				ACS+SAP (n=199)			
	Univariate		Multivariate ^a		Univariate		Multivariate ^b		Univariate		Multivariate ^c	
	r	P-value	β	P-value	r	P-value	β	P-value	r	P-value	β	P-value
Age	0.66	<0.0001	0.56	<0.0001	0.31	0.0007	0.23	0.013	0.47	<0.0001	0.44	<0.0001
Male	0.18	0.12			0.18	0.052			0.024	0.75		
Acute coronary syndrome									0.23	0.0011	0.3	<0.0001
Systolic blood pressure	0.19	0.095			0.037	0.15			0.037	0.61		
Diastolic blood pressure	0.11	0.36			0.11	0.25			0.072	0.33		
Body mass index	0.064	0.59			0.3	0.0014	-0.22	0.018	0.21	0.004	-0.045	0.55
Diabetes mellitus	0.11	0.35			0.11	0.24			0.098	0.18		
Hypertension	0.36	0.0016	0.25	0.036	0.14	0.14			0.048	0.51		
Dyslipidemia	0.18	0.13			0.057	0.54			0.13	0.075		
Smoking	0.23	0.048	0.18	0.09	0.049	0.61			0.065	0.38		
No. of coronary risk factors	0.026	0.82			0.016	0.87			0.013	0.86		
No. of stenotic coronary vessels	0.094	0.42			0.025	0.79			0.0014	0.98		
Left ventricular ejection fraction	0.12	0.32			0.017	0.85			0.13	0.07		
Inter-ventricular septum thickness	0.0096	0.94			0.12	0.23			0.07	0.37		
Left atrium diameter	0.16	0.21			0.076	0.46			0.13	0.11		
Intima-media thickness	0.36	0.0031	0.093	0.35	0.13	0.22			0.19	0.014	0.11	0.12
Triglyceride	0.15	0.21			0.11	0.25			0.16	0.029	0.072	0.35
LDL-cholesterol	0.12	0.3			0.069	0.47			0.11	0.14		
HDL-cholesterol	0.19	0.11			0.069	0.47			0.095	0.2		
Fasting plasma glucose	0.13	0.27			0.098	0.3			0.13	0.75		
Hemoglobin A1c	0.18	0.15			0.077	0.47			0.12	0.12		
Estimated glomerular filtration rate	0.45	<0.0001	-0.17	0.15	0.076	0.42			0.22	0.0019	-0.0042	0.96
C-reactive protein	0.052	0.7			0.036	0.7			0.079	0.31		
Peak serum creatine kinase	0.13	0.26										
Antihypertensive agents	0.29	0.012	0.012	0.92	0.077	0.41			0.031	0.67		
Statins	0.045	0.7			0.019	0.84			0.07	0.34		
Oral antidiabetics/insulin	0.078	0.51			0.1	0.27			0.082	0.26		

Abbreviations: ACS, acute coronary syndrome; CAVI, cardio-ankle vascular index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; r, Pearson's correlation coefficient; SAP, stable angina pectoris; β , standardized coefficient.

^aAdjusted $R^2 = 0.47$.

^bAdjusted $R^2 = 0.12$.

^cAdjusted $R^2 = 0.25$.

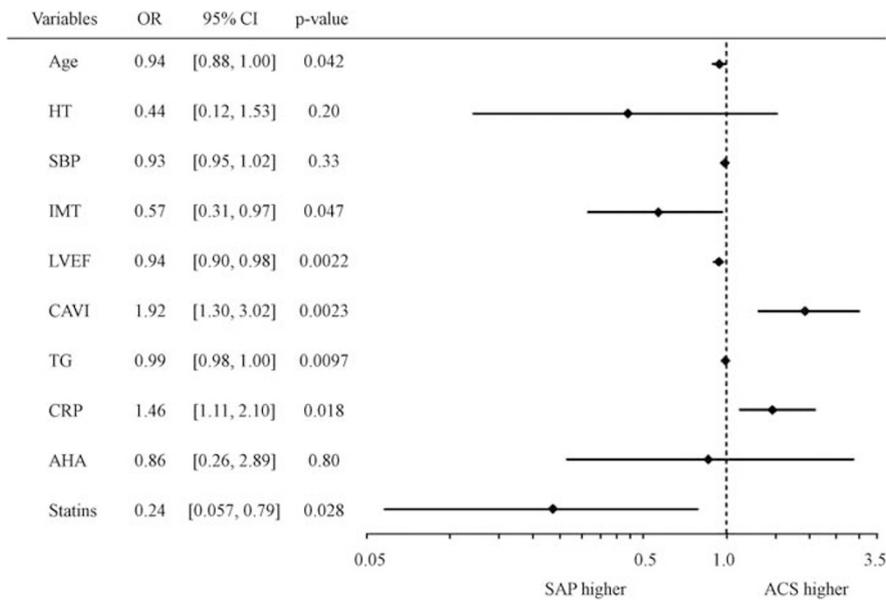


Figure 1 Multivariate odds ratio estimates of the clinical predictors of ACS vs. SAP. AHA, antihypertensive agent; CAVI, cardio-ankle vascular index; CRP, C-reactive protein; HT, hypertension; IMT, intima-media thickness; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TG, triglyceride.

the chronic phase. This result may suggest a transient increase in CAVI caused by acute myocardial ischemia. The possible mechanisms of the transient increase in CAVI were assumed to be as follows: (1) It is reported that severe myocardial ischemia induces LV diastolic dysfunction ahead of LV systolic dysfunction.^{15,16} LV diastolic dysfunction is associated with an increased CAVI.^{7,17-19} Thus, the ACS patients, who would have an abrupt and severe myocardial ischemia, could have a higher CAVI than SAP patients. (2) Systemic acute inflammation and an elevated level of interleukin-18 are strongly associated with increased arterial stiffness.^{20,21} Therefore, as the level of interleukin-18 is higher in ACS patients than in SAP patients,²² arterial stiffness could be increased in ACS patients compared with SAP patients. (3) The nitric oxide synthase inhibitor, asymmetric dimethylarginine, increases the arterial stiffness.²³ Thus, because the level of asymmetric dimethylarginine in patients with unstable angina pectoris is significantly higher than that in patients with SAP,²⁴ arterial stiffness could be increased more in ACS patients than in SAP patients. These factors associated with acute myocardial ischemia may solely and/or multifactorially contribute to the increase in CAVI in ACS patients.

CAVI, an arterial stiffness parameter, is known to increase parallel to the progression of the carotid arterial thickness.³⁻⁶ However, despite having a lower IMT, ACS patients had a rather higher CAVI compared with SAP patients. This discrepancy may be explained by the transient increase in CAVI observed in ACS patients. That is, as a reflection of the cardiovascular condition in the acute phase of an abrupt episode of myocardial ischemia, CAVI may increase as we have demonstrated, whereas IMT would not to be affected by the transient change in the cardiovascular condition. This difference in response to the transient change in the cardiovascular condition may be related in part to the fact that CAVI is a physiological parameter, whereas IMT is a morphological one.

We observed more variables with a significant correlation to CAVI in the univariate analysis in ACS patients than in SAP patients, and among those variables, age was the only variable that was associated with CAVI in both patient groups. Furthermore, as many studies have

reported,^{3-6,17} it was the strongest predictor variable of CAVI in the multivariate linear regression analysis in both patient groups. The result that ACS was another strong independent determinant of CAVI in the entire study group highlights the significant increase in CAVI in ACS patients as compared with SAP patients.

In ACS patients, there was no correlation between CAVI and LVEF, which may support the results of the previous studies that were conducted on subjects with a normal LV systolic function.^{18,19} Furthermore, CAVI was not associated with the peak creatine kinase level in ACS patients. These results may suggest that CAVI would not be directly affected by the myocardial infarct size.

Several studies have shown that statins, pioglitazone and antihypertensive agents, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and calcium channel blockers, decrease the arterial stiffness assessed by CAVI.²⁵⁻²⁸ However, although the frequency of use of these medications differed in the two groups in this study, no significant correlation between CAVI and the frequency of use of these medications was observed in the entire study group. Possible explanations for this result are that (1) as the majority of our study subjects were taking at least one of these medications, the interindividual variability of the effect of those medications on CAVI might have been small, (2) this study differed from previous studies²⁵⁻²⁸ in that all our study subjects had significant CAD and several coronary risk factors, which might have resulted in an even smaller favorable effect on arterial stiffness with such medications in this study as compared with previous studies.

Our study had several limitations. First, it was a single-center study with a small number of patients, and furthermore, the number of patients who underwent a follow-up measurement of CAVI was even smaller. Second, we did not enroll any patients with any peripheral artery disease with an ankle-brachial pressure index of <0.9, because the CAVI in those patients was reported to show inaccurate data.² Third, the prognosis of patients with a transient increase in CAVI was not shown in this study.

Despite these limitations, to the best of our knowledge, this is the first study on CAVI in ACS patients. In addition, our finding of a

transient increase in CAVI observed in the patient with ACS provided new insight into the pathological vascular condition of acute myocardial ischemia. As several investigators have reported, an increased arterial stiffness is an independent predictor of cardiovascular events and mortality in subjects with coronary risk factors.^{8–11} Therefore, patients with a transient increase in arterial stiffness caused by acute myocardial ischemia should be followed up with extreme caution. To establish the clinical importance of measuring CAVI in ACS patients, large-scale prospective studies on the relationship between CAVI and prognosis in patients who have experienced ACS would be required.

In conclusion, CAVI was significantly higher in patients with ACS than in those with SAP independent of any other parameters related to arteriosclerosis, which might result from the transient increase in CAVI caused by acute myocardial ischemia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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