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ORIGINAL ARTICLE

Correlation of Arterial Stiffness With Left Atrial Volume Index and Left Ventricular Mass Index in Young Adults: Evaluation by Coronary Computed Tomography Angiography

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Background Increased arterial stiffness is reportedly associated with cardiac remodelling, including the left atrium and left ventricle, in middle-aged and older adults. However, little is known about this association in young adults.

Methods In total, 73 patients (44 (60%) men) aged 25 to 45 years with suspected coronary artery disease were included in the analysis. The left atrial volume index (LAVI), left ventricular volume index (LVVI), and left ventricular mass index (LVMI) were measured using coronary computed tomography angiography (CCTA). Arterial stiffness was assessed with the cardio-ankle vascular index (CAVI). An abnormally high CAVI was defined as that above the age- and sex-specific cut-off points of the CAVI.

Results Compared with patients with a normal CAVI, those with an abnormally high CAVI were older and had a greater prevalence of diabetes mellitus, higher diastolic blood pressure, greater coronary artery calcification score, and a greater LAVI (33.5 ± 10.3 vs. 43.0 ± 10.3 mL/m^2, $p < 0.01$). In contrast, there were no significant differences in the LVVI or LVMI between the subgroups with a normal CAVI and an abnormally high CAVI. Multivariate linear regression analysis showed that the LAVI was significantly associated with an abnormally high CAVI (standardised regression coefficient = 0.283, p = 0.03).

Conclusions The present study demonstrated that increased arterial stiffness is associated with the LAVI, which reflects the early stages of cardiac remodelling, independent of various comorbidity factors in young adults with suspected coronary artery disease.

Keywords Cardio-ankle vascular index (CAVI) • Left atrial volume index (LAVI) • Left ventricular volume index (LVVI) • Left ventricular mass index (LVMI) • Coronary computed tomography angiography (CCTA)

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Introduction

The cardio-ankle vascular index (CAVI) is an index of the overall stiffness of the artery from the origin of the aorta to the ankle. It is independent of blood pressure at the time of measurement [1]. The CAVI is also a surrogate marker of atherosclerotic disease [2–4]. Previous studies have shown that the CAVI has a close association with left ventricular (LV) diastolic function [2,5–7]. Arterial stiffening and subsequent increased stiffness or noncompliance of the left ventricle following LV diastolic dysfunction is associated with left atrial (LA) enlargement [8,9] and increased LV mass [10]. In clinical practice, measurements of LA volume and LV mass are effective methods for identifying high-risk individuals because they are established markers of the risk of cardiovascular outcomes [11–17]. Thus, the CAVI is a promising risk predictor of cardiac structural remodelling and cardiovascular risk. Despite the advantages of the CAVI, whether this index is associated with cardiac structural remodelling parameters in young adults remains unclear. We hypothesised that the CAVI has an impact on cardiac structural remodelling, such as LA enlargement and increased LV mass, in young adults with suspected coronary artery disease (CAD). Exposing people to excess radiation for study purposes is not permitted. Therefore, in the present study, we evaluated this association only in subjects in whom measurement of the cardiac structural volume was performed for CAD screening.

Methods

Study Population

The initial surveyed population comprised 85 consecutive young patients aged 25 to 45 years with suspected CAD. All patients presented with angina and underwent coronary computed tomography angiography (CCTA) and measurement of the CAVI for suspected CAD at Los Angeles Biomedical Research Institute at Harbor UCLA (Torrance, CA, USA) or Okayama University Hospital (Okayama, Japan) from March 2012 to October 2017. Patients were excluded if they had a history of CAD (n = 2), significant coronary artery stenosis evaluated with CCTA (n = 1), persistent atrial fibrillation (n = 3), known significant valvular disease (n = 2), or insufficient CCTA image quality (n = 4). In total, 73 patients were included in the analysis. This study was approved by the ethics committees of Los Angeles Biomedical Research Institute and Okayama University Hospital. This study was conducted according to the principles expressed in the Declaration of Helsinki. All patients gave written informed consent before taking part in the study.

Computed Tomography Imaging Acquisition Protocol

Computed tomography (CT) scans were performed with a 64-slice CT scanner (Lightspeed VCT; General Electric Healthcare Technologies, Milwaukee, WI, USA), a 256-slice CT scanner (Revolution CT; General Electric Healthcare Technologies), and SOMATOM Definition Flash instrument (Siemens Medical Solutions, Erlangen, Germany). All patients with a heart rate of >65 beats per minute received beta blockers. Sublingual nitroglycerine or nitroglycerine spray (0.4 mg) was administered prior to the scan. A test CT acquisition was performed at the level of the ascending aorta after administration of 10 to 15 mL of contrast medium (Omnipaque 350; General Electric Healthcare Technologies) followed by 20 mL of normal saline. The delay before the formal scan was calculated as the time to peak enhancement in the ascending aorta plus 5 seconds. Electrocardiography (ECG)-gated CCTA was performed beginning with 20 to 25 mL of intravenous contrast medium injected at 5.5 to 5.7 mL/s, followed by 60 mL of contrast medium at 5.4 mL/s, followed by 35 to 40 mL of contrast medium diluted to 50% at 5.5 mL/s, and finally a 35- to 40-mL chaser bolus of saline at 5.0 mL/s. During ECG-gated CCTA, the centre of the imaging window was set at 75% of the R–R interval. If the heart rate was unstable, retrospective ECG-gated CCTA was performed.

LA Volume, LV Volume, and LV Mass Analysis

Quantitative data analyses were performed using automated methods on a workstation and software (AW 4.6; GE Medical Systems, Waukesha, WI, USA) that used a Hounsfield unit-based endocardial border detection technique. Images were reconstructed with a 1.25 mm slice thickness. The mid-diastolic phases were chosen for measurements of LA and LV volume and LV mass. The LA appendage and pulmonary veins were not included in the LA volume measurement. Left ventricular mass was also simultaneously calculated automatically. After adjustment for the body surface area, the LA volume index (LAVI), LV volume index (LVVI), and LV mass index (LVMI) were estimated using the DuBois formula [18].

CAVI Measurement

The CAVI was measured the same day of the CCTA using a VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan) with the patients in the supine position after 5 minutes of rest. The protocol was the same as described previously [2]. The mean of the right and left CAVI values were used for analysis. Blood pressure (systolic and diastolic in mmHg) and ECG were simultaneously recorded. An abnormally high CAVI was defined as that above the age- and sex-specific cut-off points of the CAVI [19]. The cut-off CAVI scores were 7.39 for 25- to 29-year-old men, 7.80 for 30- to 39-year-old men, 8.29 for 40- to 45-year-old men, 7.23 for 25- to 29-year-old women, 7.42 for 30- to 39-year-old women, and 7.95 for 40- to 45-year-old women.

Statistical Analysis

Data are presented as mean ± standard deviation. Categorical variables are expressed as n (%). Differences between any two groups were evaluated using Pearson's χ^2 test for categorical variables and Student's *t*-test for continuous variables. Relationships between variables were tested by Pearson and Spearman correlations. Factors independently associated with the CAVI were assessed using a multivariate linear regression analysis. Multivariate linear regression analysis was performed to evaluate the relationships among an abnormally high CAVI, LAVI, LVVI, and LVMI with adjustments for age; sex; hypertension; dyslipidaemia; diabetes mellitus; body mass index; use of anti-hypertensive agents, lipid-lowering agents, and hypoglycaemic agents; and systolic blood pressure. All statistical analyses were performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was defined as a p value of <0.05 (two-sided).

Results

In our study of 73 patients, 29 (40%) were Hispanic, 12 (16%) were Caucasian, 29 (40%) were Asian, and 3 (4%) were African-American. The patients' clinical characteristics are shown in Table 1. Of the 73 patients (age range, 25–45 years), 44 (60%) were men, 12 (16%) had hypertension, 18 (25%) had dyslipidaemia, and 20 (27%) had diabetes mellitus. The mean LAVI, LVVI, and LVMI were 35.2 ± 10.9 mL/m^2, 67.9 ± 11.7 mL/m^2, and 53.2 ± 9.6 g/m^2, respectively. The mean CAVI and ankle-brachial index (ABI) were 6.77 ± 1.27 and 1.14 ± 0.09, respectively. All patients had an ABI of >0.90. The number of patients with an abnormally high CAVI was 13 (18%). The dose–length product for cardiac CT examination was 162.1 ± 109.2 mGy-cm. Univariate and multivariate analyses were performed using clinical variables to assess the factors determining the CAVI. The univariate analysis showed that the CAVI was significantly correlated with age, diabetes mellitus, current smoking, and systolic blood pressure (Table 2). The multiple linear regression analysis demonstrated that the CAVI was independently associated with age, diabetes mellitus, and systolic blood pressure (Table 2). When patients were divided into normal CAVI and abnormally high CAVI groups, patients in the latter group were older and had a greater prevalence of diabetes mellitus, higher diastolic blood pressure, and greater coronary artery calcification score. With respect to CCTA parameters, patients with an abnormally high CAVI had a significantly greater LAVI than patients with a normal CAVI (43.0 ± 10.3 vs. 33.5 ± 10.3 mL/m^2, $p < 0.01$) (Figure 1). In contrast, there were no significant differences in the LVVI or LVMI between the abnormally high CAVI group and the normal CAVI group (68.5 ± 11.6 vs. 65.1 ± 12.3 mL/m^2, $p = 0.35$ and 52.3 ± 9.6 vs. 57.5 ± 8.9 g/m^2, $p = 0.08$, respectively) (Figure 1). The CAVI was moderately correlated with the LAVI ($r = 0.439$, $p < 0.01$) but not with the LVVI ($r = -0.128$, $p = 0.28$) or LVMI ($r = 0.188$, $p = 0.11$) (Figure 2). After adjustment for age; sex; hypertension; dyslipidaemia; diabetes mellitus; use of anti-hypertensive agents, lipid-lowering agents, and hypoglycaemic agents; and systolic blood pressure, the multivariate linear regression analysis showed that an abnormally high CAVI was independently associated with the LAVI (standardised regression coefficient = 0.283, $p = 0.03$). No associations between the LVVI or LVMI and an abnormally high CAVI were found (Table 3).

Table 1 **Patient characteristics.**

	All (n = 73)	Normal CAVI (n = 60)	Abnormally high CAVI (n = 13)	P-value
Age (years)	35 ± 5	34 ± 5	38 ± 5	0.02
Men, n (%)	44 (60)	35 (58)	9 (69)	0.47
Hypertension, n (%)	12 (16)	9 (15)	3 (23)	0.48
Dyslipidaemia, n (%)	18 (25)	15 (25)	3 (23)	0.88
Diabetes mellitus, n (%)	20 (27)	12 (20)	8 (61)	< 0.01
Current smoking, n (%)	10 (14)	10 (17)	0 (0)	0.11
Body mass index (kg/m^2)	28 ± 6	28 ± 6	27 ± 6	0.31
Systolic blood pressure (mmHg)	120 ± 12	119 ± 12	124 ± 6	0.18
Diastolic blood pressure (mmHg)	75 ± 11	73 ± 10	84 ± 8	<0.01
Heart rate (beats per minute)	64 ± 9	64 ± 9	64 ± 11	0.77
CAC score	0 [0,0]	0 [0,0]	0 [0,105]	0.03
ABI	1.14 ± 0.09	1.13 ± 0.09	1.18 ± 0.09	0.08
CAVI	6.77 ± 1.27	6.34 ± 0.86	8.73 ± 0.96	<0.01
Medication				
Anti-hypertension agents, n (%)	9 (12)	6 (10)	3 (23)	0.19
Lipid lowering agents, n (%)	9 (12)	8 (13)	1 (18)	0.58
Hypoglycaemic agents, n (%)	14 (19)	8 (13)	6 (46)	<0.01

All comparisons between the normal and abnormally high CAVI groups were performed using Pearson's χ^2 test or Student's *t*-test.
Abbreviations: CAC, coronary artery calcification; ABI, ankle-brachial index; CAVI, cardio-ankle vascular index.

Table 2 Correlations between clinical parameters and cardio-ankle vascular index.

	Univariate		Multivariate	
	r	P-value	β	P-value
Age	0.466	< 0.001	0.326	0.005
Male sex	0.101	0.397	0.105	0.295
Hypertension	0.076	0.522	-0.078	0.462
Dyslipidaemia	0.041	0.733	-0.067	0.530
Diabetes mellitus	0.375	0.001	0.253	0.024
Current smoking	0.233	0.047	-0.139	0.185
Systolic blood pressure	0.389	0.001	0.219	0.049

Abbreviation: β, standardised regression coefficient

Discussion

The results of the present study show that an abnormally high CAVI is associated with the LAVI, which reflects the early stages of cardiac remodelling, independent of various comorbidity factors in young adults with suspected CAD. Early detection of increased arterial stiffness using the CAVI may be important for prevention of cardiovascular disease. The current study is partially unique because we examined a population of young adults (age of 25–45 years); the cross-sectional association of atrial stiffness and cardiac structure remodelling has not been well studied in these individuals.

Limited investigations have been performed to examine the longitudinal observational relationship between cardiac structure remodelling and factors associated with a high risk of cardiovascular disease among young individuals [20,21]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study among adults aged 18 to 30 years over a 20-year follow-up, African-American men and glycaemic abnormalities were found to be strongly associated with impaired LV function [20,21]. Vascular stiffening of the large arteries is a common feature of ageing [22], which is accelerated by atherosclerotic risk factors such as hypertension and diabetes [23,24] and results in an augmented cardiac afterload [25]. The increased cardiac afterload results in impaired LV relaxation and increased LV filling pressure. Given the cross-sectional observational nature of the current study, we did not show associations between a high CAVI and abnormal LVVI or LVMI; such associations could be affected by long-term exposure to these cardiovascular risk factors. In the present study, a moderate correlation was found between the LAVI and a high CAVI. With worsening LV compliance, LA pressure increases to maintain adequate LV filling pressure, which results in LA enlargement. LA size may increase

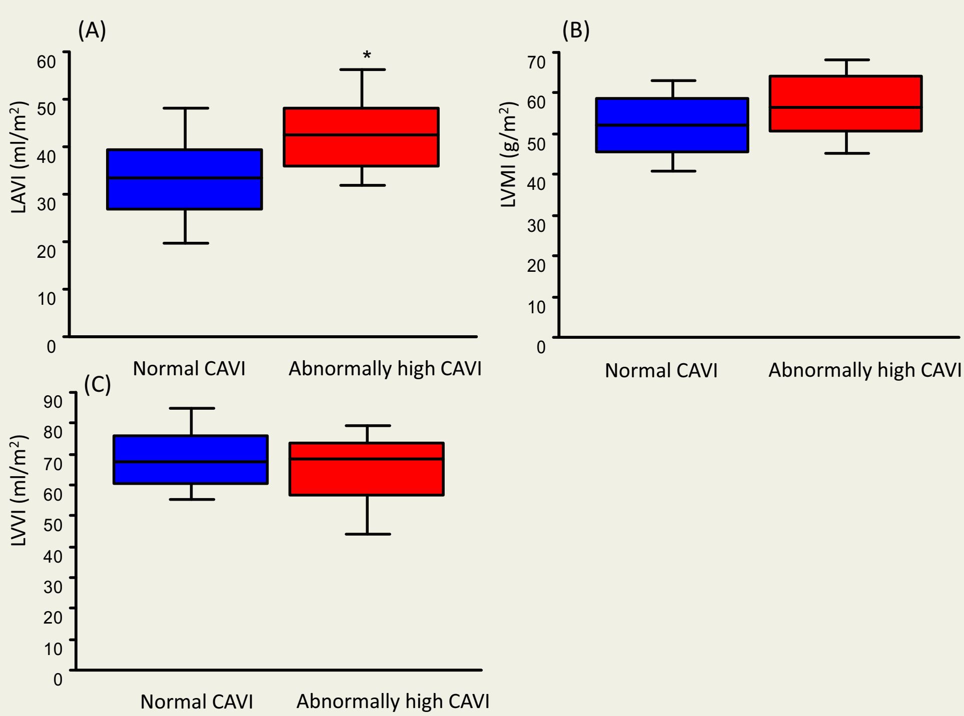

Figure 1 Box plots representing the estimated (A) LAVI, (B) LVMI, and (C) LVVI. In all plots, the top and bottom of the box represent the 75th and 25th percentiles, respectively, and the line in the box represents the median value. The upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. The p value was obtained from one-way analysis of variance. *$p < 0.05$ vs. those with a normal CAVI.
Abbreviations: CAVI, cardio-ankle vascular index; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVVI, left ventricular volume index.

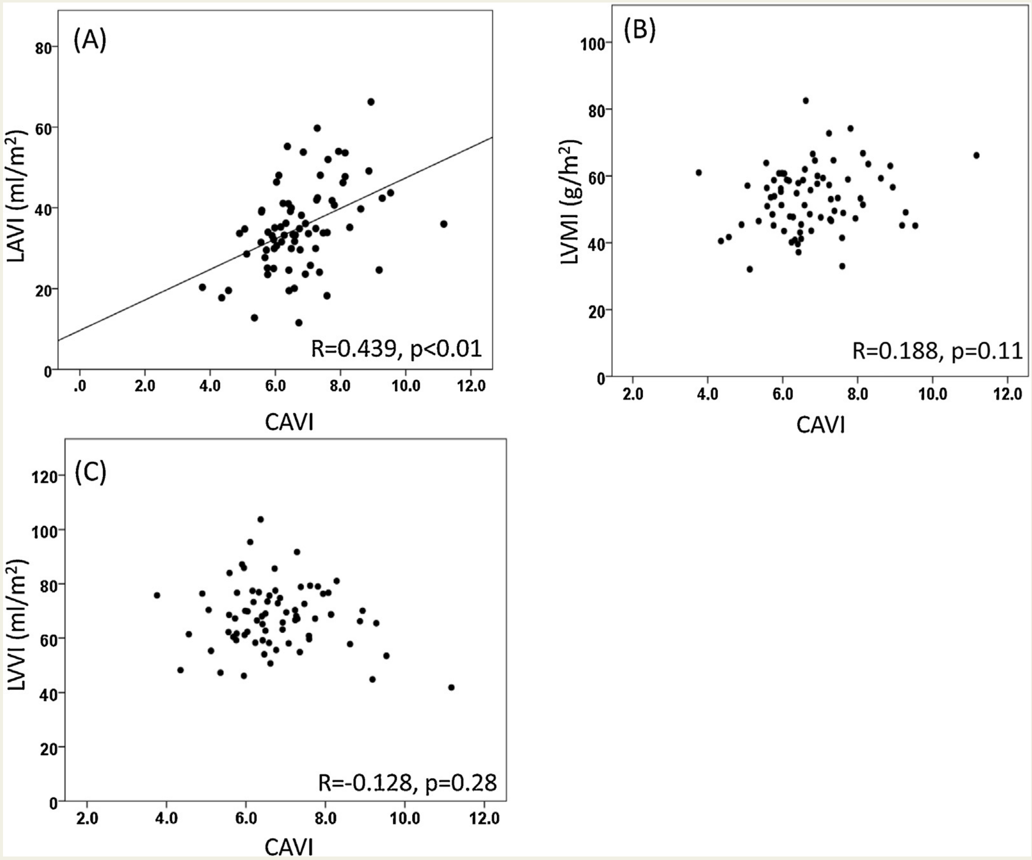

Figure 2 Correlation of the CAVI with the (A) LAVI, (B) LVMI, and (C) LVVI.
Abbreviations: CAVI, cardio-ankle vascular index; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVVI, left ventricular volume index.

Table 3 Univariate and multivariate linear regression of LAVI, LVMI, and LVVI on CAVI for young adults.

	LAVI				LVMI				LVVI			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	r	p value	β	p value	r	p value	β	p value	r	p value	β	p value
Age	0.248	0.034	0.103	0.416	0.070	0.555	-0.012	0.923	0.009	0.939	0.066	0.627
Male sex	0.058	0.628	-0.084	0.473	0.252	0.032	0.255	0.034	0.088	0.458	0.070	0.573
Hypertension	0.052	0.665	-0.107	0.509	0.063	0.596	0.102	0.532	0.139	0.239	-0.162	0.350
Dyslipidaemia	0.045	0.708	-0.081	0.589	0.229	0.051	-0.140	0.352	0.103	0.387	-0.012	0.938
Diabetes mellitus	0.137	0.247	0.006	0.977	0.165	0.164	-0.260	0.192	0.296	0.011	-0.144	0.494
Systolic blood pressure	0.388	0.001	0.315	0.011	0.193	0.102	0.216	0.079	0.132	0.266	0.170	0.191
Abnormally high CAVI	0.336	0.004	0.283	0.028	0.209	0.077	0.218	0.091	0.110	0.353	-0.044	0.741
Medication												
Antihypertensive agents	0.042	0.724	-0.009	0.956	0.110	0.354	0.036	0.835	0.034	0.778	0.081	0.657
Lipid-lowering agent	0.013	0.911	0.086	0.587	0.140	0.236	-0.103	0.518	0.001	0.990	0.047	0.780
Hypoglycaemic agents	0.095	0.425	-0.020	0.919	0.159	0.179	0.25	0.896	0.309	0.008	-0.914	0.343

Abbreviations: β, standardised regression coefficient; CAVI, cardio-ankle vascular index; LAVI, left atrial volume index; LVVI, left ventricular volume index; LVMI, left ventricular mass index.

much more than LV volume and LV mass because the left atrium is a thin-walled structure [26].

Coronary computed tomography angiography can be used to evaluate cardiac chamber sizes. Walker et al. [27] recently reported the normal values of cardiac chamber volumes in the mid-diastolic phase, which usually provides the best image quality of the coronary arteries at slow and regular heart rates. In their analysis, the normal values for the chamber volume index in the mid-diastolic phase were 20.8 to 49.8 mL/m^2 for LA volume, 44.5 to 87.6 mL/m^2 for LV volume, and 35.8 to 82.1 g/m^2 for LV mass. In our population, the mean value of the LAVI, LVVI, and LVMI corresponded to these normal ranges. In contrast, the LAVI only in the patients with an abnormally high CAVI (43.0 mL/m^2) was relatively higher of normal range, suggesting a high risk of heart failure. Few investigations have addressed the association between cardiac size measured by CT and cardiovascular events [28]. Further studies are warranted to confirm the clinical implication of the cardiac volume evaluated by CCTA.

Patients in the abnormally high CAVI group had more cardiovascular risk factors such as diabetes or high coronary artery calcification. Although glycaemic abnormality itself is known to be associated with impaired LV function [20] as well as impaired LA function and LA enlargement in young adulthood [29], high glucose exposure potentially results in systemic advanced atherosclerosis and subsequently impaired atrial stiffness [30]. The progression of atherosclerotic changes in large vessels could result in a large increase in arterial stiffness and afterload, reflecting cardiac structural changes.

Our study has several limitations. First, this study was conducted at only two institutions with a small number of patients. Even after exclusion of CAD, patients included in our study had more risk factors for cardiovascular disease, such as hypertension, dyslipidaemia, and diabetes, than did the general young population; thus, the results cannot be applied to young adults in general. Second, all analyses were cross-sectional, which complicates the casual interpretation of observed associations. Third, radiation exposure in this study was relatively low, but application of CT to younger adults should be limited. Finally, this study did not collect data on the patients' history of exercise, which could affect LA volume [31] and LV mass [32].

In conclusion, the present study demonstrated that an abnormally high CAVI was significantly associated with an increased LAVI as detected by CCTA in young adults with suspected CAD. Measurement of the CAVI is easy to perform and may be informative for identifying young adults who are at high risk of heart failure.

Conflicts of Interest

This study was funded by Fukuda Denshi, Co Ltd.

Matthew J. Budoff has received research funds from N.I.H. and GE Healthcare.

The other authors have no conflict of interest.

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