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CLINICAL INVESTIGATIONS

The relationship between cardio-ankle vascular index and subclinical atherosclerosis evaluated by cardiac computed tomographic angiography

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Background: The cardio-ankle vascular index (CAVI) is a new noninvasive index to evaluate arterial stiffness. We investigated whether CAVI can predict severity, extent, and burden of coronary artery disease by comparing results with cardiac computed tomographic angiography (CCTA).

Hypothesis: CAVI may predict the presence of subclinical atherosclerosis.

Methods: We prospectively enrolled 95 patients (66% male; mean age, 50 ± 16 years) who underwent both CCTA and CAVI consecutively. We evaluated if CAVI correlated with (1) severe stenosis (≥50%); (2) plaque extent, determined by a segment-involvement score (SIS), defined by the total number of coronary artery segments containing any plaque; and (3) plaque burden, determined by a segment-stenosis score (SSS), defined by the extent of obstruction of coronary luminal diameter in individual coronary artery segments.

Results: Bivariate analysis showed a statistically significant relationship not only between CAVI and SIS, but also between CAVI and SSS (r^2 = 0.4, P < 0.0001 for SIS; r^2 = 0.36, P < 0.0001 for SSS). Multivariable logistic analysis demonstrated that CAVI is significantly associated with SSS >5 (odds ratio [OR]: 2.3, 95% confidence interval [CI]: 1.1-7.8, P = 0.03) and SIS >5 (OR: 2.3, 95% CI: 1.1-5.8, P = 0.02), but not severe stenosis (OR: 1.7, 95% CI: 0.9-4.3, P = 0.13), after adjusting for age, sex, chest pain, hypertension, dyslipidemia, family history, diabetes, and current smoking.

Conclusions: We demonstrated that CAVI had a significant relationship with subclinical coronary atherosclerosis evaluated by CCTA, especially in relation to plaque burden and plaque extent, but not severe stenosis. Thus, CAVI may reflect coronary atherosclerosis burden more than severity.

KEYWORDS

cardio-ankle vascular index, subclinical atherosclerosis, cardiac computed tomography angiopgaphy

1 | INTRODUCTION

In 2010, nearly 800 000 Americans died of cardiovascular, cerebrovascular, and renal disease.[1] Therefore, it is very important to detect these high-risk patients in their subclinical status.

Changes in vascular integrity and properties are implicated in the pathogenesis of these diseases. Data from the Framingham cohort have shown that arterial stiffness correlates with the first cardiovascular event.[2] There are several methods to evaluate arterial stiffness, with cardio-ankle vascular index (CAVI) being one such method. Previous studies have indicated that CAVI has a significant relationship with atherosclerosis. Specifically, studies that compared CAVI with invasive coronary artery angiography or cardiac computed tomography angiography (CCTA) indicated a significant relationship between CAVI and

coronary artery disease (CAD).[3,4] Although CAVI has been extensively studied and recognized as a tool to predict cardiovascular risk, most studies have been conducted in Asian countries.[3–9] This is a pilot study to investigate whether CAVI can predict severity, extent, and burden of CAD by comparing results with CCTA in a US population.

2 | METHODS

2.1 | Patients

Eligible participants were age 18 to 80 years and presented to obtain a CCTA for clinical reasons at the outpatient center of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Torrance, CA). From April 2014 to March 2015, 106 consecutive patients were prospectively recruited, with each patient obtaining his or her CAVI measurements before the CCTA. Patients with a history of CAD and/or peripheral arterial disease (ankle-brachial arterial index of <0.9) were excluded. As a result, we enrolled 95 patients (66% male; mean age, 50 ± 16 years) for this study. The racial composition was as follows: White, 33 (34.7%); Hispanic, 29 (30.5%); Asian, 11 (11.5%); African American, 9 (9.4%); Asian Indian, 2 (2.1%); American Indian, 1 (1%); Hawaiian, 1 (1%); and other, 9 (9.4%). The investigational review board of the Los Angeles Biomedical Research Institute approved this research project. All subjects signed an informed written consent after receiving a careful explanation and review of the protocol.

2.2 | Measurement of CAVI

The CAVI readings were measured on the same day of the CCTA scan using the VaSera VS-1500 AU vascular screening system (Fukuda Denshi, Tokyo, Japan). Methods were previously described in detail.[7] Briefly stated, specialized blood pressure cuffs were applied bilaterally to the patient's upper arms and ankles, with the subject lying supine and the head maintained in the midline position. The examination was performed after a 10-minute supine rest period. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure from 30 to 50 mm Hg was applied to minimize the effect of cuff pressure on hemodynamics at the measurement site. The cuff was then deflated to complete the measurement. The formula for CAVI is:

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

where Ps and Pd are systolic blood pressure and diastolic blood pressure, PWV is heart-to-ankle pulse wave velocity, ΔP is Ps – Pd, ρ is blood density, and a and b are constants that normalize the resultant value to a physiologic range similar to that seen for carotid-femoral pulse wave velocity measurements in humans.

2.3 | CCTA data acquisition

A 64-slice multidetector CT scanner (GE Healthcare, Milwaukee, WI) was used to acquire images. Sublingual nitroglycerin or nitroglycerin spray 0.4 mg was administered before the scan. A prescan β-blocker was also given to achieve a resting heart rate <60 bpm. The following imaging and reconstruction parameters were applied: collimation 64 × 0.625 mm, tube voltage 100 kV to 120 kV, tube current 350 to 780 mA. Prospective studies were performed if the heart rate was sufficiently controlled (<60 bpm) with images acquired from 65% to 75% of the R-R interval. An iodinated contrast material (350 mg/mL; Omnipaque, GE Healthcare) was injected intravenously depending on the expected scan time. Scan times were detected by a timing bolus technique and was followed by 50 mL of saline flush.

2.4 | CCTA interpretation

Certified, expert readers blinded to the cohort's CAVI values interpreted the CCTA images. All CCTA images were evaluated on a 3-dimensional image analysis workstation (GE Advantage; GE Healthcare). The CCTA readers were permitted to use any or all of the available postprocessing image-reconstruction algorithms, including 2-dimensional axial and 3-dimensional maximal intensity projection, multiplanar reformatting, cross-sectional analysis, and volume-rendered techniques.

Coronary arteries were evaluated using a 17-segment Society of Cardiovascular Computed Tomography model.[10] A semiquantitative scale was used by the CCTA readers to grade the extent of luminal stenosis as a percentage of the vessel diameter using visual estimations. Stenosis severity was recorded in the following 5 gradations: normal, 1% to 29% stenosis, 30% to 49% stenosis, 50% to 69% stenosis, 70% to 99% stenosis, and 100% stenosis. The extent of an obstructive lesion was defined as being ≥50% in 0, 1, 2, or 3 coronary artery vessels. In addition, 2 coronary artery plaque scores were evaluated for quantitative analysis, as previously reported: (1) segment-stenosis score (SSS) and (2) segment-involvement score (SIS).[11] The SSS was used to measure the overall coronary artery plaque burden. Each individual segment was scored based on the extent of stenosis of coronary luminal diameter from 0 to 3 (0 = normal, 1 = 1%–49%, 2 = 50%–69%, 3 = 70%–100%). Then, scores of all 17 individual segments were summed to give a total score ranging from 0 to 51. The SIS was used to measure the CAD distribution and was scored based on the presence of plaque within a segment, irrespective of the severity of stenosis, ranging from 0 to 17. Predefined cutoff values of SIS >5 and SSS >5 were used for further analysis, based on previous study.[11]

2.5 | Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as counts and percentages. A predefined CAVI cutoff value of 8 was used, based on previous studies.[3,4] We investigated whether CAVI ≥8 predicted coronary stenosis, quantitative coronary plaque distribution, and extent of stenosis. The χ^2 test, Fisher exact test, and Student *t* test were used to compare the continuous variables and categorical variables, respectively. The Levine test was done and the Wilcoxon test was used if the variables did not distribute normally. By multivariate logistic regression analyses, we evaluated whether CAVI values predict severe stenosis, SSS, and SIS adjusting for age, sex, chest pain, hypertension, dyslipidemia, family history, diabetes, and current smoking. A value of $P < 0.05$ (2-sided) was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Baseline characteristics and CCTA findings

The difference in baseline characteristics between the CAVI <8 and CAVI ≥8 groups is shown in Table 1. Patients in the CAVI ≥8 group were likely of older age and higher blood pressures. In addition, patients among the CAVI ≥8 group tended to have a history of hypertension and hyperlipidemia. Therefore, patients in this group were more inclined to take medication to lower blood pressure and lipids.

The CCTA findings are shown in Table 2. Patients whose CAVI was ≥8 tended to have severe stenosis. Correlation analysis showed a statistically significant relationship between CAVI and SIS or SSS (r^2 = 0.4, P < 0.0001 for SIS; r^2 = 0.36, P < 0.0001 for SSS), and both values were significantly higher in patients with CAVI ≥8 (Table 2, Figure 1). The details of the extent of obstructive lesion were shown in Figure 2. This population did not have 3-vessel disease (VD) or left main artery disease. CAVI was significantly higher in the 1-VD group and 2-VD group compared with the 0-VD group (P < 0.0001 for 0-VD vs 1-VD, P = 0.03 for 0-VD vs 2-VD). CAVI was also higher among the patients who had any obstructive CAD (P < 0.0001). However, there was no significant difference for 1-VD vs 2-VD group comparison (0.62).

Multivariable logistic analysis demonstrated that CAVI is significantly associated with SSS >5 and SIS >5, but not severe stenosis, after adjusting for age, sex, chest pain, hypertension, dyslipidemia, family history, diabetes, and current smoking. CAVI ≥8 failed to show the relationship between these values (Table 3).

4 | DISCUSSION

This study indicated that CAVI has a significant relationship between coronary plaque scores using CCTA. In addition, this study revealed that CAVI scores tend to be higher in patients with any obstructive disease. Our results indicate that CAVI can stratify the potential cardiovascular risk in the general population of the United States, although a larger population would need to be studied to provide more conclusive evidence of this.

CAVI is a parameter that evaluates the arterial stiffness of the coronary tree by inputting the patient's pulse wave velocity and blood pressure into the CAVI equation previously mentioned (and widely established). Due to its complicated and heterogeneous anatomy, the arterial tree does not always correlate with its own short segments. However, previous studies have shown that CAVI shared a significant correlation with short aortic segments in cases such as cerebral artery, renal artery, or carotid artery disease.[12–14] A recent study has also investigated and indicated the nice correlation between aortic stiffness and coronary flow reserve.[15] Therefore, it is reasonable to think that arterial stiffness can be reflected in coronary arteries as well.

Several previous studies have demonstrated a relationship between an increase in CAVI and coronary stenosis. Nakamura et al compared CAVI with invasive coronary catheterization and demonstrated that CAVI ≥8 may be associated with significant relationship with significant coronary stenosis (cutoff value: 8.81, area under the curve [AUC]: 0.775, P = 0.004).[3] Park et al have shown that CAVI ≥8 is associated with significant stenosis (≥50%) on CCTA and calcium scores ≥300 (cutoff value: 7.6, AUC: 7.68, P = 0.004; and cutoff value: 8.1, AUC: 0.67, P < 0.001, respectively).[4] In this study, we indicated that CAVI had a significant relationship between plaque extent and severity, as seen in SIS and SSS. Notably, Min et al showed that individuals whose plaque scores were SIS >5 or SSS >5 had higher mortality rates (5.9% and 5.0% worse, respectively) compared with those whose scores were SIS ≤5 and SSS ≤5.[11]

CAVI did not, however, predict the presence of obstructive stenosis in ≥50% of our cohort, which is inconsistent with previous study findings. There might be several reasons for this. First, as data from calcium scores show, the burden of coronary artery atherosclerosis

TABLE 1 Baseline characteristics according to CAVI score

	All, N = 95	CAVI <8, n = 52	CAVI ≥8, n = 43	*P* Value
Age, y	50 ± 16	41 ± 12	61 ± 14	<0.001
Male sex	63 (66)	30 (58)	33 (77)	0.08
DM	14 (15)	4 (7)	10 (23)	0.04
SBP, mm Hg	132 ± 18	127 ± 13	139 ± 21	<0.001
DBP, mm Hg	82 ± 10	81 ± 11	85 ± 9	0.05
Family history	33 (35)	18 (35)	15 (35)	1.0
Dyslipidemia	36 (38)	11 (21)	25 (58)	<0.001
HTN	33 (35)	12 (23)	21 (49)	0.01
Current smoking	9 (9)	5 (10)	4 (9)	1.0
Chest pain	21 (22)	9 (17)	12 (28)	0.23
Medications				
ASA	8 (8)	3 (6)	5 (12)	0.46
Antihypertensive meds	17 (18)	5 (29)	12 (28)	0.03
Antidyslipidemia meds	17 (18)	3 (6)	14 (33)	<0.001
Antidiabetic meds	6 (6)	1 (2)	5 (12)	0.08

Abbreviations: ASA, acetylsalicylic acid (aspirin); CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; meds, medicine; SBP, systolic blood pressure; SD, standard deviation.

Values are presented as n (%) or mean ± SD.

TABLE 2 Details of CCTA findings

	All, N = 95	CAVI <8, n = 52	CAVI ≥8, n = 43	*P* Value
Severe stenosis ≥50%, n (%)	17 (18)	3 (5)	14 (33)	<0.001
SIS, median (IQR)	1 (0–6)	0 (0–1))	5 (1–8)	<0.001
SSS, median (IQR)	1 (0–8)	0 (0–1)	7 (1–14)	<0.001

Abbreviations: CAVI, cardio-ankle vascular index; CCTA, cardiac computed tomography angiography; IQR, interquartile range; SD, standard deviation; SIS, segment-involvement score; SSS, segment-stenosis score.

does not always translate to coronary stenosis.[16] Other factors such as local shear stress, plaque rupture, or other unknown causes may play a role in developing severe coronary stenosis.[17] Because CAVI is measured by arterial stiffness, SIS or SSS may be more directly relative to CAVI, as both include factors to the extent of CAD. Second, our data indicated that CAVI tends to be high (Figure 2) in patients with any moderate or severe coronary stenosis. Therefore, our cohort, which has a relatively small sample size, may have lost the power to predict significant stenosis with a clear cutoff value.

Although there are several methods to estimate cardiovascular risk, such as the Framingham Risk Score or the atherosclerotic cardiovascular risk equation by the American College of Cardiology/American Heart Association,[18] such methods are known to overestimate the patient's potential cardiovascular risk.[19–21] Stress tests, such as treadmill stress echocardiography or stress perfusion imaging, are effective tools to stratify patient risk; however, from a cost-effectiveness perspective, it is not practical for all patients to undergo these tests. On the other hand, CAVI appears to be an attractive alternative, as the procedure is both feasible and easy to implement in general-medicine and primary-care clinics. Thus, it would be beneficial for general practitioners and patients to use CAVI for evaluating patients for CAD, if only on a screening level, to catch early-stage involvement.

4.1 | Study limitations

This study has several limitations. First, our cohort did not have blood-test data, including the patients' cholesterol profiles. Therefore, we could not show the relationship among conventional risk factors, CAVI, and the coronary findings. Second, we could not define an ideal

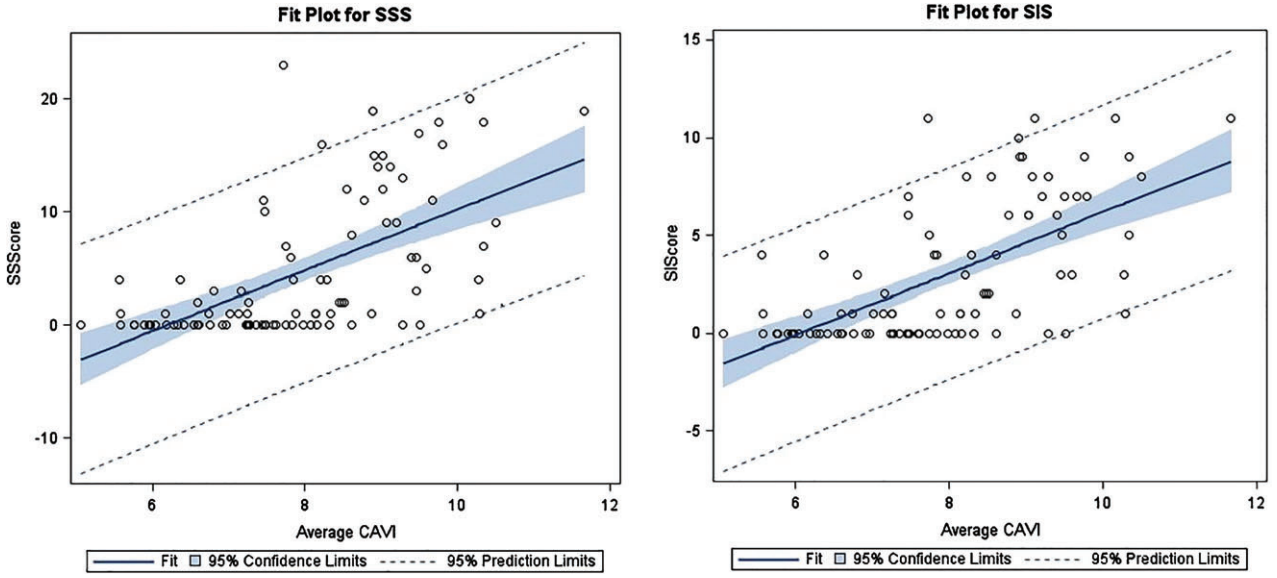

FIGURE 1 The relationships between CAVI and SSS and CAVI and SIS. Abbreviations: CAVI, cardio-ankle vascular index; SIS, segment-involvement score; SSS, segment-stenosis score.

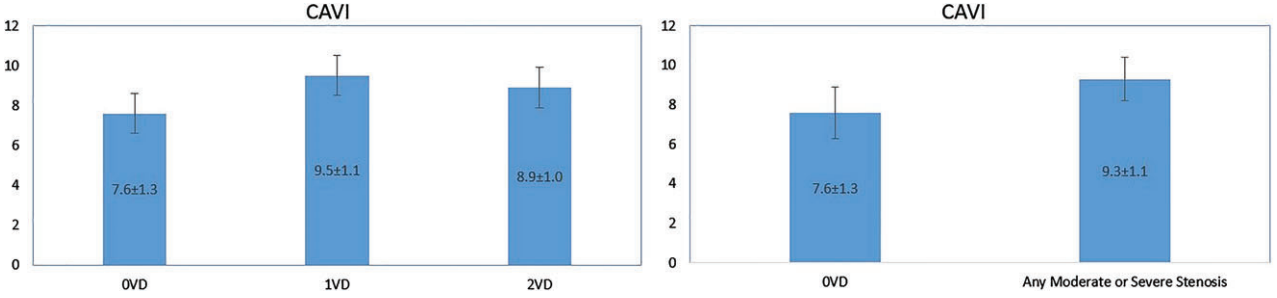

FIGURE 2 Details of the extent of obstructive lesion. Values are presented as mean ± SD. Abbreviations: SD, standard deviation; VD, vessel disease.

TABLE 3 Multiple logistic regression analyses

	OR (95% CI)	*P* Value
SIS >5		
CAVI ≥8	5.4 (0.9-41.1)	0.06
CAVI	2.5 (1.1-7.8)	0.03
SSS >5		
CAVI ≥8	2.2 (0.5-10.8)	0.32
CAVI	2.3 (1.1-5.8)	0.02
Severe stenosis ≥50%		
CAVI ≥8	1.6 (0.3-10.6)	0.61
CAVI	1.7 (0.9-4.3)	0.13

Abbreviations: CAVI, cardio-ankle vascular index; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio; SIS, segment-involvement score; SSS, segment-stenosis score.

ORs were adjusting for age, sex, chest pain, HTN, dyslipidemia, family history, DM, and current smoking.

cutoff value due to the study's relatively small sample size. Specifically, the choice for cutoff of CAVI ≥8, based on previous studies, did not have a significant relationship with SIS, SSS, and coronary artery stenosis after adjusting for general cardiovascular risk factors. A larger sample size and longitudinal study are warranted. Third, it is well known that age is one of the important confounding factors. In this current study, age was significantly higher in the CAVI ≥8 group (Table 1). We did not perform separate analysis based on different cutoff ages because of small sample size. However, we performed multivariate analysis and demonstrated that CAVI was an independent predictor regarding coronary a plaque burden and plaque extent. Finally, there is marked variation regarding SIS, and SSS depends on CAVI value, especially the SSS with CAVI values between 8 and 10 -(Figure 1), and this might make the prognostic value of CAVI worse in this current study. We suggest that it is more important to combine risk equations and CAVI if needed to predict patients at risk of future cardiovascular disease events.

5 | CONCLUSION

We demonstrated that CAVI could predict subclinical coronary atherosclerosis as evaluated by CCTA, especially in relation to plaque burden and plaque extent. Thus, CAVI could prove to be a significantly useful tool to stratify potential CAD risk.

Conflicts of Interest

Dr. Budoff receives funding from Fukuda Denshi. The other authors declare no conflicts of interest.

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