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ORIGINAL RESEARCH

IMAGING

Association Between Progression of Arterial Stiffness and Left Ventricular Remodeling in a Community-Based Cohort

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ABSTRACT

BACKGROUND Cross sectionally measured, elevated arterial stiffness is associated with unfavorable left ventricular (LV) remodeling, suggesting its important role in the pathophysiology of heart failure. However, data linking the degree of arterial stiffness progression with LV remodeling are scarce.

OBJECTIVES The purpose of this study was to investigate the association between longitudinal change in arterial stiffness and changes in LV remodeling.

METHODS Serial measurements of arterial stiffness by cardio-ankle vascular index (CAVI) were performed in 317 participants without cardiovascular disease and with normal arterial stiffness. LV size, mass, and function were assessed by transthoracic echocardiography and including LV global longitudinal strain (LVGLS) by speckle-tracking and tissue Doppler velocity (e') of the mitral annulus (diastolic function).

RESULTS During a median follow-up of 26.8 mo, there was a significant increase in CAVI ($P < 0.001$). Generalized estimating equation analyses showed that longitudinal increase in CAVI was associated with impaired LVGLS (estimate 0.46, 95% CI: 0.11-0.82; $P = 0.010$) after adjustment for demographics and baseline cardiovascular factors, but not with changes of LV mass index and e' velocity. When controlling for longitudinal change of covariates, CAVI progression remained associated with change in LVGLS (estimate 0.50, 95% CI: 0.16-0.85; $P = 0.004$). In sex stratified analysis, progression of CAVI was significantly associated with LVGLS deterioration only in women (estimate 0.92, 95% CI: 0.27-1.58; $P = 0.006$).

CONCLUSIONS Longitudinal increase in arterial stiffness is associated with deterioration in LVGLS. Vascular-ventricular coupling plays an important role in the progressive decline in ventricular function even at an early, subclinical stage. (JACC Adv 2023;2:100409) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

CAVI = cardio-ankle vascular index

EF = ejection fraction

GLS = global longitudinal strain

HF = heart failure

LV = left ventricle

PWV = pulse wave velocity

Heart failure (HF) is a global public health issue, with a prevalence of more than 23 million cases worldwide, prompting efforts for the clarification of HF mechanisms.[1] Previous cross-sectional studies demonstrated that arterial stiffening is associated with increased left ventricular (LV) afterload, and LV morphological and functional abnormalities[2-4] suggesting an important role of vascular-ventricular coupling in the pathophysiology of HF.[5,6] However, the contribution of increased arterial stiffness to incident HF is not fully established and the studies on the topic have provided conflicting results.[7-10] The Framingham Heart Study identified increased arterial stiffness, assessed by pulse wave velocity (PWV), as a significant risk factor for HF.[9] In contrast, the Health ABC (Health, Aging, and Body Composition) study, which examined 2,290 participants without prevalent HF, showed that PWV was not an independent predictor for HF occurrence.[7,10] This discrepancy may be partially explained by a lack of information on longitudinal trajectories of arterial stiffness; namely, the progression of arterial stiffness substantially varied among individuals,[11-13] which may limit the predictive value of arterial stiffness for incident HF. The Progression of Early Subclinical Atherosclerosis (PESA) study found that progression of subclinical atherosclerosis was observed in nearly 40% of healthy participants over the relatively short period of 3 years.[14] Given these observations, we hypothesized that the greater progression in arterial stiffness may adversely affect LV mechanics, possibly leading to subsequent HF even in the subjects with normal arterial stiffness at baseline. LV global longitudinal strain (LVGLS), a novel measure of LV myocardial deformation, provides the ability to detect early LV dysfunction in the presence of normal LV ejection fraction (LVEF) and has an excellent predictive value for incident HF.[15] We, therefore, investigated the degree of arterial stiffness progression over time and its impact on LV remodeling assessed by 2-dimensional and speckle-tracking echocardiography in individuals free of overt cardiovascular disease with normal arterial stiffness at baseline. Additionally, we examined the possibility of sex disparities in this association.

METHODS

STUDY POPULATION. Consecutive 435 individuals who voluntarily underwent repeated extensive cardiovascular health checkup including echocardiograms and cardio-ankle vascular index (CAVI)

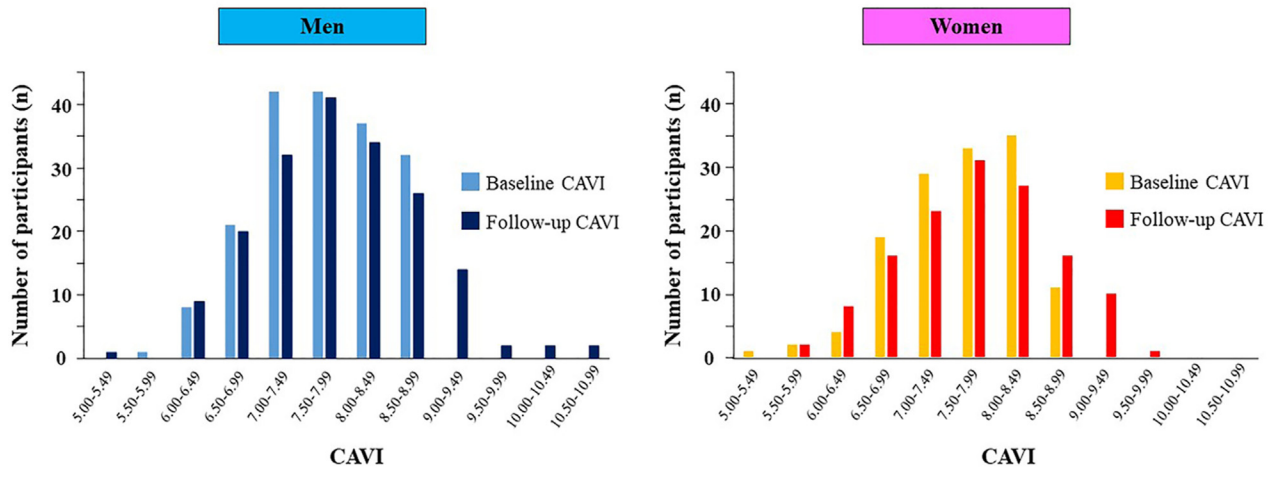
TABLE 1 Clinical and Biochemical Characteristics at Baseline and Follow-Up According to Sex

	Entire Group (n = 317)			Men (n = 183)			Women (n = 134)		
	Baseline	Follow-Up	*P* Value	Baseline	Follow-Up	*P* Value	Baseline	Follow-Up	*P* Value
Age, y	63 (53-70)	65 (56-72)	<0.001	59 (52-67)	62 (54-69)	<0.001	65 (56-71)[a]	68 (59-73)[a]	<0.001
BMI, kg/m^2	23.2 (21.3-25.4)	23.3 (21.2-25.5)	0.017	24.1 (22.5-25.9)	24.2 (22.3-26.3)	0.431	22.0 (19.9-23.7)[a]	22.0 (19.9-24.2)[a]	0.007
Systolic BP, mm Hg	117 ± 14	117 ± 15	0.933	118 ± 14	118 ± 14	0.990	116 ± 14	116 ± 15	0.908
Diastolic BP, mm Hg	74 (68-81)	74 (67-81)	0.038	76 (70-82)	75 (69-82)	0.040	73 (66-79)[a]	72 (66-80)[a]	0.380
Heart rate, beats/min	70 (65-76)	70 (64-77)	0.557	69 (62-76)	69 (63-76)	0.731	72 (66-76)[a]	71 (66-78)[a]	0.578
Hypertension	91 (28.7)	99 (31.2)	0.157	56 (30.6)	61 (33.3)	0.251	35 (26.1)	38 (28.4)	0.405
Diabetes mellitus	20 (6.3)	29 (9.1)	0.013	16 (8.7)	23 (12.6)	0.035	4 (3.0)[a]	6 (4.5)[a]	0.157
Hyperlipidemia	117 (36.9)	130 (41.0)	0.047	54 (29.5)	64 (35.0)	0.041	63 (47.0)[a]	66 (49.3)[a]	0.491
Current smoking	38 (12.0)	31 (9.8)	0.071	29 (15.8)	25 (13.7)	0.206	9 (6.7)[a]	6 (4.5)[a]	0.180
Antihypertensive medication	66 (20.8)	85 (26.8)	<0.001	38 (20.8)	52 (28.4)	<0.001	28 (20.9)	33 (24.6)	0.059
Lipid lowering medication	76 (24.0)	95 (30.0)	<0.001	35 (19.1)	49 (26.8)	<0.001	41 (30.6)[a]	46 (34.3)	0.166
Examination interval, mo	26.8 ± 9.2		-	26.7 ± 9.1		-	26.9 ± 9.3		-
Glucose, mg/dL	94 (88-101)	96 (91-104)	<0.001	96 (90-106)	98 (93-106)	<0.001	91 (87-96)[a]	93 (89-100)[a]	<0.001
Total cholesterol, mg/dL	204 ± 33	203 ± 32	0.283	200 ± 33	198 ± 31	0.314	211 ± 32[a]	210 ± 31[a]	0.646
LDL cholesterol, mg/dL	124 ± 30	120 ± 28	0.001	124 ± 31	119 ± 28	0.009	124 ± 30	120 ± 28	0.057
HDL cholesterol, mg/dL	64 (53-77)	63 (53-76)	0.124	59 (48-68)	58 (48-67)	0.220	73 (61-87)[a]	74 (61-86)[a]	0.364
eGFR, mL/min/1.73 m^2	71 (63-80)	71 (63-80)	0.294	72 (63-81)	72 (63-82)	0.940	71 (64-80)	70 (63-78)	0.139
BNP, pg/mL	16.1 (8.9-25.5)	13.4 (8.0-24.8)	0.288	12.9 (7.3-21.4)	11.3 (6.9-18.9)	0.067	19.1 (12.5-29.5)[a]	20.0 (10.8-34.5)[a]	0.670
CAVI	7.70 (7.15-8.20)	7.80 (7.31-8.42)	<0.001	7.70 (7.15-8.35)	7.86 (7.35-8.50)	<0.001	7.68 (7.10-8.15)	7.75 (7.23-8.32)	0.001
haPWV, m/s	7.40 ± 0.66	7.58 ± 0.77	<0.001	7.52 ± 0.65	7.69 ± 0.79	<0.001	7.24 ± 0.64[a]	7.42 ± 0.71[a]	<0.001

Values are median (25th-75th percentile), mean ± SD, or n (%). [a]$P < 0.05$ vs men.

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CAVI = cardio-ankle vascular index; eGFR = estimated glomerular filtration rate; haPWV = heart-to-ankle pulse wave velocity; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

FIGURE 1 Baseline and Follow-Up CAVI Values Stratified by Sex



CAVI = cardio-ankle vascular Index.

measurements as a new arterial stiffness index from 2014 to 2018 at the University of Tokyo Hospital were retrospectively recruited in this study. Our clinic provides an extensive health check for the promotion of health and prevention of cardiovascular disease. Participants were then excluded if they had atrial fibrillation or atrial flutter at baseline or follow-up (n = 8), history of coronary artery disease or abnormal ankle-brachial index (<0.9 or ≥1.4; n = 14), LVEF <52% for men and <54% for women,[16] and significant valvular disease or suboptimal image quality (n = 18). We further excluded 78 participants with abnormal CAVI (≥9) at baseline to evaluate the impact of deterioration of arterial stiffness on LV function in participants with normal arterial stiffness. Thus, the final study population of this study consisted of 317 participants free of cardiovascular disease and with normal CAVI at baseline. The investigation conformed to the principles outlined in the Declaration of Helsinki and the Institutional Review Boards of the University of Tokyo approved the study. There was no significant difference in the demographics and laboratory and echocardiographic parameters between subjects with and without serial examination except for sex (61% vs 54%; $P = 0.034$).

RISK FACTOR ASSESSMENT AND LABORATORY MEASUREMENTS. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg, or the use of antihypertensive medications. Diabetes mellitus was defined by a fasting blood glucose ≥126 mg/dL or the current use of insulin or oral hypoglycemic agents. Hyperlipidemia was defined as total serum cholesterol >240 mg/dL or the use of lipid-lowering medications. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Fasting serum glucose, cholesterol, creatinine, and BNP (B-type natriuretic peptide) levels were measured in all participants.

ARTERIAL STIFFNESS MEASUREMENT. CAVI was measured on the same day as the echocardiographic examination using a Vasera VS-1500 (Fukuda Denshi). The electrocardiogram, SBP and DBP of the brachial and ankle arteries were simultaneously recorded with subjects in the supine position after 5 min of rest. CAVI was determined using the validated following formula[17-19]: $CAVI = a\{(2\rho/\Delta P) \times \ln(SBP/DBP) \times haPWV^2\}+b$, where $\Delta P = SBP - DBP$, ρ = blood density, haPWV = PWV from the heart to the ankle, and a and b are constants. The mean of the right and left CAVI values was used for analysis and abnormal CAVI was defined as ≥9 based on the current recommendations.[17] Participants with an ankle-brachial index <0.9 or ≥1.4 were excluded from our analyses as mentioned above.[18] Change in CAVI was calculated as follows; follow-up CAVI value - baseline CAVI value.

ECHOCARDIOGRAPHIC EXAMINATION. Standard echocardiographic measurements. Transthoracic echocardiography was performed using a commercially available system (Aplio 300, Toshiba Medical Systems) by experienced and certified cardiac sonographers blinded to the participant's clinical

TABLE 2 Echocardiographic Parameters at Baseline and Follow-Up

	Entire Group (n = 317)			Men (n = 183)			Women (n = 134)		
	Baseline	Follow-Up	*P* Value	Baseline	Follow-Up	*P* Value	Baseline	Follow-Up	*P* Value
LVEDV, mL	66.1 (55.1-80.8)	65.9 (55.5-80.4)	0.140	76.9 (63.7-89.5)	75.6 (62.9-86.8)	0.108	57.0 (47.7-66.1)[a]	57.0 (48.4-65.7)[a]	0.785
LVEDV index, mL/m^2	41.2 (34.1-47.8)	40.8 (34.3-46.4)	0.136	42.9 (35.9-49.7)	42.7 (35.7-48.7)	0.099	39.3 (32.3-43.8)[a]	38.7 (33.5-43.4)[a]	0.763
LVESV, mL	24.0 (18.7-30.5)	23.3 (18.8-29.4)	0.256	27.9 (22.2-34.1)	26.7 (21.9-32.5)	0.120	19.3 (16.0-24.5)[a]	19.7 (15.8-23.6)[a]	0.790
LVESV index, mL/m^2	14.8 (11.7-18.0)	14.1 (11.6-17.3)	0.267	15.8 (13.0-19.0)	15.1 (12.3-18.3)	0.115	13.1 (10.8-16.0)[a]	13.4 (10.7-15.5)[a]	0.780
LVEF, %	63.4 (59.9-68.5)	63.8 (60.7-68.0)	0.392	63.1 (59.2-68.1)	63.7 (60.8-67.1)	0.961	64.2 (60.8-69.5)[a]	64.2 (60.5-68.8)	0.211
LV mass index, g/m^2	68.3 (58.6-78.3)	70.5 (60.5-79.9)	<0.001	71.2 (62.5-80.3)	74.2 (65.4-83.0)	<0.001	62.5 (55.0-74.8)[a]	65.4 (57.5-73.1)[a]	0.008
E-wave, cm/s	69.3 (60.9-78.7)	67.7 (59.2-77.3)	0.195	66.3 (58.9-75.2)	66.3 (57.4-73.1)	0.179	72.9 (63.4-81.8)[a]	71.9 (63.1-83.6)[a]	0.689
A-wave, cm/s	64.3 (54.1-76.3)	66.8 (55.1-81.1)	<0.001	60.6 (50.5-71.0)	60.9 (51.1-75.2)	0.055	70.4 (59.2-84.1)[a]	75.6 (63.4-85.4)[a]	<0.001
E/A ratio	1.06 (0.86-1.31)	0.96 (0.83-1.24)	<0.001	1.09 (0.86-1.32)	1.00 (0.85-1.27)	0.016	1.01 (0.85-1.29)	0.91 (0.81-1.22)[a]	<0.001
e', cm/s	8.30 (6.85-9.60)	7.95 (6.70-9.50)	0.014	8.38 (7.05-9.91)	8.15 (6.85-9.55)	0.040	8.10 (6.48-9.40)	7.68 (6.54-9.45)	0.194
E/e' ratio	8.36 (6.94-10.03)	8.23(6.98-10.16)	0.396	7.79 (6.55-9.66)	7.76 (6.59-9.34)	0.507	9.00 (7.51-10.86)[a]	9.18 (7.38-11.04)[a]	0.562
LVGLS, %	−21.2 (−23.3 to −20.0)	−20.8 (−22.5 to −19.2)	<0.001	−20.6 (−21.8 to −19.5)	−20.2 (−21.7 to −18.9)	<0.001	−22.4 (−24.8 to −20.7)[a]	−21.4 (−23.3 to −19.8)[a]	<0.001

Values are median (25th-75th percentile). [a]$P < 0.05$ vs men.

A = late diastolic transmitral flow velocity; E = early diastolic transmitral flow velocity; e' = early diastolic mitral annular velocity; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; LV = left ventricle.

information. The dimensions of the cardiac chambers were obtained according to the recommendations of the American Society of Echocardiography (ASE).[16] LV mass was calculated with a validated formula[20] and then indexed for body surface area (LV mass index). LV diastolic parameters were assessed according to the current guideline.[21] Pulsed-wave Doppler examination of mitral inflow was performed to obtain early (E) and late (A) peak velocity. Tissue Doppler mitral annular early diastolic velocity (e') of the septal and lateral sides were measured and averaged to calculate the mean early diastolic velocity. The ratio of early transmitral velocity to mean value of mitral annular early diastolic velocity (E/e') was calculated.

TABLE 3 Univariable Association Between Change in Cardio-Ankle Vascular Index and Changes in Left Ventricular Indices

Changes in LV Parameters	Estimate (95% CI)	*P* Value
LV EDV, mL	−2.13 (−5.04 to 0.77)	0.150
LV EDV index, mL/m^2	−1.22 (−2.77 to 0.32)	0.120
LV ESV, mL	−0.74 (−2.35 to 0.88)	0.371
LV ESV index, mL/m^2	−0.39 (−1.24 to 0.46)	0.370
LV ejection fraction, %	0.09 (−0.79 to 0.97)	0.843
LV mass index, g/m^2	2.30 (0.09-4.51)	0.041
E-wave, cm/s	−1.64 (−5.24 to 1.95)	0.370
A-wave, cm/s	3.41 (−0.01 to 6.83)	0.051
E/A ratio	−0.10 (−0.17 to −0.04)	<0.001
e' velocity, cm/s	−0.54 (−0.95 to −0.14)	0.008
E/e' ratio	0.36 (−0.23 to 0.95)	0.238
LVGLS, %	0.53 (0.14-0.93)	0.008

A = late diastolic transmitral flow velocity; E = early diastolic transmitral flow velocity; e' = early diastolic mitral annular velocity; EDV = end-diastolic volume; ESV = end-systolic volume; GLS = global longitudinal strain; LV = left ventricular.

Speckle-tracking echocardiography. Quantitation of LV strain was performed offline using vendor-independent commercially available speckle tracking-based software (2D Cardiac Performance Analysis, TomTec Imaging Systems). Semiautomated border detection was performed using the software and LV borders were tracked throughout the entire cardiac cycle. The integrity of tracking was visually confirmed, and manual correction was performed in case of inaccurate endocardial detection. LVGLS was calculated by averaging the negative peak of longitudinal strain from all 3 apical views.[22] Intra- and interobserver reproducibility was evaluated in 30 randomly selected patients by 2 independent and blinded observers (Y.Y. and K.N.) using an intraclass correlation coefficient. Good intra- and interobserver variability was observed: intraclass correlation coefficients were 0.90 (95% CI: 0.81-0.95) and 0.83 (95% CI: 0.62-0.92), respectively.

STATISTICAL ANALYSIS. Data are presented as numbers and proportions for categorical variables and as mean ± SD or median (IQR) for continuous variables. Distribution was evaluated by the Shapiro-Wilk test. Categorical variables were compared by the Chi-square test, and continuous variables were compared using *t*-test or Wilcoxon rank sum test, as appropriate. Change in the variables between the follow-up and the baseline was compared by the paired *t*-test or Wilcoxon signed rank test for continuous measures and McNemar's test for categorical measures. The generalized estimating

TABLE 4 Association Between Change in Cardio-ankle Vascular Index and Changes of Left Ventricular Parameters in Multivariable Model

	LV Mass Index, g/m²		E/A Ratio		e' Velocity, cm/s		LVGLS, %	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Model 1	1.29 (−0.88 to 3.47)	0.244	−0.06 (−0.10 to −0.01)	0.012	−0.27 (−0.63 to 0.10)	0.155	0.46 (0.11-0.82)	0.010
Model 2	1.56 (−0.48 to 3.61)	0.134	−0.04 (−0.08 to 0.002)	0.064	−0.12 (−0.46 to 0.23)	0.508	0.50 (0.16-0.85)	0.004

Model 1; adjusted for sex, baseline variables of age, CAVI, BMI, heart rate, systolic BP, antihypertensive medications, diabetes mellitus, hyperlipidemia, current smoking, eGFR, and BNP. Model 2; adjusted for sex, baseline age and CAVI, and longitudinal variables of BMI, heart rate, systolic BP, anti-hypertensive medications, diabetes mellitus, hyperlipidemia, current smoking, eGFR, and BNP.

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CAVI = cardio-ankle vascular index; eGFR = estimated glomerular filtration rate.

equation approach includes baseline CAVI and the change in CAVI during follow-up as covariates with identity link and working independence correlation structure. Parameters known to be associated with adverse LV remodeling (age, sex, BMI, heart rate, SBP, antihypertensive medication use, diabetes mellitus, hyperlipidemia, current smoking status, estimated glomerular filtration rate, and BNP level) were entered as covariates in multivariable model (model 1). In a separate model, we adjusted for changes in these covariables (model 2). Analyses were performed in the entire group as well as sex subgroups. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed with JMP 14 statistical software (SAS Institute).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION. The characteristics of the study population are presented in Table 1. The median age was 63 (IQR: 53-70) years and 183 (58%) of the study participants were men. Men had significantly larger BMI and higher prevalence of diabetes and current smoker, whereas women were older and had higher prevalence of hyperlipidemia (all $P < 0.05$). Baseline CAVI value did not differ between men and women (7.70 [IQR: 7.15-8.35] vs 7.68 [IQR: 7.10-8.15]; $P = 0.307$; Figure 1). Echocardiographic data are shown in Table 2. In the entire population, LV mass index significantly increased and LVGLS decreased (both $P < 0.001$). On the other hand, there was no change in LVEF. In terms of LV diastolic parameters, E/A ratio and e' velocity decreased (both $P < 0.05$), but E/e' ratio did not change during follow-up. Men had larger LV size, LV mass index and worse LVGLS compared with women, while significantly higher E/e' ratio was observed in women (all $P < 0.05$).

ASSOCIATION BETWEEN ARTERIAL STIFFNESS PROGRESSION AND LV FUNCTIONAL ALTERATION. Univariable association between change in CAVI and changes in LV indices is presented in Table 3. Generalized estimating equation analyses showed that change in CAVI was associated with LV mass index, E/A ratio, and e' velocity, and LVGLS (all $P < 0.05$), but not with LVEF and E/e' ratio. In multivariable model after adjustment for demographics and baseline cardiovascular risk factors, CAVI progression was independently associated with impaired LVGLS (estimate 0.46, 95% CI: 0.11-0.82; $P = 0.010$) (Table 4, model 1) and lower E/A ratio (estimate −0.06, 95% CI: −0.10 to −0.01; $P = 0.012$) (Table 4, model 1) When controlling for longitudinal change in covariates, CAVI progression remained significantly associated with LVGLS (estimate 0.50, 95% CI: 0.16-0.85; $P = 0.004$) (Table 4, model 2). Sex-subgroup analyses demonstrated that progression of CAVI was significantly associated with LVGLS deterioration in women independent of cardiovascular risk factors (estimate 0.92, 95% CI: 0.27-1.58; $P = 0.006$) (Table 5, model 1), but not in men (Central Illustration). On the other hand, change in CAVI was related to lower E/A ratio (estimate −0.06, 95% CI: −0.11 to −0.02; $P = 0.010$) in men. Similar results were obtained in multivariable model adjusting for change in cardiovascular risk factors (Table 5, model 2).

DISCUSSION

The present study reports on the association between longitudinal change in arterial stiffness and changes in LV morphology and function in a community-based cohort without prevalent cardiovascular disease. The greater progression in arterial stiffness was significantly associated with adverse LV remodeling even at an early, subclinical stage before LVEF decreases. In addition, sex-specific differences existed in the relationship. Our findings highlight the important role of vascular-ventricular coupling in the progressive decline in ventricular function.

ARTERIAL STIFFNESS AND INCIDENT HF. Arterial stiffening plays a pivotal role in the pathogenesis of cardiovascular diseases[6]; however, the association

TABLE 5 Association Between Change in Cardio-Ankle Vascular Index and Changes of Left Ventricular Parameters in Multivariable Model in Sex Subgroups

	LV Mass Index, g/m²		E/A Ratio		e' Velocity, cm/s		LVGLS, %	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Women								
Model 1	1.92 (−1.74 to 5.58)	0.304	−0.05 (−0.14 to 0.03)	0.196	−0.28 (−0.72 to 0.15)	0.205	0.92 (0.27 to 1.58)	0.006
Model 2	2.08 (−1.58 to 5.74)	0.265	−0.04 (−0.11 to 0.04)	0.338	−0.09 (−0.54 to 0.36)	0.698	0.86 (0.26 to 1.46)	0.005
Men								
Model 1	1.28 (−1.34 to 3.90)	0.337	−0.06 (−0.11 to −0.02)	0.010	−0.26 (−0.74 to 0.23)	0.304	0.24 (−0.14 to 0.63)	0.217
Model 2	1.20 (−1.23 to 3.63)	0.333	−0.05 (−0.10 to −0.004)	0.035	−0.14 (−0.61 to 0.33)	0.563	0.21 (−0.17 to 0.58)	0.280

Model 1; adjusted for baseline variables of age, CAVI, BMI, heart rate, systolic BP, anti-hypertensive medications, diabetes mellitus, hyperlipidemia, current smoking, eGFR, BNP. Model 2; adjusted for baseline age and CAVI and longitudinal variables of BMI, heart rate, systolic BP, anti-hypertensive medications, diabetes mellitus, hyperlipidemia, current smoking, eGFR, BNP.

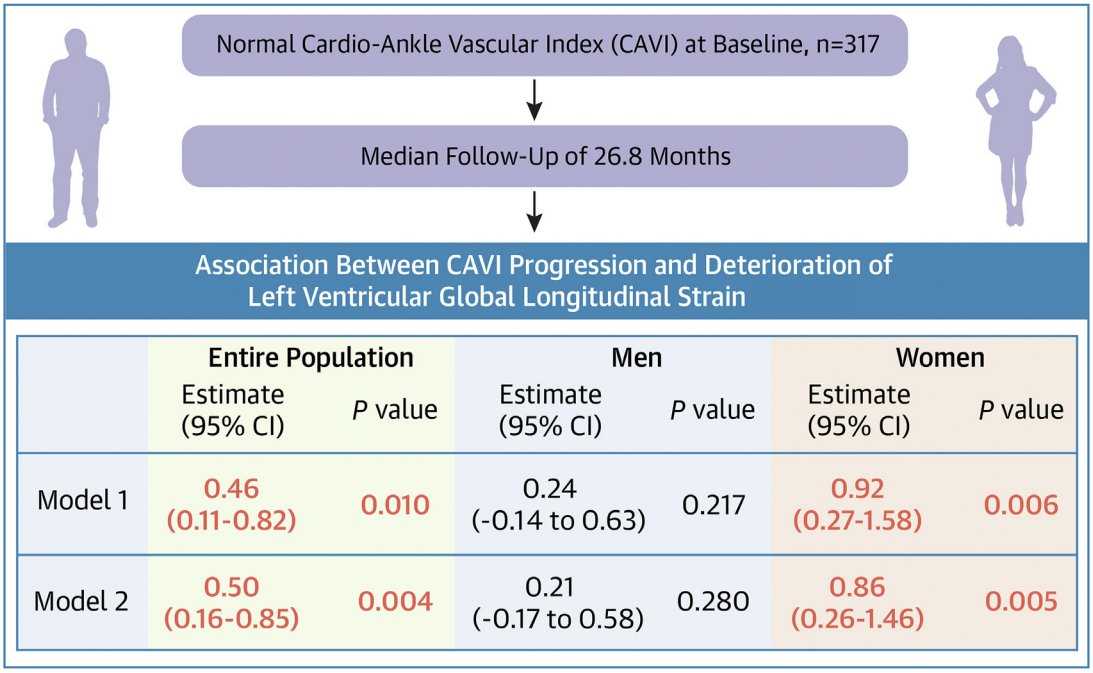
BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CAVI = cardio-ankle vascular index; eGFR = estimated glomerular filtration rate.

between arterial stiffness and incident HF still remains an area of controversy.[7-10] The Framingham Heart study reported that increased arterial stiffness conferred a 29% greater risk of incident HF during a follow-up of 10 years.[9] Chirinos et al[8] also identified arterial stiffness as a predictor for HF in 2,602 chronic kidney disease patients. In contrast, Health ABC study including 2,290 participants without overt HF showed that PWV was not an independent predictor for HF occurrence during mid- (5 years) and long-term (11 years) follow-ups.[7,10] Most of these prior studies examined PWV at one point in time and did not account for longitudinal trajectories of arterial stiffness, which may explain at least in part the lack predictive ability. Indeed, the progression of arterial stiffness differs substantially between individuals depending on the population risk profiles.[11-14] CAVI is derived from the concept of stiffness parameter β index and is less dependent on BP changes than PWV, and shows an excellent correlation with atherosclerotic burden and has an independent prognostic value.[6]

TRAJECTORIES OF ARTERIAL STIFFNESS AND LV FUNCTIONAL REMODELING. Cross-sectional data showed that increased arterial stiffness was associated with LV hypertrophy,[4] LV systolic[3] and diastolic[2] impairment, and was considered as a mediator of HF development. However, data examining the impact of longitudinal trajectories of arterial stiffness on ventricular morphological and functional changes are scarce. Cauwenberghs et al[23] reported that higher baseline PWV was associated with a longitudinal increase in LV wall thickness, but changes in PWV did not predict LV structural alteration during a follow-up of 4 years. In the current study, we demonstrated that the progression of arterial stiffness was independently associated with LVGLS and E/A ratio, but not with LV size or LV mass index. The different results might be mainly explained by the fact that the present study only included individuals with normal arterial stiffness at baseline. Coronary microvascular dysfunction may be one mechanism by which arterial stiffening leads to worsening LVGLS. When the arterial tree stiffens, reflected waves arrive at the heart in mid-to-late systole instead of diastole, leading to the impairment of coronary flow reserve, and this ultimately may decrease LV performance.[6] Our longitudinal study confirms previous cross-sectional studies and further strengthens that the progression of arterial stiffening is an important mediator of LV remodeling. Consistent with our hypothesis, Lam et al[24] showed that longitudinal increases in aortic root diameter, a robust marker of arterial remodeling, were associated with the incident HF independent of baseline aortic properties.

We further investigated the sex-specific association between arterial stiffening and LV functional alteration, and found that CAVI progression was independently associated LVGLS deterioration in women, but not in men. The effect of sex on the association between increased arterial stiffness and LV remodeling has been investigated in previous cross-sectional studies. The Multi-Ethnic Study of Atherosclerosis (MESA) study reported that PWV was independently associated with LV systolic and diastolic dysfunction in both men and women.[4] The LIFE (Losartan Intervention For Endpoint reduction in hypertension) study also showed that arterial stiffness by the pulse pressure/stroke index ratio was associated with diastolic function independent of sex.[25] On the contrary, Countinho et al[26] reported that arterial compliance was linked to LV dysfunction only in women. The enhanced association between CAVI progression and LVGLS deterioration in women in our population might be partially explained by the coronary microvascular dysfunction. Lower arterial compliance is an independent determinant of

CENTRAL ILLUSTRATION **Association Between CAVI Progression and Deterioration of LVGLS**



	Entire Population		Men		Women	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Model 1	0.46 (0.11-0.82)	0.010	0.24 (-0.14 to 0.63)	0.217	0.92 (0.27-1.58)	0.006
Model 2	0.50 (0.16-0.85)	0.004	0.21 (-0.17 to 0.58)	0.280	0.86 (0.26-1.46)	0.005

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reduced myocardial flow reserve only in women.[27] Although both e' velocity and E/e' ratio are established parameters as LV diastolic function and are known to be well correlated with an elevated LV filling pressure, increase in arterial stiffness in our cohort was neither associated with change in e' velocity nor E/e' ratio in adjusted model. The lack of independent association may be due to the limitation of these markers for the detection of subtle LV diastolic dysfunction in the general population with relatively preserved diastolic capacity.[28,29]

CLINICAL IMPLICATION. Progression of arterial stiffness was independently associated with deterioration in LVGLS in individuals with normal CAVI at baseline and normal LVEF. Vascular-ventricular coupling may play a key role in the progression of LV remodeling from an early, subclinical stage. Future research is required to evaluate whether early interventions to prevent arterial stiffening may reverse or slow the progression of the LV remodeling and possibly prevent subsequent HF. Recent studies exploring the effect of newly developed pharmacological approaches for vascular impairment such as inorganic nitrite may offer promise in enhancing therapeutic options.[30] Furthermore, although this study showed that sex difference may exist in vascular-ventricular uncoupling, we should acknowledge that a sex-specific difference in LV geometry and function may affect our observation. Kerkhof[31] and Handly et al[32] clearly mentioned that smaller LV size in women has serious implications for several metrics such as LVEF.

STRENGTH AND LIMITATIONS. The strengths of the present study include the repeated measurements of CAVI as well as LV mechanics by using speckle-tracking echocardiography. Several limitations should be noted. Because of the relatively short-term follow-up, we could not study clinical HF as an endpoint. However, we showed an independent association between trajectories of arterial stiffness and deterioration in LVGLS, with the latter being a strong prognostic marker for incident HF.[15] Although CAVI is less BP dependent than PWV and exhibits an excellent correlation with atherosclerotic burden, it has a potential disadvantage relative to carotid-femoral

PWV because it includes a long muscular arterial segment, which may confound large artery stiffness measurements. Finally, this study enrolled relatively healthy participants, which may not directly apply to individuals with different demographic composition and risk profiles, but longitudinal data of a low-risk population, which may be of help for the primary prevention are frequently underrepresented in clinical studies.

CONCLUSIONS

Increase in arterial stiffness is independently associated with worsening LVGLS in individuals free of cardiovascular disease. Our findings highlight the important role of vascular-ventricular coupling in the progressive decline in ventricular function. Strategies to prevent increases in arterial stiffness may help prevent deterioration in LV function and, perhaps, clinical HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a community-based cohort study free of overt cardiovascular disease, longitudinal increase in cardio-ankle vascular index was independently associated with worsening global longitudinal strain, and this association was observed only in women. Our findings highlight the important role of vascular-ventricular coupling in the progression of LV remodeling.

TRANSLATIONAL OUTLOOK: Future research is warranted to investigate whether early therapeutic intervention for cardiovascular risk factors may reverse decreased LV global longitudinal strain and possibly prevent subsequent HF occurrence through improvement of vascular function. Furthermore, the pathophysiological mechanisms behind the observed sex differences in vascular-ventricular uncoupling should be addressed.

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KEY WORDS **arterial stiffness, cardio-ankle vascular index, global longitudinal strain, left ventricular function, sex-differences**