The Relationships Between the Arterial Stiffness Index Measured at the Radial Artery and Left Ventricular Diastolic Dysfunction in Asymptomatic High Risk Patients Without Atherosclerotic Cardiovascular Disease

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SUMMARY

Arterial stiffness is associated with atherosclerosis and left ventricular (LV) diastolic function in general or hypertensive patients. However, the relationships between the arterial stiffness index measured at the radial artery and LV diastolic dysfunction in asymptomatic high-risk patients without atherosclerotic cardiovascular disease (ASCVD) have not been fully established.

A total 532 statin-naïve patients (male:female ratio, 230:302, mean age, 56.0 ± 9.2 years) without ASCVD were enrolled from among subjects who simultaneously underwent transthoracic echocardiography and noninvasive semiautomated radial artery applanation tonometry from July 2011 to May 2014. Of these patients, 213 were categorized as the statin benefit group (Benefit) according to guidelines for blood cholesterol treatment, and the rest were placed in the non-benefit control group (NoBenefit). Each group was subdivided into two groups (Y or N) according to antihypertensive medication administration. Thus, there were 4 groups: BenefitN ($n = 80$), BenefitY ($n = 133$), NoBenefitN ($n = 251$), and NoBenefitY ($n = 68$). There were significant differences in echocardiographic parameters of LV function and indices of arterial stiffness between the Benefit and NoBenefit groups. After adjusting for several risk factors, independent significant associations between echocardiographic parameters of LV diastolic function and arterial indices were identified with multivariate linear regression analysis in the Benefit patients.

Parameters of arterial stiffness measured at the radial artery are associated with echocardiographic indices of LV diastolic function in asymptomatic high-risk patients without ASCVD. Therapies that prevent progression of arterial stiffness and reduce late-systolic pressure overload may help to reduce the prevalence of LV diastolic dysfunction in this population. (Int Heart J 2016; 57: 73-79)

Key words: Central blood pressure, Augmentation index, Statin benefit group

Congestive heart failure with preserved left ventricle ejection fraction (LVEF) caused by diastolic dysfunction is common (40% or more), and causes significant morbidity and mortality.¹⁾ Patients who have heart failure with preserved LVEF tend to be older and female, and have a history of hypertension. Diastolic dysfunction is associated with elevated arterial stiffness caused by increased LV afterload, which mainly affects wave reflections arising in peripheral arteries that return to the proximal aorta during mid-to-late systole.^{2,3)} In adults with hypertension, early return of reflected waves may lead to increasing LV afterload and central pulse pressure (PP).⁴⁾ When the arteries stiffen, reflected wave acceleration increases central PP, which is associated with adverse clinical events.⁵⁾

Direct measurement of central pressures is ideal, but requires the use of invasive devices. Central hemodynamic parameters measured by several noninvasive methods have been

independently associated with organ damage and incident cardiovascular disease.⁵⁾ Unlike diastolic blood pressure (BP) and mean pressures, systolic BP is amplified when moving from the aorta to the periphery. Central BP relative to peripheral BP is significantly higher in people at risk for heart failure or disease compared with healthy people.⁶⁾

A recent study found significant relationships between a surrogate marker of arterial stiffness (a carotid artery measurement) and subclinical atherosclerosis in a primary prevention population.⁷⁾ Intensive cholesterol reduction is reportedly beneficial in the treatment of patients with isolated systolic hypertension and normal lipid levels, through a reduction in large artery stiffness.⁸⁾ Previous clinical and animal studies have suggested beneficial effects of statin therapy on diastolic heart failure.⁹⁻¹¹⁾ One possible mechanism, demonstrated in hypertensive diastolic heart failure in rats, is that statin therapy ameliorates cardiac fibrosis and improves LV diastolic function.¹²⁾

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but conclusive evidence is lacking. Furthermore, the relationship between arterial stiffness and diastolic function in patients with dyslipidemia remains unknown.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for blood cholesterol treatment to reduce atherosclerotic cardiovascular disease (ASCVD) in adults¹³⁾ identified statin benefit groups: 1) primary elevation of low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL; 2) diabetes mellitus (DM) aged 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD; or 3) without clinical ASCVD or DM, with LDL-C 70 to 189 mg/dL, and an estimated 10-year ASCVD risk $> 7.5\%$. We sought to elucidate the relationships between the arterial stiffness index measured at the radial artery and LV diastolic function in asymptomatic high-risk patients without ASCVD and no history of statin treatment.

METHODS

Study population: The study population consisted of subjects referred for echocardiography between July 2011 and May 2014. A total 532 subjects without ASCVD who simultaneously underwent two-dimensional, Doppler echocardiography and noninvasive semi-automated radial artery applanation tonometry (HEM-9000AI, Omron Healthcare, Kyoto, Japan) in the Department of Internal Medicine, St. Vincent's Hospital (male:female ratio, 230:302, mean age, 56.0 ± 9.2 years) were enrolled in this study. High-risk patients were defined as: 1) primary elevation of LDL-C ≥ 190 mg/dL; 2) DM aged 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD; or 3) without clinical ASCVD or DM, with LDL-C 70 to 189 mg/dL, and an estimated 10-year ASCVD risk $> 7.5\%$. Exclusion criteria were: 1) history or findings of cardiovascular disease, including heart failure symptoms or systolic dysfunction (LV EF $\leq 50\%$), significant valvular heart disease (ie, greater than mild valvular insufficiency or stenosis), hypertrophic cardiomyopathy, and evidence of coronary artery disease (defined as history and/or treatment of angina and/or myocardial infarction, history of coronary artery revascularization procedures and/or coronary angiography, with $> 50\%$ stenosis in one or more of the major coronary arteries, and/or regional wall motion abnormalities on resting echocardiography; 2) history of statin therapy; 3) serum creatinine level > 1.4 mg/dL; 4) pregnant or lactating; 5) major systemic illness (ie, chronic inflammatory disease, active malignancy, and others); and 6) current atrial fibrillation (radial tonometry is not accurate in these patients). There was no industry involvement in the design, conduct, or analysis of the study. The Ethics Committee of our institution approved the use of clinical data for this study, and all patients provided written informed consent.

Measurement of brachial BP and central BP: The participants rested for at least 5 minutes in a quiet room. The patients were comfortably seated with their legs uncrossed and their back and arms supported. Brachial BP was measured using a HEM-907 automatic cuff oscillometric device (Omron Healthcare). The average of three readings was used to determine systolic BP, diastolic BP, mean arterial pressure, and PP. Next, the radial pulse wave was obtained with a model HEM-9010AI automated applanation tonometer (Omron Healthcare). The device consists of a sensor unit, pulse measurement unit, and personal

computer. The wristwatch-shaped sensor unit has a pressure sensor with an array of 40 microtransducer elements on its inner surface. Once the sensor is placed on the left wrist over the radial artery, the device automatically flattens the artery, adjusts the applanation hold-down pressure, and selects an optimal sensing element to record the pulse wave appropriately. The obtained pressure signals are digitized at 500 Hz inside the pulse measurement unit and then transmitted to a personal computer.¹⁴⁾ In this study, radial arterial pressure waveforms were obtained for 30 seconds. Peripheral or central pulsatile stress (pPS or cPS) was calculated as the product of resting heart rate (HR) and peripheral or central PP (pPP or cPP). A radial augmentation index (RaAIx) was calculated as follows: [(second peak radial systolic pressure [SBP2]-diastolic pressure)/(first peak radial systolic pressure-diastolic pressure)*100].¹⁵⁾ Systemic hypertension was defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg, based on more than three measurements or current use of antihypertensive drugs.

Clinical and biochemical assessment: Blood specimens were obtained after a 12- to 14-hour fast (8:00 pm to 9:30 am) to reduce the influence of circadian variation. Total cholesterol (TC) and triglyceride (TG) concentrations were assessed by using standard enzyme methods. High-density lipoprotein (HDL) cholesterol level was measured after precipitation of very-low-density lipoproteins and low-density lipoprotein (LDL) with phosphotungstic acid, and LDL was calculated using the Friedewald formula. Fasting glucose levels were enzymatically measured by the hexokinase method. A blood sample from every patient was drawn and centrifuged within 30 minutes. The serum samples were stored at -80°C , and high sensitivity C-reactive protein (hs-CRP) was determined using an immunoturbidity assay (Liatest; Stago, Asnieres-sur-Seine, France), with an interassay variability coefficient of variation of 6.25%.

Transthoracic Doppler echocardiography: Two-dimensional, M-mode, pulsed Doppler, and tissue Doppler echocardiography were performed using a Vivid Seven ultrasound machine (GE Medical Systems, Horten, Norway) with a 2.5 MHz transducer. Standard two-dimensional measurements (LV diastolic and systolic dimension, ventricular septum and posterior wall thickness, and left atrial volume) were assessed as recommended by the American Society of Echocardiography.¹⁶⁾ The mitral inflow velocities were traced and the following variables were obtained: peak velocity of early diastolic mitral inflow (E), late diastolic mitral inflow (A), and deceleration time of the E velocity. Early diastolic mitral annular (Em), late diastolic (Am), and systolic velocities (Sm) of the mitral annulus were measured from the apical 4-chamber view at the septal corner of the mitral annulus.

Statistical analyses: Continuous variables are presented as the mean $\pm$ standard deviation, and categorical variables are presented as absolute and relative frequencies (%). Data for groups of diastolic function were compared using the Wilcoxon rank sum test for continuous variables. Categorical variables were compared using the chi-square test. Independent predictors of diastolic dysfunction were examined with multivariate regression analysis after adjustment. All reported *P* values were two-sided, and *P* values ≤ 0.05 were considered to indicate statistical significance. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Cary, NC, USA).

RESULTS

The 532 statin-naïve patients without ASCVD were grouped according to whether they fit any of the criteria of one of the statin benefit groups, according to the 2013 ACC/AHA guidelines for blood cholesterol treatment. A total of 213 subjects were categorized as the statin benefit group (Benefit), and the rest were in the non-benefit control group (NoBenefit). Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics were more frequently prescribed in the statin benefit group. There was no difference in the use of beta-blockers or vasodilators between groups. However, to minimize the influence of these drugs, each group was divided into two groups (Y or N) according to antihypertensive medication administration. There were 4 groups: BenefitN ($n = 80$), BenefitY ($n = 133$), NoBenefitN ($n = 251$), and NoBenefitY ($n = 68$).

There were significant differences between the Benefit and NoBenefit groups with respect to age (54 ± 16 versus 59 ± 10 years, $P < 0.0001$), gender (males, 99 versus 131, $P < 0.0001$), weight (62.3 ± 10.2 versus 66.1 ± 11.0 kg, $P <$

0.0001), height (161 ± 8 versus 164 ± 9 cm, $P < 0.0001$), and fasting plasma glucose (103 ± 25 versus 125 ± 64 mg/mL, $P < 0.0001$); there was also a greater prevalence of history of smoking (33 versus 70, $P < 0.0001$), high blood pressure (HBP) (73 versus 125, $P < 0.0001$), and DM (0 versus 82, $P < 0.0001$) in the Benefit patients. TC and LDL levels were similar between the Benefit and NoBenefit groups, but TG level (110 ± 66 versus 134 ± 107 mg/mL, $P < 0.0001$) was higher in the Benefit group. The baseline characteristics of the 4 groups are shown in Table I. In subgroup analysis, there were significant differences in body mass index (BMI) and HBP between the NoBenefitN and NoBenefitY groups. In the two Benefit groups, there were significant differences in sex, BMI, and HBP.

Subjects in the Benefit group had greater LV wall thickness (10.2 ± 1.4 versus 10.7 ± 1.3 mm, $P < 0.0001$) and LV mass index (99.8 ± 20.8 versus 105.5 ± 19.6 mm, $P = 0.008$), lower E wave velocity (67.1 ± 16.6 versus 63.0 ± 15.6 cm/s, $P = 0.017$), higher A wave velocity (68.1 ± 18.1 versus 73.2 ± 15.4 cm/s, $P = 0.006$), and lower Em velocity (8.4 ± 3.0 versus 7.0 ± 2.1 cm/s, $P < 0.0001$). There were no significant differ-

Table I. Baseline Characteristics of the 532 Statin-Naïve Participants Without ASCVD

	No benefit ($n = 319$) Antihypertensive medication			Benefit ($n = 213$) Antihypertensive medication		
	No ($n = 251$)	Yes ($n = 68$)	<i>P</i>	No ($n = 80$)	Yes ($n = 133$)	<i>P</i>
Age, years	54 ± 8	55 ± 10	0.212	58 ± 9	60 ± 10	0.155
Male, number (%)	78 (31.1)	21 (30.9)	0.551	56 (69.9)	75 (56.4)	0.017
Weight, kg	61.8 ± 10.3	64.1 ± 9.8	0.118	64.9 ± 11.4	67.4 ± 10.5	0.096
Height, cm	161 ± 8	160 ± 8	0.390	164 ± 9	162 ± 9	0.090
Body mass index, kg/m ²	23.9 ± 3.4	25.0 ± 3.3	0.013	23.9 ± 3.1	25.5 ± 2.9	< 0.0001
Fasting plasma glucose, mg/dL	103 ± 27	103 ± 18	0.962	133 ± 78	117 ± 39	0.062
Hemoglobin A1c, %	5.7 ± 0.4	6.1 ± 0.6	0.149	8.2 ± 2.9	7.3 ± 1.5	0.102
Total cholesterol, mg/dL	193 ± 37	192 ± 38	0.855	191 ± 42	188 ± 35	0.654
Triglyceride, mg/dL	114 ± 68	93 ± 54	0.082	134 ± 124	134 ± 81	0.985
High density lipoprotein cholesterol, mg/dL	47 ± 11	48 ± 13	0.645	45 ± 14	44 ± 11	0.483
Low density lipoprotein cholesterol, mg/dL	118 ± 29	119 ± 28	0.821	115 ± 34	114 ± 31	0.815
hsCRP, mg/dL	0.8 ± 1.9	0.5 ± 0.8	0.510	0.3 ± 0.6	0.4 ± 0.7	0.395
Smoking, number (%)	26 (11.4)	7 (11.1)	0.999	31 (38.7)	39 (29.3)	0.301
Diabetes mellitus, number (%)	0 (0)	0 (0)	0	32 (40.5)	48 (36.1)	0.572
Hypertension, number (%)	32 (12.7)	41 (60.3)	< 0.0001	27 (33.6)	98 (73.6)	< 0.0001

Table II. Echocardiographic Parameters of the 532 Statin-Naïve Participants Without ASCVD

	No benefit ($n = 319$) Antihypertensive medication			Benefit ($n = 213$) Antihypertensive medication		
	No ($n = 251$)	Yes ($n = 68$)	<i>P</i>	No ($n = 80$)	Yes ($n = 133$)	<i>P</i>
LVEDD, mm	46.2 ± 5.3	48.3 ± 4.7	0.007	47.6 ± 3.8	47.5 ± 3.8	0.947
LVESD, mm	29.2 ± 3.5	29.5 ± 4.6	0.560	29.8 ± 3.8	29.9 ± 3.4	0.824
IVSd, mm	10.0 ± 1.2	10.7 ± 1.8	0.011	10.6 ± 1.3	10.8 ± 1.4	0.393
LVPWd, mm	9.6 ± 1.1	10.2 ± 1.5	0.004	10.2 ± 1.2	10.4 ± 1.2	0.424
LV mass index, g/m ²	96.8 ± 17.4	112.1 ± 28.1	< 0.0001	105.3 ± 19.3	105.8 ± 19.9	0.883
LV ejection fraction, %	63.8 ± 4.2	64.0 ± 4.5	0.707	62.6 ± 3.9	62.9 ± 4.6	0.642
Left atrial volume index, mL/m ²	24.0 ± 8.8	36.1 ± 33.6	0.150	27.3 ± 12.2	32.5 ± 16.2	0.293
Transmitral E wave velocity, cm/s	66.7 ± 16.3	68.7 ± 17.9	0.433	61.1 ± 13.7	65.4 ± 17.6	0.116
Transmitral A wave velocity, cm/s	66.7 ± 17.5	74.3 ± 19.3	0.006	71.1 ± 16.3	75.9 ± 13.8	0.079
Transmitral E wave/A wave velocity, cm/s	1.05 ± 0.34	0.96 ± 0.28	0.113	0.89 ± 0.25	0.89 ± 0.28	0.988
Systolic tissue velocity (Sm), cm/s	8.1 ± 6.1	7.8 ± 1.9	0.682	7.4 ± 1.3	7.1 ± 1.3	0.249
Early diastolic tissue velocity (Em), cm/s	8.4 ± 2.9	8.3 ± 3.3	0.766	7.4 ± 2.2	6.5 ± 1.7	0.017
Late diastolic tissue velocity (Am), cm/s	9.1 ± 1.9	9.9 ± 2.0	0.013	9.9 ± 1.7	9.4 ± 2.1	0.131
Transmitral E wave deceleration time, ms	202 ± 94	216 ± 59	0.290	210 ± 37	208 ± 48	0.718
E/Em	8.6 ± 2.6	9.7 ± 7.4	0.252	8.9 ± 2.6	10.4 ± 2.7	0.001

Table III. Peripheral and Central Arterial Hemodynamic Parameters of the 532 Statin-Naïve Participants Without ASCVD

	No benefit (<i>n</i> = 319) Antihypertensive medication			Benefit (<i>n</i> = 213) Antihypertensive medication		
	No (<i>n</i> = 251)	Yes (<i>n</i> = 68)	<i>P</i>	No (<i>n</i> = 80)	Yes (<i>n</i> = 133)	<i>P</i>
Peripheral, mmHg						
Systolic blood pressure	127 ± 16	130 ± 16	0.173	133 ± 20	139 ± 21	0.036
Diastolic blood pressure	78 ± 10	79 ± 10	0.764	79 ± 13	81 ± 14	0.217
Pulse pressure	49 ± 11	52 ± 13	0.051	54 ± 13	57 ± 13	0.065
Pulsatile Stress	3484 ± 1005	3712 ± 1249	0.117	3854 ± 1058	4230 ± 1225	0.017
Heart rate, beats/minute	72 ± 12	72 ± 15	0.823	72 ± 12	74 ± 13	0.207
Central						
Late systolic peak pressure (SBP2)	119 ± 17	121 ± 16	0.318	123 ± 21	127 ± 22	0.117
Radial augmentation index, %	83 ± 12	82 ± 12	0.384	80 ± 12	80 ± 14	0.999
Pulse pressure	41 ± 12	42 ± 14	0.264	43 ± 14	46 ± 15	0.243
Pulsatile Stress	2871 ± 855	2991 ± 960	0.319	3057 ± 950	3321 ± 1011	0.051

Table IV. Associations Between Echocardiographic Parameters of Left Ventricular Diastolic Function and Indices of Arterial Stiffness in Statin Benefit Group Using Univariate Linear Regression Analysis

Dependent variable / Independent variable	β	95%CI	<i>P</i>
Em			
SBP	-0.237	-0.041 to -0.007	0.006
Peripheral PP	-0.243	-0.061 to -0.011	0.004
Peripheral PS	-0.363	-0.001 to 0.000	< 0.0001
SBP2	-0.201	-0.036 to -0.003	0.019
Central PP	-0.192	-0.051 to 0.003	0.025
Central PS	-0.359	-0.001 to 0.000	< 0.0001
RaAIX	-0.033	-0.035 to 0.024	0.707
E/Em			
SBP	0.381	0.030 to 0.074	< 0.0001
Peripheral PP	0.429	0.055 to 0.118	< 0.0001
Peripheral PS	0.378	0.001 to 0.001	< 0.0001
SBP2	0.387	0.030 to 0.073	< 0.0001
Central PP	0.437	0.054 to 0.114	< 0.0001
Central PS	0.478	0.001 to 0.002	< 0.0001
RaAIX	0.191	0.004 to 0.082	0.029
LV mass index			
SBP	0.268	0.098 to 0.421	0.002
Peripheral PP	0.348	0.267 to 0.732	< 0.0001
Peripheral PS	0.249	0.001 to 0.007	0.004
SBP2	0.212	0.040 to 0.357	0.014
Central PP	0.262	0.129 to 0.582	0.002
Central PS	0.224	0.001 to 0.008	0.009
RaAIX	-0.033	-0.335 to 0.229	0.711

E indicates peak transmitral early diastolic inflow velocity; Em, peak early mitral annular velocity in septal mitral annulus; LV, left ventricle; SBP: systolic blood pressure; PP, pulse pressure; PS, pulsatile stress; SBP2, central systolic blood pressure; and RaAIX, augmentation index measured at the radial artery.

ences in LV end-systolic and end-diastolic dimensions (LVEDD), left atrial (LA) volume index, Sm velocity or deceleration time between the NoBenefit and Benefit groups. Table II shows a comparison of the echocardiographic findings of the 4 groups. NoBenefitY subjects had larger LVEDD, greater LV wall thickness, and LV mass index, higher A wave velocity, and higher Am wave velocity. BenefitY subjects had only lower Em velocity and higher E/Em.

There were significant differences in peripheral and central hemodynamic parameters and the indices of arterial stiffness according to the presence of statin benefit, including

Table V. Associations Between Echocardiographic Parameters of Left Ventricular Diastolic Function and Indices of Arterial Stiffness in Statin Benefit Group Using Multivariate Linear Regression Analysis

Dependent variable / Independent variable	β	95%CI	<i>P</i>
Em			
SBP	-0.277	-0.045 to -0.010	0.002
Peripheral PP	-0.131	-0.046 to 0.007	0.147
Peripheral PS	-0.272	-0.001 to 0.000	0.002
SBP2	-0.225	-0.040 to -0.004	0.016
Central PP	-0.056	-0.034 to 0.019	0.563
Central PS	-0.247	-0.001 to 0.000	0.012
RaAIX	0.044	-0.026 to 0.040	0.657
E/Em			
SBP	0.351	0.026 to 0.071	< 0.0001
Peripheral PP	0.309	0.030 to 0.096	< 0.0001
Peripheral PS	0.259	0.000 to 0.001	0.002
SBP2	0.329	0.022 to 0.067	< 0.0001
Central PP	0.292	0.022 to 0.090	0.001
Central PS	0.327	0.000 to 0.001	< 0.0001
RaAIX	0.052	-0.032 to 0.055	0.598
LV mass index			
SBP	0.404	0.208 to 0.539	< 0.0001
Peripheral PP	0.383	0.281 to 0.764	< 0.0001
Peripheral PS	0.233	0.001 to 0.007	0.014
SBP2	0.407	0.199 to 0.526	< 0.0001
Central PP	0.403	0.273 to 0.754	< 0.0001
Central PS	0.349	0.003 to 0.011	0.011
RaAIX	0.140	-0.104 to 0.531	0.186

Multivariate linear regression analysis with adjustment for age, gender, height, diabetes mellitus, hypertension, body mass index, and fasting plasma glucose. E indicates peak transmitral early diastolic inflow velocity; Em, peak early mitral annular velocity in septal mitral annulus; LV, left ventricle; SBP, systolic blood pressure; PP, pulse pressure; PS, pulsatile stress; SBP2, central systolic blood pressure; and RaAIX, augmentation index measured at the radial artery.

systolic BP (128 ± 16 versus 136 ± 20 mmHg, *P* < 0.0001), pPP (49 ± 11 versus 55 ± 13 mmHg, *P* < 0.0001), pPS (3532 ± 1064 versus 4025 ± 1150, *P* < 0.0001), SBP2 (119 ± 17 versus 125 ± 22 mmHg, *P* = 0.002), RaAIX (83 ± 12 versus 80 ± 13%, *P* = 0.005), cPP (41 ± 12 versus 44 ± 15 mmHg, *P* = 0.004), and cPS (2896 ± 878 versus 3178 ± 985, *P* = 0.001). There were no differences in diastolic BP and HR. Table III shows a comparison of peripheral and central hemodynamic parameters and the indices of arterial stiffness between the 4

Figure. Correlation between the diastolic function and RaAIX (A), SBP2 (B) in the statin benefit group ($n = 80$). RaAIX indicates radial augmentation index; E, peak velocity of early diastolic mitral inflow; Em, early diastolic mitral annular velocity; and E/Em, ratio of E/Em.

groups. There were no differences in the two NoBenefit groups. However, in the two Benefit groups, there were significant differences in systolic BP and pPP.

Table IV shows the associations between the echocardiographic parameters of left ventricular diastolic function and indices of arterial stiffness using univariate analysis in Benefit patients. There were significant correlations in several echocardiographic parameters of left ventricular diastolic function and indices of arterial stiffness.

Table V shows a multivariate linear regression analysis. After adjusting for age, gender, height, DM, HBP, BMI, and fasting plasma glucose, Em was significantly correlated with systolic BP, pPS, SBP2, and cPS. E/Em and LV mass index were significantly correlated with systolic BP, pPP, pPS, SBP2, cPP, and cPS. However, RaAIX was not correlated with Em, E/Em, and LV mass index.

In a subgroup analysis using bivariate correlation, RaAIX and SBP2 were significantly associated with Em and E/Em in BenefitN subjects ($n = 80$) without ASCVD (Figure). However, in multivariate linear regression analysis, after adjusting for age, gender, height, DM, HBP, BMI, and fasting plasma glucose, Em was not correlated with any parameters. E/Em was associated with only pPP ($\beta = 0.251$, 95% confidence interval [CI], 0.001–0.097, $P = 0.045$). LV mass index was significantly correlated with systolic BP ($\beta = 0.376$, 95% CI, 0.136–0.606, $P = 0.002$), pPP ($\beta = 0.409$, 95% CI, 0.221–0.908, $P = 0.002$), pPS ($\beta = 0.278$, 95% CI, 0.000–0.009, $P = 0.032$), SBP2 ($\beta = 0.372$, 95% CI, 0.116–0.579, $P = 0.004$), cPP ($\beta = 0.397$, 95% CI, 0.170–0.834, $P = 0.004$), and cPS ($\beta = 0.363$, 95% CI, 0.002–0.012, $P = 0.012$).

In NoBenefit ($n = 319$) subjects, Em was not correlated

with any parameters in multivariate linear regression analysis, after adjusting for age, gender, height, HBP, BMI, and fasting plasma glucose. E/Em was associated with only cPP ($\beta = 0.153$, 95% CI, 0.008–0.115, $P = 0.024$). LV mass index was significantly correlated with only RaAIX ($\beta = 0.178$, 95% CI, 0.058–0.586, $P = 0.017$).

In the subgroup NoBenefitN ($n = 251$) subjects, Em was not correlated with any parameters in multivariate linear regression analysis, after adjusting for age, gender, height, HBP, BMI, and fasting plasma glucose. E/Em was associated with only SBP2 ($\beta = 0.183$, 95% CI, 0.003–0.054, $P = 0.029$). LV mass index was significantly correlated with pPS ($\beta = -0.278$, 95% CI, -0.006–0.000, $P = 0.046$), cPP ($\beta = 0.234$, 95% CI, 0.096–0.631, $P = 0.008$), and RaAIX ($\beta = 0.322$, 95% CI, 0.209–0.714, $P < 0.0001$).

DISCUSSION

This study sought to clarify the relationships between the arterial stiffness index measured at the radial artery and LV diastolic function, in asymptomatic high-risk patients without ASCVD or history of statin treatment, who were seen at a teaching hospital. Central hemodynamic parameters were associated with diastolic dysfunction in this population. Interestingly, RaAIX was not correlated with diastolic dysfunction in the Benefit subjects. However, in the NoBenefit and NoBenefitN subjects, RaAIX was related to LV mass index. We can partially explain the differences in these results by the increasing pulse pressure in Benefit subjects, and the increasing denominator in the equation used for the calculation of RaAIX.

Accordingly, we suggest that arterial stiffness measured at the radial artery is associated with diastolic function in patients with subclinical atherosclerosis, a useful finding for the primary prevention of ASCVD.

Our findings are similar to those of an earlier report that RaAIx could serve as a surrogate marker of carotid atherosclerosis in routine clinical practice,⁷⁾ although the previous study did not evaluate diastolic function. In the Strong Heart Study, noninvasively determined central PP was related more to vascular hypertrophy, the extent of atherosclerosis as assessed by carotid artery ultrasound, and cardiovascular events, than to brachial BP in the general population.¹⁷⁾

Arterial wave reflection, not augmentation index, has been independently associated with incident cardiovascular events, and is strongly associated with incident congestive heart failure in the general population.¹⁸⁾ In patients with LV systolic dysfunction, aortic wave reflections and cardio-ankle vascular index negatively interfere with LV function and induce a shortening of EF.^{19,20)} In a previous study, wave reflection was assessed by wave separation analysis, and was generated predominantly near muscular (medium-sized) and smaller arterial segments. It should be noted that wave reflection is highly modifiable by vasoactive drugs despite small effects on brachial pressure.²¹⁾ RaAIx is not only influenced by the magnitude of wave reflections but also confounded by their timing, as well as HR, body height, and other factors. In this study, RaAIx was associated with LV mass index in the NoBenefit group, after adjusting for several confounding factors.

Diastolic dysfunction is associated with older age, female gender, and a history of hypertension. Despite similar peripheral PP, the central hemodynamics reflecting arterial stiffness differ between men and women.²²⁾ Wide variation in brachial-aortic systolic BP differences can occur between patients with similar brachial systolic BP.²³⁾ The magnitude of pressure amplification may vary and is influenced by several demographic variables, including age, gender, and height, as well as clinical and physiological factors, such as hypercholesterolemia and heart rate. Patients with hypercholesterolemia (defined as TC $\geq$ 250 mg/dL) have a higher central pulse pressure and stiffer blood vessels than matched controls, despite similar peripheral BP.²⁴⁾ In the present study, the mean TC level of all patients was 191 mg/dL, which is lower than seen in a previous study. According to 2013 ACC/AHA guidelines,¹³⁾ the statin benefit group did not refer to only those with higher lipid levels, but also intended a disease-specific approach.

A few studies have examined the relationship between arterial stiffness and diastolic dysfunction in various populations.^{25,26)} We previously reported²⁷⁾ that amplification of BP and higher RaAIx are associated with diastolic dysfunction in subjects without hypertension, after adjusting for age and sex. The results of the present study are similar to those of our previous study. Increased arterial stiffness may contribute to the development of LV diastolic dysfunction through increased PP and LV afterload. Greater LV afterload and an increase in late systolic augmentation may slow LV relaxation. There appears to be a significant relationship between arterial stiffness and diastolic dysfunction, independent of age, sex, and risk factors. In addition, noninvasive estimation of central hemodynamic parameters offers a useful method for routine clinical practice.

Beta-blockers and ACE inhibitors improve survival in patients with heart failure and a normal EF,²⁸⁾ and statin therapy

is similarly associated with improved survival in the same patients.⁹⁾ However, the mechanism behind the beneficial effects of statins on diastolic heart failure remains unknown. We included antihypertensive medication and vasoactive drugs in our analysis because of their different effects on peripheral and central BP.^{21,29,30)} After we controlled for patients taking medications, and after adjusting for age, gender, height, DM, HBP, BMI, and fasting plasma glucose, central hemodynamic parameters were associated with diastolic dysfunction in asymptomatic high-risk patients without ASCVD. We used the newly defined concept of ASCVD in this study, because risk estimates for a more broadly based ASCVD outcome are more relevant to contemporary populations, according to the ACC/AHA guidelines for cardiovascular risk assessment in 2013.³¹⁾

Our study has a few limitations. First, it was cross-sectional, so the causal relationship observed between arterial stiffness and diastolic dysfunction in the statin benefit group without ASCVD remains to be fully established by prospective studies. However, in the statin benefit group with various risk factors or medical treatments, arterial stiffness and diastolic function in statin-naïve subjects were evaluated. In addition, enrolled patients ranged in age from 40 to 75 years old. Second, the augmentation index (AI) was obtained directly from radial pressure waveforms instead of aortic or carotid pulse waves. Although this method is not the gold standard, RaAIx has been significantly associated with carotid AI in an adult population with a wide age range, and gives information equivalent to carotid AI measurements.³²⁾ In addition, noninvasive estimation of RaAIx and central BP by using automated applanation tonometry is simple and inexpensive.

In conclusion, we found that central hemodynamic parameters (eg, SBP2, cPP, and cPS) were associated with diastolic function in statin benefit patients without ASCVD, after adjusting for age, gender, height, DM, HBP, BMI, and fasting plasma glucose, or after excluding the effect of antihypertensive medication. However, RaAIx should not be considered for use as an isolated index of arterial stiffness. We suggest that arterial stiffness is associated with diastolic function in patients with subclinical atherosclerosis, a useful finding for the primary prevention of ASCVD. Although further studies are required, therapies that prevent progression of arterial stiffness and reduce late-systolic pressure overload may help reduce the prevalence of LV diastolic dysfunction in asymptomatic high-risk patients.

DISCLOSURES

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The authors declare that there is no conflict of interest.

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