CLINICAL STUDY

Coronary Artery Calcium Is Associated with Left Ventricular Diastolic Function Independent of Myocardial Ischemia

Assessment by Myocardial Perfusion Single-Photon Emission Computed Tomography

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Summary

It has been shown in several studies that coronary artery calcium (CAC) burden or CAC progression is associated with heart failure. We tested the hypothesis that the extent of CAC is associated with left ventricular (LV) diastolic parameters derived from gated myocardial perfusion single-photon emission computed tomography (SPECT) in patients with no evidence of myocardial ischemia.

157 patients undergoing coronary computed tomography (CT), gated SPECT, and transthoracic echocardiography (TTE) were enrolled in this study. The CAC score was calculated according to the Agatston method. The peak filling rate (PFR) and the one-third mean filling rate (1/3MFR) were obtained as LV diastolic parameters.

There were 139 patients with CAC and 18 patients without. The CAC score ranged from 0 to 4,976. There were no significant differences in the LV end-diastolic volume (LVEDV) (61 ± 21 mL versus 62 ± 22 mL, P = 0.79) and LV ejection fraction (LVEF) (66 ± 9% versus 68 ± 9%, P = 0.43). Patients with CAC had lower PFR than those without (2.2 ± 0.5 EDV/s versus 2.6 ± 0.7 EDV/s, P = 0.03). Multivariate linear regression analysis showed that ln (CAC score + 1) was significantly associated with PFR (β = −0.20, P = 0.01) and 1/3MFR (β = −0.18, P = 0.049).

Our data suggest that the extent of CAC is inversely associated with LV diastolic parameters derived from gated SPECT independent of myocardial ischemia.

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Key words: Myocardial imaging, Coronary calcium

Coronary artery calcium (CAC) score derived from coronary computed tomography (CT) is a well-known surrogate for predicting future cardiovascular events.[1,2] It has been shown in several studies that CAC burden or CAC progression is associated with a risk of heart failure, suggesting a possible linkage between CAC and left ventricular (LV) diastolic function.[3,4] It should be further evaluated whether CAC is linked with LV diastolic function independent of myocardial ischemia. Gated myocardial perfusion single-photon emission computed tomography (SPECT) is a suitable modality for examining this clinical question because it can provide information about myocardial perfusion and LV function simultaneously.[5-7]

In the present study, we tested the hypothesis that the extent of CAC is associated with LV diastolic parameters derived from gated SPECT in patients with no evidence of myocardial ischemia.

Methods

Study population: Between July 2012 and May 2017, 617 patients with angina-like symptoms underwent coronary CT, gated SPECT, and transthoracic echocardiography (TTE) within one year of each examination for evaluating coronary artery disease. Patients with summed stress score (SSS) of > 3, suggesting the presence of myocardial ischemia, were excluded[8] because the purpose of this study was to clarify the relation between CAC and LV diastolic function independent of myocardial ischemia. Patients with previous cardiac or aortic surgeries, reduced LV ejection fraction (LVEF) of < 50%,[9] hemodynamically significant valvular heart disease, atrial fibrillation, ventricular pacing, and hemodialysis were also excluded because these could affect the LV diastolic parameters. Finally, 157 patients with no evidence of myocardial ischemia were enrolled in this study. The study protocol was

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approved by the Ethical Committee for Epidemiology of Hiroshima University. Informed consent was obtained from all patients.

CAC analysis: CAC was assessed using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan). All patients were given sublingual nitroglycerin just before scanning.[10,11] An unenhanced scan with prospective electrocardiogram triggering was performed to measure the CAC score (slice thickness: 3.0 mm; maximum tube current: 270 mA; tube voltage: 120 kV). The CAC score was calculated using a commercially available software package (SmartScore, version 3.5; GE Healthcare, Chicago, IL, USA) according to the Agatston method.[12] CAC was considered absent when the CAC score was zero. The patients were divided into two groups according to the presence or absence of CAC. The CAC score was also analyzed as a continuous variable transformed into the natural logarithm (ln) of (CAC score + 1) to better normalize the CAC score distribution.[13,14]

Gated SPECT: All patients fasted overnight and underwent gated SPECT. Adenosine was infused over 6 minutes (120 μg/kg/minute), and thallium-201 (Tl-201) (111 MBq [3.0 mCi]) was injected 3 minutes after the initiation of adenosine infusion. Stress Tl-201 SPECT acquisition was started 5 minutes after the pharmacological stress test. After 4 hours, a redistribution image was obtained. Gated SPECT images were acquired using a dual-detector 90° γ-camera (BrightView X; Philips Healthcare, Milpitas, CA, USA). Images were acquired with the following parameters: 36 total projections; 180° from right anterior oblique to left posterior oblique and a noncircular orbit; 64 × 64 matrix; 6.4 mm pixel size; 16 frames per cardiac cycle; low-energy, high-resolution collimation; and 40 seconds per step. Images were reconstructed using ordered-subset expectation maximization (iteration: 2, subset: 9) with a Butterworth filter (order: 8; cutoff frequency: 0.34 cycles/cm for the redistribution image).

SPECT interpretation: Semiquantitative visual interpretation of SPECT images was performed with the short and vertical long axes divided into 17 segments for each study. Each segment was scored using a five-point scoring system (0: normal uptake; 1: mildly reduced uptake; 2: moderately reduced uptake; 3: severely reduced uptake; 4: absence of detectable radiotracer in a segment). Two experienced nuclear cardiologists performed the semiquantitative analysis independently, and consensus was reached on all analyses.

LV volume and function: LV end-diastolic volume (LVEDV) and LVEF were obtained on redistribution images using the widely adopted algorithm (quantitative gated SPECT; Cedars-Sinai Medical Center, Los Angeles, CA, USA).[5] The transient ischemic dilation (TID) ratio was defined as the ratio of LVEDVs on stress and redistribution images. The following LV diastolic parameters were obtained from the redistribution images. The peak filling rate (PFR) was defined as the maximum dV/dt divided by LVEDV.[6,7] The one-third mean filling rate (1/3 MFR) was defined as the average of dV/dt in the first third of the filling time.[6,7]

TTE: A comprehensive echocardiographic assessment was performed by three experienced sonographers blinded to the patients' clinical status, using a Vivid E9 ultrasound system with a 2.5 MHz transducer (GE Vingmed Ultrasound, Horten, Norway). All imaging data were digitized and saved on an optical disk for offline analysis (EchoPAC software version 112; GE Vingmed Ultrasound). LV internal dimension (LVID), interventricular septal thickness (IVS), and posterior wall thickness (PWT) were measured at end diastole. LV mass was calculated with the following formula:[15] LV mass (g) = 0.8 × 1.04 [(LVID + IVS + PWT)^3 − (LVID)^3] + 0.6. The LV mass index (LVMI) was calculated by dividing the LV mass by the body surface area.

Statistical analysis: Continuous variables are expressed as the mean ± standard deviation, and categorical variables are presented as percentages. Categorical variables were compared using the chi-squared test, and continuous variables were compared using the Mann-Whitney U test. Pearson's correlation was used to analyze the correlations of ln (CAC score + 1) with PFR and 1/3MFR. A linear regression analysis was performed using clinical variables including ln (CAC score + 1) to determine the factors associated with PFR and 1/3MFR. P-values < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP 12 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics: The patient characteristics are shown in Table I. There were 139 patients with CAC and 18 patients without. The CAC score ranged from 0 to 4,976. There were no significant differences in terms of age, sex, systolic blood pressure, heart rate, serum creatinine, lipid profile, medications, and LVMI between patients with CAC and those without. Patients with CAC had diabetes mellitus (P = 0.04) and New York Heart Association Functional Classification II or III (P = 0.02) more frequently than those without.

The time interval between coronary CT and gated SPECT was 82 ± 121 days. LVEDV (61 ± 21 mL versus 62 ± 22 mL, P = 0.79), TID ratio (1.1 ± 0.1 versus 1.1 ± 0.1, P = 0.31), and LVEF (66 ± 9% versus 68 ± 9%, P = 0.43) were similar between the two groups. However, patients with CAC had lower PFR than those without (2.2 ± 0.5 EDV/s versus 2.6 ± 0.7 EDV/s, P = 0.03).

Effects of CAC on LV diastolic parameters: The Figure shows correlations between ln (CAC score + 1) and LV diastolic parameters. ln (CAC score + 1) was inversely associated with PFR (r = −0.30, P < 0.001) and 1/3MFR (r = −0.24, P = 0.002). There were no correlations between ln (CAC score + 1) and LVEDV (P = 0.43) or between ln (CAC score + 1) and LVEF (P = 0.17).

Multivariate linear regression analysis was performed to determine the factors associated with LV diastolic parameters. LVEDV (β = −0.35, P = 0.002) and ln (CAC score + 1) (β = −0.20, P = 0.01) were significantly associated with PFR (Table II). Furthermore, LVMI (β = −0.25, P = 0.03) and ln (CAC score + 1) (β = −0.18, P = 0.049) were significantly associated with 1/3MFR (Table III).

Table I. Patient Characteristics.

Variables	Presence of CAC (n = 139)	Absence of CAC (n = 18)	P-value
Age (years)	71 ± 8	66 ± 13	0.13
Male	95 (68%)	9 (50%)	0.18
Body mass index (kg/m^2)	23 ± 3	23 ± 4	0.47
Systolic blood pressure (mmHg)	137 ± 23	133 ± 30	0.59
Heart rate (bpm)	66 ± 11	69 ± 12	0.30
Hypertension	105 (76%)	12 (67%)	0.40
Diabetes mellitus	50 (36%)	2 (11%)	0.04
Dyslipidemia	98 (71%)	13 (72%)	1.00
Smoking	83 (60%)	10 (56%)	0.80
Prior myocardial infarction	0 (0%)	0 (0%)	1.00
Prior coronary intervention	8 (6%)	1 (6%)	0.97
Serum creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.12
HDL cholesterol (mg/dL)	59 ± 18	65 ± 18	0.26
LDL cholesterol (mg/dL)	106 ± 34	113 ± 38	0.50
Triglycerides (mg/dL)	128 ± 76	115 ± 60	0.41
Hemoglobin A1c (%)	6.2 ± 1.0	5.8 ± 0.7	0.04
NYHA classification			0.02
Functional class I	11 (8%)	5 (28%)	
Functional class II	104 (75%)	12 (67%)	
Functional class III	24 (17%)	1 (5%)	
Medications			
ACEIs or ARBs	61 (44%)	6 (33%)	0.39
Beta-blockers	31 (22%)	1 (6%)	0.10
CCBs	69 (50%)	5 (28%)	0.08
Statins	76 (55%)	6 (33%)	0.09
LVMI (g/m^2)	90 ± 23	82 ± 17	0.11
QGS variables			
LVEDV (mL)	61 ± 21	62 ± 22	0.79
Transient ischemic dilation ratio	1.1 ± 0.1	1.1 ± 0.1	0.31
LVEF (%)	66 ± 9	68 ± 9	0.43
PFR (EDV/s)	2.2 ± 0.5	2.6 ± 0.7	0.03
1/3MFR (EDV/s)	1.3 ± 0.4	1.5 ± 0.5	0.12

CAC indicates coronary artery calcium; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LVMI, left ventricular mass index; QGS, quantitative gated single-photon emission computed tomography; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PFR, peak filling rate; and 1/3MFR, one-third mean filling rate.

Discussion

In this study, it was demonstrated that, in patients with no evidence of myocardial ischemia, the extent of CAC was inversely associated with LV diastolic parameters derived from gated SPECT, and ln (CAC score + 1) was an independent predictor of these parameters.

Numerous studies have shown that the CAC score offers incremental information beyond traditional risk factors for predicting future cardiovascular events.[16-19] Moreover, several studies have recently shown an association between CAC and the development of heart failure.[3,4] Leening, *et al*. reported that the extent of CAC had a clear association with the development of heart failure independent of overt coronary artery disease.[3] Bakhshi, *et al*. showed that CAC progression assessed by serial CAC measurement was associated with incident heart failure independent of overt coronary artery disease.[4] However, in these studies, no assessments of the functional significance of coronary artery disease have ever been performed (i.e., the presence or absence of myocardial ischemia). It remains unclear whether CAC is associated with the development of heart failure independent of myocardial ischemia or not. Approximately half of the patients with heart failure have preserved LVEF, and impaired LV diastolic function is a major cause of heart failure.[20] From this point of view, it is clinically important to clarify the effects of CAC on LV diastolic function independent of myocardial ischemia.

Gated SPECT is a unique modality that allows us to evaluate both myocardial perfusion and LV function by a single test. Myocardial ischemia is one of the major factors inducing impaired LV diastolic function.[21] In the present study, we included only patients with no evidence of myocardial ischemia on the basis of SSS with TID ratio. We demonstrated that patients with CAC had lower PFR compared with those without, although the LVMI and LVEF were similar between the two groups. Thus, gated SPECT was useful in selecting the study population and in assessing the effects of CAC on the LV diastolic func-

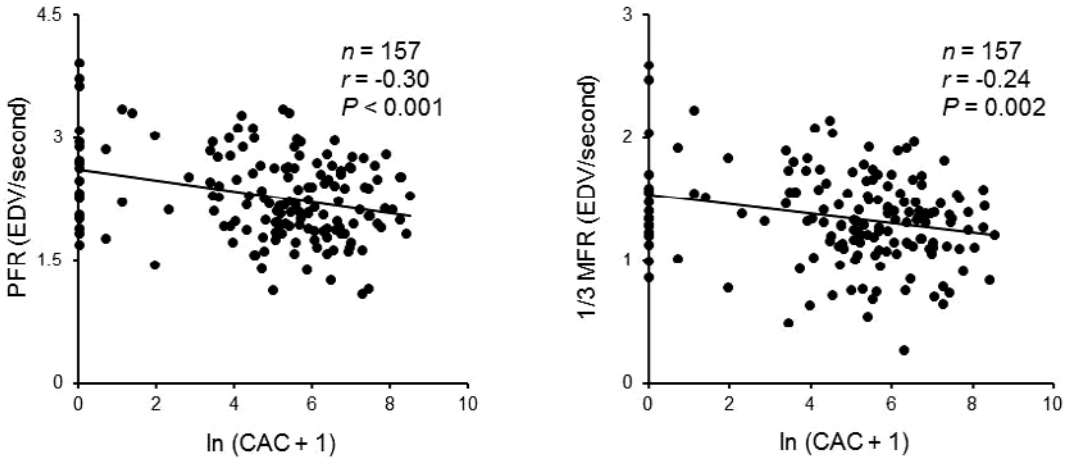

Figure. ln (CAC score + 1) was inversely associated with PFR ($r = -0.30$, $P < 0.001$) (left) and 1/3MFR ($r = -0.24$, $P = 0.002$) (right).

Table II. Linear Regression Analysis to Determine the Factors Associated with PFR.

Variables	Univariate		Multivariate	
	β	*P*-value	β	*P*-value
Age	−0.14	0.08	−0.14	0.11
Male	−0.24	0.003	−0.10	0.29
Body mass index	−0.19	0.02	−0.03	0.67
Hypertension	−0.21	0.008	−0.10	0.20
Diabetes mellitus	0.11	0.18	0.15	0.052
Serum creatinine	−0.14	0.09	−0.03	0.75
LVMI	−0.29	< 0.001	−0.10	0.32
LVEDV	−0.27	< 0.001	−0.35	0.002
ln (CAC score + 1)	−0.30	< 0.001	−0.20	0.01

LVMI indicates left ventricular mass index; LVEDV, left ventricular end-diastolic volume; CAC, coronary artery calcium; and PFR, peak filling rate.

Table III. Linear Regression Analysis to Determine the Factors Associated with 1/3MFR.

Variables	Univariate		Multivariate	
	β	*P*-value	β	*P*-value
Age	−0.16	0.04	−0.04	0.70
Male	−0.14	0.09	−0.08	0.45
Body mass index	−0.12	0.13	−0.05	0.56
Hypertension	−0.24	0.002	−0.12	0.18
Diabetes mellitus	0.04	0.64	0.03	0.72
Serum creatinine	−0.03	0.74	0.02	0.82
LVMI	−0.32	< 0.001	−0.25	0.03
LVEDV	−0.12	0.12	−0.07	0.60
ln (CAC score + 1)	−0.24	0.002	−0.18	0.049

LVMI indicates left ventricular mass index; LVEDV, left ventricular end-diastolic volume; CAC, coronary artery calcium; and 1/3MFR, one-third mean filling rate.

tion. In agreement with our results, Maragiannis, *et al*. showed a higher incidence of impaired LV diastolic function in patients with CAC compared to those without.[22] Their study comprised younger patients compared with our study, and only 49 out of 114 patients had CAC. Therefore, they did not evaluate the graded association between the extent of CAC and LV diastolic function. Osawa, *et al*. recently showed that patients with a CAC score of ≥400 had impaired LV diastolic function on TTE more frequently than those with a CAC score of 0-9.[23] They assessed the presence or absence of impaired LV diastolic function but did not evaluate its severity. In contrast, in the present study, we assessed the CAC and LV diastolic function as continuous variables using coronary CT and gated SPECT, respectively, and showed that the extent of CAC was inversely associated with LV diastolic parameters such as PFR and 1/3MFR. Because we included only patients with no evidence of myocardial ischemia, our results suggest that the extent of CAC is inversely associated with LV diastolic function independent of myocardial ischemia.

Our findings of the linkage between CAC and LV diastolic function may be explained by some possible mechanisms. One possible mechanism is the strong and graded associations among CAC, aortic calcification, and arterial stiffness.[24-27] Oei, *et al*. demonstrated that there was an 11-fold increase in CAC from the lowest category of aortic calcification to the category of severe calcification in men, with a 20-fold increase in CAC in women.[24] van Popele, *et al*. and Kullo, *et al*. reported that carotid-femoral pulse wave velocity, the gold-standard measurement of arterial stiffness, was associated with ln (CAC score + 1) in elderly people[26] and in a community-based sample of adults,[13] respectively. We also recently showed that the radial augmentation index, one of the indices of arterial stiffness, was associated with ln (CAC score + 1).[14] Based on these findings, patients with CAC may have increased arterial stiffness leading to impaired LV diastolic function. The other possible mechanism is the association between CAC and microvascular function. Coronary flow reserve (CFR) is considered as a composite marker for macro- and microvascular function. Several studies have shown an inverse correlation between the extent of CAC and CFR in patients with no obstructive coronary artery disease, indicating an association between CAC and microvascular function.[28] On the other hand,

Blomster, *et al*. demonstrated that CFR measured by TTE reflected LV diastolic function well in patients with angina-like symptoms.[29] Konerman, *et al*. also showed similar results using positron emission tomography.[30] Taken together, the results have shown that patients with CAC may have impaired CFR leading to impaired LV diastolic function. Our findings suggest that, especially in patients with severe CAC, the LV diastolic function should be examined using some modality in order to prevent the development of heart failure.

There were several limitations in this study. First, we conducted this study on patients with no evidence of myocardial ischemia. It remains unclear whether CAC has additive effects on LV diastolic function in patients with myocardial ischemia. Second, there was a time interval of 82 days between coronary CT and gated SPECT. This indicates that the CAC score and LV diastolic parameters were not assessed at the same time. However, according to a recent study, the annual change in the CAC score is only 24.9.[27] This time interval would be acceptable for the purpose of our study. Third, we used Tl-201 for gated SPECT. Compared with Tl-201, a higher dose of technetium agents can provide a better image quality without increasing the radiation burden and would be suitable for assessing the LV diastolic function. Fourth, there was a possibility of selection bias because we enrolled patients undergoing coronary CT, gated SPECT, and TTE. Finally, the small sample size was a major limitation of this study.

Conclusion

In conclusion, our data suggest that the extent of CAC is inversely associated with LV diastolic parameters derived from gated SPECT independent of myocardial ischemia.

Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest.

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