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Retrospective Study

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Chest Pain Without Coronary Artery Obstruction and Calcification in Young Women May Indicate Left Ventricular Diastolic Dysfunction

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ABSTRACT

Background: Left ventricular diastolic dysfunction (LVDD) and coronary artery calcification become worse with increasing age. However, it is unclear whether there is a gender difference in patients with chest pain but no obstructive coronary artery disease (CAD).
Aim: This study's aim was to investigate whether gender and age differences existed in the association between LVDD and the coronary artery calcium score (CACS) in patients with chest pain but no obstructive CAD.
Methods: We retrospectively studied a total of 705 patients (age 65±13 years; men 342, 49%) who had chest pain, normal LV ejection fraction on echocardiography, and no obstructive CAD on computed tomography (CT) coronary angiography. LVDD was defined by the American Society of Echocardiography recommendation of septal e'<8. Abnormal CACS was defined as CACS of >0.
Results: Although, there was a significant difference in LVDD prevalence among patients with normal and abnormal CACS (76.1% *vs*. 88.9%; $p<0.001$), in a multiple logistic regression analysis, LVDD was not significantly associated with abnormal CACS. When the patients were divided according to gender and age (decades; 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 years), the proportion of men and women with abnormal CACS increased with age. On the other hand, young women (age 20-39 years) with normal CACS showed a high LVDD prevalence, although older women (age 60-69 years) and young men (age 20-39 years) had a low LVDD prevalence.
Conclusions: Young women with chest pain but no obstructive and no calcified CAD, which associated with LVDD. LV diastolic function assessment by echocardiography should be performed in young women with chest pain even with normal CT coronary angiogram.

KEY WORDS: Diastolic heart failure; Left ventricular diastolic dysfunction; Coronary artery calcium score; Gender difference.

ABBREVIATIONS: LVDD: Left Ventricular Diastolic Dysfunction; CAD: Coronary Artery Disease; CACS: Coronary Artery Calcium Score; CAC: Coronary Artery Calcification; HFpEF: Heart Failure with Preserved Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; HDL: High-density lipoprotein cholesterol; DT: Deceleration Time; LAD: Left Atrial Diameter; PWT: Posterior Wall Thickness; IVST: Interventricular septal thickness.

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INTRODUCTION

Epidemiologic studies report that 30-50% patients with heart failure have left ventricular diastolic dysfunction (LVDD), for which no effective treatment yet exists.[1,2] The proportion of heart failure caused by LVDD increases with age.[3] Previous studies have shown that LVDD is a predictor for cardiovascular disease and mortality.[4,5] Groups at high risk for LVDD include the elderly; women; and patients with hypertension, diabetes mellitus, metabolic syndrome, chronic kidney disease, or coronary artery disease (CAD). LVDD is closely related to heart failure with preserved ejection fraction (HFpEF), and the early detection of LVDD is important for preventing HFpEF. Two recent studies reported a significant association between LVDD and coronary artery calcification (CAC) in patients without CAD.[6,7] In one study, the coronary artery calcium score (CACS) was associated with LVDD with an odds ratio of 1.96 for CACS of ≥400 compared with that of 0-9.[6] LVDD and CACS become worse with increasing age. CACS is known to be higher in men than women.[8,9] Meanwhile, LVDD prevalence increases with age, especially in women. Therefore, we hypothesized that the association between LVDD and CACS would be affected by gender and age. Furthermore, the association between LVDD and CACS is unknown in patients with chest paint but no coronary artery stenosis. The current study's aim was to evaluate the effect of gender and age in the association between LVDD and CACS in patients with chest pain but no obstructive CAD.

METHODS

Study Population

The study was retrospective in design. We enrolled patients into the study if they were aged ≥20 years and had been admitted to the National Center for Global Health and Medicine with chest pain between August 2010 and October 2015. All patients underwent computed tomography (CT) coronary angiography, from which CACS was obtained. Echocardiography was performed within 1 month before CT coronary angiography. Patients with coronary artery stenosis (>70%) as observed on CT coronary angiography were excluded. Other exclusion criteria were as follows: CAD, defined as history of acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass graft surgery; LV ejection fraction (LVEF) <50%; atrial fibrillation; moderate to severe aortic or mitral valve disease; pericardial disease; and inadequate echocardiographic studies. In addition, patients who had undergone mitral valvuloplasty, mitral valve replacement, or aortic valve replacement as well as those on hemodialysis were excluded. A total of 705 patients with normal LVEF and without current or past obstructive CAD or major valve disease were included in the analysis.

This study was approved by the institutional review board of the National Center for Global Health and Medicine (Approval No. NCGM-G-002112-00). The study was conducted in accordance with the principles of the Declaration of Helsinki.

CT Protocol

All patients underwent scanning with a 320-row multi-detector computed tomography (MDCT) scanner (Aquilion, Toshiba Medical Systems, Tochigi, Japan). Angiographic scan parameters were as follows: detector collimation 320×0.5 mm; rotation times adapted to heart rate (0.35, 0.375, and 0.40 ms); tube voltage 120 kVp; and X-ray exposure dose set using auto exposure control (maximum tube current 400 mA and image noise set to "standard deviation (SD)=25" per 0.5-mm-thick slice).

Before CT angiography, CACS was measured. We performed a non-contrast enhanced, prospective electrocardiography-gated CT scans to measure CACS, which was calculated using the Agatston method.[10] CACS was quantified on a workstation (Ziostation ver 2.0.X, Ziosoft, inc. Tokyo, Japan) with calcium-scoring software. For these analyses, we defined an abnormal CACS as CACS>0.

Echocardiography

We performed echocardiography using one of two systems (Artida SSH-880-CV or Aplio 400 TUS-A400 equipment with 2.5-MHz and 3.5-MHz transducers, Toshiba Medical Systems, Tochigi, Japan). A two-dimensional, guided M-mode echocardiography was performed by experienced cardiac ultrasonologists who were blinded to the patients' CACS and laboratory data. M-mode measurements included LV end-diastolic diameter (LVDd); LV end-systolic diameter (LVDs); LV posterior wall thickness (PWT), and interventricular septal thickness (IVST); left atrial diameter (LAD); and LVEF. LV mass (LVM) was calculated using the Devereux formula, and the LV mass index (LVMI) was derived by indexing LV mass to patient height.[11] We assessed diastolic function by pulsed-wave Doppler examination of mitral flow and tissue Doppler imaging of the mitral annulus. From the mitral inflow profile, we determined E-wave and A-wave peak velocities, mitral deceleration time (DT) and the E/A ratio. We measured mitral annular motion septal velocity obtained using tissue Doppler technique and calculated septal e' and the E/e' ratio. LVDD was defined as septal e' of <8, according to the standard algorithm recommended by the American Society of Echocardiography.[12] The variables lateral e' and LA volume index were not available in all patients; hence, we did not incorporate that data into the LV diastolic function assessment.

Statistical Analysis

Data are presented as the mean±standard deviation (SD) for continuous variables and percentages (total number) for categorical variables. Categorical and continuous variables were compared between the groups by chi-square analysis, variance analysis, and Wilcoxon rank sum test, respectively. Multivariable analysis was performed by logistic regression analysis for independent variables related to CACS. A p value of <0.05 was considered significant. Statistical analysis was performed using the JMP software package (version 10, SAS Institute Inc., Cary, NC, USA).

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RESULTS

CACS and LVDD

We analyzed data obtained for 705 patients (342 men, 363 women; mean age 65±13 years). We divided the subjects into two groups according to the absence (CACS=0, n=418, 59.3%) or presence (CACS>0, n=287) of abnormal CACS. Patient characteristics and echocardiography results for the two groups are shown in Table 1. There were no differences in dyslipidemia prevalence, E-wave, and EF between the groups. Patients with an abnormal CACS were older and more likely to be male and have hypertension, diabetes mellitus, and a smoking history. Triglycerides, hemoglobin A1c, and brain natriuretic peptide were significantly higher in patients with abnormal CACS than in those with normal CACS. LV diastolic diameter (LVDd), LA diameter (LAD), and LVMI were significantly larger in patients with abnormal CACS than in those with normal CACS. In addition, IVST and PWT were greater in patients with abnormal CACS than in those with normal CACS. However, creatinine clearance (CCr), total cholesterol, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) were significantly lower in patients with abnormal CACS than in those with normal CACS. Factors such as A-wave, E/A ratio, DT, septal e' velocity, septal E/e', and LAD (an index of LVDD) were also related to abnormal CACS. LVDD prevalence was 88.9% (n=255) in patients with abnormal CACS and 76.1% (n=318) in patients with normal CACS (p<0.001). We divided the subjects into two groups according to the absence (LVDD (-), n=132, 18.7%) or presence (LVDD (+), n=573) of LVDD. Patient characteristics and echocardiography results for the two groups are shown in Table 2. Patients with LVDD were older, more likely to have hypertension and diabetes mellitus than those without LVDD. Patients with LVDD had higher body mass index, hemoglobin A1c levels and lower CCr levels than those without LVDD. Among the cardiac echocardiography parameters, there were significant differences between with LVDD and without LVDD except LVDd. Abnormal CACS prevalence was 44.5% (n=255) in patients with LVDD and 24.2% (n=32) in patients without LVDD (p<0.001). In a multiple logistic regression analysis adjusted for variables associated with abnormal CACS, age, male gender, history of smoking, and LVMI were

Table 1: Characteristics and Echocardiography Results of Study Population According to Coronary Artery Calcium Score (CACS).

	Total	CACS = 0	Abnormal CACS	
Variables	n=705	n=418	n=287	*p* value
Age (years)	65.2±12.6	62.0±13.7	69.9±8.9	<0.001
Male, n(%)	342 (48.5%)	182 (43.5%)	160 (55.9%)	<0.01
Body mass index (kg/m^2)	23.1±3.8	22.9±3.7	23.5±3.8	0.04
Hypertension, n(%)	351 (50.0%)	176 (42.3%)	175 (61.2%)	<0.001
Dyslipidemia, n (%)	361 (51.7%)	202 (48.7%)	159 (56.2%)	0.05
Diabetes Mellitus, n (%)	113 (16.1%)	55 (13.3%)	58 (20.3%)	0.01
History of smoking, n (%)	262 (45.1%)	142 (39.3%)	120 (54.5%)	<0.01
CCr (ml/min)	80.0±27.2	85.5±27.8	72.2±25.7	<0.001
Total cholesterol (mg/dl)	200.4±37.9	203.4±38.7	196.3±36.4	0.02
Triglycerides (mg/dl)	132.8±95.8	130.1±107.0	136.8±77.2	0.03
HDL cholesterol (mg/dl)	58.8±16.9	60.5±18.0	56.3±14.7	<0.01
LDL cholesterol (mg/dl)	115.4±31.0	118.2±31.8	111.2±29.3	<0.01
Hemoglobin A1c (%)	5.8±0.9	5.7±0.9	5.9±0.9	0.04
BNP (ng/ml)	44.2±112.4	39.7±134.8	50.8±67.4	<0.001
E (cm/s)	66.4±16.4	67.2±16.0	65.2±16.9	0.07
A (cm/s)	75.5±19.3	73.3±19.6	78.7±18.4	<0.001
E/A ratio	0.9±0.4	1.0±0.5	0.9±0.3	<0.001
DT (ms)	230.6±45.5	226.1±45.0	237.1±45.6	<0.01
Septal e' velocity (cm/s)	6.4±2.0	6.8±2.2	5.9±1.6	<0.001
Septal E/e'	10.9±3.0	10.5±2.9	11.5±3.1	<0.001
LVDd (mm)	45.5±4.8	45.1±4.9	46.1±4.6	<0.01
IVST (mm)	9.5±1.7	9.2±1.6	9.9±1.7	<0.001
PWT (mm)	9.5±1.4	9.3±1.4	9.8±1.4	<0.001
LAD (mm)	36.5±5.3	35.8±5.0	37.5±5.6	<0.001
Ejection Fraction (%)	65.9±5.6	65.9±5.8	65.8±5.3	0.88
LV mass index (g/m^2)	90.5±33.0	84.5±28.9	99.0±36.4	<0.001
Diastolic dysfunction (septal e'<8)	573 (81%)	318 (76.1%)	255 (88.9%)	<0.001

Values are mean±SD, or number (percent).

BNP: Brain Natriuretic Peptide; CCr: Creatinine clearance; DT: Deceleration Time; LVDd: Left Ventricular Diastolic Diameter; IVST: Interventricular Septal Thickness; PWT: Posterior Wall Thickness; LAD: Left Atrial Diameter; LV: Left Ventricle.

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significantly associated with abnormal CACS. However, LVDD (septal e'<8) and septal E/e' were not significantly associated with abnormal CACS (Table 3).

Distribution of CACS

Figure 1 shows the distribution of CACS in the two groups.

Table 2: Characteristics and Echocardiography Results of Study Population According to Left Ventricular Diastolic Dysfunction.

Variables	Total n=705	LVDD (-) n=132	LVDD (+) n=573	*p* value
Age (years)	65.2±12.6	54.2±14.8	67.8±10.5	<0.001
Male, n(%)	342 (48.5%)	66 (50.0%)	276 (47.9%)	0.7
Body mass index (kg/m^2)	23.1±3.8	22.1±4.0	23.4±3.7	<0.001
Hypertension, n(%)	351 (50.0%)	26 (20.0%)	325 (56.8%)	<0.001
Dyslipidemia, n(%)	361 (51.7%)	64 (49.6%)	297 (52.2%)	0.6
Diabetes Mellitus, n(%)	113 (16.1%)	13 (10.2%)	100 (17.5%)	0.04
History of smoking, n(%)	262 (45.1%)	49 (41.9%)	213 (45.9%)	0.43
CCr (ml/min)	80.0±27.2	91.1±29.2	77.4±26.7	<0.001
Total cholesterol (mg/dL)	200.4±37.9	202.2±39.8	200.0±37.4	0.67
Triglycerides (mg/dL)	132.8±95.8	129.4±153.0	133.6±78.3	0.28
HDL cholesterol (mg/dL)	58.8±16.9	60.7±18.9	58.4±16.4	0.21
LDL cholesterol (mg/dL)	115.4±31.0	115.0±30.6	115.4±31.1	0.92
Hemoglobin A1c (%)	5.8±0.9	5.5±0.5	5.8±1.0	<0.001
BNP (ng/ml)	44.2±112.4	50.1±236.6	43.0±61.6	0.8
E(cm/s)	66.4±16.4	80.2±14.5	63.2±15.1	<0.001
A(cm/s)	75.5±19.3	64.8±19.7	78.0±18.3	<0.001
E/A ratio	0.9±0.4	1.3±0.5	0.8±0.3	<0.001
DT (ms)	230.6±45.5	207.2±33.9	235.9±46.2	<0.001
Septal e' velocity (cm/s)	6.4±2.0	9.8±1.4	5.7±1.2	<0.001
Septal E/e'	10.9±3.0	8.3±1.7	11.5±3.0	<0.001
LVDd (mm)	45.5±4.8	45.5±4.6	45.5 ±4.8	0.97
IVST (mm)	9.5±1.7	8.8±1.5	9.7±1.7	<0.001
PWT (mm)	9.5±1.4	8.8±1.2	9.6±1.4	<0.001
LAD (mm)	36.5±5.3	34.5±5.0	37.0±5.3	<0.001
Ejection Fraction (%)	65.9±5.6	64.3±5.4	66.2±5.6	<0.001
LV mass index (g/m^2)	90.5±33.0	76.8±24.8	93.7±33.8	<0.001
Abnormal CACS , n (%)	287 (40.7%)	32 (24.2%)	255 (44.5%)	<0.001

Values are mean±SD, or number (percent).
LVDD: Left Ventricular Diastolic Dysfunction; BNP: Brain Natriuretic Peptide; CCr: Creatinine Clearance; DT: Deceleration Time; LVDd: Left Ventricular Diastolic Diameter; IVST: Interventricular Septal Thickness; PWT: Left Ventricular Posterior Wall Thickness; LAD: Left Atrial Diameter; LV: Left Ventricle; CACS: Coronary Artery Calcium Score.

Table 3. The Results of Multiple Logistic Regression Analysis for Associations with Abnormal Coronary Artery Calcium Score (CACS).

Variable	Odds ratio (95% CI)	*p* value
Age	1.08 (1.06-1.10)	<0.001
Men	1.62 (1.04-2.55)	0.04
History of smoking	1.81 (1.19-2.79)	<0.01
Left ventricular mass index (LVMI)	1.01 (1.00-1.02)	<0.01
Diastolic dysfunction (septal e'<8)	0.87 (0.39-1.94)	0.73
E/E'	1.00 (0.93-1.08)	0.90

CACS:Coronary Artery Calcium Score; CI: Confidence Interval.

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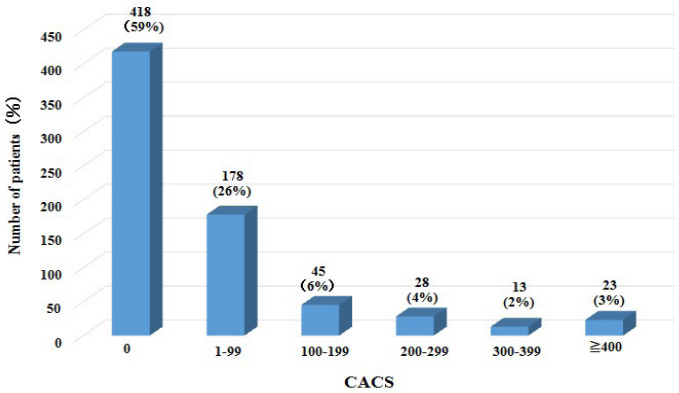
Figure 1: Distribution of Coronary Artery Calcium Score (CACS).



CACS=0 was found in 418 patients (59.3%). Of the 287 patients with CACS of >0, 178 (62%) had mild calcification (CACS=1-99), followed by 45, 28, and 13 patients displaying CACS in increments of 100; only 23 patients had CACS of ≥400.

Distribution of CACS and LVDD and relationship of chest pain to gender and age

We next divided the patients according to gender and decades of age between 20 and 79 years. Because septal e' decreases with aging, we defined LVDD as less than normal values of septal e' which depend on age, as recommended by the Japanese Normal Values for Echocardiographic Measurements Project (JAMP) study.[13] Figure 2A shows that with increasing age, there was a gradual increase in the proportion of subjects with abnormal CACS in both genders, although women had lower CACS than men in each age group. Figure 2B shows that 100% women had LVDD in the 20-29 years age group and 67% women had LVDD in the 30-39 years age group. However, only 10% women in the 60-69 years age group had LVDD. On the other hand, 25% men had LVDD in the 20-29 years age group and 36% men had LVDD in the 30-39 years age group. Men in all age groups had an LVDD prevalence of approximately 20-40%, and no associations with the age of patients were observed. Table 4 shows existence of risk factors related to a presence of LVDD with separated by gender and age. In women 20-39, 50-59 years age group with LVDD, there was positively but weak correlated with dyslipidemia. But, in group with LVDD of men 20-39 years age group and women 40-49 years age group, no significant risk factors related to presence of LVDD except chest pain were found. The LVMI was significantly higher in women 50-59, 70-79 years age group and men 60-69, 70-79 years age group. Ratio of hypertension was significantly higher in women 50-59 years age group and men 50-59 years age group.

DISCUSSION

We first examined the association between LVDD and CACS in patients with chest pain but no obstructive CAD and concluded that there was no association between LVDD and CACS in

Figure 2A: Number of Patients with CACS=0 and Abnormal CACS Described as Percent of the Total Variance by Gender and Age. CACS, Coronary Artery Calcium Score.

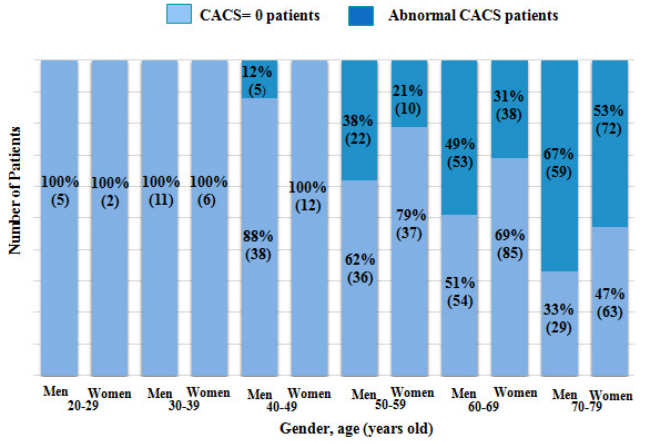
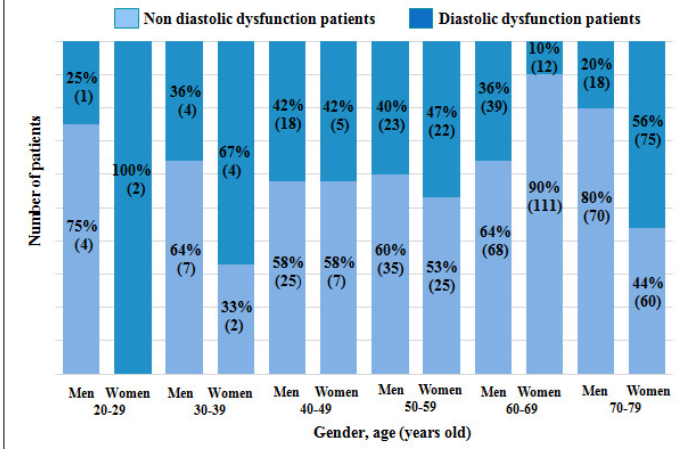


Figure 2B: Number of Patients with Non-Left Ventricular Diastolic Dysfunction and Left Ventricular Diastolic Dysfunction Described as Percent of the Total Variance by Gender and Age.



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Age group (years) Women	20-39				40-49				50-59				60–69				70–79			
	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	p value	Overall	LVDD (+)	LVDD (−)	p value
	n=8	n=6	n=2		n=12	n=5	n=7		n=47	n=22	n=25		n=123	n=12	n=111		n=135	n=75	n=60	
Body mass index (kg/m^2)	21.5±2.1	21.5±1.6	21.4±4.1	0.94	24.2±4.4	27.1±12.8	21.9±4.1	0.07	22.8±3.9	24.3±3.0	21.5±4.2	0.03	22.4±3.8	24.1±5.3	22.2±3.6	0.12	22.6±3.5	23.0±3.9	22.2±2.8	0.24
Hypertension, n (%)	1 (12.5%)	1 (16.7%)	0 (0%)	1	5 (41.7%)	4 (80.0%)	1 (14.3%)	0.07	16 (34.0%)	12 (54.5%)	4 (16.0%)	0.01	50 (41.0%)	8 (66.7%)	42 (38.2%)	0.06	71 (53.0%)	39 (52.0%)	32 (54.2%)	0.86
Dyslipidemia, n (%)	2 (25.0%)	0 (0.0%)	2 (100.0%)	0.04	5 (41.7%)	4 (80.0%)	1 (14.3%)	0.07	25 (53.2%)	16 (72.7%)	9 (36.0%)	0.02	74 (61.2%)	7 (58.3%)	67 (61.5%)	1	78 (58.2%)	43 (57.3%)	35 (59.3%)	0.86
Diabetes Mellitus, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	2 (16.7%)	2 (40.0%)	0 (0.0%)	0.15	5 (10.6%)	3 (13.6%)	2 (8.0%)	0.65	20 (16.5%)	1 (8.3%)	19 (17.4%)	0.69	15 (11.2%)	12 (16.0%)	3 (5.1%)	0.06
History of smoking, n (%)	3 (50.0%)	2 (50.0%)	1 (50.0%)	1	3 (30.0%)	2 (50.0%)	1 (16.7%)	0.5	12 (30.8%)	4 (23.5%)	8 (36.4%)	0.49	32 (30.0%)	1 (14.3%)	31 (31.0%)	0.67	24 (20.7%)	16 (25.4%)	8 (15.1%)	0.25
CCr (ml/min)	123.4±17.5	126.6±15.7	113.8±25.6	0.36	135.5±43.5	169.1±37.5	107.5±24.2	0.06	105.0±28.6	108.3±25.5	102.1±31.3	0.47	88.9±23.9	85.5±27.8	88.0±23.5	0.24	74.7±18.3	76.8±19.0	72.2±17.3	0.16
LVDd (mm)	44.4±4.8	44.8±5.6	43.5±1.8	0.74	44.9±4.2	46.6±3.4	43.7±4.6	0.24	44.6±4.0	44.8±3.1	43.5±4.5	0.06	44.1±4.6	45.1±4.9	44.1±4.5	0.81	43.7±4.1	43.9±4.4	43.4±3.5	0.43
IVST (mm)	7.6±0.6	7.5±0.7	7.7±0.3	0.74	8.4±1.0	8.7±0.8	8.2±1.1	0.44	9.1±1.8	9.6±1.6	8.7±1.9	0.09	8.7±1.2	9.2±1.6	8.6±1.2	0.02	9.2±1.5	9.4±1.6	9.0±1.3	0.08
PWT (mm)	7.4±0.6	7.3±0.6	7.7±0.7	0.36	8.6±1.0	8.9±1.0	8.4±1.1	0.47	9.0±1.3	9.5±1.3	8.6±1.2	0.03	8.9±1.2	9.3±1.4	8.8±1.1	< 0.01	9.2±1.3	9.3±1.4	9.0±1.0	0.14
LAD (mm)	33.1±3.4	33.4±4.0	32.4±0.0	0.71	35.4±5.0	39.0±3.9	32.9±4.2	0.08	34.8±4.5	36.9±4.4	33.0±3.8	<0.01	35.2±4.3	35.8±5.0	35.0±4.3	0.32	35.9±5.1	36.8±5.5	34.8±4.2	0.02
Ejection Fraction (%)	65.0±5.8	63.3±5.7	70.1±2.4	0.19	66.4±4.3	66.9±4.4	66.0±4.5	0.75	66.9±6.3	66.2±5.3	67.5±7.1	0.49	66.4±5.5	65.9±5.8	66.1±5.2	0.06	66.9±5.1	67.2±5.0	66.3±5.3	0.27
LV mass index (g/m^2)	56.8±9.1	56.8±10.5	57.0±4.7	0.98	70.1±14.5	69.9±9.2	70.3±18.8	0.95	81.5±26.9	93.3±31.0	71.6±18.4	0.01	79.7±24.1	84.5±28.9	78.3±23.5	0.05	87.3±31.2	92.9±37.7	80.5±19.0	0.03
Age group (years) Men	20-39				40-49				50-59				60-69				70-79			
	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value	Overall	LVDD (+)	LVDD (−)	*p* value
	n=16	n=5	n=11		n=43	n=18	n=25		n=58	n=23	n=35		n=107	n=39	n=68		n=88	n=18	n=70	
Body mass index (kg/m^2)	24.1±5.1	29.3±5.7	21.8±2.7	0.06	24.5±4.2	24.3±4.8	24.7±3.8	0.78	24.4±4.2	25.5±5.0	23.8±3.6	0.16	23.6±3.8	25.2±3.7	22.6±3.5	<0.01	23.3±3.3	23.6±4.0	23.2±3.1	0.7
Hypertension, n (%)	3 (18.8%)	1 (20.0%)	2 (18.2%)	1	12 (27.9%)	7 (38.9%)	5 (20.0%)	0.3	29 (50.0%)	18 (78.3%)	11 (31.4%)	<0.01	66 (61.7%)	28 (71.8%)	38 (55.9%)	0.15	52 (59.1%)	12 (66.7%)	40 (57.1%)	0.59
Dyslipidemia, n (%)	5 (35.7%)	1 (20.0%)	4 (44.4%)	0.58	20 (46.5%)	8 (44.4%)	12 (48.0%)	1	33 (57.9%)	14 (60.9%)	19 (55.9%)	0.79	49 (45.8%)	19 (48.7%)	30 (44.1%)	0.69	38 (43.7%)	7 (38.9%)	31 (44.9%)	0.79
Diabetes Mellitus, n (%)	2 (14.3%)	2 (40.0%)	0 (0.0%)	0.11	2 (4.7%)	1 (5.6%)	1 (4.0%)	1	9 (15.5%)	4 (17.4%)	5 (14.3%)	1	27 (25.2%)	12 (30.8%)	15 (22.1%)	0.36	18 (20.5%)	4 (22.2%)	14 (20.0%)	1
History of smoking, n (%)	5 (45.5%)	2 (66.7%)	3 (37.5%)	0.05	23 (63.9%)	9 (60.0%)	14 (66.7%)	0.74	33 (71.7%)	14 (82.4%)	19 (65.5%)	0.32	64 (71.1%)	25 (78.1%)	39 (67.2%)	0.34	46 (73.0%)	8 (61.5%)	38 (76.0%)	0.31
CCr (ml/min)	110.8±22.8	133.6±23.0	100.5±13.8	0.09	99.2±22.1	99.8±25.4	98.9±20.1	0.9	91.7±26.8	97.9±29.8	87.6±23.9	0.18	71.6±16.9	76.2±19.1	68.8±15.0	0.03	55.5±11.9	53.9±13.0	56.0±11.6	0.5
LVDd (mm)	47.9±5.4	48.5±7.6	47.5±4.6	0.73	48.1±3.5	46.8±3.7	49.1±3.0	0.04	48.3±3.7	47.8±3.6	48.6±3.9	0.39	46.9±4.4	47.3±4.0	46.7±4.7	0.51	46.6±4.8	46.0±5.0	46.8±4.4	0.5
IVST (mm)	9.5±1.4	10.6±2.1	9.0±0.7	0.11	10.1±1.7	11.0±1.9	9.5±1.3	0.01	9.7±1.7	10.0±1.4	9.5±1.9	0.27	10.1±1.7	10.7±1.8	9.8±1.6	<0.01	10.0±1.6	10.9±1.8	9.8±1.4	0.01
PWT (mm)	9.5±1.4	10.4±2.2	9.0±0.7	0.12	10.1±1.7	10.7±1.9	9.6±1.3	0.04	9.8±1.4	10.1±1.3	9.6±1.4	0.12	10.0±1.4	10.5±1.4	9.6±1.3	< 0.01	9.9±1.5	10.7±2.0	9.6±1.3	<0.01
LAD (mm)	34.9±5.8	37.6±8.5	33.6±3.9	0.22	36.5±4.5	36.7±4.0	36.3±4.8	0.79	36.8±5.7	36.9±5.7	36.7±5.9	0.89	37.7±5.3	39.5±4.3	36.6±5.5	<0.01	38.8±6.1	40.9±8.1	38.2±5.3	0.09
Ejection Fraction (%)	62.2±5.1	64.0±6.6	61.4±4.3	0.34	63.3±6.6	66.0±8.1	61.3±4.3	0.04	64.2±5.1	64.9±5.0	63.7±5.3	0.39	66.2±5.3	66.3±5.9	66.1±5.0	0.77	64.8±5.0	62.6±5.0	65.4±4.9	0.04
LV mass index (g/m^2)	86.1±28.2	101.5±42.0	79.1±17.7	0.18	97.8±40.6	114.2±55.5	85.6±17.8	0.06	92.7±37.1	95.6±25.8	90.8±43.2	0.64	98.3±34.3	110.0±39.5	91.5±29.2	0.01	100.0±36.2	120.0±48.5	94.7±30.6	0.01

Values are mean±SD, or number (percent).
CCr, creatinine clearance; LVDd, Left ventricular diastolic diameter; IVST, Interventricular septal thickness; PWT, left ventricular posterior wall thickness; LAD, Left atrial diameter; LV, Left ventricle; LVDD, Left ventricular diastolic dysfunction.

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patients who had chest pain and relatively mild calcification of coronary arteries. Furthermore, by using the standard value of septal e' for Japanese populations, we examined age and gender differences in LVDD and CACS. It became easily understood that coronary calcification gradually increased with age in both men and women. In contrast, LVDD prevalence was remarkably high in women in the 20-39 years age group. The major finding of the present study was the existence of a difference in the progression rate of coronary calcification and LVDD by gender and age. We also suggested that in young women, chest pain without obstructive CAD associated with LVDD regardless of coronary calcification, unlike in men.

There has not been any effective medical treatment for HFpEF so far. However, HFpEF prevalence in patients with heart failure is reported to be 30-50%. In the I-PRESERVE trial, two-thirds of patients with HFpEF showed LVDD.[14] LVDD is closely related to HFpEF, and the early detection of LVDD patients is important for prevention of HFpEF.

In the recent study, LVDD was significantly associated with CACS after adjusting for Framingham Risk Score or clinical risk factors.[7] On the other hand, Eleid et al reported that there was a trend toward a positive correlation between CACS and increasing LVDD severity, but this relationship did not reach statistical significance.[15] Eleid et al also reported in a sub-analysis of younger patients that men aged <55 years and women aged <65 years revealed no significant correlation between CACS and LVDD grade.[15] Recently in a Japanese study, Osawa et al showed that high CACS (≥400) was associated with LVDD.[6] In the present study, we examined the association between LVDD and CACS in patients with chest pain, and normal LV systolic function without coronary stenosis, in whom angina was suspected. We performed multivariate analysis including several clinical risk factors, and we showed that CACS did not show significant association with LVDD. In our study, approximately 85% of the population showed CACS 0-99, and high calcification (CACS ≥400) was only 3%. Most subjects showed a mild calcification. It may be one the causes that did not association for LVDD and CACS. The findings of our study are consistent with those of a previous study, which indicated that men generally show more calcification than women, and this increases with age.[16] However, the proportion of LVDD was different by gender or age. Factors such as hypertension, old age, obesity, diabetes mellitus, and female gender are related to LVDD.[17,18] We examined the association between LVDD and risk factors by every age group and gender. In women and men group of 50-59, 60-69, 70-79 years, LVMI and hypertension were risk factor of LVDD. It was consistent with the risk factor of known LVDD. Angina has traditionally been thought to be caused by obstructive CAD. Nevertheless, some patients with angina symptoms have a normal coronary angiogram. Various studies have shown that in patients who are undergoing clinically indicated coronary angiography, up to 49% do not have significant coronary stenosis.[19] Of these patients, 22-64% may have coronary microvascular dysfunction (CMD).[20,21] CMD is well-documented in microvascular angina (MVA) and responsible for the decreased coronary flow reserve (CFR) frequently observed in this condition. We did not conduct invasive measurements of CFR in this study, but CMD might be a factor in chest pain onset. It has been reported that CACS is statistically significantly lower in syndrome X patients than in CAD patients.[22] Thus, apart from CAD, CMD must be considered as a cause of chest pain because our study was limited to patients with mild calcification. Young women (20-39 years age group) with chest pain but no obstructive and no calcified CAD could have LVDD, which may be associated with CMD. But risk factor for CMD are similar to the traditional CVD risk factor, including hyperlipidemia.[23] The findings of our study are not consistent with those of a previous study. There was not influence of medication in all of young women (20-39 years age group). CFR measurement is necessary for the definitive diagnosis of CMD and to rule out pain arising from noncardiac etiologies, such as esophageal and other gastrointestinal diseases, musculoskeletal diseases, hyperventilation syndrome, and psychiatric disease, as well as other cardiac etiologies such as cardiomyopathy, coronary spasm, and mitral valve prolapse. However, for differential diagnosis, knowledge of diseases that cause LVDD and chest pain is limited. Recent studies suggest that CMD might play a key role also in HFpEF. The hypothesis of a common origin for MVA and HFpEF appears to be endorsed by the clinical observation that dyspnea is present in a large proportion of patients with MVA and, *vice versa*, angina-like symptoms are reported in about 50% of patients with HFpEF.[24] There are several reports about the association between CMD and LVDD as well as between MVA and LVDD.[25,26] Pepine et al reported that recurrent cycles of ischemia–reperfusion impair myocyte relaxation, thereby producing LVDD and HFpEF.[27] A recent study also showed decreased CFR in patients with HFpEF.[28] Because CMD has been reported to have a poor prognosis,[29] the cause of LVDD is what, young women with chest pain but no obstructive and no calcified CAD could have LVDD, which careful follow-up is required.

LIMITATIONS

First, this study was a cross-sectional study that enrolled consecutive patients at a single institution. Second, detailed information concerning variables such as lateral e' and LA volume index were not available in all patients and were not incorporated into diastolic function assessment. Therefore, we did not exclude the athlete's heart. In addition, the correlation of septal e' to LA volume index is defined by preload (LA pressure). Thus, the influence of preload is an issue for using septal e' as an index for LV relaxation. In case LV relaxation is normal, septal e' decreases after dialysis and e' increases in patients with severe mitral valve regurgitation because of increased flow. In the relaxation abnormality example, septal e' does not accept influence from preload, and septal e' decreases as relaxation is affected. Third, we were unable to consider how drugs administration and the period of drug administration influenced LVDD among patients. This remains as a future research topic. Fourth, we cannot exclude the possibility of the effects of non-calcified plaques because a cal-

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cium score of 0 can be seen in non-calcified plaques.

CONCLUSIONS

We found no association between CACS and LVDD in a patient population with mild coronary calcification. The proportion of patients with LVDD and CACS and their progression with age showed differences between genders. Even if there are no obstructive and no calcified CAD, we recommend that clinicians consider LVDD and perform echocardiography, particularly in young women with chest pain.

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DISCLOSURES

The authors declare that they have no conflicts of interest.

REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006; 355(3): 251-259. doi: 10.1056/NEJMoa052256

2. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. *Circulation*. 2012; 126: 65-75. doi: 10.1161/CIRCULATIONAHA.111.080770

3. Thomas JD, Weyman AE. Echocardiographic doppler evaluation of left ventricular diastolic function: Physics and physiology. *Circulation*. 1991; 84: 977-990. doi: 10.1161/01.CIR.84.3.977

4. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. *Am J Cardiol*. 2007; 99: 1643-1647. doi: 10.1016/j.amjcard.2007.01.041

5. Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) Trial. *Circulation*. 2010; 121: 1393-1405. doi: 10.1161/CIRCULATIONAHA.109.909614

6. Osawa K, Miyoshi T, Oe H, et al. Association between coronary artery calcification and left ventricular diastolic dysfunction in elderly people. *Heart Vessels*. 2016; 31: 499-507. doi: 10.1007/s00380-015-0645-5

7. Maragiannis D, Schutt RC, Gramze NL, et al. Association of left ventricular diastolic dysfunction with subclinical coronary atherosclerotic disease burden using coronary artery calcium scoring. *J Atheroscler Thromb*. 2015; 22: 1278-1286. doi: 10.5551/jat.29454

8. Makaryus AN, Sison C, Kohansieh M, Makaryus JN. Implications of gender difference in coronary calcification as assessed by CT coronary angiography. *Clin Med Insights Cardiol*. 2015; 8: 51-55. doi: 10.4137/CMC.S18764

9. Jairam PM, de Jong PA, Mali WP, Gondrie MJ, Jacobs PC, van der Graaf Y; PROVIDI Study Group. Age and sex based reference values for incidental coronary artery and thoracic aorta calcifications on routine clinical chest CT: A powerful tool to appreciate available imaging findings. *Atherosclerosis*. 2014; 235: 546-553. doi: 10.1016/j.atherosclerosis.2014.05.949

10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15: 827-832. doi: 10.1016/0735-1097(90)90282-T

11. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the heart failure and echocardiography associations of the European Society of Cardiology. *Eur Heart J*. 2007; 28: 2539-2550. doi: 10.1093/eurheartj/ehm037

12. Negueh SF, Appleton CP, Gillebert TC, et al. Reccomendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009; 10: 165-193. doi: 10.1016/j.echo.2008.11.023

13. Daimon M, Watanabe H, Abe Y, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: The JAMP study. *Circ J*. 2008; 72: 1859-1866. doi: 10.1253/circj.CJ-08-0171

14. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011; 124: 2491-2501. doi: 10.1161/CIRCULATIONAHA.110.011031

15. Eleid MF, Appleton CP, Lopez AG, Cha S, Hurst RT. Coronary artery plaque burden does not affect left ventricular diastolic function in asymptomatic adults with normal ejection fraction. *J Am Soc Echocardiogr*. 2011; 24: 909-914. doi: 10.1016/j.echo.2011.03.017

16. Makaryus AN, Sison C, Kohansieh M, Makaryus JN. Implications of gender difference in coronary calcification as assessed by CT coronary angiography. *Clin Med Insights Cardiol*. 2015; 8: 51-55. doi: 10.4137/CMC.S18764

17. Okura H, Takada Y, Yamabe A, et al. Age- and gender –specific changes in the left ventricular relaxarion: A Doppler echocar-

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diographic study in healthy individuals. *Circ Cardiovasc Imaging*. 2009; 2: 41-46. doi: 10.1161/CIRCIMAGING.108.809087

18. Lju JE, Palmieri V, Roman MJ, et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: The Strong Heart Study. *J Am Coll Cardiol*. 2001; 37: 1943-1949. doi: 10.1016/S0735-1097(01)01230-X

19. Bradley SM, Maddox TM, Stanislawski MA, et al. Normal coronary rates for elective angiography in the veterans affairs healthcare system: Insights from the VA CART program (Veterans Affairs Clinical Assessment Reporting and Tracking). *J Am Coll Cardiol*. 2014; 63: 417-426. doi: 10.1016/j.jacc.2013.09.055

20. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A, Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv*. 2015; 8: 1445-1453. doi: 10.1016/j.jcin.2015.06.017

21. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near normal coronary arteries. *Am J Cardiol*. 2009; 103: 626-631. doi: 10.1016/j.amjcard.2008.10.033

22. Chen LC, Chen JW, Wu MH, et al. Differential coronary calcification on electron-beam CT between syndrome X and coronary artery disease in patients with chronic stable angina pectoris. *Chest*. 2001; 120: 1525-1533. doi: 10.1378/chest.120.5.1525

23. Cheng C, Wei J, AlBadri A, Zarrini P, Bairey Merz CN. Coronary microvascular dysfunction- Epidemiology, pathogenesis, prognosis, diagnosis, risk factors and therapy. *Circ J*. 2016; 81: 3-11. doi: 10.1253/circj.CJ-16-1002

24. Shah AM, Claggett B, Sweitzer NK, et al. Cardiac structure and function in heart failure with preserved ejection fraction. Baseline findings from the echocardiographic study of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail*. 2014; 7: 104-115. doi: 10.1161/CIRCHEARTFAILURE.114.001583

25. Wei J, Mehta PK, Shufelt C, et al. Diastolic dysfunction measured by cardiac magnetic resonance imaging in women with signs and symptoms of ischemia but no obstructive coronary artery disease. *Int J Cardiol*. 2016; 220: 775-780. doi: 10.1016/j.ijcard.2016.06.198

26. Moreno R, Garcia-Fernandez MA, Moreno M, et al. Regional diastolic function in microvascular angina studied by pulsed-wave Doppler tissue imaging. *Echocardiography*. 1999; 16(3): 239-244. doi: 10.1111/j.1540-8175.1999.tb00808.x

27. Pepine CJ, Peterson JW, Bairey Merz CN. A microvascular-myocardial diastolic dysfunctional state and risk for mental stress ischemia. A revised concept of ischemia during daily life. *JACC Cardiov Imaging*. 2014; 7: 362-365. doi: 10.1016/j.jcmg.2013.11.009

28. Srivaratharajah K, Coutinho T, dekemp R, et al. Decreased myocardial flow in heart failure patients with preserved ejection fraction. *Circ Heart Fail*. 2016; 9(7).

29. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and enodothelial dysfunction. *Circulation*. 2000; 101: 948-954. doi: 10.1161/01.CIR.101.9.948