Original Article

Association of Left Ventricular Diastolic Dysfunction with Subclinical Coronary Atherosclerotic Disease Burden Using Coronary Artery Calcium Scoring

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Aim: Diastolic dysfunction is a common problem in patients with obesity, hypertension, diabetes, or coronary artery disease. The purpose of this study was to evaluate the association of left ventricular diastolic dysfunction with an abnormal coronary artery calcium score (CAC score).

Methods: This study considered a cohort of patients ≥ 18 years of age with normal ejection fraction who were admitted to the hospital with chest pain. All patients underwent regadenoson myocardial perfusion stress imaging and had no evidence of ischemia or infarction. Patients then underwent cardiac CT for measurement of CAC score. Patients were excluded if they had prior history of coronary artery disease, ECG findings diagnostic of an acute coronary syndrome, an elevated troponin level, or hemodynamic instability.

Results: A total of 114 patients were included and 52 (45.6%) patients had echocardiographic evidence of diastolic dysfunction. Patients with diastolic dysfunction were more likely to have an abnormal calcium score (79.6% vs 20%; OR 15.10, 95% CI 5.70 to 43.85; $p < 0.001$). In multivariable analysis, the presence of diastolic dysfunction on echocardiogram was significantly associated with an abnormal calcium score (OR 13.82, 95% CI 5.57 to 37.37; $p < 0.001$) after adjusting for Framingham Risk Score or clinical risk factors (age, gender, diabetes mellitus, dyslipidemia, and obesity; OR 19.06, 95% CI 4.66 to 107.97; $p < 0.001$).

Conclusions: Our study demonstrates that left ventricular diastolic dysfunction is associated with an abnormal CAC score even after adjusting for Framingham Risk Score or clinical risk factors. Patients without known coronary artery disease that present with chest pain and have normal perfusion imaging with evidence of abnormal diastolic function on echocardiogram may warrant more thorough evaluation for coronary atherosclerotic disease with CAC score assessment.

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Key words: Coronary Artery Calcium score, Diastolic Dysfunction, Coronary Artery Atherosclerosis

Introduction

Left ventricular diastolic dysfunction is a recognized pattern of myocardial dysfunction in which patients may develop overt clinical signs of heart failure despite a normal ejection fraction¹. Age, hyper-

tension, obesity, and diabetes are established risk factors for the development of diastolic dysfunction²⁻⁶. Subclinical coronary artery disease is often associated with the development of diastolic dysfunction. The CAC score is used to non-invasively evaluate cardiovascular risk in asymptomatic patients with a low to intermediate pre-test probability for coronary artery disease⁷. CAC score is correlated with coronary artery plaque burden, and prior studies have demonstrated a link between CAC score and all-cause mortality independent of other established risk factors^{8, 9}. The purpose of this study was to determine if the presence of

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Table 1. Patient demographics stratified by the presence of an abnormal CAC score

	Total <i>n</i> = 114	Abnormal CAC score		<i>P</i> value
		(+) <i>n</i> = 49	(−) <i>n</i> = 65	
Age (years)	56.1 ± 13.7	64.3 ± 10.6	50.0 ± 12.6	<0.001
Male (%)	51 (44.7%)	26 (53.1%)	25 (38.5%)	0.132
Body mass index (kg/m ²)	28.8 (25.4–33.1)	28.8 (25.9–33.5)	28.1 (24.9–32.6)	0.637
Body surface area (m ²)	2.0 ± 0.3	2.0 ± 0.3	1.9 ± 0.3	0.320
Hypertension	68 (59.6%)	33 (67.3%)	35 (53.8%)	0.179
Dyslipidemia	42 (36.8%)	25 (51.0%)	17 (26.2%)	0.010
Diabetes Mellitus	17 (14.9%)	6 (12.2%)	11 (16.9%)	0.599
History of smoking	16 (14.0%)	6 (12.2%)	10 (15.4%)	0.909
eGFR [†] (mL/min/1.73 m ²)	74.7 (66.3–87.6)	74.0 (66.3–87.2)	77.2 (66.8–87.7)	0.695
Framingham CHD risk (% per 10 years)	7.0 (1.0–16.0)	12.0 (6.0–16.0)	2.0 (1.0–14.0)	<0.001
Medications				
ACE-inhibitors or ARBs	38 (33.3%)	17 (34.7%)	21 (32.3%)	0.842
B-blockers	25 (21.9%)	15 (30.6%)	10 (15.4%)	0.068
Statins	31 (27.2%)	18 (36.7%)	13 (20.0%)	0.057
Aspirin	26 (22.8%)	16 (32.7%)	10 (15.4%)	0.042
Nitrates	1 (0.9%)	1 (2.0%)	0 (0%)	0.430
Diuretics	22 (19.3%)	12 (24.5%)	10 (15.4%)	0.240
Calcium channel antagonists	23 (20.2%)	12 (24.5%)	11 (16.9%)	0.353

ACE, Angiotensin-converting-enzyme; ARB, Angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate. [†]The reported eGFR is an estimated value based on the MDRD formula.

left ventricular diastolic dysfunction was independently associated with an abnormal coronary artery calcium score. To the best of our knowledge, assessment of left ventricular diastolic dysfunction is not associated with the presence of coronary artery calcium independent of known atherosclerotic risk factors. Identifying an association between diastolic dysfunction and CAC score may have significant implications for screening patients for atherosclerotic coronary artery disease.

Methods

The study design was a cohort study of participants who met the study inclusion criteria from a previously described group of patients¹⁰. Analysis of this cohort was approved by the local Institutional Review Board and all patients provided written informed consent. Included patients had a predominantly low to intermediate Framingham Risk Score (FRS), were admitted to the hospital with chest pain, and underwent regadenoson myocardial perfusion stress imaging during hospitalization without evidence of ischemia or infarction. Patients were excluded if they had an elevated troponin T level in the initial blood sample (defined as >0.10 ng/mL), ischemic ECG findings,

clinically significant atrial or ventricular arrhythmias, hemodynamic instability, a history of coronary artery disease based on prior coronary angiography or non-invasive stress testing, history of coronary revascularization, atrial fibrillation during echocardiography, or more than moderate valvular heart disease. Of these patients we included those who also underwent echocardiographic imaging within 7 months from the hospitalization. Echocardiography and cardiac computed tomography studies were performed at the discretion of the patient's treating physician. The FRS was used to estimate a 10-year risk of coronary heart disease (CHD) defined as angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency, and coronary heart disease death¹¹. The FRS score included age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, and anti-hypertensive use as individual components. The estimated glomerular filtration rate (eGFR) at admission was determined using the MDRD equation¹².

Echocardiography

Standard transthoracic echocardiogram was performed within 7 months of the cardiac CT study, using commercially available ultrasound systems. All studies were analyzed at an offline workstation

Table 2. Echocardiographic characteristics stratified by the presence of an abnormal CAC score

	Total <i>n</i> = 114	Abnormal CAC score		<i>P</i> value
		(+) <i>n</i> = 49	(-) <i>n</i> = 65	
E (cm/s)	73.8 (62.9–85.5)	75.5 (64.3–90.7)	73.1 (62.8–83.3)	0.489
A (cm/s)	70.6 (56.9–84.2)	75.8 (65.8–93.2)	65.9 (54.0–75.0)	<0.001
E/A ratio	1.1 (0.9–1.3)	1.0 (0.8–1.2)	1.2 (1.0–1.4)	0.002
Dec Time (ms)	228.0 ± 43.3	244.7 ± 46.1	215.2 ± 36.5	<0.001
IVRT (ms)	86.0 ± 13.8	91.0 ± 15.0	82.5 ± 11.8	0.004
Average e' velocity (cm/s)	9.1 (6.9–11.4)	7.2 (6.6–8.1)	10.3 (9.0–12.6)	<0.001
Average a' velocity (cm/s)	9.7 ± 2.2	10.0 ± 2.0	9.5 ± 2.4	0.236
E/e' average	8.5 (6.2–10.6)	10.1 (8.2–12.3)	7.4 (5.4–9.1)	<0.001
S (cm/s)	55.1 (47.3–63.0)	55.8 (46.8–62.0)	54.4 (47.4–63.3)	0.618
D (cm/s)	44.6 (38.3–52.1)	43.0 (37.3–51.0)	46.5 (40.4–52.4)	0.218
S/D ratio	1.2 (1.0–1.4)	1.3 (1.1–1.4)	1.2 (1.0–1.3)	0.240
LVEDd (cm)	4.5 ± 0.6	4.7 ± 0.6	4.4 ± 0.5	0.007
IVSEDd (cm)	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.1)	0.003
PWEDd (cm)	1.1 (0.9–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.1)	0.012
LA volume index (ml/m ²)	28.8 (23.0–34.9)	33.0 (26.2–37.7)	27.0 (21.3–32.9)	<0.001
LV mass index (gr/m ²)	81.9 (68.4–95.2)	88.8 (76.5–109.6)	77.4 (62.5–87.0)	<0.001
Ejection Fraction (%)	66.3 (63.9–68.9)	65.8 (63.4–70.7)	66.6 (64.2–68.3)	0.911
PA systolic pressure (mmHg)	26.0 (24.2–30.0)	28.0 (26.0–33.0)	26.0 (23.5–29.5)	0.094
Diastolic dysfunction	52 (45.6%)	39 (79.6%)	13 (20.0%)	<0.001

Dec Time, Deceleration time; IVRT, Isovolumic relaxation time; LVEDd, Left ventricular end diastolic diameter; IVSEDd, Intraventricular septum end diastolic diameter; PWEDd, Posterior wall end diastolic diameter; LA, Left atrium; LV, Left ventricle; PA, Pulmonary artery.

(Digisonics; Houston, TX) by an experienced investigator blinded to the CT results. Measurements of left ventricular (LV) dimensions, mass, and the left atrial volume (LA vol) were performed according to the American Society of Echocardiography guidelines^{13–15}. Measured Doppler parameters of diastolic function included mitral inflow velocity, pulmonary venous flow velocity, tissue Doppler annular early and late diastolic velocity, and other surrogates of diastolic relaxation including isovolumic relaxation time (IVRT). Deceleration time (DT) as a surrogate of LV stiffness was measured. E/e' was measured to estimate LV filling pressures. The presence and grade of diastolic dysfunction was determined according to the American Society of Echocardiography guidelines, with an E/A <0.8, deceleration time (DT) >200 ms, and average E/e' <8 representing Grade 1 diastolic dysfunction; an E/A between 0.8 and 1.5, DT between 160 and 200 ms, and average E/e' of 9–12 representing Grade II diastolic dysfunction; an E/A >2, DT <160 ms, and average E/e' >12 representing Grade III diastolic dysfunction. A septal e' >8, lateral e' >10, or LA volume <34 ml/m² was defined as normal diastolic function¹⁵.

Multi-detector Computed Tomography

Participants underwent a non-contrast cardiac CT on a 16-slice MDCT scanner (Phillips Precedence, Philips Healthcare, Eindhoven, Netherlands). The scan was performed with an inspiratory breath-hold using prospective ECG gating with imaging trigger at 75% of the R-R interval (collimation 8 × 0.5 mm, voltage 120 keV). CAC score was calculated with reconstructed axial images of 2.5 mm thickness by the Agatston method¹⁶. A single experienced cardiologist, with more than 10 years of experience in interpreting cardiac CT images, analyzed the studies and was blinded to the echocardiography results. CAC score was measured on a Philips Extended Brilliance Workspace Workstation, version 4.02.145 (Philips Healthcare, Cleveland, OH) on the previously acquired non-contrast cardiac CT scans. To perform these analyses an abnormal CAC score was defined as an Agatston score >0. Protocols for the measurement of CAC score and regadenoson myocardial perfusion stress imaging were optimized to reduce potential patient exposure and minimize radiation-related risks to the patient. The mean radiation dose for CAC score was 2.5 mSv and the mean radiation dose for myocardial

Table 3. Frequency of patients with diastolic dysfunction stratified by CAC score

CAC score	Total <i>n</i> = 114	Diastolic dysfunction		<i>P</i> value
		(+) <i>n</i> = 52	(-) <i>n</i> = 62	
0	65 (57.0%)	13 (25.0%)	52 (83.9)	< 0.001
1 – 99	17 (14.9%)	12 (23.1%)	5 (8.1%)	
100 – 399	18 (15.8%)	13 (25.0%)	5 (8.1%)	
400 +	14 (12.3%)	14 (26.9%)	0 (0%)	< 0.001
100 +	32 (28.1%)	27 (51.9%)	5 (8.1%)	

Table 4. Two multivariable logistic regression models that include the Framingham Risk Score and diastolic dysfunction for patients with an abnormal calcium score (CAC score greater than 0 and CAC score greater than 100)

Outcome	Covariable	Odds Ratio	2.5%	97.5%	<i>P</i> value
CAC score > 0	Framingham CHD risk (% per 10 years)	1.03	0.97	1.09	0.338
	Diastolic dysfunction	13.82	5.57	37.37	< 0.001
CAC score ≥ 100	Framingham CHD risk (% per 10 years)	1.05	0.98	1.12	0.133
	Diastolic dysfunction	10.34	3.75	33.82	< 0.001

perfusion imaging using a stress-only protocol was 5.2 mSv and for stress/rest or rest/stress protocol was 12.8 mSv.

Statistical Methods

The Wilcoxon rank-sum test for independent samples was used to identify differences between continuous variables that were not normally distributed. Student's *t*-test was used to identify differences between normally distributed continuous variables. The Shapiro–Wilk test was used to assess normality¹⁷. Differences between categorical variables were evaluated with the Fisher exact test. The Spearman rank correlation coefficient was used to describe correlations between continuous variables. Multivariable logistic regression modeling was used to model the relationship between CAC score and the presence of diastolic dysfunction by echocardiography. Covariates for the model were selected on the basis of biologic plausibility to model a hypothesized association between CAC score and diastolic dysfunction. Two multivariable models were used to evaluate the association between diastolic dysfunction and an abnormal coronary calcium score. The first model included the FRS score and diastolic dysfunction as covariables. The second model included the age, diabetes mellitus, dyslipidemia, hypertension, obesity, and diastolic dysfunction as covariables. Receiver operating characteristic (ROC)

curve analysis was used to assess the performance of the modeled associations. The DeLong method was used to identify differences between ROC curves¹⁸. Net reclassification improvement was determined for both models¹⁹. All statistical analyses were performed using R, release 3.1.3²⁰.

Results

From the initial cohort study, 114 patients met study inclusion criteria and had an echocardiographic study at a median of 1 (1–9) day after myocardial perfusion imaging. Included patients had a mean age of 56.1 ± 13.7 years and 63 (55.3%) were women. Sixty-eight (59.6%) patients had hypertension, 17 (14.9%) patients had diabetes mellitus, and 42 (36.8%) had dyslipidemia. Diastolic dysfunction was present in 52 (45.6%) patients. Patients with an abnormal CAC score were older (mean age 64.3 years vs 50.0 years, *p* < 0.001), more likely to have dyslipidemia (51.0% vs 26.2%, *p* = 0.010) and had a higher 10-year CHD risk (median 12.0% vs 2.0%, *p* < 0.001). Complete demographic characteristics of patients are shown in **Table 1** and echocardiography results are summarized in **Table 2**. The frequency of patients with diastolic dysfunction was significantly different between patients stratified by CAC score (**Table 3**).

Patients with diastolic dysfunction were more

Fig. 1. Receiver operating characteristic curve showing the sensitivity and specificity for both the Framingham 10 year coronary heart disease (CHD) risk and a model of the 10-year CHD risk with the addition of diastolic dysfunction.

likely to have an abnormal CAC score (79.6% vs 20.0%; OR 15.10, 95% CI 5.70 to 43.85; $p < 0.001$). In multivariable analysis, the presence of diastolic dysfunction on echocardiogram was significantly associated with an abnormal CAC score (OR 13.82, 95% CI 5.57 to 37.37; $p < 0.001$) after adjusting for FRS. Furthermore, this association remained significant for patients with a CAC score > 100 (Table 4). When diastolic dysfunction was added to a model that included the FRS, it resulted in a significant improvement of the ability to identify abnormal CAC score (AUC 82.8, $p < 0.010$) (Fig. 1). The addition of diastolic dysfunction to the FRS resulted in a net reclassification improvement of 47% (Table 5).

The presence of diastolic dysfunction was significantly associated with an abnormal CAC score (OR 19.06, 95% CI 4.66 to 107.97; $p < 0.001$) even after adjusting for other clinical variables (Table 6). The model using clinical variables in addition to diastolic dysfunction demonstrated significantly increased area

under the curve (AUC 90.8, $p = 0.017$) (Fig. 2) and a net reclassification improvement of 8% (Table 5).

Moreover, a positive CAC score was correlated with surrogates of diastolic dysfunction. Both left atrial volume index (OR 1.09, 95% CI 1.04 to 1.15; $p = 0.001$) and the E/e' ratio (OR 1.25, 95% CI 1.11 to 1.44; $p = 0.001$) were associated with an abnormal CAC score. In addition, left ventricular mass index was correlated with an abnormal CAC score (OR 1.03, 95% CI 1.01 to 1.05; $p = 0.001$).

Discussion

This study describes an important and novel association between diastolic dysfunction and an abnormal coronary artery calcium score. We found that patients with diastolic dysfunction were more likely to have an abnormal CAC score and this association was significant after adjusting for a 10-year CHD risk by FRS and the clinical risk factors. This

Table 5. The net reclassification improvement for identifying an abnormal CAC score by adding diastolic dysfunction to a model that includes the Framingham Risk Score (1) and clinical variables (2)

1. Net reclassification improvement by adding diastolic dysfunction to the Framingham Risk Score						
Patients with abnormal CAC score						
	FRS + DD		Higher risk (%)	Lower risk (%)	Net correctly reclassified (%)	Net reclassification improvement (%)
FRS	7	23	77	16	41	
	3	16				
Patients with CAC score = 0						
	FRS + DD					47
FRS	42	6	13	59	6	
	10	7				
2. Net reclassification improvement by adding diastolic dysfunction to clinical variables [†] (CVs)						
Patients with abnormal CAC score						
	CVs + DD		Higher risk (%)	Lower risk (%)	Net correctly reclassified (%)	Net reclassification improvement (%)
CVs	7	5	42	11	2	
	4	33				
Patients with CAC score = 0						
	CVs + DD					8
CVs	49	2	4	43	6	
	6	8				
[†] Clinical variables include age, diabetes mellitus, hypertension, dyslipidemia, sex, and obesity (defined as a body mass index > 30 kg/m ²)						
<div>Improved classification</div> <div>No classification change</div> <div>Worse classification</div>						

finding has important clinical implications and suggests that patients with diastolic dysfunction on echocardiogram and those who are low to intermediate risk for CHD based on clinical criteria may benefit from further risk assessment with coronary calcium score CT imaging.

One challenge for clinicians is patients with diastolic dysfunction have diverse characteristics with several comorbid conditions. The mechanisms causing preclinical diastolic dysfunction are unclear; however, associations with age, myocardial mass and composition, intracellular changes in titin or microtubule structure, extracellular collagen content, neurohormonal activity, and oxidative stress are known²¹. Patients with an abnormal calcium score may share several of these factors.

In a prior study of CAC score and diastolic dys-

function, Eleid *et al.* did not find an association between CAC score and left ventricular diastolic dysfunction²². However, similar to our findings, they reported an association between LA volume index (a surrogate for diastolic dysfunction) and CAC score. One possible explanation is the patient population in their study was different than our population. Specifically, our study had a larger percentage of female participants (55.3% vs 14.0%) and had a higher prevalence of hypertensive patients (59.6% vs 36.0%).

To further support our conclusions, other echocardiographic parameters of diastolic dysfunction, including the LA volume index, average E/e', and left ventricular mass index were all associated with the CAC score. LA volume index is a marker of atrial remodeling that is specific for left ventricular diastolic dysfunction in the absence of mitral valve disease and

Table 6. Multivariable logistic regression model that include the clinical risk factors and diastolic dysfunction for patients with an abnormal CAC score (CAC score greater than 0)

	Odds Ratio	2.50%	97.50%	P value
Age	1.11	1.04	1.19	0.002
Diabetes Mellitus	0.34	0.06	1.55	0.175
Hypertension	0.20	0.03	0.85	0.044
Male gender	4.72	1.39	18.80	0.018
Dyslipidemia	3.11	1.03	10.28	0.051
Obesity [†]	2.42	0.78	8.40	0.139
Diastolic dysfunction	19.06	4.66	107.97	<0.001

[†] defined as a body mass index > 30 kg/m²

Fig. 2. Receiver operating characteristic curve showing the sensitivity and specificity for a model including only clinical variables (age, gender, hypertension, dyslipidemia, diabetes mellitus, obesity) and a model including the clinical variables with the addition of diastolic dysfunction.

atrial arrhythmias²³⁾. A recent study reported that the extent of coronary artery plaque burden as defined by cardiac CT angiography was associated with echocardiographic measures of increased left ventricular filling pressure in patients with and without prior coronary artery disease²⁴⁾. The authors observed that the pres-

ence of non-obstructive coronary artery disease was associated with increased left ventricular filling pressures. These results support our observations, although the mechanisms of such correlations are yet unclear. Similar to the left atrial volume, the left ventricular mass has been associated with diastolic dysfunction²⁵⁾.

Mehta *et al.* have shown that patients with concentric left ventricular hypertrophy have increased coronary atherosclerotic burden as assessed by CAC score with evidence of an inflammatory state as measured by the plasma C-reactive protein levels²⁶⁾.

It should be noted that our study likely underestimated the presence of atherosclerotic plaque burden amongst our patient population. The patients in our analysis underwent CT calcium scoring as a part of a clinical evaluation resulting from a hospital presentation for chest pain. Several studies have shown a greater preponderance of non-calcified or partially calcified atherosclerotic plaque in patients evaluated for acute coronary syndromes that would not have been detected by our method²⁷⁻²⁹⁾. Investigation for the presence of non-calcified atherosclerotic plaque likely would have identified further coronary atherosclerotic disease.

We believe our study has important implications for clinical practice. Because the examination of a patient with chest pain often involves imaging studies to evaluate left ventricular performance, the results of this study suggests further investigation should be considered in patients with diastolic dysfunction. Thus, patients discharged with reassurance of the absence of acute coronary ischemia (as determined by an electrocardiogram, a normal regadenoson myocardial perfusion stress test, and negative cardiac biomarkers) could warrant ongoing evaluation for coronary atherosclerotic disease burden in the presence of diastolic dysfunction. In addition, outpatient echocardiography is a routine test ordered in the setting of various disorders. Our study suggests that in patients with chest pain, the identification of diastolic dysfunction may warrant further investigation for coronary artery disease, despite normal myocardial perfusion stress imaging is performed.

Limitations

Due to the limitations of observational study design the identified associations do not confirm causation. Furthermore, the study included a relatively small sample size, and we were not able perform stratified analyses on subpopulations of the initial cohort. Nevertheless, our study had sufficient power to demonstrate an association between left ventricular diastolic dysfunction and CAC score. We used multivariable analysis for FRS and incorporated major coronary artery disease risk factors such as age, hypertension, and diabetes that would reasonably be associated with left ventricular diastolic dysfunction. However, we did not explicitly adjust for other non-traditional risk factors for coronary artery disease, and there may be

alternative risks for the development of coronary artery calcium deposition that are pertinent to this population. In addition there may be undetectable or non-quantifiable risks amongst patients with non-cardiac chest pain that limits the interpretation. Therefore, the results of this study should be confirmed in a larger cohort.

Conclusion

The presence of left ventricular diastolic dysfunction was associated with an abnormal coronary artery calcium score (defined as a CAC score >0). This association was significant after adjustment for FRS and clinical risk factors. Clinicians may consider assessment of coronary artery calcium as a part of the clinical evaluation for patients with left ventricular diastolic dysfunction without a history of coronary atherosclerotic disease.

Conflicts of Interest

None.

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