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Original Article

Association Between Stress-Induced Left Ventricular Diastolic Dysfunction and Ischemic Heart Disease in Myocardial Perfusion Imaging

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ABSTRACT

Background: Myocardial perfusion imaging (MPI) via gated single-photon emission computed tomography is an effective tool in the evaluation of left ventricular (LV) perfusion and function. The purpose of this study was to determine the association between stress-induced left ventricular diastolic dysfunction (LVDD) and ischemic heart disease (IHD) via MPI.

Methods: The present study recruited 103 patients, all of whom underwent a standard 2-day stress/rest gated MPI study according to predefined protocols. Perfusion quantitative and semiquantitative indices and diastolic functional parameters were recorded.

Results: The study population comprised 88 male patients (85%) and 15 female patients (15%) at a mean age of 56.3 ± 10.7 years. The thresholds of stress-induced LVDD were calculated as post-stress to rest differences in diastolic parameters and defined as a reduction of 0.21 end-diastolic volumes per second (EDV/s) in the peak filling rate (PFR), an increase of 0.32 in the PFR2/PFR ratio, and an increase of 25 milliseconds of time-to-peak filling. The patients were categorized into 2 groups based on the presence or absence of stress-induced LVDD. The comparison of perfusion parameters depicted no significant changes between the 2 groups (all *P*-values >0.05). No significant differences were also detected concerning IHD burden (*P* =0.714).

Conclusions: Although LV diastolic dysfunction is deemed one of the earliest indicators of coronary artery disease, we found no significant association between stress-induced LVDD and the burden of IHD. ***(Iranian Heart Journal 2021; 22(3): 95-103)***

KEYWORDS: Myocardial perfusion gated SPECT, Myocardial perfusion imaging, Diastolic dysfunction, Coronary artery disease

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Coronary artery disease (CAD) and left ventricular diastolic dysfunction (LVDD) are conjoined insofar as LVDD is usually one of the earliest indicators of CAD and both myocardial ischemia and myocardial infarction (MI) are known as the leading causes of diastolic dysfunction. [1, 2] Regional systolic and diastolic dysfunction may occur in CAD; be that as it may, it has been proposed that the functional recovery of the systolic function occurs at an earlier period after reperfusion of a transiently occluded artery than diastolic dysfunction, which may persist for a longer period. [3] Furthermore, since in response to an ischemic insult, LVDD develops prior to systolic dysfunction, stress-induced LVDD has been introduced as a more sensitive indicator of CAD. [4, 5] Therefore, observing stress-induced LVDD could confer the early detection of myocardial ischemia.

Several studies have depicted the role of echocardiography with either dobutamine or exercise stress in discriminating patients with ischemic heart disease (IHD) from those without CAD using LV diastolic function assessment. [5, 6] Myocardial perfusion imaging (MPI) via gated myocardial single-photon emission computed tomography (SPECT) provides simultaneous information regarding both the perfusion and function of the left ventricle (LV) in a single study. [7] Recently, the diastolic functional indices of the LV via gated SPECT MPI have been introduced. [2, 8] Seeking the role of stress-induced LVDD as a diagnostic indicator of IHD and its severity and extension, we studied the relationship between the deterioration of the LV diastolic function in the post-stress phase as compared with the resting state and the extent and severity of stress-induced ischemia in MPI.

METHODS

Patients

The study population consisted of 103 patients referred to the Department of Nuclear Medicine and Molecular Imaging of Rajaie Cardiovascular Medical and Research Center, which is a tertiary referral center, between March and August 2019. All the patients were referred to our department for MPI study on account of clinical indications by cardiologists. Each participant underwent a standard 2-day stress/rest protocol and was stressed by either exercise or dipyridamole administration in keeping with standard protocols. [9] The entire study population had normal sinus rhythms without any significant arrhythmias. Each individual in the study population received a standard dose of 12 to 15 mCi of ^{99m}Tc-Sestamibi in each phase of the study.

Image Acquisition

Acquisition intervals between the completions of the stress tests were 10 to 15 and 45 to 60 minutes for the exercise and pharmacologic stress tests, respectively, and 45 to 60 minutes after the ^{99m}Tc-Sestamibi injection at resting state.

All the acquisitions were performed by using dual-detector SPECT/CT cameras (Symbia T2 and T6, Siemens Medical Systems) with low-energy high-resolution collimators, 90° detector configuration, and a noncircular body contoured at a 180° acquisition arc from right anterior oblique to left posterior oblique. Each phase of the gated SPECT MPI study was performed in the step-and-shoot mode with a zoom factor of 1.4, a matrix size of 64 × 64 (pixel size =6.6 mm), and 64 projections, 30 seconds per projection. A fixed acceptance window of 30% and 16-frame fixed temporal resolution forward-backward gating per R-R intervals were set as gating parameters to ensure a sufficient frame rate for the assessment of diastolic function. [10] The energy window was also set to 20% centered over a 140 keV photopeak,

accepting gamma rays of 126 to 154 keV. Each patient's electrocardiogram was monitored during the acquisitions to make sure that there was no gating error throughout the acquisition period. No respiratory motion correction was applied. [11]

Image Processing

The rotating raw images and heartbeat histogram diagrams of all the participants were visually assessed to ensure the quality of perfusion and gating acquisitions. [12] The projection summed and gated images were reconstructed by filtered back projection using post-reconstruction Butterworth filtering (cutoff frequency =0.4; order =5). In order to decrease the impact of attenuation artifacts on MPI, we applied attenuation correction by using non-uniform low-dose computed tomographic-based attenuation correction. The reconstructed images were further analyzed by Cedar-Sinai's quantitative perfusion and gated SPECT (QPS and QGS) so as to provide LV perfusion and functional indices based on the software's predefined algorithm. [13]

Once the processing was completed, the time-volume curve of each gated study and the endocardial and epicardial surfaces of all the perfusion and gated studies were evaluated visually to ensure the accuracy of all the regions of interest and gating quality. [14] Afterward, LV systolic (the LV ejection fraction) and diastolic functional parameters, including the peak filling rate (PFR), the time-to-peak filling rate (TTPFR), and the secondary peak filling rate (PFR2)-to-PFR ratio (PFR2/PFR) were derived for both resting state and post-stress MPI studies. Perfusion semiquantitative data, composed of the summed stress score (SSS), the summed rest score (SRS), and the summed difference score (SDS), as well as perfusion quantitative data, including the defect extent and the total perfusion deficit (TPD) of both stress and resting phase images, were also derived. The SSS, the SDS, and the SRS were calculated on the basis of a 17-segment model and a 5-point scoring system, which was derived automatically by the quantification software. [15, 16] The TPD was designed to provide both defect severity and extent in 1 single parameter in the QPS and was calculated as the percentage of the total LV surface area of less than the predefined uniform mean deviation threshold. [17, 18]

Statistical Analysis

The one-sample Kolmogorov–Smirnov test was used to assess the normal distribution of the variables. Numeric data were described as the mean ± the standard deviation and the median interquartile range (Q_1–Q_3), and categorical data were expressed as frequencies (percentages). The associations between diastolic dysfunction parameters and MPI indices were assessed via the Mann–Whitney *U* test and χ^2 for trend tests. The correlations between interval data were determined by using the Spearman correlation coefficient (the Spearman rho). A Bland-Altman plot was also carried out to evaluate the intraobserver reliability. The statistical analyses were performed with IBM SPSS Statistics, version 20, for Windows (IBM Inc, Armonk, NY). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Patients

Of the total 103 subjects, who were recruited in the study, 88 (85%) were male and 15 (15%) were female. The patients' characteristics and risk factors are presented in Table 1, and the calculated functional parameters are shown in Table 2. There were 6 patients (5.8%) with a history of percutaneous coronary intervention and 9 patients (7.8%) with a previous history of coronary artery bypass graft surgery. Twenty-three patients (23.3%) were also on medial therapy with anti-ischemic agents.

Table 1. Characteristics of the study population

Male, %	88/103 (85%)
Age, y	56.3 ± 10.7
Weight, kg	85.4 ± 18.5
Height, cm	170.6 ± 11.5
Diabetes mellitus	26/103 (25.2%)
Hypertension	57/103 (55.3%)
Family history	18/103 (17.5%)
Smoking	15/103 (14.6%)
Hypercholesterolemia	46/103 (44.7%)

Statistics are frequencies (%) or the mean ± the standard deviation.

Reproducibility of the Measured Data

For the evaluation of the reproducibility of the measured data, 30 raw images were randomly selected, reconstructed, and reoriented twice, and the measured diastolic parameters (viz, the PFR, the TTPFR, and the PFR2/PFR) were reordered again. The agreement of the measured data was analyzed by using the Bland-Altman plot, which yielded a good agreement between the measurements (Fig. 1).

Evaluation of Stress-Induced LVDD and Its Relationship With Perfusion Parameters

For the assessment of diastolic function in each phase of the study, diastolic parameters, encompassing the PFR, the PFR2/PFR ratio, and the TTPFR, were used. Furthermore, the deterioration of each of the abovementioned parameters in the post-stress phase as compared with the resting phase of more than a preset threshold was considered stress-induced LV diastolic dysfunction. In pursuance of setting an appropriate threshold for stress-induced LVDD, the interquartile range of the post-stress-rest differences was calculated. A reduction of 0.21 end-diastolic volumes per second (EDV/s) (Q1), an increase of 0.32 in the PFR2/PFR ratio (Q3), and an increase of 25 milliseconds in the TTPFR (Q3) were considered the thresholds for stress-induced LVDD. Stress-induced LVDD was defined as having at least 1 of the aforementioned criteria. Subsequently, the patients were categorized into 2 groups based on the presence (LVDD-Presence) or absence of LVDD (LVDD-Absence). Thereafter, the distributions of the median and interquartile range of the SSS, the SRS, and the summed difference score SDS, as well as the TPD, were calculated in each group by using the Tukey Hinges. The independent samples Mann–Whitney *U* test was employed to detect differences between the 2 groups, who performed the exercise stress: those with pharmacologic stress and all the study population irrespective of the stress type. The results demonstrated no significant differences (Table 3).

Seeking to find the association between stress-induced LVDD and the burden of IHD, we also categorized the patients on the basis of the SSS into 4 groups of normal (SSS <4), mild (4≤ SSS <9), moderate (9≤ SSS <12), and severe (SSS ≥13) IHD. Then, the LVDD-Absent and LVDD-Present patients were compared in each group by using the χ^2 test (Table 4). The results indicated no obvious relationships in terms of stress-induced LVDD and the severity of IHD (*P* =0.714).

Table 2. Patients' calculated functional parameters

Exercise Stress (n = 69)	Stress	Rest
HR, BPM	81.53 ± 13.39	68.55 ± 11.48
LVEF, %	67.92 ± 12.07	65.79 ± 11.49
ESV, mL	25.35 ± 17.11	28.89 ± 16.16
EDV, mL	72.98 ± 22.62	80.19 ± 24.32
PFR, EDV/s	2.90 ± 1.04	2.67 ± 0.82
TTPFR, ms	161 ± 43.52	157.85 ± 25.49

Pharmacologic Stress (n = 34)		
HR, BPM	69.39 ± 11.07	66.54 ± 14.97
LVEF, %	69.06 ± 13.63	70.12 ± 11.66
ESV, mL	23.45 ± 16.23	22.63 ± 15.73
EDV, mL	69.18 ± 22.09	69.18 ± 22.64
PFR, EDV/s	2.60 ± 1.13	2.60 ±1.23
TTPFR, ms	161.78 ± 39.65	169.33 ± 47.10
Overall (N =103)		
HR, BPM	77.50 ± 13.66	67.98 ± 12.62
LVEF, %	68.35 ± 12.55	67.27 ± 11.92
ESV, mL	24.78 ± 16.77	26.87 ± 16.34
EDV, mL	71.91 ± 22.46	76.61 ±24.21
PFR, EDV/s	161.09 ± 41.82	2.66 ± 0.96
TTPFR, ms		161.48 ± 33.94

Statistics are presented as the mean ± the standard deviation.

BPM, Beats per minute; LVEF, Left ventricular ejection fraction; ESV, End-systolic volume; EDV, End-diastolic volume; PFR, Peak filling rate; TTPFR, Time-to-peak filling rate; EDV/S, End-diastolic volumes per second

Table 3. Comparison of the distribution of the perfusion quantitative parameters based on the presence or absence of LVDD

	LVDD-Present	LVDD-Absent	*P*-value
Exercise Stress			
SSS	4 (2-7.5)	3.5 (2-6)	0.478
SRS	1 (0-2.5)	0 (0-3)	0.398
SDS	3 (1-5.5)	2 (1-4)	0.438
Pharmacologic Stress			
SSS	4.5 (4-6.5)	6 (3-10)	0.359
SRS	1 (0-2)	2 (0-6)	0.306
SDS	3 (0-4.5)	2 (1-4)	0.769
Overall			
SSS	4 (2-7)	5 (2.6.5)	0.905
SRS	1 (0-2)	1 (0-4)	0.980
SDS	2 (1-5)	2 (1-4)	0.416
Stress TPD	4 (2-9)	4 (2-7)	0.775
Rest TPD	1 (0-3)	1 (0-5)	0.381

SSS, Summed stress score; SRS, Summed rest score; SDS, Summed difference score

Table 4. Comparison of the burden of ischemic heart disease based on the presence or absence of LVDD

	LVDD-Absent	LVDD-Present	*P*-value
	(n =40)	(n =63)	
SSS<4	17 (42.5%)	20 (31.7%)	
4≤SSS<9	16 (40.0%)	31 (49.2%)	
9≤SSS<13	3 (7.5%)	6 (9.5%)	
SSS≥13	4 (10.0%)	6 (9.5%)	
			0.714

LVDD, Left ventricular diastolic dysfunction; SSS, Summed stress score

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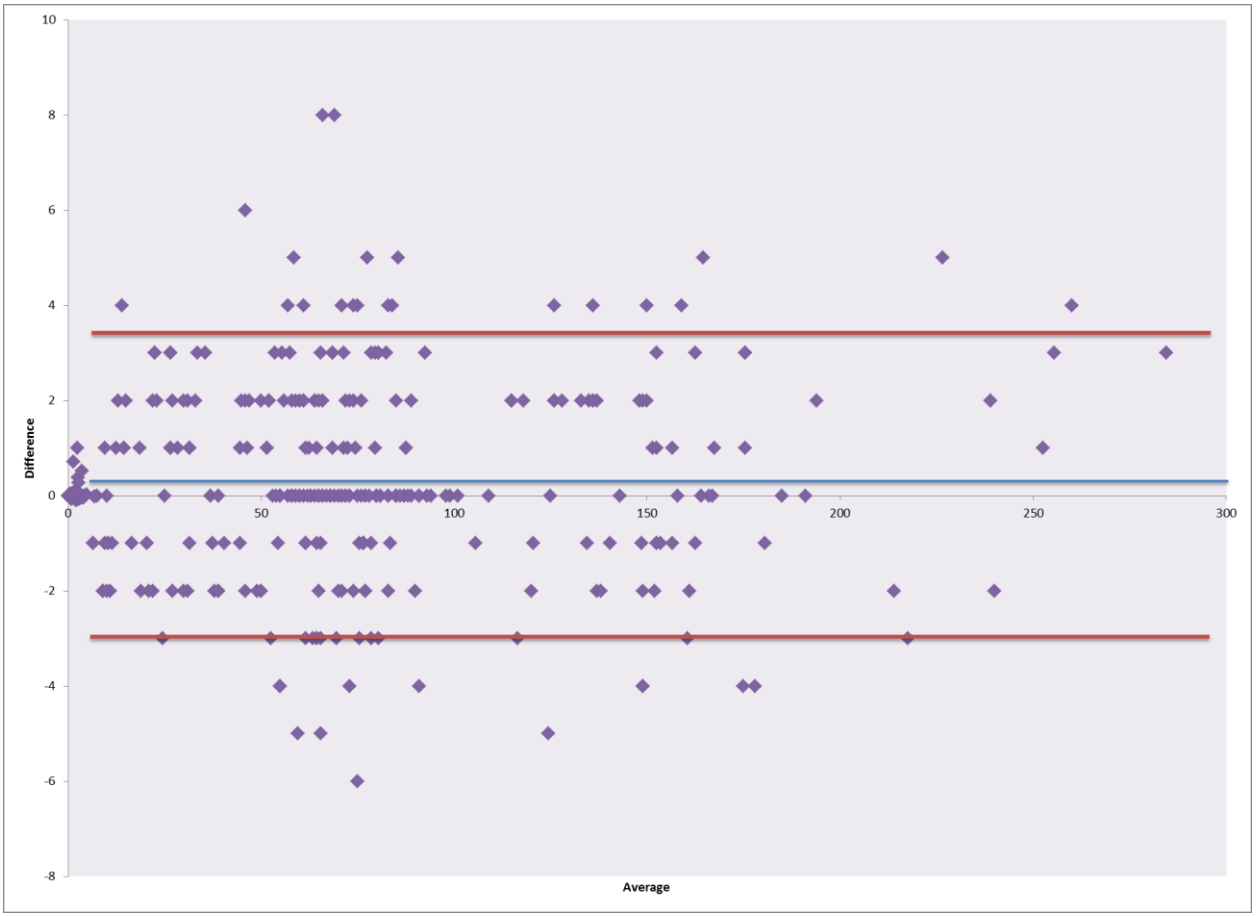

Figure 1. The image depicts the Bland–Altman plot of the repeated measurements of 30 randomly selected patients to determine the intraobserver reliability.

DISCUSSION

Our study evaluated the relationship between the deterioration of the LV diastolic function induced by the exercise or dipyridamole stress test and IHD. We found no significant differences between patients without stress-induced LVDD and those who experienced deterioration in diastolic function after stress in terms of ischemic or infarction burden.

Noninvasive cardiac imaging, including MPI, plays an important role in predicting the risk of major adverse cardiac events. Further, post-stress LV systolic dysfunction, assessed by gated SPECT MPI, has been recognized as a marker of high-grade CAD. [19, 20] Nonetheless, it appears that the role of stress-induced LVDD has been evaluated to a lesser degree in the literature than post-stress LV systolic dysfunction.

Nakano et al [21] found that LVDD induced by stress could be employed as an accurate marker to detect significant restenosis following coronary artery stenting by using pharmacologic stress MPI with adenosine. In their study, the diagnostic accuracy of the detection of significant stent restenosis was only 72%, and it improved to 92% when the presence of LVDD was taken into account along with perfusion findings.

More recently, Pawhay et al [22] studied 201 patients who underwent a 1-day protocol adenosine stress-rest ^{99m}Tc-tetrofosmin MPI.

Their study showed that increasing CAD severity, which was evaluated by either invasive or computed tomographic coronary angiography, was correlated with stress-induced LVDD. The stress-to-rest TTPFR difference and the stress TTPFR value were also introduced as the independent determinants of CAD presence and extension in their study.

Contrary to the findings of the 2 abovementioned studies, we found no significant correlations between the presence of stress-induced LVDD and perfusion parameters. One reason could be related to the different stress types as there was no adenosine stress MPI study in our investigation.

Sakamoto et al [23] evaluated the impact of exercise-induced LVDD by measuring the peak ejection rate (PER), the PFR, and the TTPFR in resting state and 30-minute post-exercise in patients with angina pectoris or old MI and compared the results with those of a control group. They found that QGS software successfully measured the changes in systolic and diastolic parameters in resting and post-stress phases by using 32-frame gating per R-R intervals and a single-day protocol. In that study, post-stress LVDD was identified 30 minutes after exercise in patients with angina pectoris or old MI as compared with the control group. Although 69 patients (67%) in our study performed the exercise stress test, we did not reach the same conclusion. This inconsistency could be related to different stress-rest protocols (ie, single-day vs 2-day protocols); nonetheless, a logical explanation for this incongruity might be different temporal sampling methods (ie, 32 frame rate gating per R-R intervals vs 16). Functional measurements can be adversely affected by temporal undersampling, [24] and higher frame-rate gating (ie, 32) has been proposed for the accurate evaluation of the LV diastolic function. [23, 25] While 32-frame gating provides more accurate LV diastolic function evaluation than 16-frame gating, longer acquisition periods are mandatory, which could be less bearable, particularly in the elderly population. Furthermore, it has been suggested that the measurement of LV functional parameters may be less jeopardized by using fewer frame rates than was previously thought. [26] In our study, the diastolic indices of post-stress and resting states were derived from studies of exactly the same temporal resolution. Therefore, it appears that our measurements are likely to be less affected by temporal undersampling.

CONCLUSION

Despite the fact that LV diastolic dysfunction has been reported as one of the earliest indicators of CAD, there appears to be no significant relationship between stress-induced LVDD and the burden of ischemia or infarction in MPI studies. Hence, it appears that stress-induced LVDD cannot be used as an index with the same power as stress-induced LV systolic dysfunction. Nevertheless, the clinical benefits of these findings mandate further investigation.

Disclosures

The authors report no conflicts of interest.

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