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ORIGINAL RESEARCH ARTICLE

Evaluation of the relationship between cardiovascular risk factors and left ventricular diastolic function parameters in myocardial perfusion scan

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ABSTRACT

Introduction: Heart failure is an important life-threatening problem, with left ventricular diastolic dysfunction as a major initial pathophysiologic process and identification and treatment of related risk factors lead to better prognosis. Gated single-photon emission computed tomography (G-SPECT) myocardial perfusion imaging (MPI) is a feasible tool to evaluate the diastolic function. The aim of this study was to assess the correlation of cardiovascular risk factors with the diastolic function parameters in G-SPECT MPI.

Methods: This is a cross-sectional retrospective study including 274 patients with normal ejection fraction (EF) and no previous history of heart disease. Demographic data and history of cardiovascular risk factors were collected. Correlation of quantitative functional parameters of G-SPECT including diastolic indices (peak filling rate (PFR), time to peak filling rate (TTPF), mean filling rate at the first third of diastolic phase (MFR/3), and second peak filling rate (PFR2)) with cardiovascular factors was studied using SPSS software.

Results: In this study, 274 patients with a mean age of 56 years (with 172 females) were evaluated. There was a significant relationship between age and all diastolic parameters. Diabetic patients had a significantly lower TTPF, and hypertensive patients revealed a significantly lower MFR/3. Hyperlipidemia and chronic kidney disease were not associated with any diastolic parameters. PFR was significantly lower in smokers, and family history had a significant relationship with PFR2.

Conclusion: Most of CAD risk factors, except for CKD and hyperlipidemia, had a significant relationship with at least one parameter of the left ventricular diastolic function in G-SPECT MPI.

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INTRODUCTION

Left ventricular diastolic dysfunction (LVDD) can be the earliest manifestation of LV dysfunction in many diseases, including coronary artery disease (CAD), congestive heart failure (HF), hypertension, and diabetes mellitus [1]. Diastolic dysfunction, defined as HF with normal ejection fraction, constitutes 40% to 50% of all HF cases and has a prognosis and mortality, almost as worse as systolic HF [2]. Impaired filling and prolonged relaxation time are the main steps in development of LVDD [3].

In addition to CAD, as an important cause of LVDD, previous studies showed the independent relationship of cardiovascular risk factors in the development and prognosis of LVDD, regardless of their role in the development of CAD. It has been suggested that there is a decline in diastolic function in normal people by aging when using echocardiography or invasive techniques [4, 5]. In addition, heart failure is the most common cause of death in diabetic patients who have a myocardial infarction, and LVDD is an early indicator of cardiomyopathy [6, 7]. Hypertension is also considered as another important risk factor of LVDD and HF [8]. A high prevalence of LVDD was also noticed in patients with COPD and smoking, independent of its known association with CAD [9, 10]. LVDD is also a harmful clinical condition in patients with chronic kidney disease (CKD), who are more prone to fluid overload during hemodialysis [11]. Gated single-photon emission computed tomography (G-SPECT) myocardial perfusion imaging (MPI) is a widely used technique for evaluation of left ventricular perfusion and function, especially in suspected CAD patients. Furthermore, if performed with 16-frame gating, G-SPECT MPI can also provide information about the left ventricular diastolic function by analyzing volumetric changes during cardiac cycles [7]. Although there is evidence regarding the association of different echocardiographic diastolic indices with CAD risk factors [12], there is scant data according to the impact of different CAD risk factors on the pattern of diastolic dysfunction and diastolic parameters obtained from G-SPECT MPI. Since it is helpful to discover diastolic function disorders at an early stage, identification of more important risk factors and mode of their contribution to LVDD development is essential for better patient management. In this study, the association of diastolic function parameters derived by G-SPECT MPI with cardiovascular risk factors including age, diabetes mellitus, hypertension, CKD, smoking, family history of CAD and hyperlipidemia was investigated.

METHODS

Study population

This is a cross-sectional retrospective study, which evaluated consecutive patients who had been referred to our nuclear medicine department in a one-year period. Those patients with normal EF and no history of previous CAD were enrolled. However, patients with arrhythmia, evidence of other structural heart diseases such as valvular or congenital cardiac diseases, and those with abnormal perfusion in G-SPECT MPI or low quality G-SPECT images were excluded. Detailed history including demographic data and classical cardiac risk factors such as a positive history of DM, hypertension, CKD, smoking, family history of CAD and hyperlipidemia was recorded, and quantitative perfusion and functional parameters of G-SPECT MPI were also extracted. This study was approved by the local ethics committee of the Shiraz University of Medical Sciences.

G-SPECT MPI

The routine protocol in our center was a 2-day stress-rest study. For the stress phase of the study, patients underwent either exercise or pharmacological stress tests based on appropriate indications. Patients capable of exercise underwent exercise treadmill test with the Bruce protocol, and 15-20 mCi 99mTc-sestamibi was injected intravenously at peak exercise. In the pharmacological stress test, dipyridamole was infused with a rate of 0.56 mg/kg/min for 4 minutes, and the radiopharmaceutical injection was administered 2-3 minutes later. G-SPECT images were obtained 45 to 90 minutes after radiotracer injection in pharmacologic stress and rest phases and 15 minutes after radiotracer injection in exercise test. G-SPECT acquisition was performed with a dual-head cardiac-dedicated gamma camera, by covering a 180° arc from 45° left posterior oblique to 135° right anterior oblique in 32 steps (30s for each projection) with a matrix size of 64 × 64. For gated acquisition, R-r window of 30% and 16 frame per cycle were used. An ordered subset expectation maximization (OSEM) algorithm was used to reconstruct the images. All images were assessed by a nuclear medicine specialist, and those with suboptimal quality and evidence of abnormal perfusion were excluded.

Quantification of images was performed by quantitative perfusion SPECT (QPS)/quantitative gated SPECT (QGS) software. Diastolic parameters of G-SPECT parameters were extracted for each patient including: peak filling rate (PFR), expressed in units of end-diastolic volume (EDV)/second, which is the first positive peak in the derivative function of the time-volume curve of LV; time to peak filling rate (TTPF), which is the time from end-systole to the time of the peak filling rate; second peak filling rate, which is the second positive peak after PFR; mean filling rate at the first third of diastole (MFR/3), which is the average of filling rate in the first third of the diastolic phase. Total perfusion deficit at stress (TPDs) and rest (TPDr), EF, EDV and end-systolic volume (ESV) were also extracted.

Statistical analysis

Statistical analysis was performed using SPSS software. Quantitative data are expressed as mean±SD and qualitative data as a number (%). Independent sample t-tests or Mann-Whitney nonparametric test were used for the comparison of diastolic parameters of G-SPECT MPI between the groups of each risk factor. The coefficient of correlation between age and diastolic variables was performed using Pearson correlation test. Regression analysis was also used to evaluate the correlation of different cardiac risk factors with diastolic parameters. $P<0.05$ was considered as the level of significance.

RESULTS

Finally, 274 patients were included with a female/male ratio of 172/102. The mean age of the total patient population was 56±10 (30-90 years). The baseline features of patients are displayed in Table 1. The comparison of left ventricular diastolic parameters between the groups with and without cardiac risk factors is presented in Table 2. There was a significantly lower MFR/3 in hypertensive patients as compared to normotensive ones ($p<0.001$), but PFR, PFR2, and TTPF were not significantly different between the two groups. Female patients also showed significantly higher PFR than male ones with no significant difference in other parameters. The TTPF was found to be lower in patients with DM than those without DM. Other diastolic function markers were not statistically different in the two groups. There was a significant difference between the nonsmoker and smoker groups in PFR. The PFR2 parameter was higher in patients with a family history of CAD in comparison to those without this risk factor. There was no significant difference in the diastolic parameters between patients with or without CKD, and the same result for the hyperlipidemia (Table 2).

Table 1. Baseline clinical and imaging characteristics of the patients

Variable	Mean±SD or number (%)
Age (years)	56.8±12.6
Sex (m/f)	105(37.2%)/172 (62.8%)
Diabetes mellitus	70 (25.5%)
Hypertension	151 (55.1%)
Hyperlipidemia	112 (40.9%)
Smoking	48 (17.5%)
Family history	34 (12.4%)
CKD	7 (2.6%)
TPDs	3.8±5.4
TPDr	0.9±3.1
EF (%)	69.4±7.2
EDV (ml)	72.8±22.1
ESV (ml)	22.9±11.8
PFR(EDV/s)	2.9±1.0
TTPF (ms)	164.6±55.9
MFR/3 (EDV/s)	1.2±0.5
PFR2 (EDV/s)	1.6±1.3

CKD, chronic kidney disease; TPDs, total perfusion deficit at stress; TPDr, total perfusion deficit at rest; EF, ejection fraction; EDV, end-diastolic volume ESV, end-systolic volume; PFR, peak filling rate; TTPF, time to peak filling; MFR/3, mean filling rate at first third of diastole; PFR2, second peak filling rate.

Regression analysis was used for the evaluation of independent effect of each risk factor that had significant correlation in previous analysis with the same diastolic parameter (Table 3). For each parameter, the risk factors with significant correlation with the result of regression analysis are shown in Table 3. We found that age and smoking had a significant correlation with PFR, while age had more effect on PFR than smoking. Age and DM can both affect TTPF at the same time but in different directions, while age had less effect than DM. Hypertension and age had a significant negative correlation with MFR/3, equally. Age and family history had a positive correlation with PFR2, while age had a stronger correlation than smoking.

DISCUSSION

This study showed a significant relationship between all diastolic parameters of G-SPECT MPI and age, indicating that with increasing age, all diastolic indices would be affected. Nonetheless, PFR2 showed no significant difference between the patients aged over and under 60 years old. Besides, regression analysis showed a non-significant weak correlation between TTPF and age.

Table 2. Comparison of Left ventricular diastolic parameters between the groups with and without cardiac risk factors

Risk factors		PFR mean±SD	P value	TTPF mean±SD	P value	PFR2 mean±SD	P value	MFR/3 mean±SD	P value
Age	≤60y	3.0±1.0	0.015	158.3±51.6	0.010	1.6±1.3	0.234	1.3±0.5	0.004
	>60y	2.7±1.0		176.9±162.2		1.8±1.2		1.1±0.5	
Gender	M	2.6±0.9	0.002	162.7±47.8	0.558	1.7±1.3	0.801	1.2±0.4	0.363
	F	3.0±1.1		167.9±58.0		1.6±1.3		1.2±0.5	
DM	Yes	3.0±1.4	0.496	150.5±62.3	0.013	1.7±1.6	0.656	1.2±0.5	0.178
	NO	2.8±0.8		171.3±50.5		1.6±1.1		1.3±0.4	
Hypertension	Yes	2.9±1.1	0.779	168.9±61.3	0.302	1.7±1.4	0.137	1.1±0.4	0.001
	NO	2.9±0.9		162.3±44.4		1.5±1.1		1.3±0.5	
Hyperlipidemia	Yes	2.9±1.1	0.933	169.3±62.9	0.394	1.8±1.3	0.208	1.2±0.5	0.151
	No	2.9±0.9		163.6±47.6		1.6±1.2		1.3±0.4	
CKD	Yes	2.9±0.8	0.971	180.7±47.0	0.470	1.1±1.0	0.260	1.1±٠.4	0.608
	No	2.9±1.0		165.6±54.6		1.7±1.3		1.2±٠.5	
Family history of CAD	Yes	2.7±1.0	0.414	156.4±72.1	0.274	2.1±1.5	0.024	1.3±0.5	0.581
	No	2.9±1.0		167.3±51.4		1.6±1.2		1.2±0.5	
Smoking	Yes	2.6±0.7	0.047	163.1±36.2	0.693	1.6±1.2	0.995	1.2±0.4	0.516
	No	2.9±1.0		166.6±57.5		1.6±1.3		1.2±0.5	

P < 0.05 is significant. PFR, Peak filling rate; TTPF, Time to Peak filling rate; PFR2, Second Peak filling rate; MFR/3, Mean Filling Rate at first third of diastole; DM, diabetes mellitus; CKD, Chronic kidney disease.

Table 3. Comparison of correlation coefficient of two risk factors and left ventricular diastolic parameter

		Standardized Coefficients Beta	P value
PFR	Age	-0.208	0.001
	Smoke	-0.119	0.050
TTPF	Age	0.118	0.054
	DM	-0.178	0.004
MFR3	Age	-0.188	0.002
	Hypertension	-0.187	0.002
PFR2	Age	0.177	0.004
	Family history of CAD	0.166	0.007

P < 0.05 is significant. PFR, Peak filling rate; TTPF, Time to Peak filling rate; PFR2, Second Peak filling rate; MFR/3, Mean Filling Rate at first third of diastole; DM, diabetes mellitus

The diastolic function assessment is one of the relatively new and less discussed areas of MPI [13]. Contributing to the interpretation of perfusion findings, MPI can help with early detection of undiagnosed diastolic dysfunction as a guide for further investigation. Wide availability of modern G-SPECT imaging software with higher framing gated acquisition (16 vs 8 frames) makes the calculation of diastolic function more feasible in most nuclear medicine centers [14]. Thus, further investigation regarding the interaction and relationship of clinical factors with these parameters are

needed for optimal application of this technique in routine clinical setting.

In this study, among all the diastolic parameters, the strongest association with age belonged to PFR followed by MFR/3. The relationship between PFR and aging has also been reported in other previous studies; Akincioglu et al. studied 90 patients with no cardiac diseases and reported a decrease in PFR with aging, whereas TTPF did not show any correlation with age [1]. However, another study suggested a positive association between TTPF and age [15]. In 2010, Nakajima and their co-workers observed a significant correlation between age and PFR2 and MFR/3 [16]. These results are in accordance with prolonged relaxation and increased myocardial and chamber stiffness that has been observed with advanced age in previous studies [4, 5].

In this study, we found that the TTPF, obtained using G-SPECT MPI, was significantly lower in patients with DM than those without it, while other parameters were similar in both groups. There was also a significant, but weak, negative correlation between this parameter and DM. A study conducted by Korkmaz et al. [7] showed that PFR parameter was the most sensitive marker of diastolic function that globally reflects diastolic properties of the ventricle; they also reported that there was a negative relationship between PFR and DM, but not for TTPF. However, in our study negative correlation of TTPF with DM contradicts the relationship of diastolic dysfunction and DM, as described in previous studies. Since in the current study only those with normal perfusion and systolic function were selected, it might be suggested that diastolic dysfunction in DM patients is more likely correlated with other cardiac abnormalities, and in the absence of other factors, this relationship is non-significant. Another study on 126 diabetic patients reported that 26% of diabetic patients had abnormal SPECT results, and diastolic dysfunction (A>E) in echocardiography was diagnosed in 61% of patients, which was significantly associated with abnormal SPECT results [17]. On the other hand, it might indicate the lower sensitivity of G-SPECT MPI in detection of diastolic function in DM patients with normal perfusion and systolic function. Diastolic dysfunction in diabetic patients can be a result of Insulin resistance, glyco- and lipo-toxicity, and increased cytokine activity, which may all affect the myocardial function, and the result, is increasing arterial stiffness and energy demand. Given that diastolic dysfunction is an established early pathological mechanism in development of diabetic cardiomyopathy [6], further studies are needed to better characterize the diastolic parameters of G-SPECT MPI in DM patients.

Comparison of the normotensive and hypertensive patients revealed that MFR/3 was significantly lower in hypertensive patients (1.18 vs. 1.38 EDV/s). Sayed et al. reported similar results with significantly lower MFR/3 in hypertensive patients [18]. They also found a significant negative correlation between hypertension and PFR. However, this study included just 30 selected patients. In another study with echocardiography, patients with hypertension were shown to have reduced LV diastolic and systolic longitudinal function assessed by tissue tracking and strain rate in Doppler imaging [19]. This can be the result of hypertension-induced stiffening of larger arteries such as the aorta that causes an increase in aortic systolic pressure, and consequent reductions in diastolic blood pressure. These events can reduce LV coronary perfusion during diastole, which may develop LVDD [8].

In our study, there was no correlation between diastolic dysfunction parameters and CKD; in contrast, a study carried out by Sato et al. suggested that impaired renal function was a major factor that caused LV diastolic dysfunction in patients with suspected CAD associated with reduced PFR and MFR/3 [20]. This correlation has been also shown by echocardiography. Another study indicated that diastolic dysfunction was a common and potentially destructive clinical condition in ESRD patients [11]. Increasing myocardial calcium level, lipid peroxides level, oxidative stress, and reduced antioxidants in CKD patients may affect the LV myocardial functions and cause LV hypertrophy and high filling pressure. However, in our study in patients with normal systolic function, no difference was found between the CKD and non-CKD groups. Although the small number of CKD patients in this study might be associated with some degree of uncertainty in statistical analysis, this may also partly be related to selection of only patients with normal perfusion and function. It should be further investigated whether diastolic dysfunction in CKD patients occurs in the absence of other associated cardiac abnormalities.

Previously, there was no study on the effect of smoking on diastolic parameters of G-SPECT MPI, but, based on our data, smoker patients had lower PFR than the non-smoker group. Some studies mentioned the correlation between smoking and diastolic dysfunction by

echocardiography. It has been shown that smoking remarkably affects the LV diastolic function by prolonging the relaxation time due to shifting the mitral blood flow from early (E wave) to late (A wave) diastole [9, 10]. Nonetheless, our study found that the most affected parameter in G-SPECT MPI was the PFR. Our data showed that hyperlipidemia did not correlate with diastolic parameters. However, lately, some reports mentioned that hyperlipidemia was associated with impaired relaxation in patients with normal ejection fraction and the absence of heart failure. In heterozygous familial hypercholesterolemia (FH) patients, increased low-density lipoprotein (LDL) cholesterol leads to endothelial dysfunction, adverse changes in vascular morphology, and increased intima-media thickness in the peripheral arteries. In our study, however, there might be heterogenous characteristics of hyperlipidemic patients including those with and without therapy that might influence the result.
Patients with a family history of CAD have been shown to have a significant increase in the LV mass and relaxation time leading to LVDD [21]. In our study, the PFR2 parameter, which is considered as the index of left atrial contribution in diastolic phase, was higher in the patients who had a positive family history of CAD. The heritability of the LV structure and function as determined by echocardiography has been studied in a research conducted in 2013, and it suggested that there is overall moderate to small heritability for the LV structure which was reported to be 48% for systolic function and 25-53% for diastolic function [22]. It can be suggested that genetic pathways involved in CAD may also contribute to expression of other associated features of cardiac diseases such as diastolic dysfunction.
There are also some limitation with the current study. The main limitation is the retrospective design that can interfere with optimal selection of patients and precise evaluation of baseline risk factors. However, considering the selection of all patients who met the inclusion criteria in a specific duration of time (one year), the selection bias could be partly reduced. The small number of patients in some subgroups such as CKD and positive family history may also affect the reliability of results in these groups. Finally, the lack of follow up data for assessing the effect of diastolic dysfunction in different subgroup on prognosis and outcome is another limitation which is recommended to be evaluated in the studies with dedicated prospective design.

CONCLUSION

According to our results, it seems that all cardiovascular risk factors except CKD and hyperlipidemia had a significant relationship with at least one parameter of left ventricular diastolic function in G-SPECTMPI. Aging was the most important risk factor in this study, affecting all diastolic parameters. Involving different diastolic parameters by different risk factors can imply the different pathophysiological mechanism by which they contribute to development of diastolic dysfunction.

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