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Original article

Evaluation of Diastolic Function in Patients with Normal Perfusion and Type 2 Diabetes Mellitus with Gated Single-photon Emission Computed Tomography

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Abstract

Early identification of diastolic dysfunction of patients with diabetes is important in preventing cardiac events. In this study, we aimed to show that both myocardial perfusion and diastolic function parameters can be evaluated in diabetic patients with possible silent cardiac symptoms using gated single-photon emission computed tomography (G-SPECT). We examined eighty patients: Forty with and forty without diabetes. The patients were compared in terms of systolic and diastolic parameters obtained using G-SPECT. ^{99m}Tc-sestamibi was used to obtain 8-frame images in each cardiac cycle, with calculation of the left ventricular ejection fraction (LVEF), peak filling rate (PFR), mean filling rate during the first third of diastolic time (MFR/3), and time to peak filling (TTPF) using the QGS software. G-SPECT results were compared in forty diabetic and forty nondiabetic patients of similar age and sex. Of the diastolic function parameters, PFR was found to be lower in patients with than without diabetes (2.31 ± 0.68 vs. 2.76 ± 0.68, respectively; $P = 0.004$). The TTPF and MFR/3 in both groups were similar. PFR was negatively correlated with end-diastolic volume and end-systolic volume (ESV) and positively correlated with LVEF. This correlation was stronger in patients with diabetes. The diastolic parameter PFR, obtained using G-SPECT, was significantly lower in patients with than without diabetes. We believe that these parameters should be noted for the early diagnosis or prevention of heart disease in patients with a risk of diastolic dysfunction.

Keywords: Diastolic function, myocardial perfusion scintigraphy, peak filling rate, tip 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is one of the major risk factors for cardiovascular disease. In patients with DM, heart disease may remain silent until an advanced stage. As a result, early diagnosis of patients at risk is important in preventing cardiac events.[1] In patients with DM, left ventricular (LV) diastolic dysfunction is an early finding of cardiomyopathy and reportedly may be accompanied by increased cardiac mortality.[2] In patients with clinically asymptomatic DM and normal systolic function, it is thus important to identify diastolic function disorders in the early period. In patients with DM, invasive (angiography) and noninvasive (echocardiography, radionuclide ventriculography, and myocardial perfusion scintigraphy [MPS]) methods may be used to identify myocardial dysfunction. Due to limitations such as the invasiveness of angiography, the requirement for experienced personnel for echocardiography, and the inability to obtain sufficient image quality

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in situations such as obesity and chronic obstructive pulmonary disease, nuclear medicine methods have often been chosen as an alternative.[3] Radionuclide ventriculography (RNV) has long been used in the evaluation of systolic and diastolic functions of the left ventricle, and studies correlated with echocardiography have confirmed its value.[4] Currently, however, it is used less often and does not provide information about myocardial perfusion. MPS is an ideal method with which to provide diagnostic and prognostic information about myocardial perfusion effectively and at low cost. In addition, gated MPS provides information about systolic function (e.g., LV ejection fraction [LVEF], end-diastolic volume [EDV], and end-systolic volume [ESV]) and diastolic function (e.g., peak filling rate [PFR], mean filling rate during the first third of diastolic time [MFR/3], and time to peak filling [TTPF]) as well as about myocardial perfusion.[5,6]

In this study, we compared diastolic function parameters obtained with gated single-photon emission computed tomography (G-SPECT) in patients with DM without known coronary artery disease (CAD) and no ischemia with those of the individuals without DM. We assessed whether G-SPECT can be used to evaluate both myocardial perfusion and systolic and diastolic functions in patients with DM with atypical cardiac symptoms.

Materials and Methods

This retrospective study included eighty patients (forty with and forty without DM, all without known CAD and all with complaints of atypical chest pain) who were referred to our department from January 2014 to December 2015. The records were scanned for patient histories, effort test results, and G-SPECT results. Demographic information and risk factors for CAD were noted. Written consent was obtained from all patients for scintigraphic studies.

Exclusion criteria

The following patients were excluded from the study: Those with irregular heart rhythms (atrial fibrillation, branch blocks, frequent paroxysmal atrial contraction, or frequent paroxysmal ventricular contraction), CAD, cardiomyopathy, severe valve diseases, comorbid diseases (kidney, lung, and liver diseases), aneurysm findings, heart failure diagnosis, electrocardiography and effort test abnormalities linked to ischemia, and ischemia and scar findings on MPS).

Patients with normal myocardial perfusion were included in the study. For all patients, systolic (LVEF, ESV, and EDV) and diastolic (PFR, MFR/3, and TTPF) parameters were calculated from the G-SPECT records. The patients were divided into two groups: Those with and without DM. The systolic and diastolic parameters were compared between the two groups.

Gated single-photon emission computed tomography protocol

G-SPECT ^{99m}Tc-sestamibi was performed in a single-day stress-rest protocol. Beta blockers, calcium channel blockers, and long-effect nitrates were not taken for 2 days before the study. Patients capable of exercise underwent an effort test with the Bruce protocol, and 296–370 MBq ^{99m}Tc-sestamibi was injected intravenously at peak exercise. Patients incapable of exercise underwent a pharmacological stress test with adenosine. During adenosine infusion at 0.14 mg/kg/min for 6 min, the radiopharmaceutical injection was administered at the 3rd min. About 30–45 min after the stress injection, images were obtained. About 2 h later, the patients underwent injection of 888–1110 MBq of ^{99m}Tc-sestamibi at rest, and nearly 1 h after the injection, rest images were obtained. All data acquisitions were performed with a 90° dual-head SPECT system (E.cam, Siemens) equipped with a low-energy, high-resolution collimator. A 20% window was centered the 140 keV energy photopeak. The acquisition matrix size was 64 × 64. Image taking began at 45° right anterior oblique with a 180° semicircular orbit. Acquisition was synchronized with the electrocardiogram R wave, with 8 frames per cardiac cycle. Frames were reconstructed with a gamma camera using filtered back projection (Butterworth filter, order 5, cut-off frequency 0.5). No correction was made for attenuation or scatter. To quantify the perfusion and wall thickening, the left ventricle was divided into 17 segments, each of which was assigned a score from 0 to 4 for both perfusion (0 = normal perfusion, 1 = mild hypoperfusion, 2 = moderate hypoperfusion, 3 = severe hypoperfusion, and 4 = no uptake) and wall motion and thickening (0 = normal, 1 = mildly impaired, 2 = moderately impaired, 3 = severely impaired, 4 = no wall motion and/or thickening). The summed rest score, summed stress score, and summed difference score for perfusion were calculated. Myocardial ischemia criteria were considered to exist when the summed difference score was ≥ 2. Calculation of the LVEF and ventricular volumes was performed automatically during stress-G-SPECT. Endocardial and epicardial boundaries were traced automatically using the quantitative QGS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA). The LV filling rate/time curve was calculated from the first derivative of the volume/time curve. Specifically, PFR was defined as the greatest filling rate in early diastole and complies with the peak value of the first derivative of the diastolic portion of the time–activity curve. The unit for PFR is EDV/s. The TTPF is expressed in milliseconds. For

systolic function, EDV (mL), ESV (mL), and LVEF (%) were calculated from the LV volume–time curve.[7]

Statistical analysis

All data analyses were performed with the SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Distribution of data was assessed with the Kolmogorov–Smirnov test. Continuous variables with normal distributions are given as mean ± standard deviation, while those with nonnormal distributions are given as median (minimum–maximum). Categorical data are given as frequency and percentage. To compare groups with normal distributions, the independent-sample *t*-test was used, while the Mann–Whitney U-test was used for those with nonnormal distributions. Categorical data were analyzed with the χ^2 test. The correlations between PFR and ESV, EDV, LVEF, and age were evaluated with Pearson's correlation or Spearman correlation analyses. $P < 0.05$ was considered to indicate statistical significance. Significant PFR values between the groups are shown on a mean value error bar graphic.

Results

The study included forty patients with and forty patients without DM with G-SPECT performed for suspicion of CAD and no ischemia or scar findings on MPS. Age, gender, smoking, hypertension, hyperlipidemia, and CAD family history were similar in the two groups [Table 1].

EDV and ESV values were higher in patients with than without DM [Table 2]. The diastolic parameter of PFR was found to be significantly lower in patients with than without DM [Table 3 and Figure 1]. Other diastolic function markers, MFR/3 and TTPF, were similar in both groups [Table 3].

When a correlation analysis was performed in patients with DM for the most important marker of diastolic function, PFR, there was a moderate negative correlation between PFR and ESV and EDV, a moderate positive correlation between poststress LVEF, and no correlation with age [Figure 2]. Similarly, in patients without DM, there was a weaker negative correlation between PFR and ESV, while the correlations between PFR and EDV and stress EF were not statistically significant. Again, there was no correlation between age and PFR [Table 4].

Table 1: Differences between patients with diabetes mellitus and nondiabetes mellitus

	DM (*n*=40)	Non-DM (*n*=40)	*P*
Age (years)	60±8	57±11	0.123*
Gender, female (%)	16 (40)	21 (52)	0.262
Smoking, *n* (%)	7 (18)	10 (25)	0.581
Hypertension, *n* (%)	32 (80)	25 (62)	0.084
Hyperlipidemia, *n* (%)	17 (42)	12 (30)	0.245
Family history, *n* (%)	23 (58)	19 (48)	0.370

*Independent sample *t*-test; Chi-square test. DM: Diabetes mellitus

Table 2: Left ventricular systolic function parameters in patients with diabetes mellitus and nondiabetes mellitus

	DM (*n*=40)	Non-DM (*n*=40)	*P*
LVEF (%)	64.78±14.45	67.35±9.77	0.078*
EDV (ml)	86 (10-300)	68.5 (43-138)	0.030
ESV (ml)	33.5 (10-239)	22.5 (7-59)	0.002

*Independent sample *t*-test; Mann-Whitney U-test. DM: Diabetes mellitus; LVEF: Left ventricular ejection fraction; EDV: End-diastolic volume; ESV: End-systolic volume

Table 3: Left ventricular diastolic function parameters in patients with diabetes mellitus and nondiabetes mellitus

	DM (*n*=40)	Non-DM (*n*=40)	*P**
PFR (EDV/s)	2.31±0.68	2.76±0.68	0.004
MFR/3 (EDV/s)	1.15±0.41	1.27±0.34	0.134
TTPF (ms)	160.4±60.3	174.7±43.5	0.228

*Mann-Whitney U-test; Independent sample *t*-test. DM: Diabetes mellitus; PFR: Peak filling rate; MFR/3: Mean filling rate during the first third of diastolic time; TTPF: Time to peak filling

Table 4: Correlations between peak filling rate and age, end-diastolic volüme, end-systolic volüme, left ventricular ejection fraction

	DM (*n*=40)		Non-DM (*n*=40)	
	r	*P*	*r*	*P*
Age	−0.258	0.107	−0.164	0.311
EDV*	−0.542	<0.001	−0.290	0.070
ESV*	−0.521	0.001	−0.352	0.026
LVEF	0.569	<0.001	0.289	0.071

*Spearman correlation analyze; Pearson correlation analyze. PFR: Peak filling rate; DM: Diabetes mellitus; EDV: End-diastolic volüme; ESV: End-systolic volüme; LVEF: Left ventricular ejection fraction

Discussion

In this study of patients with DM but without a CAD diagnosis, PFR was found to be lower than that of patients without DM. In addition, EDV, ESV, and LVEF were correlated more clearly with PFR in patients with than without DM. Cardiovascular diseases are the most common cause of failure and death in patients with DM. DM is responsible for a variety of cardiovascular complications, such as increased coronary atherosclerosis and LV dysfunction. In these patients, LV dysfunction is the earliest marker of diastolic dysfunction.[8,9]

In patients with DM, disrupted diastolic reserve is an early finding of LV involvement.[8] Although both patients with and without DM with CAD have similar atherosclerotic plaques, the development of more severe and diffuse lesions is possible in patients with

DM. This event, termed diabetic cardiomyopathy, is believed to be responsible for microvascular angina, autonomous dysfunction, interstitial fibrosis, and metabolic disorders.[10] When the high mortality of patients with DM is noted, it is important to identify diastolic filling disorders in the early period with noninvasive methods in asymptomatic patients with normal systolic function.

In a study investigating diastolic function in patients with DM using cardiac magnetic resonance imaging, Graça *et al*.[9] found that the PFR values in patients with Type 2 DM were significantly lower than those in the control group. In our study with G-SPECT, the PFR in patients with DM was also significantly lower than that in patients without DM.

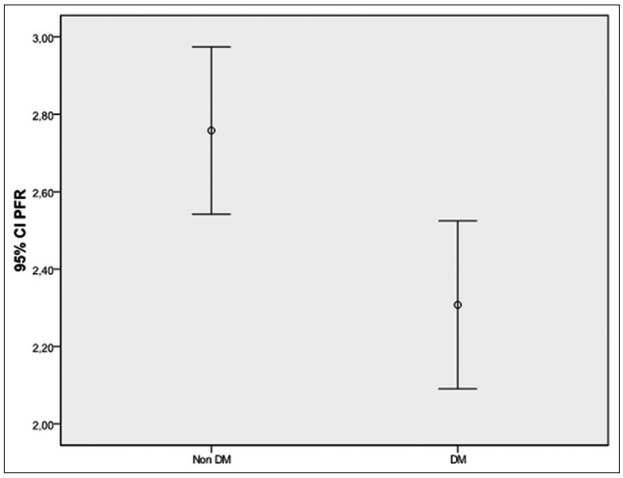

Figure 1: Peak filling rate values in patients with diabetes mellitus and nondiabetes mellitus

Echocardiography is a frequently used noninvasive method with which to evaluate LV function. Depending on the operator, this method can assess both systolic and diastolic function. In nuclear medicine, RNV has been frequently used to measure these parameters. G-SPECT allows the calculation of LV volume changes during each cardiac cycle. In addition to providing ischemic, metabolic, and prognostic information, G-SPECT can quantitatively and objectively assess systolic (LVEF, ESV, and EDV) and diastolic (PFR, MFR, and TTPF) function.[11] When compared with echocardiography, it has significant advantages of not being affected by body structure, minimal intra- and inter-observer variability, repeatable results, and providing quantitative data.

In a study comparing LV end-diastolic pressure (LVEDP) obtained using the invasive method of cardiac catheterization with PFR, TPFR, and MFR/3 values obtained with 16-frame G-SPECT, the values were significantly correlated.[12] When diastolic dysfunction worsens, LVEDP increases with a negatively correlated reduction in PFR and MFR/3, whereas there is a positive correlation with increasing TPFR. In our study, the PFR

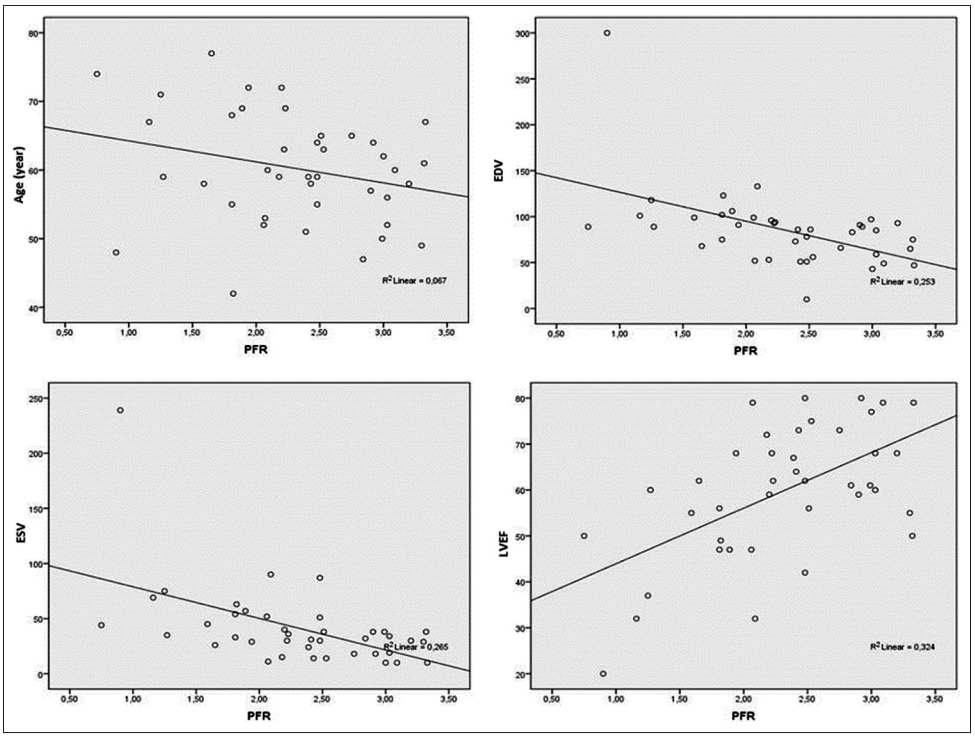

Figure 2: Correlations between peak filling rate and age, end-diastolic volume, end-systolic volume, left ventricular ejection fraction in patients with diabetes mellitus

in patients with DM was significantly lower than that in patients without DM.

In a study by Akincioglu *et al.*,[7] MPS in 90 normal healthy individuals revealed that the PFR was negatively correlated with age, EDV, and ESV and positively correlated with EF. Again, the diastolic parameter TTPF reportedly increased with age. Similar to the present study, the PFR was negatively correlated with ESV and EDV and positively correlated with EF. Although there was a reduction in the PFR with age, it was not statistically significant.

Another study reported that the diastolic function parameter PFR was the most sensitive marker of diastolic function.[13] PFR globally reflects diastolic properties of the ventricle. In addition to PFR, TTPF is another important G-SPECT parameter for diastolic function. In situations where the relaxation of the heart is disrupted, TTPF increases as PFR decreases. In our study of patients with DM with normal myocardial perfusion, the PFR was clearly lower in patients with than without DM (matched for age and sex). The other parameter, TTPF, was similar in both groups.

When evaluating diastolic function with G-SPECT, 16-frame images are generally recommended for each cardiac cycle. In a study comparing 8-, 16-, and 32-frame G-SPECT with RNV, although 32-frame G-SPECT showed better correlation with radionuclide angiography, the lengthened acquisition time with an increasing frame number was reported as a limitation of the study.[5] Another study found a statistically significant correlation between functional indices (LVEF, PFR, and TTPF) obtained with G-SPECT using an 8-frame volume curve and those obtained with 32-frame radionuclide angiography.[7] In our study, although our acquisition was 8 frames per cardiac cycle, the statistically significant differences observed in PFR are, especially important in terms of showing the value of G-SPECT as an indicator. Another limitation of the study is that the data were evaluated retrospectively. As a result, our G-SPECT data cannot be compared with other methods, such as RNV and echocardiography. However, correlations between G-SPECT and RNV and echocardiography values have been observed in many studies.

Conclusions

In the present study, patients with DM with normal myocardial perfusion were shown to have disrupted cardiac relaxation and a low PFR compared with patients without DM using G-SPECT. These results illustrate the disruption in diastolic function in patients with DM in the early period and earlier occurring cardiac events. G-SPECT is frequently used in daily practice at most nuclear medicine centers, and because it is a repeatable, highly accurate test independent of the operator, it can be used to evaluate diastolic function parameters in addition to myocardial perfusion with no time or financial loss. Thus, we believe that the evaluation of diastolic function parameters with G-SPECT may help to identify patients with DM requiring more aggressive treatment in the early period. Completion of prospective studies with larger patient numbers will provide important data on this topic.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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