Original Article

Impact of Diabetes Mellitus on Left Ventricular Synchrony by Gated Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging Phase Analysis

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ABSTRACT

Background: Phase analysis assesses left ventricular (LV) dyssynchrony from gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT-MPI). This study aimed to determine the impact of diabetes mellitus (DM) on phase parameters.

Methods: The study population consisted of 121 diabetic patients with no history of coronary artery disease, hypertension, or dyslipidemia and no evidence of perfusion abnormalities or systolic dysfunction in GSPECT-MPI. The resting-state images of MPI were further analyzed using the Cedar–Sinai quantitative GSPECT, and LV phase parameters, including phase histogram bandwidth (PHB), phase standard deviation (PSD), and entropy, were derived. The results were compared with the corresponding figures previously defined in a control group, consisting of 100 subjects with low likelihoods of coronary artery disease, in our center.

Results: Significant differences existed in the derived values for PHB, PSD, and entropy between the DM and control groups concerning global whole LV synchrony (P>.05). Likewise, PHB and PSD demonstrated no significant differences between the 2 groups regarding the regional wall-based analysis (P>.05). In contrast, the entropy indices of the LV septum (P= .019) and anterior wall (P= .022) were significantly higher in the DM group.

Conclusions: It appears that except for the regional wall-based entropy of the septum and the anterior wall, DM does not inherently impose any significant alterations on the mechanical synchrony indices of GSPECT-MPI. Consequently, the provided normal databases for GSPECT-MPI-derived synchrony parameters could be utilized in DM patients. ***(Iranian Heart Journal 2023; 24(1): 54-61)***

KEYWORDS: Diabetes mellitus, Single-photon emission computed tomography, Myocardial perfusion imaging

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Received: October 12, 2021 **Accepted:** January 9, 2022

Heart failure is a growing health problem with high morbidity and mortality rates. Despite advances in treatment, the related mortality rate has increased steadily. [1] Several large and well-designed clinical trials have demonstrated the significant role of cardiac resynchronization therapy in treating moderate-to-severe heart failure over the past decade. [2] Not only does cardiac resynchronization therapy improve the quality of life and increase the left ventricular (LV) ejection fraction, but also it decreases heart failure-related symptoms and hospitalization rates. Be that as it may, the response to cardiac resynchronization therapy is clinically variable, and some patients may not respond adequately. [3] Therefore, defining appropriate criteria for patient selection for cardiac resynchronization therapy by different imaging modalities seems mandatory. [4] Tissue Doppler imaging is the most commonly used means to assess mechanical dyssynchrony with a more accurate prediction of reverse remodeling after cardiac resynchronization therapy treatment than strain rate imaging. [5, 6]

On the other hand, coronary artery disease (CAD) is the leading cause of morbidity and mortality in adults, and diabetes mellitus (DM) is a major risk factor for CAD, accounting for increased incidence rates of heart failure, myocardial infarction, and cardiac death. [7,8]

Gated single-photon emission computed tomography myocardial perfusion imaging (GSPECT-MPI) is a feasible and well-established method for the evaluation and risk stratification of ischemic heart disease and the assessment of LV function and myocardial viability. [9] Recently, phase analysis has also been introduced, allowing the assessment of LV mechanical dyssynchrony simultaneously with LV myocardial perfusion and function. [10] Since then, phase analysis has been incorporated into different quantitative GSPECT software packages with nearly good correlations between the results. Despite the fact that modest correlations have been observed between the GSPECT phase analysis and tissue Doppler imaging results, the former confers low intra- and interobserver variabilities as a result of being automated and 3D (encompassing the entire LV) and fewer perplexing indices. [11,12] More recently, the normal range of phase analysis parameters has also been introduced. [13] There is also a growing body of literature on the evaluation of different factors with potential impacts on phase-analysis results, spanning from patient-related to acquisition-related factors. [12,14-18] However, little attention has been paid to the potential impact of DM on GSPECT-MPI phase-analysis results. Hence, the present study was undertaken to determine the independent impact of DM global and regional phase analysis parameters.

METHODS

Patients

The study population consisted of a prospective cohort of 121 patients with type II DM with a mean duration of 6.85±5.72 years and no known CAD (the DM group) referred to the Department of Nuclear Medicine and Molecular Imaging of Rajaie Cardiovascular Medical and Research center, a tertiary hospital, for the assessment of ischemic heart disease via GSPECT-MPI. All the patients were referred on account of clinical indications by cardiologists and DM documentation based on at least 2 fasting plasma glucose tests exceeding 125 mg/dL. The inclusion criteria were the absence of hypertension, dyslipidemia, and smoking in the past medical history and normal LV perfusion and function according to GSPECT-MPI results, defined as the absence of any appreciable perfusion

abnormalities in visual assessment by an expert nuclear physician, summed stress scores <4, LV ejection fractions ≥50%, and summed motion thickening scores of zero. The exclusion criteria were the presence of valvulopathy in the patients' echocardiographic study within 8 weeks before MPI or any atrial or ventricular arrhythmias, including atrial fibrillation or premature atrial or ventricular contractions.

As normal ranges for global whole-ventricle and regional wall-based LV synchrony parameters had previously been defined in a group of 100 nondiabetic subjects with low pretest likelihoods for CAD in our center (the LLK group), the corresponding phase analysis data were drawn upon as the control group. [13]

Image Acquisition

A standard 2-day stress/rest protocol was performed for all the patients. However, for the elimination of the stress effect on the results, only rest-phase data were incorporated into the study. Furthermore, all the patients received a fixed dose of 10 to 12 mCi of ^{99}mTc-Sestamibi in the rest phase of MPI to reduce the dose-related impact on the phase-analysis results. Seeking to decrease interfering subdiaphragmatic activity, we instructed the patients to drink 125 mL of milk 10 minutes after radiotracer injection. [19]

Acquisitions were performed 45 to 60 minutes after radiotracer injection with a dual-detector SPECT/CT camera (Symbia T6, Siemens Medical Systems) in a 90° detector configuration and a non-circular body-contoured 180° acquisition arc from the right anterior oblique view to the left posterior oblique view. The acquisition parameters were set to the step-and-shoot mode with a matrix size of 64×64 (pixel size =6.6 mm), sixty-four 25-second projections, and 16-frame fixed temporal resolution forward-backward gating per R-R interval, using a fixed acceptance window of 30%. The energy window was centered over the 140-keV photopeak using a window of 20%.

Image Processing

For the enrollment of GSPECT-MPI studies with good quality, the rotating raw images and heartbeat histograms of all the patients were assessed visually. All the projection images were reconstructed by filtered back projection using post-reconstruction Butterworth filtering with a cutoff frequency of 0.4 and order of 5. With the aim of providing LV phase indices, the reconstructed images were further analyzed using the Cedar–Sinai quantitative GSPECT on the basis of the software's predefined algorithm. [20] All endocardial and epicardial automated-drawn region of interest contours were meticulously quality controlled. [21]

After the completion of processing, global whole ventricular and regional wall-based LV synchrony parameters, including phase histogram bandwidth (PHB; the width of histogram including 95% of the elements in the phase distribution), phase standard deviation (PSD; the standard deviation of the phase distribution), and entropy (defined by the summation of $[f_i*\log(f_i)]/\mathrm{Log}(n)$], in which f and n represent the frequency in the i^{th} bin and the number of bins, respectively), were derived. [22]

Statistical Analysis

The Mann–Whitney *U* test was employed to compare the synchrony parameters between the diabetic and nondiabetic subjects. The statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, version 22.0. IBM Inc, Armonk, NY). The quantitative continuous variables were presented as the mean ± the standard deviation, whereas the categorical variables were expressed by numbers (percentages). A *P* value of < .05 was considered statistically significant.

RESULTS

Of the total 121 patients enrolled in the study from March 2019 through April 2020, 66 (54.5%) were male and 55 were female (45.5%). The mean duration of DM was 6.85±5.72 years. The fasting plasma glucose levels of all the patients were under control by medical treatment, either with insulin injection (81.8%) or metformin (18.2%).

The patients' demographic data are presented in Table 1. The LV phase parameters of both DM and LLK groups were derived in the resting phase and are presented in Table 2 and Table 3 based on global whole LV and regional wall-based synchrony parameters, respectively. No significant differences were noted in the derived values for PHB, PSD, and entropy between the DM and LLK groups concerning global whole LV synchrony (*P*>.05). Likewise, PHB and PSD demonstrated no significant differences between the 2 groups regarding the regional wall-based analysis (*P*> .05). Nonetheless, the entropy indices of the LV septum and anterior wall were significantly higher in the DM group (*P*= .019 and *P*= .022, respectively). Furthermore, PHB and entropy demonstrated no significant changes (*P*>.05) in patients with more prolonged DM (>5 y) compared with patients who had shorter disease duration (<5 y), either in global or regional wall-based analyses (Table 4). The PSD values of the septum and the apex were the only parameters with significant differences (*P*= .04 and *P*= .01, respectively) vis-à-vis DM duration. Furthermore, no significant differences were noticed in the phase-analysis parameters according to the DM treatment type (*P*>.05).

Table 1: Demographic and baseline GSPECT data of the study population

Demographic Parameter		LLK Group (n=100)	DM Group (n=121)
Sex	male	56 (56%)	66 (54.5%)
	female	44(44%)	55 (45.5%)
Body weight, kg		83.3±17	82 ±15.1
Height, cm		167.2 ±9.3	167.9±10.2
BMI, kg/m^2		29.7±5.2	29±4.9
Age, y		48.5 ±9.8	59.9±10.6
Treatment for DM With oral agents		Not applicable	99 (81.8%)
Treatment for DM With insulin		Not applicable	22 (18.2%)

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

GSPECT, Gated single-photon emission computed tomography; LLK, Nondiabetic subjects with low likelihoods of coronary artery disease; DM, Diabetes mellitus; BMI, Body mass index

Table 2: Global whole LV phase parameters

Phase Parameter	LLK Group	DM Group	*P* value
PHB	30 (24-36)	30 (24-36)	.452
PSD	6.3 (4.9-8.58)	6.4 (5.25-9.25)	.354
Entropy	34 (27-40)	33 (24-40)	.323

Data are presented as the median (the interquartile range). Additionally, PHB and PSD are presented in degrees and entropy in percentages.

LLK, Nondiabetic subjects with low likelihoods of coronary artery disease; DM, Diabetes mellitus; LV, Left ventricular; PHB, Phase histogram bandwidth; PSD, Phase standard deviation

Table 3: Regional wall-based phase parameters

Region	Parameter	LLK Group (n=100)	DM Group (n=121)	*P* value
Apex	PHB	12 (12-18)	12 (12-18)	.815
	PSD	2.9 (2.23-3.18)	2.8 (2.4-3.4)	.651
	Entropy	16 (11-18)	15 (13.5-17.5)	.116
Lateral	PHB	24 (18-30)	24 (18-35.5)	.534
	PSD	5.8 (4.2-8.85)	5.9 (4.2-8.95)	.793
	Entropy	30 (23.25-38.75)	28 (18-36)	.114
Inferior	PHB	21 (18-30)	24 (18-30)	.149
	PSD	5.1 (3.9-7.3)	5.3 (3.8-7.5)	.511
	Entropy	26 (19-32)	23 (13-32.5)	.324
Septum	PHB	18 (18-24)	18 (15-30)	.753
	PSD	4.6 (3.23-6.58)	4.7 (3.3-7.1)	.965
	Entropy	26 (19-32)	23 (13-32.5)	.019
Anterior	PHB	24 (18-30)	24 (18-30)	.534
	PSD	5.55 (4.13-8.3)	5.1 (3.75-7.85)	.588
	Entropy	30 (23-36.75)	26 (17-34)	.022

Data are presented as the median (the interquartile range). Additionally, PHB and PSD are presented in degrees and entropy in percentages.

LLK, Nondiabetic subjects with low likelihoods of coronary artery disease; DM, Diabetes mellitus; PHB, Phase histogram bandwidth; PSD, Phase standard deviation

Table 4: Regional wall-based phase parameters based on diabetes mellitus duration

Region	Parameter	< 5 y (n=70)	>5 y (n=51)	*P* value
Global whole LV	PHB	30 (24-42)	24 (24-36)	.206
	PSD	6.8 (5.4-9.5)	6.15 (4.8-8.6)	.202
	Entropy	34 (27.8-42)	30.5 (16.638.2)	.056
Apex	PHB	12 (12-18)	12 (12-12)	.186
	PSD	2.9 (2.5-3.5)	2.7 (2.2-3.2)	.151
	Entropy	16 (9.8-21)	12.5 (0.2-17)	.01
Lateral	PHB	24 (18-35.3)	24 (18-36)	.335
	PSD	6.3 (4.3-9.1)	5.4 (4.1-8.9)	.271
	Entropy	29 (19-36)	26.5 (10.6-36.5)	.221
Inferior	PHB	24 (18-30)	24 (18-30)	.423
	PSD	5.5 (4-7.7)	5.3 (3.5-7.3)	.11
	Entropy	29.5 (19.8-36)	24.5 (9.1-33.5)	.368
Septum	PHB	18 (10.5-30)	18 (12-24)	.115
	PSD	5 (3.4-7.8)	4.3 (3-6.3)	.04
	Entropy	25.5 (16-35.5)	21.5 (0.4-31)	.622
Anterior	PHB	24 (18-30)	18 (18-30)	.277
	PSD	5.7 (3.9-7.9)	4.4 (3.7-8.1)	.169
	Entropy	27 (18-36)	23.5 (6.1-34)	.335

Data are presented as the median (the interquartile range). Additionally, PHB and PSD are presented in degrees and entropy in percentages.

LV, Left ventricular; PHB, Phase histogram bandwidth; PSD, Phase standard deviation

DISCUSSION

In this study, we found no significant impact exerted by DM on PHB and PSD phase parameters, either in the global whole-body analysis or in the regional wall-based analysis. Therefore, the previously presented normal range for PHB and PSD values can be applied to the interpretation of diabetic patients as

well. Nevertheless, the regional entropy values of the anterior wall and the septum may be increased somewhat in diabetic subjects. Consequently, entropy could be used as the primary indicator of LV dyssynchrony in diabetic patients with preserved LV systolic function and with no evidence of abnormal perfusion in their MPI. The unique feature of our study is the selection of patients suffering only from DM and the exclusion of all patients with other CAD risk factors with a potential impact on phase-analysis results.

There is a growing body of literature on the evaluation of the effect of different factors on GSPECT-MPI phase-analysis parameters. These factors could be either patient-related, including demographics, myocardial ischemia, heart rate during imaging, and hypertension, or technical, such as radiotracer injected dose, reconstruction method, acquisition orbit type, processing software package, and the type of gamma camera. [11,12,14-18,23]

Hypertension and DM are major risk factors for the development of CAD. [24] As the majority of patients referred for GSPECT-MPI have suspected CAD, it is not surprising that most of them suffer from hypertension and DM. Diabetic patients are much more likely to develop congestive heart failure than nondiabetic individuals, particularly in younger age groups. [25] Age, DM duration, insulin use, elevated serum creatinine, and the presence of ischemic heart disease are independent risk factors for the incidence and prevalence of congestive heart failure. Hence, DM not only increases but also accelerates the risk of congestive heart failure.[25,26] Consequently, the early recognition and aggressive treatment of DM as a modifiable risk factor for congestive heart failure seem mandatory. Hypertension is a powerful modifiable risk factor for the incidence of heart failure among individuals with preserved or reduced ejection fractions. [27]

Still, prior investigations have demonstrated no significant associations between hypertension and phase-analysis parameters. [15] Malik et al [28] found that LV mechanical dyssynchrony was affected by the evolution time of type II DM. They also found higher prevalence rates of hypertension, obesity, and dyslipidemia in the diabetic group than in the control group. The duration of DM was statistically significant in their univariate and multivariate logistic regression analyses. As a result, they concluded that dyssynchrony could be a manifestation of long-standing DM. We found no significant impact exerted by DM duration on phase-analysis parameters in our study, which could be related to differences in patient populations and the selection of patients without any other CAD risk factors except DM. The only concordant finding of our study is the alteration of entropy in the anterior wall and the septum, which could be used as a potential indicator of LV dyssynchrony in diabetic patients.

Among other patient-related factors, Hämäläinen et al [29] found that gender, age, and body mass index exerted no influence on phase-analysis measurements. Moreover, Aljaroudi et al[14] concluded that phase-analysis indices were not prone to alterations in the presence of perfusion abnormalities, however considerable. Nonetheless, this conclusion was not reproduced in a study by Singh et al.[30]

CONCLUSIONS

Except for regional wall-based entropy in the septum and the anterior wall, DM does not inherently impose any significant alterations on the mechanical synchrony indices of normal GSPECT-MPI studies. As a result, it can be assumed that the regional-based entropy indices of the septum and the anterior wall could be used as the primary indicators of LV dyssynchrony in diabetic patients with preserved LV systolic function and with no evidence of abnormal perfusion in their MPI. Furthermore, the provided

normal databases for GSPECT-derived synchrony parameters could be drawn upon for diabetic patients as well.

Disclosures

The authors report no conflicts of interest.

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