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Original Article

Prevalence of Left Ventricular Dyssynchrony in Individuals Undergoing Gated SPECT Myocardial Perfusion Imaging Using Phase Analysis

Maryam Alvandi [1]*, MD; Seid Kazem Razavi-Ratki [2], MD; Zahra Shaghaghi[3], PhD; Abolfazl Ghafouri Khosrowshahi [4], PhD; Mohamad Ali Seif Rabiei [5], MD; Sara Zebarjadi [6], MS

ABSTRACT

Left ventricular (LV) synchrony is a clear indicator of cardiac performance. However, left ventricular dyssynchrony (LVD) is not necessarily a sign of heart malfunction. Individuals at a higher risk of developing heart failure can be identified by LVD. Gated SPECT myocardial perfusion imaging (MPI) allows the simultaneous assessment of LV perfusion, function, and mechanical dyssynchrony through phase analysis. The aim of this study was to evaluate the prevalence and predictors of LVD in patients undergoing MPI. A total of 907 consecutive patients referred to the Nuclear Medicine Department of Farshchian Heart Center, Hamadan, Iran, for diagnostic purposes were examined. The patients underwent gated SPECT MPI with a 2-day stress/rest protocol. Auto-Quant software package was used to evaluate perfusion, function, and phase analysis. Additionally, significant LVD was assessed based on the following criteria: standard deviation of the LV phase distribution > 19.6 and a phase histogram > 72.5 in the stress phase of the examination. Several variables were evaluated using univariate and multivariate analyses. The variables significantly associated with LVD were sex (male), obesity, hypertension, diabetes, QRS > 120 ms, a history of coronary artery disease, myocardial perfusion defects reported on MPI, and LV dysfunction. Our results suggested that the prevalence of significant LVD as a predictor of adverse cardiovascular events, death, and progression to heart failure was 12.9%. The multivariate analysis revealed that variables such as obesity, diabetes, hypertension, sex (male), coronary artery disease, and QRS >120 ms were highly associated with LVD. ***(Iranian Heart Journal 2019; 20(3): 66-74)***

KEYWORDS: Left ventricular dyssynchrony, Heart failure, Phase analysis

[1] Department of Nuclear Medicine and Molecular Imaging, Clinical Development Research Unit of Farshchian Heart Center, Hamadan University of Medical Sciences, Hamadan, IR Iran.
[2] Department of Radiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, IR Iran.
[3] Department of Radiology, Paramedical School, Hamadan University of Medical Sciences, Hamadan, IR Iran.
[4] Department of Medicinal Chemistry, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, IR Iran.
[5] Department of Community Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran.
[6] Department of Biostatistics and Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, IR Iran.

***Corresponding Author:** Maryam Alvandi, MD
Email: maryamalvandi@yahoo.com **Tel:** 09124146091

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Disturbances in synchrony in the left ventricle (LV) affects its contraction negatively and causes its remodeling, eventually leading to progressive ventricular dilation and cardiac function impairment. [1-3] Left ventricular dyssynchrony (LVD) can be investigated as a clear marker for the early diagnosis of progressive heart failure in patients who even do not exhibit any symptoms and signs of heart disease. [1, 2, 4] The optimal time for the detection of LVD is the subclinical stage because the symptoms typically occur late in heart failure progression. Phase analysis has shown excellent reproducibility and repeatability for assessing LVD. [1] It was first applied to investigate dyssynchrony in 2005. Myocardial perfusion imaging (MPI) can simultaneously survey perfusion, function, and dyssynchrony. In comparison with other imaging modalities such as echocardiography, magnetic resonance imaging, and equilibrium radionuclide angiography, some advantages of MPS phase analysis include its simplicity, widespread availability, superior reproducibility, applicability to retrospective data, and ability to simultaneously assess myocardial perfusion and function. [2] Despite all these advantages, however, this modality is not commonly used for the evaluation of dyssynchrony because there are no precise data on the prevalence of dyssynchrony in asymptomatic patients. The most frequently used phase analysis parameters for the assessment of LVD are the phase histogram bandwidth (PHB) and phase standard deviation (PSD). There are 4 software packages for phase dyssynchrony analysis in gated myocardial perfusion single-photon emission computed tomography (SPECT): 4DM, cREPO, ECTb, and QGS. Although the mean bandwidth and phase SD values derived from these software packages are significantly different, previous research has revealed high correlations between these parameters. [3-5]

In the present study, with the aid of QGS-derived mechanical dyssynchrony, for the first time, we aimed to study the prevalence of dyssynchrony. We also sought to report the clinical indicators for mechanical dyssynchrony in individuals undergoing MPI.

METHODS

Study Population

This clinical study recruited 907 patients who for diagnostic purposes underwent Gated SPECT MPI with a 2-day stress/rest protocol between the years 2016 and 2017 at the Nuclear Medicine Department of Farshchian Heart Center. Patients with irregular electrocardiographic rhythms (the presence of atrial or ventricular arrhythmias), implanted cardiac devices and pacemakers, and cardiac resynchronization therapy were excluded from the study.

Gated-SPECT MPI

The patients underwent MPI at rest and under stress in a 2-day protocol. The induced stress was either pharmacological (dipyridamole or dobutamine) or a treadmill exercise test. The standard radiotracer used was ^{99}Tc sestamibi, which was injected intravenously. The doses were 25 and 20 mCi at stress and rest, respectively. A standard acquisition protocol with SPET was performed using a rotating, dual-head gamma camera (Symbia T2, Siemens Healthcare), equipped with a low-energy high-resolution parallel hole collimator. During the image acquisition, the patients were in the supine position. Thirty-two projections at 30 seconds were obtained over a 180° circular orbit, from 45° right anterior to 135° left posterior oblique on a 64 × 64 × 16 matrix and a 38.5-cm detector mask. Rest phase perfusion study was carried out with a similar imaging protocol on the following day. In stress phase study, ECG-gated data acquisition was conducted at 16 frames per cardiac cycle and a 30% acceptance window for the R-R interval length using the forward-backward gating method. The raw data were reinvestigated using

ramp and Butterworth filters with a window frequency cutoff of 0.45 and order of 9. The summed stress score, the summed rest score, the summed difference score, the end-diastolic volume, the end-systolic volume, and the ejection fraction (EF %) were measured using Auto-QUANT software package (Cedars-Sinai Medical Center, Los Angeles, CA) in order to quantitatively process the images.

Phase analysis with QGS software

Using a short-axis data set, QGS computes myocardial surfaces coordinated to an ellipsoidal sampling system, along which unidimensional arrays are created for each spatial sampling point that contains the local maximum myocardial count at each interval. The phase angle of the first-harmonic Fourier transform is the basis for all the synchrony measurements. This software provides indices of LV mechanical synchrony, including PHB, which contains 95% of the phase distribution, and PSD, which is the SD of the phase distribution.

Criteria in the diagnosis of ventricular dyssynchrony

Based on a study done by Rastgou et al, [6] we considered the criteria of significant LVD diagnosis derived from QGS software as follows: PHB > 72.5 and/or PSD > 19.6. A patient was considered to have significant LVD if any of these criteria were achieved during phase analyses.

Statistical Analysis

Via descriptive statistics, the categorical variables were introduced as absolute frequencies (n), relative frequencies (n), and percentages (%). The numerical variables were presented as the mean and the SD. The χ^2 test and the Student *t*-test were used to analyze the association between the categorical and numerical variables with dyssynchrony, respectively. A multiple binary logistic regression was employed for the comparison of different variables. A *P* value < 0.05 was considered to indicate statistical significance. All the analyses were performed using SPSS software, version 17.0, for Windows.

RESULTS

The study consisted of 907 patients referred for routine gated SPECT MPI to the Nuclear Medicine Department of Farshchian Heart Center for diagnostic purposes with a 2-day stress/rest protocol between 2016 and 2017. Sixty-eight patients were excluded from the study due to irregular electrocardiographic rhythms (the presence of atrial or ventricular arrhythmias) and implanted cardiac devices. The clinical characteristics of the study population and their associations with LVD are shown in Table 1. The prevalence of LVD in the study population was 12.9%, and the average age was 59.3 ± 11 years. Additionally, 39.2% of the study patients were males, whose dyssynchrony prevalence was 8.6%, while the prevalence of dyssynchrony in the females was 3.7%, yielding a prevalence ratio of 2.3. The age of the included patients ranged from 22 to 89 years old, with an average of 59.3 years old. The statistical analyses showed no significant correlation between age and dyssynchrony (*P* = 0.112). The body mass index values in our patients were between 4.73 and 58.00, with an average of 27.06. A total of 186 (22.2%) patients had a body mass index > 30 kg/m^2, and the counted prevalence of dyssynchrony in this group was 27/2, which was approximately more than twofold that of the non-obese individuals with a prevalence ratio of 2.08. The frequency of hypertension in our study was 42%, and the prevalence of LVD in this group proved to be 17.6% with a prevalence ratio of 1.8, approximately twofold that in the unaffected individuals. There were also similar results for the patients suffering from diabetes mellitus, and a significant correlation was achieved between this variable and significant dyssynchrony. The prevalence ratio was 4.2

(P < 0.005). In contrast, no significant correlation was found between significant LVD and smoking, hyperlipidemia, and opium abuse. There was also a significant correlation between the duration of the QRS interval and dyssynchrony: 4.2% of the sample population had QRS intervals >120 mms and the prevalence of LVD in this group was 34%, while the prevalence of LVD in the patients with narrow QRS intervals (< 120 ms) proved to be 11.9%. The prevalence ratio was equal to 2.85%. Known coronary artery disease was reported in 22.2% of all the patients. According to our results, there was a significant correlation between a previous history of coronary artery disease and LVD. The prevalence of dyssynchrony among the patients with coronary artery disease proved to be 15.8%, which was 4.15 times higher than that in the patients without known coronary artery disease, whose LVD prevalence was 3.8%. After the interpretation of the myocardial perfusion scan, 138 patients had fixed perfusion defects, indicating nonviable myocardium. In addition, significant reversible perfusion defects were seen in 191 patients, suggesting jeopardized myocardium. In the patients with fixed defects, the prevalence of dyssynchrony was 47%; and in those with reversible defects, the counted prevalence of dyssynchrony proved to be 34.1%, whereas the prevalence of significant LVD in the patients without any perfusion defect was only4.16%. Hence, there were significant correlations between the existence of both nonviable and jeopardized myocardium and the disturbance of synchrony in the LV myocardium. A significant correlation existed between LV dysfunction and significant LVD (P < 0.00). A considerable percentage of the study population (89.9%) had normal LV function (LVEF > 45%). The prevalence of significant LVD in these patients was only 3.5%, whereas the prevalence of significant LVD was 93.3% in the patients with mild-to-moderate dysfunction (LVEF = 36–44%) and 100% in the patients with severe dysfunction (LVEF ≤ 35%). The patients with LVD revealed higher average amounts of end-systolic and end-diastolic volumes. Accordingly, it can be concluded that there was a significant correlation between these variables and significant LVD. A multivariate regression analysis was performed to identify the independent and dependent variables with LVD. The analysis showed that sex (male), hypertension, obesity, diabetes mellitus, QRS > 120 ms, and a history of known CAD remained associated with LVD.

DISCUSSION

The value of LVD the prognostication of patients with severe heart failure has been proven. [6] LVD is a primary sign of the progression of LV dysfunction in asymptomatic patients without coronary artery disease and with a normal LVEF. Individuals at a higher risk of developing heart failure can be identified by LVD. [7-9] Meanwhile, dyssynchrony is a predictive marker of LV remodeling [10, 11] and, in a population with impaired LV function, influences the long-term outcome. [12] MPI is widely used for the detection of myocardial ischemia, myocardial infarction, viability assessment, patient risk stratification, and anti-ischemic treatment efficacy. The use of the phase analysis of gated SPECT along with MPI for quantifying mechanical synchrony has been well-described in the literature, [1, 13-17] although not always fully utilized. [18-22] In this study, the variables most closely associated with LVD were sex (male), obesity, hypertension, diabetes, a history of coronary artery disease, QRS >120 mms, myocardial perfusion defect reported on MPI including fixed and reversible defects, and LV dysfunction. Controversial findings have been reported in the previous studies that have evaluated the relationship between age and LVD. Our results showed no significant relationship between age and the prevalence of LVD, which is compatible with the findings reported by Tavares et al [5] and in

contrast to those reported by Bader et al, [7] who revealed that older age was associated with LVD. Various recent studies have evaluated the relationship between sex and dyssynchrony; further, adverse cardiovascular events have shown diversity between women and men in terms of myocardial responses to aging and specific cardiovascular risk exposure. During the cardiac aging process, women are more likely to preserve myocardial mass and structure, whereas men tend to have greater myocyte cell loss and cellular reactive hypertrophy. [3] Therefore, it is reasonable that they become prone to more LVD. We found that, compared with men, women had a lower prevalence of LVD, which chimes in with previous studies. [3, 4] It has been shown that significant coronary artery stenotic lesions are associated with LVD. [11] In keeping with the previous findings, our study also confirmed that known coronary artery disease is significantly linked with LVD. Our statistical analysis showed that hypertension and diabetes mellitus were significantly related to LVD. Both diabetes mellitus and hypertension are important risk factors for cardiovascular diseases. Hypertension can result in the delayed activation of certain ventricular segments secondary to ventricular hypertrophy, eventually leading to uncoordinated contraction. [23] Malik et al [24] in 2017 suggested that diabetic patients had a higher incidence of LVD and might require aggressive management despite the absence of perfusion abnormalities and adequate LVEFs. Although previous studies have revealed a significant correlation between dyssynchrony and hyperlipidemia, [4] no strong association was found in our study. Moreover, smoking and opium abuse showed a weak association with LVD, which was not statistically significant. An increased body mass index has been previously reported in 11% and 14% of heart failure cases in men and women, respectively. [25] Obesity is known as an important risk factor for heart failure in both men and women, and our study showed a positive correlation between LVD and obesity (P = 0.00). This finding may indicate that such patients are likely to develop LV dysfunction in the future, so close observation would be an acceptable recommendation for this group of patients. Our results indicated that there was a significant correlation between the duration of the QRS interval and dyssynchrony. The prevalence of LVD in our patients with a QRS interval > 120 ms was 34%, approximately 4.38 times higher than that in patients with a QRS interval < 120 ms (11.9). This finding suggests that in some cases, electrical dyssynchrony can cause mechanical dyssynchrony. That a large number of the patients with a QRS interval >120 ms (67%) had fixed defects and/or LV dysfunction is indicative of myocyte damage, electrical dyssynchrony, and mechanical dyssynchrony. These variables were associated with LVD in the multivariate analysis. The results showed that, based on the pattern of myocardial perfusion in the MPI examination reports, both fixed defects (the existence of myocardial fibrosis) and reversible defects (ischemic myocardium) had statistically significant relationships with LVD, which was more prominent for fibrotic myocardium (P = 0.000). Such a reasonable finding has been found in preceding studies. [27-29] As was mentioned before, LVD prevalence in our patients with a normal LVEF, the main group of the study, was only 3.5%. In contrast, in the patients with mild-to-moderate dysfunction (4.5%) and those with severe LV systolic dysfunction (5.7%), the prevalence of LVD was 93% and 100%, respectively. An increase in the LVEF is in tandem with a rise in LVD prevalence, so that in patients with severe LV systolic dysfunction, LVD prevalence reaches 100%. Similar results have been reported by previous studies evaluating the relationship between LVD and LV contractile function. [31] Our multivariate analysis showed that diabetes, hypertension, obesity, sex (male), coronary artery disease, and QRS > 120 ms were highly associated with LVD (P = 0.000). Using QGS

software package for the first time, we evaluated the prevalence and predictors of LVD in patients undergoing MPI, while the only similar study, done by Tavares et al [4] in 2016, used Emory Tool Box software package for the evaluation. We found that patients with severe LV dysfunction always had LVD, but the prevalence of dyssynchrony was much more than what we had excepted; therefore, LVD can detect patients with normal LV systolic function in the presence of some risk factors. According to our results, further monitoring and closer observation in patients with the abovementioned risk factors, which are significantly associated with LVD even in patients with a normal LVEF, should be taken into consideration. Surely, further studies are needed to confirm our conclusion in the future and to explain this association with more details.

CONCLUSIONS

We found a noticeable relationship between LVD and some risk factors such as hypertension, diabetes, and obesity. Significant LVD is a predictive indicator of LV systolic dysfunction in the future; therefore, the use of phase analysis along with gated SPECT MPI can be a convenient and cost-effective tool for the evaluation of LVD in these patients.

Table 1. Baseline characteristics

Variable	Frequency	%	Prevalence of LVD (%)	*P* value
Gender				
Male	329	39.21	8.6	0.000
Female	510	60.78	3.7	0.112
Age				
<49 y	156	18.6	8.3	0.112
50-59 y	269	32.1	10.4	
60-69 y	259	30.9	13.8	
> 70 y	155	18.5	7.3	
Obesity (BMI >30)				
No	653	77.8	13.1	0.000
Yes	186	22.2	27.3	
Known coronary artery disease				
No	694	77.8	3.8	0.000
Yes	145	22.2	15.8	
Smoking				
No	784	93.4	12.6	0.095
Yes	55	5.5	16.3	
Hypertension				
No	487	58.0	9.4	0.000
Yes	352	42.0	17.6	
DM				
No	634	75.6	17.6	0.000
Yes	205	24.4	9.4	0.000
Dyslipidemia				
No	738	88.0	6.5	0.112
Yes	101	12.0	7.5	
Opium				
No	791	95.8	6.5	0.066
Yes	48	4.2	7.2	
QRS internal >120ms				
No	804	95.8	11.9	0.000
Yes	35	4.2	34	

LVD, Left ventricular dyssynchrony; BMI, Body mass index; DM, Diabetes mellitus

Table 2. Prevalence of LVD according to the perfusion pattern in the myocardial perfusion imaging examination report

Report	Total		LVD (No)		LVD (Yes)		*P* value (χ^2 test)
	N	%	N	%	N	%	
Normal perfusion	521	100	499	95.84	22	4.16	
Reversible defect	191	100	126	65.9	65	34.1	0.000
Fixed defect	138	100	72	53	66	47	0.000

LVD, Left ventricular dyssynchrony

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