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Original Article

Association Between Blunted Heart Rate Response to Dipyridamole and Myocardial Ischemia in Diabetic Patients as Compared With Nondiabetic Patients

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ABSTRACT

Background: Blunted heart rate response (BHR) during dipyridamole stress testing has been reported to be related to higher cardiac death. This study was performed to assess the association between BHR and perfusion abnormalities in diabetic patients undergoing dipyridamole stress ECG-gated myocardial perfusion imaging (MPI) as compared with nondiabetic patients.

Methods: A total of 2172 subjects (1602 women and 570 men) at a mean age of 61 ± 11 years who were referred for MPI to our department were studied. The subjects were divided into 2 groups on the basis of the presence or absence of diabetes mellitus (849 diabetic vs 1323 nondiabetic subjects).

Results: Dipyridamole-related BHR was noted in 471 (67.7%) patients, demonstrating a significantly higher incidence in the diabetic patients than in the nondiabetic subjects ($P < 0.05$). Both basal systolic and peak systolic blood pressures were significantly higher in the patients with diabetes mellitus ($P < 0.05$). However, no significant difference was noted in the number of segments with perfusion abnormalities in patients with BHR as compared with the subjects with a normal hemodynamic response, neither in the diabetic nor in the nondiabetic subjects.

Conclusions: The results of our study suggest that the presence of myocardial perfusion abnormalities and left ventricular dysfunction is not related to abnormal heart rate response during dipyridamole stress testing, neither in diabetic nor in nondiabetic subjects. The incidence of BHR to dipyridamole is significantly higher in diabetic patients, however. ***(Iranian Heart Journal 2020; 21(1): 67-74)***

KEYWORDS: Diabetes mellitus, Hemodynamic response, Ischemic heart disease, Myocardial perfusion imaging, Dipyridamole stress testing

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An individual's heart rate is a physiological response to autonomic, central, and peripheral reflexes as well as intrinsic cardiac control mechanisms. Different abnormalities could be responsible for an abnormal heart rate response to physiological stress including renal failure, diabetes, and intrinsic cardiac conditions such as coronary artery disease (CAD) and cardiomyopathy. [1] Dipyridamole is routinely employed for pharmacological stress testing in myocardial perfusion imaging (MPI). This vasodilator agent has also been used for the assessment of heart rate response variability. [2,3,4] Dipyridamole may cause a modest decrease in blood pressure, whereas there is a modest increase in heart rate, which have been believed to be a normal hemodynamic response to this vasodilator agent. [5] Chronotropic incompetence, which is defined as an attenuated chronotropic response to exercise, has been considered to be a predictor of increased mortality. [6,7] Likewise, it has been shown recently that blunted heart rate response (BHR) during dipyridamole stress testing is related to cardiac death. [1,6,7,8] Myocardial ischemia and left ventricular dysfunction have been shown to be in association with chronotropic incompetence during exercise, [8,3] and the same association might be present in dipyridamole-related abnormal heart rate response, despite the fact that the underlying mechanisms are not yet understood. [9] Furthermore, BHR to dipyridamole has been associated with a higher mortality risk, even in the presence of normal myocardial perfusion, [7] which could partly be explained by sudden cardiac death and ventricular arrhythmias related to an abnormal cardiac autonomic nervous system, [10,11] Diabetes mellitus is known as the most common metabolic disease in the world. [12] It is estimated that 20%–40% of diabetic patients suffer from cardiac autonomic neuropathy, which can be assessed by heart rate variability during the vasodilator stress test, [13,14] resulting in an increased risk of cardiovascular-related mortality. [2,15]

Hence, we performed the present study to assess the association between BHR and perfusion abnormalities in diabetic patients undergoing dipyridamole stress ECG-gated MPI as compared with nondiabetic patients, using single-photon emission computed tomography (SPECT).

METHODS

Study Population

Consecutive patients (N = 2172) who underwent dipyridamole stress ECG-gated SPECT MPI in Rajaie Cardiovascular, Medical, and Research Center were enrolled in this study. The exclusion criteria were pregnancy, severe obstructive lung disease, second- or third-degree atrioventricular block without a functioning pacemaker, acute myocardial infarction or unstable coronary syndrome (< 24 h), systolic blood pressure < 90 mm Hg, hypersensitivity to dipyridamole, or atrial fibrillation.

Dipyridamole Stress Protocol

All the patients were instructed to interrupt xanthine-containing compounds and dipyridamole for 24 hours and to be in a fasting state for 8 hours before testing. When possible, they were also instructed to discontinue β-blocking medications for 48 hours and calcium channel blockers as well as long-acting nitrates for 24 hours. All the patients underwent a structured interview for recording demographic data, clinical history, prior cardiac events, cardiac risk factors, therapeutic procedures, and prior diagnostic tests before the study. A 12-lead ECG was obtained before and during stress testing at 2-minute intervals. The patients underwent dipyridamole stress SPECT MPI according

to the standard protocol. [16] Dipyridamole in a dose of 0.56 mg/kg of body weight was infused intravenously over a 4-minute period.

Heart rate and blood pressure were measured at resting state in the supine position and then every 1 minute after the commencement of dipyridamole infusion for a total period of 10 minutes. Next, 99mTc-Sestamibi was injected 3 to 5 minutes after the termination of dipyridamole infusion.

The peak stress heart rate was defined as the maximum recorded heart rate during a 6-minute period after the completion of dipyridamole infusion. The peak stress to baseline heart rate ratios were calculated and the results were categorized as normal (ratios ≥ 1.2) or BHR groups (ratios < 1.2), according to the previously published data. [6,8]

Acquisition Protocol

All the patients underwent a 2-day stress-rest protocol, using 99mTc-Sestamibi with an injection dose of 10 to 15 mCi in each phase of the study. A series of 2 acquisitions, composed of a 60- to 90-minute post-stress as well as a resting-state acquisition, was carried out for all the patients. The SPECT acquisitions were conducted in the step-and-shoot mode with 32 thirty-second or 64 twenty-second projections, a zoom factor of 1.46, and in a non-circular 180° arc (45° RAO-to-LPO), using a PHILIPS BrightView dual-head gamma camera (USA), an Infinia Hawkeye dual-head SPECT/CT hybrid camera (GE Healthcare, USA), or a Symbia T2 dual-head SPECT/CT hybrid camera (Symbia T2 System; Siemens Medical Solutions, USA), equipped with low-energy, high resolution (LEHR) collimators and an automated body contour detection system.

Post-stress gated MPI with an acceptance window of 30% was carried out for all the subjects. All the data were stored in a 64×64×16 computer matrix and reconstructed with 3D ordered subset expectation maximization (3D-OSEM), using 2 iterations and 8 subsets. [17] The rotating raw images of all the participants were seen visually, and the studies with motion artifacts or low-count density were excluded.

Image Interpretation

The reconstructed and reoriented images were quality controlled and interpreted by experienced nuclear physicians, using AutoQUANT® software for cardiac quantification and functional analysis. [18] A semi-quantitative visual analysis of images was performed on the basis of standard 17-segment scoring. Each segment was considered to be normal (with no perfusion abnormality), ischemic (with reversible perfusion abnormality), or infarcted (with persistent perfusion abnormality and after the exclusion of attenuation artifacts, using the planar lateral view in the lateral decubitus portion or CT-based attenuation correction if available). [19]

Gated short-axis images were processed, and the left ventricular ejection fraction was automatically calculated. Patients with a post-stress ejection fraction < 50% were considered to have left ventricular dysfunction.

Statistical Analysis

The χ^2 test was used for the categorical and the Student *t*-test and the Mann–Whitney *U* test for the numerical variables. Multivariate logistic regression models were also performed to investigate adjusted associations between the variables.

The data were described as the mean ± the standard deviation (SD) and as counts (%) for the interval and the categorical variables, respectively. A *P* value < 0.05 was considered a statistically significant result.

The data were handled and analyzed with Statistical Program for Social Sciences

(SPSS 15.0 for Windows, SPSS Inc, Chicago, Illinois).

RESULTS

A total of 3021 patients, who were referred to Rajaie Cardiovascular, Medical, and Research Center for MPI study, were included in the study. A total of 849 patients were also excluded from the analysis due to recent intakes of beta-blockers, calcium channel blockers, known chronic renal failure, or incomplete data. Therefore, 2172 patients (1602 women and 570 men) at a mean age of 61 ± 11 years were enrolled in this study. Of this total, 520 (23.9%) patients had diabetes mellitus. The background and demographic descriptive data are shown in Table 1 and the comparisons of the demographic differences, hemodynamic response, and MPI parameters according to the presence or absence of diabetes mellitus are depicted in Table 2.

Dipyridamole-related BHR was noted in 1476 (68%) patients, demonstrating a significantly higher incidence in the diabetic patients than in the nondiabetic subjects (P = 0.008). Both basal systolic and peak systolic blood pressures were significantly higher in the patients with diabetes mellitus (P = 0.002), whereas no significant difference was noted in the peak to basal blood pressure changes. Furthermore, no significant difference was noted in the number of either ischemic or infarcted myocardial segments in the patients with BHR as compared with the subjects with a normal hemodynamic response, neither in the diabetic nor in the nondiabetic subjects (Table 3).

The adjusted association analysis by logistic regression models (Table 4) revealed no significant association between the incidence of myocardial ischemia and BHR, whereas there was a statistically significant association between ischemia and diabetes mellitus (OR = 1.574; P < 0.001) as well as hypertension (OR = 1.283; P = 0.010).

DISCUSSION

Normal hemodynamic response to dipyridamole is reflected by systemic vasodilatation, with a modest decrease in blood pressure and a modest increase in heart rate. [5,20] Despite the fact that CAD has been introduced as an intrinsic cardiac condition, responsible for BHR, [5,2,21,22] we found no association between the incidence of abnormal perfusion in patients with dipyridamole-related BHR as compared with patients with a normal response, neither in diabetic nor in nondiabetic subjects. Furthermore, BHR was not related to left ventricular dysfunction in our study as well. However, the incidence of BHR was significantly higher in diabetic patients than in nondiabetic subjects. One of the explanations for this finding could be related to the higher incidence of cardiac autonomic neuropathy in diabetes mellitus. [1314]

In a large cohort of patients undergoing adenosine stress MPI, Abidov et al [8] demonstrated that several hemodynamic variables could provide independent information in the risk assessment of patients. They found that patients with high resting heart rates were at a higher risk of cardiac death and that the peak to basal HR ratio provided incremental prognostic information over MPI results, enhancing the risk stratification of patients regarding cardiac death, particularly among those with normal perfusion. Although the authors showed that this fact might be related to heart failure, the ventricular function was not assessed in that study. Furthermore, diabetes mellitus was not regarded as a separate entity.

Bhatheja et al [6] also reached the same conclusion by showing that BHR to dipyridamole was a predictor of cardiac

death even in the setting of normal perfusion scan and normal ECG.

In a recent study by Mathur et al, [1] BHR was an independent predictor of cardiac mortality after adjustments for perfusion and function-related gated SPECT variables.

Our study is in accordance with the previously published data that found no association between myocardial ischemia or infarction and BHR, using MPI. Previous research has linked BHR to dipyridamole to higher mortality as a result of an abnormal cardiac nervous system, predisposing patients to ventricular arrhythmias and sudden death. [7,10,11]

The findings of our study are also in accordance with previous epidemiological studies, which have demonstrated that diabetic patients have a higher probability of BHR. [2,9,18]

Limitations

Our results are based on a population of patients who were referred to our department for gated SPECT MPI study; therefore, there might be a question on the implication of the results to a broader population. Moreover, the current study is retrospective, in spite of the prospective collection of all the data. Chronic renal failure and diabetic neuropathy have been concluded to cause BHR in previous studies. [2,9,18,20] However, the data concerning these conditions were unavailable and were not included in our study. Finally, this study was carried out in a single nuclear cardiology center.

Table 1. Background and demographic descriptive data (N = 2172)

Age (y)	61 ± 11
Gender (F/M)	1602/570 (73.8/26.2)
Symptoms:	
Atypical chest pain	1151 (53.0)
Typical chest pain	234 (10.8)
DOE	1068(49.2)
Palpitation	579 (26.7)
Arrhythmia	22 (1.0)
None	225 (10.4)
Risk Factors:	
Diabetes mellitus	520 (23.9)
Hypertension	1132 (52.1)
Hypercholesterolemia	885 (40.7)
Family history	286 (13.2)
Hemodynamic Variables:	
Basal HR (beat per minute)	69.6 ± 17.9
Peak HR (beat per minute)	60.6 ± 34.5
Peak HR/Basal HR <1.2 >1.2	 1471(67.7) 693 (31.9)
Basal systolic BP (mm Hg)	138.0 ± 18.0
Basal diastolic BP (mm Hg)	74.1 ± 23.5
Peak systolic BP (mm Hg)	142.0 ± 31.0
Peak diastolic BP (mm Hg)	73.8 ± 23.8
EF	66.2 ± 7.6

Statistics are numbers (%) or the mean ± the standard deviation.
HR, Heart rate; BP, Blood pressure

Table 2. Comparison of the demographic differences, hemodynamic, and MPI parameters in the patients with diabetes mellitus as compared with the nondiabetic subjects

Characteristic/ Variable	Diabetes Mellitus		*P* value
	Yes n = 520	No n = 1652	
Age (y)	62 ± 9.8	61 ± 11.3	0.015
Gender (F/M)	385/135	1217/435	0.867
Hemodynamic Variables:			
Peak HR/Basal HR ≤1.2 >1.2	 378 (72.7) 142 (27.3)	 1098 (66.5) 554 (33.5)	0.008
Peak HR (beat per minute)	61.2 ± 35.1	60.4 ± 34.4	0.199
Basal HR (beat per minute)	70.1 ± 20.4	69.5 ± 17.1	0.001
Basal systolic BP (mm Hg)	14.1 ± 1.9	13.8 ± 1.8	0.002
Basal diastolic BP (mm Hg)	73.1 ± 24.6	74.4 ± 23.1	0.586
Peak systolic BP (mm Hg)	14.6 ± 4.1	14.1 ± 2.8	0.002
Peak diastolic BP (mm Hg)	72.8 ± 24.9	74.1 ± 23.4	0.560
Basal/peak systolic BP (mm Hg)	0.9 ± 0.1	0.9 ± 0.1	0.664
Basal/peak diastolic BP (mm Hg)	1.1 ± 1.1	1.1 ± 1.01	0.795
Number of ischemic infarcted segments	348 (66.9)	856 (51.8)	<0.001
Number of ischemic segments	341 (65.6)	827 (50.1)	<0.001
Number of infracted segments	55 (10.6)	104 (6.3)	0.001
EF	66.8 ± 6.6	66.1 ± 7.8	0.298

Statistics are numbers (%) or the mean ± the standard deviation.
Significant *P* values in bold
MPI, Myocardial perfusion imaging; HR, Heart rate; BP, Blood pressure; EF, Ejection fraction

Table 3. Comparison of the number of ischemic, infarcted, or ischemic infarcted segments according to the peak to baseline heart rates in the diabetic patients

Characteristic/ Variable	Peak-to-Baseline Heart Rate		*P* value
	≤1.2 n = 378	>1.2 n = 142	
Number of ischemic infarcted segments	256 (67.7)	92 (64.8)	0.526
Number of ischemic segments	252 (66.7)	89 (62.7)	0.393
Number of infracted segments	43 (11.4)	12 (6.5)	0.296

Statistics are numbers (%).

Table 4. Multivariate logistic regression analysis for the association between ischemia and HR variability, adjusted for the EF, diabetes mellitus, hypertension, and hypercholesterolemia

Characteristic/ Variable	B	OR	95% CI for EXP(B)		*P* value
			Lower	Upper	
Diabetes mellitus	0.454	1.574	0.000	1.978	0.001
Hypertension	0.249	1.283	0.010	1.551	0.010
Hypercholesterolemia	0.172	1.188	0.083	1.443	0.083
EF	0.001	1.001	0.892	1.013	0.892
Peak to basal HR	0.032	0.969	0.753	1.182	0.753

Significant *P* values in bold
HR, Heart rate; EF, Ejection fraction

CONCLUSIONS

The incidence of BHR to dipyridamole was significantly higher in the diabetic patients in the present study; nonetheless, the results presented herein suggest that myocardial perfusion abnormalities and left ventricular dysfunction are not related to an abnormal heart rate response during dipyridamole stress testing, neither in diabetic nor in nondiabetic subjects. As previously published data indicate, given an increased risk of cardiac-related mortality in patients with BHR during dipyridamole stress testing, more attention should be paid to the risk stratification of patients with normal gated SPECT MPI but with BHR to dipyridamole stress testing.

REFERENCES

1. Mathur S, Shah AR, Ahlberg AW, Katten DM, Heller GV. Blunted heart rate response as a predictor of cardiac death in patients undergoing vasodilator stress technetium-99m sestamibi gated SPECT myocardial perfusion imaging. J Nucl Cardiol. 2010;17(4):617-24.

2. Lee KH, Yoon JK, Lee MG, Lee SH, Lee WR, Kim BT. Dipyridamole myocardial SPECT with low heart rate response indicates cardiac autonomic dysfunction in patients with diabetes. Journal of nuclear cardiology. 2001;8(2):129-35.

3. Petrucci E, Mainardi LT, Balian V, Ghiringhelli S, Bianchi AM, Bertinelli M, et al. Assessment of Heart Rate Variability Changes During Dipyridamole Infusion and Dipyridamole-Induced Myocardial Ischemia: A Time Variant Spectral Approach1. Journal of the American College of Cardiology. 1996;28(4):924-34.

4. Petretta M, Spinelli L, Marciano F, Vicario ML, Testa G, Signorini A, et al. Wavelet transform analysis of heart rate variability during dipyridamole-induced myocardial ischemia: Relation to angiographic severity and echocardiographic dyssynergy. Clinical cardiology. 1999;22(3):201-6.

5. Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, et al. Safety of dipyridamole testing in 73,806 patients: the Multicenter Dipyridamole Safety Study. Journal of nuclear cardiology. 1995;2(1):3-17.

6. Bhatheja R, Francis GS, Pothier CE, Lauer MS. Heart Rate Response During< i> Dipyridamole</i> Stress as a Predictor of Mortality in Patients With Normal Myocardial Perfusion and Normal Electrocardiograms. The American journal of cardiology. 2005;95(10):1159-64.

7. Kim YH, Lee KH, Chang HJ, Lee EJ, Chung HW, Choi JY, et al. Depressed heart rate response to vasodilator stress for myocardial SPECT predicts mortality in patients after myocardial infarction. The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging). 2006;22(5):663-70.

8. Abidov A, Hachamovitch R, Hayes SW, Ng CK, Cohen I, Friedman JD, et al. Prognostic impact of hemodynamic response to adenosine in patients older than age 55 years undergoing vasodilator stress myocardial perfusion study. Circulation. 2003;107(23):2894-9.

9. de Souza Leão Lima R, Machado L, Azevedo AB, De Lorenzo A. Predictors of abnormal heart rate response to dipyridamole in patients undergoing myocardial perfusion SPECT. Annals of nuclear medicine. 2011;25(1):7-11.

10. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. European heart journal. 2000;21(6):475-82.

11. Stein PK, Barzilay JI, Chaves PHM, Mistretta SQ, Domitrovich PP, Gottdiener JS, et al. Novel measures of heart rate variability predict cardiovascular mortality

in older adults independent of traditional cardiovascular risk factors: the Cardiovascular Health Study (CHS). Journal of cardiovascular electrophysiology. 2008;19(11):1169-74.

12. Malek H, Hedayati R, Yaghoobi N, Behnia M, Rastgou F, Bitarafan Rajabi A, et al. The relationship between retinopathy in diabetes mellitus type 2 and severity and extent of myocardial ischemia in myocardial perfusion imaging. Iranian Heart Journal. 2013;13(4):6-14.

13. Ziegler D, Gries F, Spüler M, Lessmann F. The epidemiology of diabetic neuropathy. Journal of Diabetes and its Complications. 1992;6(1):49-57.

14. Fedele D, Comi G, Coscelli C, Cucinotta D, Feldman EL, Ghirlanda G, et al. A multicenter study on the prevalence of diabetic neuropathy in Italy. Diabetes Care. 1997;20(5):836-43.

15. Ewing D, Campbell I, Clarke B. Mortality in diabetic autonomic neuropathy. The Lancet. 1976;307(7960):601-3.

16. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. Journal of Nuclear Cardiology.23(3):606-39.

17. Seret A. The number of subsets required for OSEM reconstruction in nuclear cardiology. European journal of nuclear medicine and molecular imaging. 2006;33(2):231.

18. Malek H, Yaghoobi N, Hedayati R. Artifacts in Quantitative analysis of myocardial perfusion SPECT, using Cedars-Sinai QPS Software. Journal of Nuclear Cardiology. 2017;24(2):534-42.

19. H Malek, N Yaghoobi, F Rastgou, A Bitarafan-Rajabi FR, M Alvandi, M Kargar, R Hedayati, H Amouzadeh, Sh Hosseini, H Firoozabadi. Assessment of myocardial viability in patients with left ventricular dysfunction: Correlation between CT-based attenuation correction and uncorrected quantification analysis in thallium201(201Tl)rest-redistribution SPECT study. Iranian Heart Journal. 2013;13(4):15-20.

20. Johnston DL, Daley JR, Hodge DO, Hopfenspirger MR, Gibbons RJ, editors. Hemodynamic responses and adverse effects associated with adenosine and dipyridamole pharmacologic stress testing: a comparison in 2,000 patients1995: Mayo Clinic.

21. De Lorenzo A, Lima RSL. Reduced heart rate response to dipyridamole as a marker of left ventricular dysfunction in diabetic patients undergoing myocardial perfusion scintigraphy. Clinical nuclear medicine. 2009;34(5):275.

22. Kim SB, Lee SK, Park JS, Moon DH. Prevalence of coronary artery disease using thallium-201 single photon emission computed tomography among patients newly undergoing chronic peritoneal dialysis and its association with mortality. American journal of nephrology. 2004;24(4):448-52.