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ORIGINAL RESEARCH ARTICLE

Correlation of heart rate response to dipyridamole stress during SPECT myocardial perfusion imaging with clinical factors

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ABSTRACT

Introduction: Myocardial perfusion imaging (MPI) with pharmacologic stress is a useful technique for evaluation of suspected coronary artery disease (CAD). Heart rate responses (HRR) to vasodilators such as dipyridamole mirror autonomic activity and may provide important prognostic information in CAD patients. In this study, the impact of baseline characteristics of patients including age and gender on the expected HRR has been assessed.
Methods: This retrospective study included database of 2584 patients (1575 female, 1009 male) who were referred to the nuclear medicine department for pharmacologic MPI. The HRR to dipyridamole was calculated as ratio of maximal heart rate (HR) during or shortly after dipyridamole infusion to baseline HR. The association of HRR with age, gender, presence of other known CAD risk factors and perfusion findings was evaluated.
Results: Significant correlation was found between HRR and sex, age, diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD) ($P < 0.001$) in both univariate and multivariate analysis. The mean HRR was also significantly higher in patients with normal perfusion on SPECT MPI as compared to patients with abnormal findings, however, multivariate regression analysis showed no significant correlation. In the subgroup of patients with no CAD risk factors, HRR was significantly higher in women under age 55 years.
Conclusion: The HRR during dipyridamole infusion depends on age and gender, irrespective of presence of other CAD risk factors and should be considered in the interpretation of. Besides, DM, HTN and CKD are also correlated with lower HRR to dipyridamole stress.

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INTRODUCTION

Myocardial perfusion imaging (MPI) with pharmacologic or exercise stress test is a useful noninvasive diagnostic procedure for evaluation of patients suspected of coronary artery disease (CAD) [1-4]. The pharmacologic stress usually includes a vasodilator such as adenosine or dipyridamole. Dipyridamole is a phosphodiesterase inhibitor. By inhibition of the cyclic adenosine monophosphate (cAMP) degradation and blockage of endogenous adenosine reuptake, dypiridamole can indirectly increases myocardial perfusion. This can lead to 3 to 4 times increase in the concentration of adenosine in the circulation [2, 5]. Adenosine then acts on the A receptor and regulates the production of cyclic adenosine monophosphate [2]. Then cyclic adenosine monophosphate relaxes vascular smooth muscle and causes vasodilation and increases myocardial perfusion by 3.8 to 7 times [6].

Several CAD risk factors have been suggested to be related with blunted HRR during dipyridamole or adenosine infusion such as diabetes mellitus (DM) and chronic kidney disease (CKD) [7, 8]. There has been a limited number of studies that have investigated age and gender differences in response to dipyridamole stress [9, 10]. A recent study suggested that HRR to adenosine infusion depends on age and gender so higher HRR was seen in young women with evidence of ischemia in single-photon emission computed tomography (SPECT) MPI [11]. The purpose of this study is to investigate the relationship between age, gender and other CAD risk factors with HRR to dipyridamole stress during SPECT MPI.

METHODS

The present study was conducted retrospectively on the digital database of our nuclear medicine department, including all patients who were referred for myocardial perfusion imaging during a 2-year period between Dec-2019 and Dec-2021. Inclusion criteria included people over 18 years of age who underwent MPI SPECT with dipyridamole stress test with complete registered data. In addition, the current study has been approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.544).

The gender and age of patients as well as history of CAD risk factors including DM, hypertension (HTN), CKD, dyslipidemia, obesity, smoking and the presence of ischemia in the scan were analyzed. The HRR was calculated as ratio of peak heart rate after dipyridamole infusion to baseline heart rate.

Dipyridamole SPECT MPI

All patients underwent a 2-day dipyridamole Stress/Rest [^{99m}Tc]Tc-MIBI SPECT MPI protocol. Patients were referred by cardiologists for dipyridamole stress test and it would be noteworthy that due to covid-19 pandemic most of MPI studies in our department was performed with dipyridamole stress test. Patient preparation included fasting for at least 4 hours before dipyridamole stress gated-SPECT and refraining from consuming food, beverages, and drugs containing caffeine, drugs containing methylxanthine for at least 24 hours, and oral dipyridamole for 48 hours. Beta-blockers and nitrates were also prohibited for at least 24 hours before the test. Dipyridamole was administered intravenously at a dose of 0.56 mg/kg for 4 minutes. Patients were continuously monitored by 12-lead electrocardiogram. [^{99m}Tc]Tc-MIBI was injected 4 minutes after the end of the dipyridamole injection.

To study the stress phase, dipyridamole was injected intravenously (IV) at a dose of 0.56 mg/kg over a 4-minute period followed by 15-20 mCi [^{99m}Tc]Tc-MIBI IV injection 3-5 minutes later. Stress gated-SPECT images were obtained 45-90 minutes after radiotracer injection. For the rest phase on the next day, SPECT was performed 45-90 minutes after IV injection of 15-20 mCi [^{99m}Tc]Tc-MIBI. SPECT was performed in the supine position using a double-headed gamma camera at a 90° setting and equipped with high-resolution, low-energy collimators. From right anterior oblique 45 degrees to left posterior oblique 45 degrees, 32 views were obtained in a 180-degree orbit in step and shoot image format (25 seconds per view and 8 frames per cardiac cycle). The energy window was centered on 140 ± 20 keV. The magnification factor was 1.46 and the images were stored in a 64 × 64 matrix on the computer and reconstructed with ordered subset expectation maximization 3D (OSEM3D) algorithm and Butter-worth post-filter.

Statistical analysis

Symmetrically distributed variables are presented as mean values and standard deviation. Discrete variables are described through relative and absolute frequencies. For comparison of HRR between the groups based on age, gender, scan results or cardiac risk factors independent t-test was used. Regression analysis was also utilized to evaluate the relationship of HRR and cardiac risk factors with scan findings. All statistical analysis was performed by SPSS software for windows. P value< 0.05 was considered as the level of statistical significance.

RESULTS

This study includes 2584 adults (61 % female and 39 % male) who underwent the SPECT MPI with dipyridamole stress between Dec2019-Dec2021. Baseline characteristics of patients were presented in Table 1.

Table 1. Baseline characteristics of the patients

Clinical variable	Mean±SD or Number (%)
Age	57.8±10.6
Gender(f/m)	1575(61.0%)/1009 (39.0%)
Diabetes Mellitus	762 (29.5%)
Hypertension	1527 (59.1%)
Dyslipidemia	1035 (40.1%)
Smoking	459 (17.8%)
Prior history of CAD	344 (13.3%)
Chronic kidney disease	168 (6.5%)
Dipyridamole stress variables	
Baseline HR	76.7±14.6
Peak HR	90.8±15.9
Baseline systolic BP	131.5±20.2
Baseline diastolic BP	80.9±8.8
Post stress systolic BP	124.4±19.4
Post stress diastolic BP	76.1±10.3
SPECT-MPI results	
Normal Perfusion	1646 (63.7%)
Abnormal perfusion with mild ischemia	593 (22.9%)
Abnormal perfusion with moderate/severe ischemia	280 (10.8%)
Abnormal perfusion with no ischemia	65 (2.5%)

CAD: Coronary artery disease; HR: heart rate; BP: blood pressure; SPECT-MPI: single-photon emission computed tomography myocardial perfusion imaging.

Table 2 depicts the association of HRR with gender, age, and other clinical variables. Although there was a significant association between HRR and sex, age, DM, HTN, and CKD (P < 0.001), no significant correlation was found between HRR and dyslipidemia, smoking, and prior history of CAD.

Table 2. Comparison of HRR between different groups based on clinical CAD risk factors

Variable	HRR		P-value
	Mean	SD	
Gender			0.001*
Male	1.23	0.15	
Female	1.26	0.15	
Age			0.001*
> 55	1.23	0.14	
< 55	1.27	0.16	
Diabetes mellitus			0.001*
Yes	1.21	0.13	
No	1.26	0.15	
Hypertension			0.001*
Yes	1.23	0.14	
No	1.27	0.16	
Chronic kidney disease			0.001*
Yes	1.16	0.12	
No	1.25	0.15	
Smoking			0.248
Yes	1.24	0.14	
No	1.25	0.15	
Dyslipidemia			0.994
Yes	1.25	0.14	
No	1.25	0.15	
Prior history of CAD			0.446
Yes	1.24	0.15	
No	1.25	0.15	

* P < 0.05 is considered as significant
CAD: Coronary artery disease; HRR: Heart rate response.

The mean HRR was also significantly higher in patients with normal perfusion on SPECT MPI as compared to patients with abnormal findings (Table 3).

Table 3. Comparison of HRR between different groups based on SPECT-MPI results

Variable	HRR		P-value
	Mean	SD	
SPECT-MPI result			
Normal Perfusion	1.25	0.15	
Abnormal perfusion with mild ischemia	1.24	0.15	0.001*
Abnormal perfusion with moderate/severe ischemia	1.21	0.14	
Abnormal perfusion with no ischemia	1.20	0.14	

* P < 0.05 is considered as significant
HRR: Heart rate response; SPECT-MPI: single-photon emission computed tomography myocardial perfusion imaging.

The Association of clinical variables with HRR using multivariate regression analysis at the same time is demonstrated in Table 4. Gender, age and history of DM, HTN, and CKD (P < 0.001) revealed a significant association with HRR. However, there was no significant association between HRR and smoking, prior history of CAD, and normal perfusion SPECT MPI (P < 0.05).

Table 4. Association of all variables with HRR using regression analysis

Variable	Non-standard		Standard	T	P-value
	B	SE	Beta		
Gender	0.031	0.006	0.100	4.88	0.001*
Age	0.040	0.006	0.126	6.46	0.001*
Diabetes Mellitus	0.049	0.007	0.145	7.32	0.001*
Hypertension	0.020	0.006	0.065	3.21	0.001*
Chronic kidney disease	0..078	0.012	0.126	6.44	0.001*
Smoking	0.004	0.008	0.009	0.46	0.643
Dyslipidemia	0.013	0.006	0.041	2.05	0.055
Prior history of CAD	0.013	0.009	0.030	1.47	0.140
Normal SPECT-MPI results	0.005	0.006	0.015	0.72	0.471

∗ P < 0.05 is considered as significant
CAD: Coronary artery disease; HRR: Heart rate response; SPECT-MPI: single-photon emission computed tomography myocardial perfusion imaging.

Table 5 revealed the association between different groups of sex and age with HRR using one-way ANOVA test in subgroup of 471 patients with no CAD risk factors. This analysis shows that the HRR was significantly higher in women under age 55 years (P < 0.05), in the absence of CAD risk factors.

Table 5. Association of sex and age with HRR without any risk factor

Variable	Number	HRR		P-Value
		Mean	SD	
Female≤55 y	158	1.33	0.18 [a]	
Female >55y	123	1.23	0.13	<0.001*
Male ≤ 55y	67	1.26	0.18	
Male>55y	109	1.22	0.15	

* P < 0.05 is considered as significant
[a] Post hoc analysis revealed statistically significant difference between this group with others
HRR: Heart rate response.

DISCUSSION

The results of our study showed that sex, age and history of DM, HTN, and CKD had a significant independent association with HRR to dipyridamole infusion. Besides, sex and age in participants without any CAD risk factors were also associated with HRR. We observed a significantly higher HRR response in women and younger patients. Although the HRR was significantly lower in patients with abnormal perfusion on SPECT MPI images, multivariate regression analysis showed no independent correlation.

Previous studies revealed that sex and age are important contributors to the HRR to adenosine or regadenoson as well as DM, CAD, left ventricular ejection fraction, and antagonist therapy [7, 9, 10, 12]. In the current study with dipyridamole stress, the HRR was significantly higher in women which were similarly reported in previous studies [13, 14]. Dipyridamole and adenosine, as potent vasodilators, are used to identify myocardial perfusion heterogeneity through their coronary vasodilation effects. Adenosine, or dipyridamole, is frequently used for the treatment of supraventricular tachycardia, due to its direct negative chronotropic action on sinus or atrioventricular nodes. Infusion of adenosine or dipyridamole consistently increases HR in healthy subjects, which can be observed during pharmacologic stress SPECT MPI [15, 16]. Although the exact mechanisms are not clearly understood, a reduction in peripheral vasodilator afferent nerve discharge and/or sympathetic stimulation of afferent nerve endings may contribute to this effect [17]. Adenosine may also reduce vagal activity and parasympathetic tone which can further contribute to increase HR [18].

The infusion of adenosine causes flow heterogeneity due to disparities in coronary flow response between healthy and diseased epicardial arteries, leading to perfusion defects in affected segments [19, 20]. It appears that baseline cardiac sympathetic activity is important in determining hemodynamic responses to adenosine [7, 9, 12]. Adenosine administration increases plasma norepinephrine levels as well as heart rate [18]. Furthermore, atropine premedication has been shown to reduce the chronotropic response to adenosine, suggesting that parasympathetic withdrawal can also occur during adenosine administration [18].

In the current study, the highest HRR was seen in the young female in subgroup of patients with no CAD risk factors. Previous studies suggested a disproportionate sympathetic response to vasodilator stress in young females with positive SPECT MP in the presence of ischemic cardiac processes. Vaccarino et al. found that in young female patients, the presence of ischemia is associated with higher HRR. Young females with stable CAD are also more likely to experience myocardial ischemia during mental stress [21]. Considering that cardiac sympathetic activity is positively associated with cardiovascular mortality, young women are probably at greater risk during increased cardiac oxygen demand and stress [22]. Indeed, CAD is associated with worse outcomes in young women compared with age-matched men, and this population has been reported to have higher mortality following an acute MI [23-27]. According to these findings, the application and interpretation of HRR in different age and gender groups should be more customized with different definition of abnormal values.

Concordant with our findings, Bravo et al. and lee et al. noted a significantly lower HRR in patients with DM compared with non-DM individuals [9, 28]. Cardiac autonomic neuropathy that presented in diabetic patients may contribute to lower HRR to dipyridamole or adenosine. These findings provided incremental prognostic data on top of traditional MPI findings and clinical variables [29-32]. However, the impact of age and gender in the interpretation of this effect should be considered. In addition, Abidove et al. evaluated 3444 individuals (23.5 % with DM), who had undergone SPECT MPI, for 2 years. They observed that higher basal HR and lower HRR to adenosine are strong predictor of mortality [13]. This finding is consistent with the observation that CAN is associated with an increased risk of cardiovascular complications and mortality [29-32].

In the current study, we also observed that participants with CKD had a diminished HRR compared with non-CKD participants. In line with our findings, De Lorenzo et al. also found that patients with CKD showed lower HRR [33]. As it has been explained for diabetic patients, autonomic neuropathy may also play an important role in the blunted HRR in patients with CKD [28].

CONCLUSION

The HRR during dipyridamole infusion depends on age and gender, irrespective of other baseline CAD risk factors and should be considered in the interpretation of HRR in different genders and age groups. Our findings suggest that younger women had a stronger, sympathetic-driven, hemodynamic response to dipyridamole infusion. Prospective studies are still needed to evaluate the prognostic significance of different HRR cut-offs in different genders and ages.

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