

Outcome of Patients with Discrepant Dipyridamole Stress Test and Myocardial Perfusion Study Findings

Gulam MS Syed^{1,3*}, Sleiman Naddaf¹ and Ihab Suliman²

¹Molecular Imaging Nuclear Medicine Section, Department of Medical imaging, King Abdul-Aziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

²King A Aziz Cardiac Centre, King Abdul-Aziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

³King Saud Bin A Aziz University of Health Sciences (KSAU-HS), Riyadh, Saudi Arabia

***Corresponding Author:** Ghulam MS Syed, Molecular Imaging Nuclear Medicine Section MC 1422, Department of Medical Imaging, King Fahad Hospital, King A Aziz Medical City, Riyadh, Saudi Arabia.

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Abstract

Background: Stress tests with vasodilators have been used in patients undergoing Gated myocardial perfusion Imaging using SPECT (G MPI-SPECT) for suspected coronary artery disease (CAD). Some debate exists regarding the significance of positive ECG changes in dipyridamole test despite the normal G MPI-SPECT.

Objectives: We studied the outcome of patients with normal G MPI-SPECT and ischemic ECG changes on dipyridamole Stress test to investigate the significance of these discrepant findings.

Methods: We identified patients with a positive dipyridamole stress test and normal scan findings among those who underwent G MPI-SPECT studies from January 2008 to Dec 2014 through review of the records. Findings of follow up investigations such as coronary catheterization, CT angiography (CTA), Rb 82 cardiac PET/CT or repeat G MPI-SPECT, results of cardiac enzymes and clinical follow up were recorded on these patients.

Results: A total of 87 patients among 5724 had normal G MPI-SPECT study and positive dipyridamole Stress test. Follow up information was available in 81 of 87 patients. There were 75 women and 6 men with mean age of 61 ± 11 years. History of diabetes mellitus was present in 52 patients (64%) and hypertension in 62 patients (77%). Catheterization was undertaken in 27 patients and revealed 15 patients with CAD and 12 with normal results. 11 of 15 patients with CAD on catheterization were > 65 y of age and had diabetes as well as hypertension. In remaining 54 patients, one patient had mild CAD at CTA, ten patients had normal PET/CT or CTA, or repeated G MPI-SPECT study and no hard event was observed in the remaining 43 patients over an average follow up of 23 ± 21 months.

Conclusion: The ischemic ECG changes during dipyridamole stress are nonspecific in majority of female patients with normal SPECT study, however, the patients with multiple risk factors do warrant further work up.

Keywords: Dipyridamole Stress Test; Gated Myocardial Perfusion SPECT; Coronary Artery Disease; Cardiac Catheterization; Cardiac Events

Abbreviations

CAD: Coronary Artery Disease; GMPI: Gated Myocardial Perfusion Imaging; SPECT: Single-Photon Emission Computed Tomography

Introduction

Pharmacologic vasodilator stress test utilizing dipyridamole in conjunction with Gated myocardial perfusion imaging and single-photon emission computed tomography (G MPI-SPECT) is commonly applied to assess coronary artery disease (CAD) [1,2]. The positivity of dipyridamole test with a positive G MPI-SPECT study is considered highly sensitive for the presence of CAD and several studies have reported a high sensitivity [3,4]. Even if dipyridamole test is found positive along with a normal G MPI-SPECT, such patients are usually referred for catheterization to confirm the presence of CAD and offered possible treatment [5,6]. However, the significance of discrepant findings (positive dipyridamole stress test and normal G MPI-SPECT) has not been fully investigated and only a few reports are available in the published literature [5-8].

This study was conducted in a sub-group of patients who were sent to rule out stress-induced ischemia and subsequently had positive dipyridamole test and negative G MPI-SPECT study with the aim to assess the outcome in this subgroup and also to investigate possible underlying reasons of such discrepancy.

Material and Methods

This is a retrospective study. We reviewed the charts of patients who were referred for dipyridamole MPI study between January 2008 and December 2014 and identified the sub-group with discrepant dipyridamole stress test and G MPI-SPECT findings (had positive dipyridamole test and negative G MPI-SPECT study).

Dipyridamole Stress Test

Stress tests were performed in the stress lab, supervised and interpreted by a cardiologist. The dipyridamole test was performed using standard procedure [9]. In brief, dipyridamole was infused intravenously for 4 minutes with a total dose of 0.56 mg/kg; the radiotracer was injected intravenously 3 minutes later. At the end, aminophylline was given iv to every patient. A dipyridamole test was considered positive if: patient experienced severe chest pain, horizontal or downsloping ST-segment depression ≥ 2 mm, ST-segment elevation ≥ 1.5 mm, symptomatic hypotension, supraventricular or ventricular tachyarrhythmias, and intolerable symptoms. Intravenous aminophylline (up to 240 mg) was immediately available to reverse the effects of dipyridamole.

MPI Study

Gated SPECT MPI was performed 45 - 60 minutes after the iv injection of 25 mCi of Tc-99m Sestamibi. Stress images were acquired in supine (gated) and prone position (non-gated). When stress study was entirely normal, rest study was not performed. If needed, rest study was done within 7 days only in supine position and gated as well. All patients were imaged on a single dual-head camera Philips ADAC Forte, 2007 model). Motion correction was applied when indicated. Reconstruction was carried out using filtered back projection and then processed using Cedar Sinai's AutoQuant software version 3.0.

The criteria used to label a G MPI-SPECT study as normal were as follows:

- The distribution of radiotracer in the myocardium should be homogeneous,
- LV cavity not dilated,
- Wall motion and thickening normal with LVEF more than 55%.
- When rest study was performed, transient ischemic dilation (TID) ratio should be less than 1.20.

Follow up

Patients records available at our centre were reviewed for follow up. A note was made if additional imaging investigations or cardiac catheterization was undertaken or cardiac enzymes levels were measured. Notes on clinical follow up were reviewed and patient’s status with regard to the CAD was documented.

Significant CAD on coronary angiography was defined as coronary luminal narrowing $\geq 50\%$ in at least one major branch.

If the catheterization or cardiac PET/CT was normal at any time during the follow up after negative G MPI-SPECT study, it was considered acceptable indicator of true negative study in our analysis.

Results

A total of 5724 patients underwent stress cardiac imaging at our centre from Jan 2008 to Dec 2014. A sub group of 87 patients had a normal G MPI-SPECT and positive dipyridamole test. Six patients were lost to follow up. Among remaining 81 patients, six were males and 75 were females with mean age 61 ± 11 years. Fifty-two patients were diabetic, 62 had hypertension while 44 had both. The demographics and risk factors for these 81 patients are summarized in table 1.

Total # of patients	81
Male	6
Female	75
Mean age in years \pm SD (range 39-92)	61 ± 11
Diabetes Mellitus	52 (60%)
Hypertension	62 (71%)
Chest pain	38
Shortness of Breath	18
Pre-OP evaluation	3
Known to have Coronary artery Disease	14

Table 1: Patients demographics and risk factors (n = 81).

Details on follow up were available in these 81 patients and are summarized in table 2. Only 27 patients underwent catheterization and 15 (1M, 14F) were found to have at least one major coronary branch disease. The remaining 12 cases (all females) were found to have normal coronary angiography. Results of catheterization are summarized in table 3.

Among 54 patients who did not undergo catheterization, additional imaging was performed in 11 during the follow up (table 2) and only one patient showed mild abnormality on cardiac CT angiography. In remaining ten patients, six had normal cardiac Rb-82 PET/CT, two had normal cardiac CT angiography and two had a negative G MPI-SPECT study within 4 years after the first study without an intervention between the two studies.

Catheterization	27
Normal	12
Abnormal	15
Cardiac PET/CT	6
Normal	6
Abnormal	0
CT Angiography	3
Normal	2
Abnormal	1
Repeat G MPI-SPECT Dipyridamole	2
Normal	2
Abnormal	0
Discharged from cardiology service at F/U	20
No cardiac event at F/U including	23
Total	81

Table 2: Outcome of patients with discrepant findings (n = 81).

PET/CT: Positron emission tomography/computed tomography; CT: Computed Tomography; G MPI-SPECT: Gated Myocardial Perfusion Single Photon Emission Computed Tomography.

Findings on Catheterization	Patient number
Normal	12
Abnormal	15
Triple vessel disease	1 patient
Double vessel disease	8 patients
Single vessel disease	6 patients

Table 3: Results of catheterization (n = 27).

Among the remaining 43 patients, twenty were deemed not to have a cardiac disease at follow-up with cardiac department (mean follow up period 7 ± 18 months (range 2 - 36 months) and were discharged from the cardiology service; The remaining 23 patients were followed up clinically, mean follow up period 23 ± 21 months (range 1 - 62 months) and considered not to have a significant CAD as no cardiac event was recorded.

Discussion

Dipyridamole stress test with G MPI-SPECT is a well-established methodology to evaluate CAD. Positive dipyridamole test with abnormal G MPI-SPECT findings is reported to carry a high sensitivity for CAD. However, the significance of positive dipyridamole test when G MPI-SPECT is normal has not been well studied.

Previous reports on such discrepant findings were published by Klodas, *et al.* [5], Paladugu, *et al.* [8] and Hage, *et al.* [10]. All these studies reported a higher incidence in females, a finding that was noted in our study also. The incidence of such discrepant findings was reported as 0.9% by Klodas, *et al.* [5] in a total of 5526 patients and 0.7% by Paladugu, *et al.* [8] in 2945 patients. In our study the incidence was 1.5% among 5724 patients over a period of seven years.

Previous studies considered the positive ECG changes at Dipyridamole/adenosine test as predictive of worse outcome even if accompanied by normal SPECT MPI studies [5,6,8]. One of these studies reported that the discrepant dipyridamole and G MPI-SPECT findings were uncommon and were mainly seen in older females. However they reported a higher subsequent cardiac event rate in this population [5]. Similar conclusions were drawn by authors in another study [8] and the rate of abnormal cardiac angiography was high.

In our study one-third of the patients with discrepant findings underwent coronary angiography (27/81) and about only 56% of these (15/27) had abnormal findings. In the remaining 54 patients, mild CAD was seen in one patient while rest of them remained free of any significant CAD or had no cardiac event on additional imaging during the mean follow up of 23 ± 21 months (range 1 - 62 months). Hence only about 20% (n = 16) of 81 patients with positive dipyridamole test and normal Tc-99m Sestamibi were proven to have CAD. This result is far lower than those previously reported in the literature 83% - 100% [7,8].

In our study, 43 patients were followed up by reviewing the medical records available in cardiology department. Twenty were discharged from cardiology with no evidence of CAD. In remaining 23, no cardiac event was documented at our centre. However, possibility of an event where care was provided at an outside centre could not be verified. Such a happening would be extremely rare as these patients belonged to National Guard service. Patients are referred back to our centre after providing an acute care. We did not come across any such case during the review of patient records

In our study, the patients who had abnormal angiography findings (n = 15), a majority (11/15) had two major risk factors for CAD, diabetes as well as hypertension. Thirteen of these 15 patients were elderly aged > 65 years. Similarly, fourteen out of fifteen patients with abnormal catheterization results were females.

False negative findings on G MPI-SPECT in our 15 patients (positive stress test with CAD on cardiac catheterization and normal G MPI SPECT) can be attributed to several possible factors reported by investigators previously [7,11]. The presence of collaterals and the relative coronary steal phenomenon, small vessel disease, balanced ischemia, endothelial dysfunction, or deviation from protocol by injecting the radiopharmaceutical earlier than 3 minutes after the completion of dipyridamole infusion are some of the possible factors resulting in false negative studies.

The plausible known causes of false positive Dipyridamole/adenosine test include variations in reporting the ECG results among cardiologists (2 mm versus 1 mm ST shift), presence of baseline changes, tachyarrhythmias and taking into consideration the clinical symptoms (chest pain, hypotension) and adding clinical and ECG findings. False positive ischemic changes are also reported in female gender in a higher proportion [12].

The findings of our study showed that over 2/3 of the patients who underwent catheterization and had CAD were elderly females with multiple risk factors. In younger patients with a few risk factors for CAD, the outcome during the follow up was uneventful and free of hard cardiac events. Our study agrees with previous studies in which the ECG changes associated with adenosine/dipyridamole study were not predictive of hard cardiac events [10,13,14].

Conclusion

A sub group of patients with positive dipyridamole test but normal G MPI-SPECT and has multiple risk factors will benefit from invasive procedure of catheterization. G MPI-SPECT findings in these patients are likely false negative. However, younger female patients with a low risk for CAD will have an uneventful clinical outcome. In these patients G MPI-SPECT over-rides the vasodilator test findings which are probably false positive.

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