Original Article

Higher events rate in patients with a normal gated myocardial perfusion imaging with dipyridamole than exercise: "Run for reliability"

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ABSTRACT

Objective: The aim of this is to evaluate the negative predictive value (NPV) of a normal gated myocardial perfusion imaging (NGMPI) with exercise and dipyridamole in a propensity matched population. **Materials and Methods:** This is a prospective study conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases, Karachi from December 2008 until June 2010. A total of 809 patients with a NGMPI with adequate exercise (558/809) or dipyridamole (251/809) stress were included and followed-up for 12-30 months (mean 24 ± 3 months) for fatal or non-fatal myocardial infarctions (MI). **Results:** Mean ejection fraction (%), end diastolic volume (ml), and end systolic volume (ml) in exercise and dipyridamole cohorts were (72 ± 08, 66 ± 11), (68 ± 13, 81 ± 17), and (19 ± 11, 26 ± 12) respectively. On follow-up, in dipyridamole cohort 2 fatal and 6 non-fatal MIs were reported. While in exercise cohort only 2 non-fatal MIs were reported. The NPV of a NGMPI with exercise was 99.7% (95% confidence interval [CI] 98.93-99.96%) with an event rate of 0.3% (95% CI; 0.03-0.6%) and annualized event rate of 0.15%. The NPV of NGMPI with dipyridamole was 96.80% (95% CI; 2.2-4.3%) with an event rate of 3.2% (95% CI; 1.39-3.83%) and annualized event rate of approximately 1.6%. Event free survival for dipyridamole group was significantly lower than exercise analyzed by Log-rank test (14.509, $P < 0.001$). **Conclusion:** A NGMPI with dipyridamole stress has higher event rate (low-NPV) as compared with exercise and this raises concern over its credibility to label these patients into low-risk group.

Keywords: Annualized event rate, ejection fraction, negative predictive value, normal gated myocardial perfusion imaging, Tc-99m methoxy isobutyl isonitrile

INTRODUCTION

Gated single photon emission computerized tomography (GSPECT) myocardial perfusion imaging (MPI) has enjoyed great success over the past several decades as a technique for accurately diagnosing[1] and risk-stratifying[2] patients with suspected or known coronary artery disease (CAD). Accurate risk stratification has become increasingly important to optimize patients' outcomes and contain rapidly escalating medical care cost. Tests with high-negative predictive values (NPVs) (low event rates after a negative test) are particularly useful because they identify low-risk persons who generally do not need additional tests and interventions. A large body of data has confirmed that a normal GSPECT MPI with adequate exercise has < 1% annualized event rate for major adverse cardiac events (MACE)[3,4] and accuracy is similar in both men and women[5] and it is widely assumed that normal pharmacological single photon emission computerized tomograph (SPECT) studies also identify low-risk patients.[6] However, a meta-analysis of 10 exercise and 8 pharmacological studies reported a higher event rates in patients with pharmacological stress than exercise.[7] This evidence raises a serious concern about the reliability and strength of normal pharmacological MPI for categorizing patients into low-risk group.

The goal of the present study was to compare the NPV of normal gated myocardial perfusion imaging (NGMPI) performed with dynamic exercise and dipyridamole.

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/0972-3919.112722

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MATERIALS AND METHODS

Study design, site and duration

This is a prospective study conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan from December 2008 till June 2010. The ethical committee of the institute duly approved this study. Patients with a normal MPI (with adequate dynamic exercise or dipyridamole intervention), defined as absence of perfusion defects on stress images and no transient ischemic dilatation visually, normal left ventricular ejection fraction (EF ≥ 50%), normal wall motion (WM), sum stress score (SSS), sum rest score (SRS), and sum difference score (SDS) all < 2 were included in the study. Patients with known CAD or previous history of revascularization or positive MPI were excluded. All patients/families were interviewed on telephone (12-30 months follow-up, mean 24 ± 3 months) regarding MACE like fatal or non-fatal myocardial infarction and the history of revascularization.

Study population

Study included 809 consecutive patients with NGMPI with adequate dynamic exercise or dipyridamole stress and were referred either for evaluation of chest pain or risk-factor assessment (intermediate-risk patients). The mean age of the studied population was 51 ± 08 years with a male: female ratio of 299:510 (37%:63%). On the basis of mode of stress used, patients were divided into exercise group (558/809, 69%) and dipyridamole group (251/809, 31%). In exercise cohort, mean age of population was 50 ± 11 years with M:F of 173:385 (31%:69%). Risk-factor assessment revealed that 396 (71%) were hypertensive, 181 (32%) were diabetic, 195 (35%) were dyslipidemic, 84 (15%) were smokers and positive family history for CAD was found in 212 (38%) [Table 1]. In dipyridamole cohort, mean age of population was 53 ± 10 years with M:F of 126:125 (50%:50%). Risk-factor assessment revealed that 203 (81%) were hypertensive, 94 (37%) were diabetic, 96 (38%) were dyslipidemic, 45 (18%) were smoker and positive family history for CAD was found in 104 (41%) [Table 1].

Table 1: Patients' demographic features

	Total patients	Exercise group	Dipyridamole group	*P* value
Number (*n*)	809	558 (69%)	251 (31%)	
Age in years (mean±SD)	51±0850	51±1153	51±100.341	
Male:Female	299:510	173:385	126:125	<0.05
Hypertension (%)	599 (74)	396 (71)	203 (81)	0.502
Diabetes mellitus (%)	275 (34)	181 (32)	94 (37)	0.434
Dyslipidemia (%)	291 (36)	195 (35)	96 (38)	0.277
Family h/o CAD (%)	316 (39)	212 (38)	104 (41)	0.102
Smoker (%)	129 (16)	84 (15)	45 (18)	0.151
LVEF (%)	68±0872	68±0866	68±110.06	
EDV (ml)	74±1668	74±1381	74±170.15	
ESV (ml)	24±0919	24±1126	24±120.11	

CAD: Coronary artery disease, SD: Standard deviation, LVEF: Left ventricular ejection fraction, EDV: End diastolic volume

Acquisition protocol

All patients underwent same day (rest-stress or stress-rest) myocardial perfusion GSPECT using Tc-99m labeled Methoxy IsoButyl Isonitrile (MIBI). 10-15 mCi (370-555 MBq) of Tc-99m MIBI was administered intravenously for first study (rest in rest-stress or stress in stress-rest protocol) and 25-30 mCi (925-1110 MBq) for second study (stress in rest-stress or rest in stress-rest protocol). Gated stress and non-gated rest SPECT acquisitions were performed using dedicated dual head cardiac (Cardio MD, Philips) gamma camera with low-energy all-purpose collimator, 32 projections around a 180 degree arc, a 64 × 64 matrix and 16 frames per cardiac cycle. Image reconstruction and left ventricular (LV) functional parameters (EF, end diastolic volume (EDV), end systolic volume (ESV), and WM) were contemplated by using commercially available Astonish® and Autoquan® software packages respectively. An EF ≥ 50%, ESV ≤ 70 ml and WM score of zero (in a 17 segment model) were considered normal. Similarly, gated myocardial perfusion imaging (GMPI) with SSS, SRS and SDS < 2 were considered as normal

Stress protocol

Dynamic exercise (either Bruce or Modified Bruce protocol) was performed using treadmill and exercise was considered adequate when patient achieved ≥ 85% of age predicted target heart rate (220-age) or developed typical angina or dyspnea or > 2 mm ST depressions in 2 or more leads. Beta blockers, calcium blocker, and long acting nitrate were stopped 24-48 h prior the test. Dipyridamole intervention was performed (0.567 mg/kg for 4 min) in-patients who were unable to perform dynamic exercise or having left bundle branch LBBB on resting ECG or specifically asked by the referring physicians due to limited exercise capacity. Tea, coffee, and xanthine derivatives were stopped 24 prior in patients scheduled for dipyridamole test. A rise in ≥ 10 beats (from baseline) or drop of ≥ 10 mmHg of systolic blood pressure with or without symptoms or ST changes were considered as adequate response to dipyridamole. Tc-99m MIBI was given 1 min before terminating exercise or 3-4 min after dipyridamole infusion.

Statistical analysis

Comparisons between patient groups were performed using student-*t* test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean ± standard deviation. Kaplan-meier cumulative survival analysis for major cardiac events like fatal and non-fatal Mis was performed, and survival curves were compared by the log rank test. Statistical significance was defined as $P < 0.001$

RESULTS

The mean EF (%) of studied population was 68 ± 8% while mean EDV (ml) and ESV (ml) were 74 ± 16 and 24 ± 09 respectively [Table 1, Figure 1]. In exercise cohort the mean EF (%), EDV (ml), and ESV (ml) were 72 ± 08, 68 ± 13, and 19 ± 11 respectively. In dipyridamole cohort, the mean EF (%),

EDV (ml) and ESV (ml) were 66 ± 11, 81 ± 17 and 26 ± 12 respectively [Table 1, Figure 2].

At 12-30 months follow-up, in dipyridamole cohort 2 fatal (1 male, 1 female) and 6 non-fatal MIs (4 males and 2 females) were reported. While in exercise cohort only 2 non-fatal MIs were reported. The NPV of a NGMPI with exercise was 99.7% (95% confidence interval (CI) 98.93-99.96%) over a mean follow-up of 24 ± 3 months with an event rate of 0.3% (95% CI; 0.03-0.6%) and annualized event rate of 0.15%. The NPVs of NGMPI with dipyridamole was 96.80% (95% CI; 2.2-4.3%) over a mean follow-up of 24 ± 3 months with an event rate of 3.2% (95% CI; 1.39-3.83%). The annualized event rate was approximately 1.6%. The event free survival for dipyridamole group was significantly lower than exercise group analyzed by Log rank test (14.509, $P < 0.0001$) [Figure 3].

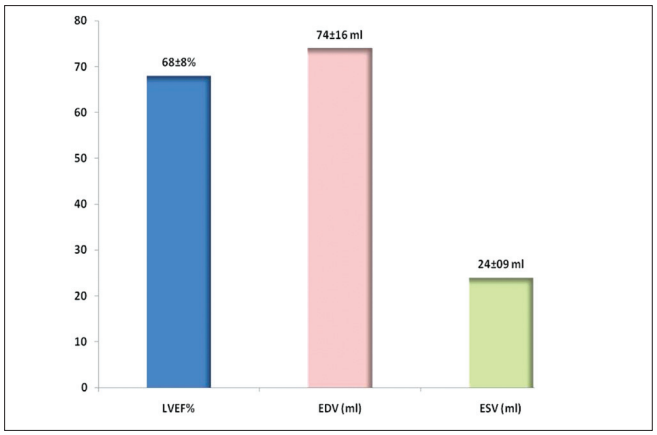

Figure 1: Overall left ventricular function parameters estimated on gated myocardial single photon emission computerized tomography

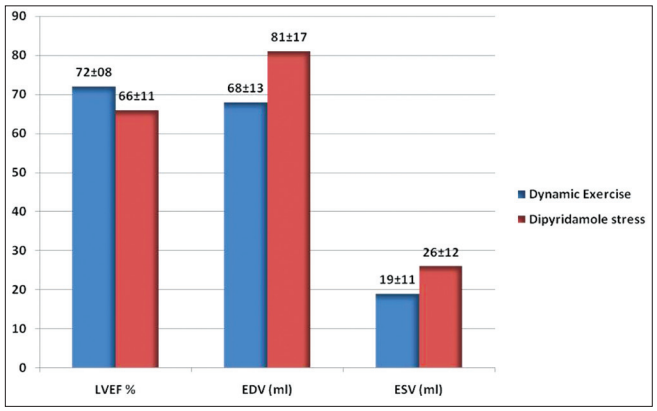

Figure 2: Left ventricular function parameters estimated on gated myocardial single photon emission computerized tomography in dynamic exercise and dipyridamole stress cohort

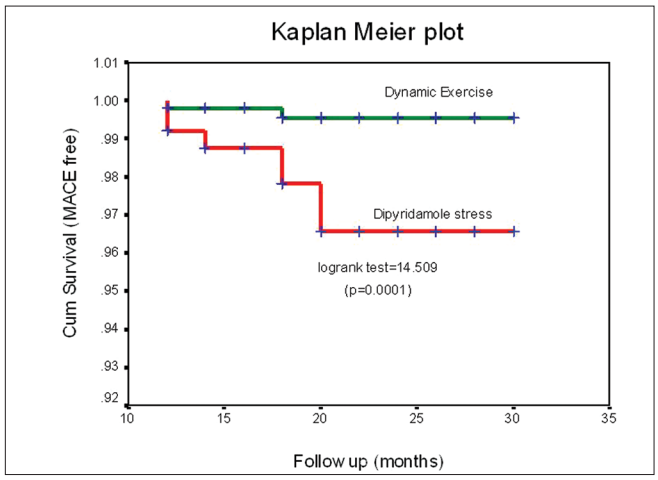

Figure 3: Kaplan Meier plot for event free cumulative survival in dynamic exercise and dipyridamole stress cohort for average 24 ± 3 months follow-up

DISCUSSION

Dynamic exercise is considered gold standard for stress MPI as it most effectively dilates the coronaries; however, a submaximal exercise reduces the sensitivity of test and gives false negative results.[8] Pharmacological stress (vasodilator using dipyridamole, adenosine and recently regadenoson) is used in patients in whom exercise is not feasible for one or the other reason; and in United States about 50% of MPIs are carried out with pharmacological stress.[9] Various initial studies comparing MPI results obtained with vasodilators stress have shown good concordance with exercise stress.[10,11] However, a meta-analysis published in 2004 by Navare, *et al*.[7] revealed increased event rates in patients with normal MPI performed with pharmacological stress and this was attributed to greater age and associated morbidities in said cohort. Our prospective study also revealed higher MACE rate in dipyridamole group than exercise. Importantly the mean age of patients in both groups was almost same and the incidence of risk-factors was also not statistically significant, which rules out possible contributory role of age and risk-factors as assumed in non-propensity matched earlier studies.[7] Our findings correlate with the results of recently published study where higher mortality was seen in propensity matched cohort with NGMPI performed with adenosine stress.[6] We don't have a tangible explanation for this observation. One plausible explanation could be inadequate vasodilatation by dipyridamole due to either variable endothelial dysfunction or idiosyncratic effect of stress agent. However, early studies have shown comparable magnitudes of ischemia induced by exercise and dipyridamole.[12,13] Other possibility might be the effects of calcium and beta blockers, which reportedly may reduce the sensitivity of stress MPI substantially.[14,15] Although, it is our routine to advice patients to stop calcium and beta blockers at least 24 h prior the test but we are not sure about non-compliance, which is a limitation of this study. However, data from recently published study[6] have re-demonstrated higher mortality in adenosines group after eliminating patients who were on these medications. The emerging data revealing higher MACE in patients with NGMPI with pharmacological stress warrants a close follow-up of these cases as compared to patients with normal exercise MPI. Furthermore, it demands a prospective study using positron emission tomography (PET) perfusion agent, comparing coronary flow reserve (CFR) during exercise and pharmacological stress in a propensity matched group of patients.

We conclude that a normal GMPI with dipyridamole stress has higher event rate (low-NPV) as compared with exercise and this raises concern over its credibility to label these patients into low-risk group. We do recommend a prospective study using PET perfusion agent, comparing CFR during exercise and pharmacological stress for precise evaluation of this important issue.

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How to cite this article: Fatima N, uz Zaman M, Ishaq M, Rasheed SZ, Baloch DJ, Wali A, *et al*. Higher events rate in patients with a normal gated myocardial perfusion imaging with dipyridamole than exercise: "Run for reliability". Indian J Nucl Med 2012;27:172-5.

Source of Support: Nil. **Conflict of Interest:** None declared.