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Original Article

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Objective: The negative predictive value of a normal single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is very high. However, prognostic implication of a normal SPECT MPI in patients with known coronary artery disease (CAD) is not clear. Objective of this study was to evaluate the cardiac event rate in patients with known CAD who had a normal stress SPECT MPI.

Methods: This prospective study accrued 428 consecutive patients with a history of CAD [revascularization or previous myocardial infarction (MI)] who had a normal stress (dynamic exercise or dipyridamole intervention) and rest Tc-99m-MIBI SPECT MPI. These patients were followed for 2-5 years (median: 3.1 years) for all-cause and cardiac mortality and non-fatal MI. Univariate and multivariate analyses were performed to identify predictors of outcome.

Results: During a follow-up period, all-cause mortality was found in 60 patients (14%) and 41 (10%) died of cardiac reasons. Non-fatal MI was found in 77 (18%) patients. Annualized cardiac mortality and non-fatal MI rates were 2% and 3.6% respectively. Smoking, congestive heart failure (CHF) and failure to achieve 85% age predicted heart rate were found to be predictors for all-cause and cardiac mortality. Diabetes, dyslipidemia, smoking and limited functional capacity (<7 METS) were found to be predictors for non-fatal MI.

Conclusions: Patients with known CAD had higher cardiac event rates despite a normal stress SPECT MPI. Diabetes, dyslipidemia, smoking and limited functional capacity were the predictors for fatal and non-fatal cardiac events. A cost effective but comprehensive surveillance strategy is warranted.

Keywords: Myocardial perfusion imaging (MPI); coronary artery disease (CAD); event rate; prognosis

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Introduction

The myocardial perfusion imaging (MPI) using gated single photon emission computerized tomography (GSPECT) has been on the horizon of clinical cardiology of last four decades. The primary reasons for this popularity are its high diagnostic capability and ability to provide prognostic information useful in risk stratification and clinical decision making (1). There is a large body of data from various part of world indicating very high negative predictive value (NPV >99%) in patients with a normal SPECT MPI study (2,3). Gated MPI being a functional imaging modality is useful in ascertaining the hemodynamic significance of an anatomical lesion seen on coronary angiogram and allows risk stratification and guides about optimal management (4). Due to this very high NPV of a normal SPECT MPI, it has been considered as an efficient gatekeeper to catheterization laboratory (5). In recent years development in medical therapy and revascularization strategies have resultedin a growing number of patients with normal MPI who have a history of coronary artery diseases (CAD). Assessment of negative predictive of a normal MPI in this group of patients is important but currently data is limited with

varied outcomes, depending upon duration of follow-up in different studies (4,6,7). This certainly creates ambiguities in decision making in this clinical scenario. The aim of this study was to find out negative predictive value of normal GMPI in patients with history of CAD.

Methods

Study design and patients' demographic

The was a prospective study conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan. Consecutive patients were accrued from December 2008 till December 2011 and followed till December 2013. The study was duly approved by the ethical committee of institute. We included 428 consecutivepatients with a history of CAD, which was defined as a healed myocardial infarct (MI) and/or previous coronary revascularization, who had a normal stress Tc-99m-MIBI (^{99m}Technetium Methoxy IsoBytyl Isonitrile) GSPECT MPI. Dynamic exercise on treadmill was used (using Bruce or modified Bruce protocol) in 255 (60%) patients while pharmacological stress using dipyridamole (0.142 mg/kg/min for 4 minutes) was adopted in 173 (40%). All patients were referred (272 inside and 156 outside referrals) for assessment of ischemia (179 patients asymptomatic; 249 patients with typical/atypical chest pain/dyspnea) Mean time interval between MPI and myocardial infarction (MI) was 3.2±4.6 years (118 patients) and revascularization was 1.9±3.2 years (310 patients). Patients with abnormal MPIs or MPI done within 60 days of coronary intervention or those with normal MPI but lost to follow-up were not included.

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 two or more leads. Beta blockers, calcium blocker and long acting nitrate were stopped 24-48 hours prior the test. Dipyridamole intervention was performed (0.567 mg/kg for 4 minutes) in patients who were unable to perform dynamic exercise or having left bundle branch block (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 minute before terminating exercise or 3-4 minutes after dipyridamole infusion.

Gated SPECT myocardial perfusion imaging

All patients underwent same day (rest-stress or stress-rest) myocardial perfusion GSPECT using Tc-99m 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 (925-1,110 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 (LEAP) collimator, 32 projections around a 180-degree arc, a 64×64 matrix and 16 frames per cardiac cycle. Image reconstruction and LV functional parameters [EF, EDV, ESV and wall motion (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, GMPI with SSS, SRS and SDS <2 were considered as normal. As per department protocol, to ensure optimal quality of scan, fatty meal with a glass of water prior the imaging was used to minimize sub-diaphragmatic activity and use of gated images (partial volume effect and wall motion) to rule out attenuation artifacts. No attenuation correction methodology was employed.

Follow-up

All patients/family were interviewed on telephone (median follow-up: 3.1 years; range: 2-5 years) regarding overall death, fatal or non-fatal MI. These events were confirmed by hospital records for those who were managed at our institute and by reviewing the discharge notes for those who were managed at other healthcare facilities. Cardiac death was defined as death caused by MI, significantcardiac arrhythmias, refractory congestive heart failure or unexplained sudden death.

Statistical analysis

Comparisons between patient groups were performed

Table 1 Patients' demographic with known coronary artery disease

Variables	With normal MPI (n=428)	*t* test/χ^2 values	P values
Age (average ± SD in years)	56±10	12.413	<0.0001*
Male:Female (%:%)	295:133 (69%:31%)	122.091	<0.0001*
BMI (average ± SD, Kg/m^2)	26.660±5.172	93.361	<0.0001*
Obese	177 (41%)	3.724	0.0002*
Hypertension	299 (70%)	16.551	<0.0001*
Diabetes mellitus	157 (37%)	5.379	<0.0001*
Dyslipidemia	143 (33%)	7.034	<0.0001*
Family history for CAD	160 (37%)	5.379	<0.0001*
Smoking	80 (19%)	12.827	<0.0001*
Exercise	255 (60%)	4.138	<0.0001*
Pharmacological stress	173 (40%)	4.138	<0.0001*
METS	8.805±4.944	172.380	<0.0001*
% target heart rate	(86±12)%	62.061	<0.0001*
LVEF (%)	64±11	26.660	<0.0001*
EDV (mL)	87±33	23.196	<0.0001*
ESV (mL)	33±24	14.654	<0.0001*

*P<0.05. MPI, myocardial perfusion imaging; SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; METs, metabolic equivalent task; LVEF, left ventricular ejection fraction; EDV, end diastolic volume; ESV, end systolic volume.

using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean ± standard deviation (SD). Kaplan-Meier cumulative survival analysis for MACE like fatal and non-fatal MIs was performed, and survival curves were compared by the Logrank test. Univariate and multivariate Cox's proportional hazard regression models were used to identify independent predictors of end points of interest. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. Statistical significance was defined as P<0.05. Commercially available packages Medcalc® and statistical package for social sciences (SPSS 17®) were used.

Results

The mean age of total 428 studied individuals was 56±10 years with a male to female ratio of 69%:31%. The average body mass index (BMI) of studied individuals was 26.660± 5.172 Kg/m^2 and 177 (41%) were found to be obese (BMI ≥30 Kg/m^2). Prevalence of hypertension, diabetes, dyslipidemia and positive family history was 70%, 37%, 33% and 37% respectively. Smoking (defined as current or left less than 05 years) was found in 80 (19%) individuals. Dynamic exercise was performed by 255 (60%) of individual while dipyridamole stress was used in 173 (40%) who were unable to perform dynamic stress. The mean age predicted heart rate achieved and functional capacity (as metabolic equivalents, METS) were (86±12)% and 8.805±4.944 METS respectively. Mean left ventricular functional parameters like ejection fraction (%), end diastolic volume (EDV in mL) and end systolic volumes (ESV in mL) were (64±11)%, 87±33 and 33±24 mL respectively (*Table 1*).

Follow-up analysis

During a median follow-up of 3.1 years (range, 2-5 years), a total number of 60 patients (14%) died (all-cause mortality) with an annualized all-cause mortality rate of 2.8% (*Figure 1*). Cardiac deaths [fatal MI, congestive heart failure (CHF) or sudden unexplained death] was reported in 41 (10%) patients with annualized cardiac mortality rate was 2.0% (*Figure 2*). Nonfatal MI was reported in 77 patients (18%) with annualized event rate of 3.6% (*Figure 3*).

Predictors of long-term outcome

Smoking, CHF and failure to achieve 85% age predicted

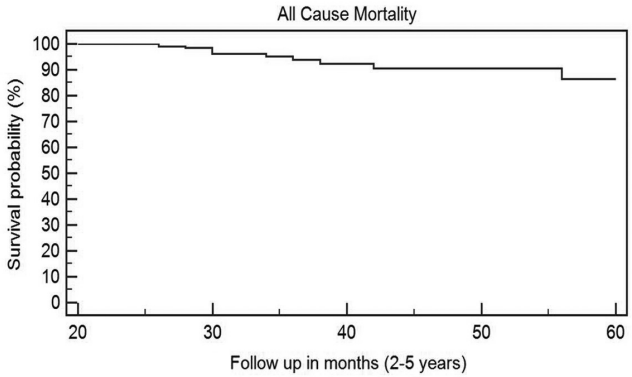

Figure 1 Kaplan-Meier survival plot for all-cause mortalities in patients with normal MPI with known CAD. Event =60 (14%); Event rate (%/year): 2.8; Survival =86%. MPI, myocardial perfusion imaging; CAD, coronary artery disease.

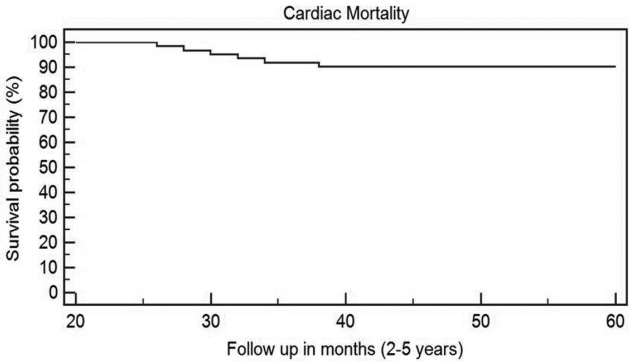

Figure 2 Kaplan-Meier survival plot for cardiac mortalities in patients with normal MPI with known CAD. Events =41 (10%); Event rate (%/year): 2; Survival =90%. MPI, myocardial perfusion imaging; CAD, coronary artery disease.

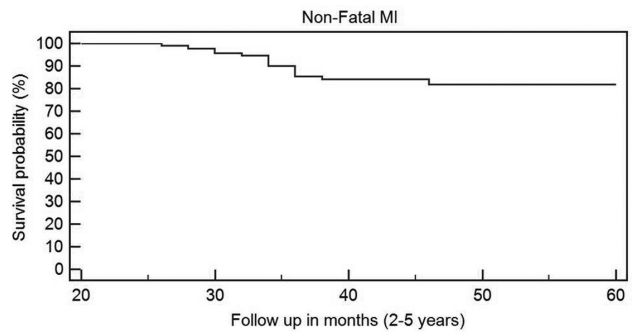

Figure 3 Kaplan-Meier survival plot for non-fatal myocardial infarction in patients with normal MPI with known CAD. Events =77 (18%); Event rate (%/year): 3.6; Survival =82%. MPI, myocardial perfusion imaging; CAD, coronary artery disease.

heart rate were found to be predictors for all-cause and cardiac mortality. Diabetes, dyslipidemia, smoking and limited functional capacity (<7 METS) were found to be predictors for non-fatal MI (*Table 2*).

Discussion

Over a long time as SPECT MPI has reached scientific and clinical maturity and we have grown to expect that the results of this test when negative, reliably predicts an excellent patients' outcome. It is a well-established fact that annual probability of hard cardiac event with a normal exercise gated MPI is <1% (1-6). On the same note there has been an increase prevalence of normal MPI in patients with known CAD and this is primarily caused by remarkable improvement in medical therapy (statins mainly) and revascularization methodologies (8).The reasons for such clinical scenarios could be a patent graft or stent, presence of a haemodynamically non-significant stenosis, or a previous small (subendocardial) MI with a patent infarct-related coronary artery (4). In our study the all-cause mortality during the study period was 2.8% per year which is comparable with other published studies (4,6). However, the annual cardiac mortality and non-fatal MI rates in our study was 2% and 3.6% which are significantly higher than established ≈0.6% of average annual event rate in patients with a normal stress MPI (9). Our findings are in concordance with study by Acampa *et al*. (10) who studied 362 patients who had post-CABG normal MPIs with 22 month follow-up with a hard event rate (both fatal and non-fatal MIs) of 4%. Annualized cardiac and non-fatal MI rate in our study (2% and 3.6%) when compared with similar studies published by Schinkel (4) (0.5% and 1.4% in first 3 years follow-up) and Ottenhof *et al*. (7) (0.9% and 1.2% with 12 years follow-up) are significantly higher. Compared with these studies, our patients were younger, predominantly female with higher incidence of diabetes (37% *vs*. 10%) and hypertension (70% *vs*. about 50%). However, important to note that in Schinkels' study (4) the annual cardiac mortality and cardiac mortality/non-fatal MI rate were increased to 1.3% and 3.1% during 4-6 years follow-up (0.5% and 1.4% in first 3-year follow-up) and closer to our findings with a median follow-up of 3.1 years. Another important aspect which draws our attention is the use of dipyridamole as mode of stress in 40% of our patients while previously mentioned studies included normal MPIs with dynamic exercise or with dobutamine stress. Recent

Table 2 Multivariate predictors of clinical outcome by Cox hazard ratio with 95% confidence interval

Variables	Cox's proportional hazard ratios with 95% confidence interval		
	All-cause motility	Cardiac mortality	Non-fatal MI/ischemia
Age >65 (years)	1.565 (0.552-4.438)	1.378 (0.408-4.648)	1.401 (0.557-3.526)
Age ≤65 (years)	0.639 (0.225-1.811)	0.726 (0.215-2.447)	0.713 (0.283-1.795)
Male gender	1.265 (0.577-2.772)	1.181 (0.467-2.985)	1.364 (0.686-2.714)
Obesity	0.481 (0.222-1.043)	0.489 (0.197-1.201)	0.895 (0.453-1.765)
Diabetes mellitus	1.426 (0.671-3.044)	1.307 (0.531-3.224)	2.579* (1.326-5.015)
Hypertension	0.758 (0.316-1.823)	0.927 (0.330-2.602)	0.505 (0.230-1.085)
Dyslipidemia	0.6839 (0.324-1.442)	1.004 (0.416-2.423)	2.156* (1.118-4.155)
Smoking	2.694* (1.098-6.609)	4.555* (1.558-13.324)	2.335* (1.053-5.178)
Family history	1.226 (0.572-2.632)	1.352 (0.547-3.339)	0.899 (0.460-1.761)
CHF	16.547* (4.397-62.271)	13.319* (2.745-64.639)	1.051 (0.314-3.511)
Previous infarction	1.189 (0.524-2.704)	1.676 (0.635-4.427)	1.016 (0.489-2.11)
Revascularization	0.588 (0.265-1.306)	0.550 (0.213-1.416)	0.724 (0.359-1.463)
MAPHR <85%	2.181* (1.028-4.626)	3.358* (1.377-8.186)	0.625 (0.332-1.215)
METS <7	0.742 (0.342-1.615)	0.466 (0.186-1.169)	7.765* (3.911-15.417)

*P<0.05. MI, myocardial infarction; CHF, congestive heart failure; MAPHR, maximal age predicted heart rate; METS, metabolic equivalent task.

reports have shown a higher event rate in patients having a normal GMPI with vasodilators (dipyridamole or adenosine) than dynamic exercise (11,12). Therefore, higher incidence of diabetes and hypertension and use of vasodilator stress in 40% of our patients are the major contributors for higher event rates in our study than other published data (4,6). Diabetes, dyslipidemia and smoking were independent risk factors for non-fatal MI while smoking, CHF and limited effort tolerance were risk factors for fatal MI. Pakistan is among the countries with highest incidence of diabetes with a reported figure of 13.14% (13). However, in our cohort, the incidence was 37% and this is due to referral bias. It is also an established fact that functional capacity of diabetics is lower as compared with non-diabetics (14) and this does explain the use of dipyridamole as stressor in 40% of participants of our study. Similarly the limited functional capacity in studied cohort who had dynamic exercise is a well-known risk factor for dismal outcome despite a normal MPI (15).

Findings of our study fuel the debate of safety profile of a normal MPI in patients with known CAD than in patients with suspected CAD where it is very high (cardiac event rate <1%). Higher event rates in this study puts a question mark over concept of warranty period in patients with known CAD and normal stress MPI (both exercise and vasodilator) as these patients had higher incidence of risk factors than patients cohorts reported in other studies (1,6). Based on multivariate analysis in this study, we suggest that patients with known CAD despite having a normal MPI need a close surveillance in the presence of risk factors like diabetes, dyslipidemia, history of smoking, limited effort tolerance and use of vasodilator as stressor. We strongly feel that in current era of effective medical and interventional strategies resulting in growing number of normal MPIs in patients with known CAD, more prospective studies are required to establish the safety profile of normal MPI in patients' subset with known CAD and to design a cost effective but comprehensive surveillance strategy.

Our study has some limitations. (I) As coronary angiography was not routinely performed, odds of inclusion of false negative cases can be ruled out; (II) lack of data about how effectively diabetes and other risk factors were controlled as inadequate control of risk factors could be the reason for higher incidence during study period despite a normal MPI as noted in second half of follow-up in Schinkle's study (4); (III) higher incidence of diabetes in studied population due to referral bias.

We conclude that patients with known CAD had higher cardiac event rates despite a normal stress SPECT MPI.

Diabetes, dyslipidemia, smoking and limited functional capacity were the predictors for fatal and non-fatal cardiac events. A cost effective but comprehensive surveillance strategy is warranted.

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