High negative predictive value of workload ≥7 METS on exercise testing in patients with normal gated myocardial perfusion imaging: Was imaging really required?

Original Article

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(Received 18 December 2013, Revised 16 January 2014, Accepted 26 January 2014)

ABSTRACT

Introduction: Good functional capacity has a high negative predictive value (NPV) in patients with known or suspected coronary artery disease (CAD) similar to a normal gated myocardial perfusion imaging (GMPI). Aim of this study was to evaluate NPV of functional capacity during treadmill exercise in patients with normal GMPI in Pakistani population.

Methods: This was a prospective study which included 1318 individuals with normal exercise GMPI. On the basis of maximal age predicted heart rate (MAPHR) and metabolic equivalents (METS) achieved, these patient were divided into Group A: ≥ 85% MAPHR and ≥7 METS (714 patients), Group B: ≥85% MAPHR and <7METS (145 patients), Group C: <85% MAPHR and ≥7 METS (289 patients) and Group D: <85% MAPHR and <7 METS (170 patients). Patients were followed up on telephone (15 ±3 months) for fatal or non-fatal myocardial infarction (FMI and NFMI).

Results: There was no MI in any group but NFMIs was reported in 2.07% in Group B and 2.35% in Group D. NPV of a normal GMPI in relation with functional capacity was found to be 100% for Group A and C (≥7METS), 97.9% and 97.6% for Group B and D (<7METS) respectively.

Conclusion: We conclude that patients with ≥7 METS with normal GMPI had 100% NPV for FMI or NFMIs and omitting GMPI in these patients would save cost and avoid radiation exposure.

Key words: Functional capacity; NPV; GMPI; METS; Peak target heart rate; Radiation exposure

Iran J Nucl Med 2014;22(2):70-76
Published: June, 2014
http://irjnm.tums.ac.ir

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INTRODUCTION

The prevalence of coronary artery disease (CAD) is staggering and its related mortality is the leading cause of death in United States [1, 2]. The primary objective of non-invasive procedures is early diagnosis and risk stratification and in this regard tests with high negative predictive values (NPV) are preferred [3]. Commonly used procedures are exercise tolerance test (ETT), stress gated myocardial perfusion imaging (GMPI) and dobutamine stress echocardiography (DSE). Stress GMPI is considered as the gate keeper for catheterization laboratory in patients with low to intermediate risk and in US alone 9.3 million MPIs were performed in 2005 [4]. The NPV of a normal stress MPI is >99% (event rate <1%) in western [5] as well as in Pakistani population [6]. It is also an undeniable fact that GMPI is accounted for 22% of all radiation exposure from medical imaging in US [7]. ETT is the most commonly performed non-invasive procedure with a sensitivity of 68% and a specificity of 77% [8]. Exercise or functional capacity measured in metabolic equivalents (METS) [9] and duration of exercise [10] in ETT or treadmill GMPI are powerful predictors of major cardiac events. Higher workloads achieved during exercise stress (≥ 10 METS) predict improved survival rates, irrespective of age and gender [9] and even in the setting of significant coronary artery disease [11]. On basis of these facts, it has been suggested that GMPI could be eliminated in patients achieving ≥ 10 METS on exercise testing without loss of prognostic capability, cost saving and avoiding undue radiation exposure to patients [12].

The aim of this prospective study was to evaluate negative predictive value of functional capacity during treadmill exercise in patients with normal GMPI in Pakistani population.

METHODS

Study design, site and duration

This prospective study was conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan from December 2008 till December 2011. The study was duly approved by the ethical committee of the KIHD. We recruited all consecutive patients presented for exercise GMPI after obtaining informed consent. Patients with a normal GMPI (no perfusion abnormality, sum stress score, SSS <2, and no evidence of transient ischemic dilatation, TID) were selected. Patients with an abnormal GMPI defined as summed stress score (SSS) >2, summed rest score, (SRS) >2 or summed difference score (SDS) >2 and transient or fixed dilated LV cavity were excluded. All patients (or a family member in case patient has expired) were interviewed on telephone (mean follow-up 15 ± 3 months) regarding coronary angiography (within 3 months after GMPI), history of revascularization and major adverse cardiac events (MACE) like fatal or non-fatal MIs.

Study population

From December 2008 till December 2011, 1347 normal exercise GMPI studies were performed while 29 lost to follow up and remaining 1318 patients constituted the study cohort. On the basis of maximal age predicted heart rate (MAPHR) and METS achieved, these patient were divided into four groups: Group A: ≥ 85% MAPHR and ≥ 7 METS (714 patients), Group B: ≥ 85% MAPHR and <7METS (145 patients), Group C: <85% MAPHR and ≥ 7 METS (289 patients) and Group D: <85% MAPHR and <7 METS (170 patients). In Group A, the mean age was 49 years with male: female ratio of 63%:37%, mean body mass index (BMI) 25.7 Kg/m^2 and risk factor assessment revealed that 435/714 (61%) were hypertensive, 196/714 (27%) diabetic, 221/714 (31%) were dyslipidemic, 87/714 (12%) were smoker and positive family history for CAD was found in 302/714 (42%). In Group B, the mean age was 54 years with male: female ratio of 28%:72%, mean BMI was 26.3 Kg/m^2 and risk factor assessment revealed that 105/145 (72%) were hypertensive, 50/145 (34%) diabetic, 581/145 (40%) were dyslipidemic, 20/145 (14%) were smoker and positive family history for CAD was found in 52/145 (36%). In Group C, the mean age was 48 year with male: female ratio of 52%:48%, mean BMI 26.4 Kg/m^2 and risk factor assessment revealed that 188/289 (65%) were hypertensive, 73/289 (25%) diabetic, 99/289 (34%) were dyslipidemic, 41/289 (14%) were smoker and positive family history for CAD was found in 122/289 (42%). In Group D, the mean age was 53 year with male: female ratio of 19%81%, mean BMI 26.5 Kg/m^2 and risk factor assessment revealed that 118/170 (69%) were hypertensive, 58/170 (34%) diabetic, 54/170 (32%) were dyslipidemic, 29/170 (17%) were smoker and positive family history for CAD was found in 75/170 (44%) (Table 1).

Acquisition protocol

All patients underwent same day (rest-stress or stress-rest) GMPI single photon emission computerized tomography (SPECT) using Technetium-99m (Tc-99m) labeled Methoxy IsoButyl Isonitrile (MIBI). 10–15 mCi (millicurie) of Tc-99m MIBI was administered intravenously for first study (rest in rest-stress or stress in stress-rest protocol) and 25–30 mCi for second study (stress in rest-stress or rest in stress-rest protocol).

Table1: Demographic distribution among different patients' groups according to effort tolerance.

Variables	GROUP A ≥85%MAPHR &≥ 7 METs (714)	GROUP B ≥85%MAPHR & <7 METs (145)	P value	GROUP C <85%MAPHR &≥ 7 METs (289)	GROUP D <85%MAPHR & <7 METs (170)	P value
Age in years (mean ± SD)	49± 9.6	54±10.5	<0.0001*	48 ±9.4	53±9.8	<0.0001*
BMI (Kg/m^2)	25.7 ±4.3	26.3±18.6	0.443	26.4±4.9	26.5±5.9	0.845
Male: Female	449:265 (63%:37%)	41:104 (28%:72%)	<0.0001*	151:138 (52%:48%)	33:137 (19%:81%)	<0.0001*
MPHR (%) (mean ± SD)	93±6	91±6	0.0003*	78±4	77±6	0.033*
METS (mean ± SD)	9.6±1.9	5.9±0.8	<0.0001*	8.8±1.5	5.7±0.9	<0.0001*
Hypertension	435(61%)	105 (72%)	0.016*	188 (65%)	118 (69%)	0.439
Diabetes Mellitus	196 (27%)	50 (34%)	0.108	73 (25%)	58 (34%)	0.050
Dyslipidemia	221 (31%)	58 (40%)	0.044*	99 (34%)	54 (32%)	0.736
F/H of CAD	302 (42%)	52 (36%)	0.213	122 (42%)	75 (44%)	0.749
Smoking	87 (12%)	20 (14%)	0.597	41 (14%)	29 (17%)	0.464
LV function						
LVEF%	68±07	70±07	0.002*	66±08	68±09	0.013*
EDV (ml)	75±19	68±16	0.000*	80±21	74±19	0.002*
ESV (ml)	24±12	20±09	0.000*	26±12	24±12	0.048*
MACE						
Fatal MI	0%	0%	--	0%	0%	--
Non-Fatal MI	0%	2.07% (03)	0.002*	0%	2.35% (04)	0.033*
%Annualized Event rate	0%	1.38%	0.028*	0%	1.56%	0.043*

*p<0.05; SD= Standard Deviation; F/H =family history of CAD; BMI=Basal Metabolic Index; LVEF=Left Ventricular Ejection Fraction; MAPHR=Maximum Age Predicted Heart Rate; EDV=End Diastolic Volume; METs= Metabolic Equivalent; ESV=Send Systolic Volume; MACE=Major Acute Cardiac Even; MI=Myocardial Infarction

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 x 64 matrix and 16 frames per cardiac cycle.

Image reconstruction and LV functional parameters [LV ejection fraction (LVEF), end diastolic volume (EDV), end systolic volume (ESV), wall motion (WM) and TID] were assessed by using commercially available Astonish® and Autoquan® software packages respectively (using 20 segments scoring system). All scans were reported by two board certified nuclear cardiologists incorporating visual assessment with quantitative parameters.

Stress protocol

All patients underwent treadmill exercise using standard protocols (Bruce or Modified Bruce) and beta blockers, calcium blocker and long acting nitrate were stopped 24–48 hour prior the test after consultation with referring physicians. Stress test was symptom-limited unless prematurely terminated for reasons recommended in ACC/AHA guidelines [13].

Functional capacity or exercise workload was defined as the total metabolic equivalents (METS) achieved (1 METS = 3.5 ml Oxygen/ml/min).

Significant ST-depression was defined as ≥1mm horizontal or down-sloping depression of the ST-segment ≥ 80ms after the J-point for 3 consecutive beats.

Tc-99m MIBI was given intravenously 1 min before terminating exercise on treadmill.

Statistical analysis

Comparisons between patient groups were performed 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.

Statistical significance was defined as P<0.05. Commercially available packages Medcalc® and statistical package for social sciences (SPSS 17®) were used.

RESULTS

The gated myocardial perfusion imaging (GMPI) revealed normal perfusion, left ventricular ejection fraction and volumes within normal limits in all four groups (significant p values on inter group analysis). Mean MAPHR (%) achieved by patients in group A and B were 93 ±6% and 91 ±6% with a mean work load (METS) of 9.6 ±1.9 and 5.9 ±0.8 respectively (p value significant). Mean MAPHR (%) achieved by patients in group C and D were 78 ±4% and 77 ±6% with a mean work load (METS) of 8.8 ±1.5 and 5.7 ±0.9 respectively (p value significant). Risk factor analysis shows a significant correlation of hypertension and dyslipidemia in Group B cohort having functional capacity <7 METS. While no significant correlation was found for any risk factor in other groups. Follow-up data revealed no evidence of fatal MI in any group and non-fatal MI in Group A and Group C (groups with good functional capacity, i.e. ≥ 7 METS whether achieved or not achieved 85% mean MAPHR). Non-fatal MI was reported in 2.07% (03 patients) in Group B and 2.35% (04 patients) in Group D with significant p values (patients with low functional capacity, i.e. <7 METS whether achieved or not achieved 85% mean MAPHR) (Table 1). Kaplan Meier's survival analysis revealed an annualized event rate of 1.38% and 1.56% in Group B and D with significant p values (Figure 1). NPV of a normal GMPI in relation with functional capacity was found to be 100% for Group A and C (groups with good functional capacity, i.e. ≥ 7 METS whether achieved or not achieved 85% mean MAPHR), 97.9% and 97.6% for Group B and D respectively (patients with low functional capacity, i.e. <7 METS whether achieved or not achieved 85% mean MAPHR) (Figure 2).

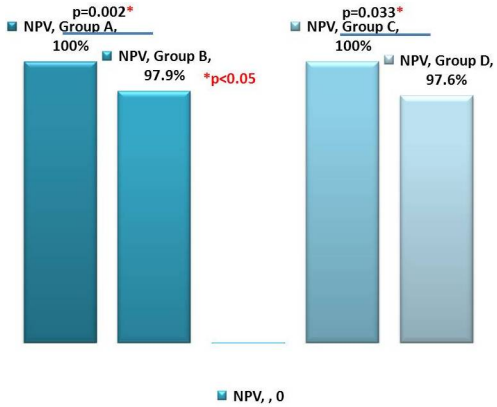

Fig 1. Negative predictive values of normal MPI in relation with effort tolerance during stress among different groups {Group A ≥85% MAPHR & ≥ 7 METs (714); Group B ≥85% MAPHR & < 7 METs (145); Group C <85% MAPHR & ≥ 7 METs (289); Group D <85% MAPHR & < 7 METs (170)}

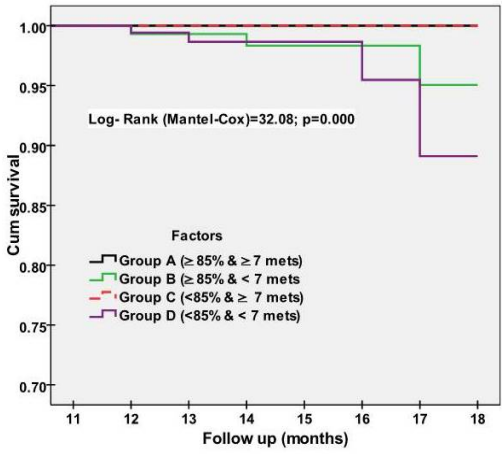

Fig 2. Comparative analysis of survival functions of different groups by Kaplan Meier's.

DISCUSSION

In this study better functional capacity (≥ 7 METS) of patients in Group A and C can be explained as they were younger (mean age <50years) with a male predominance particularly in Group C. While patients in Group B and D (functional capacity <7 METS) were older (5 year older than patients in Group A and C) with a very remarkable female dominance in both cohorts. The mean functional capacity in our studied population was lower as compared to same age western cohort in published data [12] and likely due to physique and relatively sedentary life style in Pakistani urban population [14]. Interestingly impact of known risk factors upon functional capacity has been found non-significant except hypertension and dyslipidemia in Group B. However, we can't neglect the higher prevalence of diabetes in studied cohort compared with western population [15] and known association of reduced functional capacity with impaired glycemic control, subclinical LV dysfunction, and impaired heart rate recovery (HRR) in diabetics [16]. Unfortunately, we don't have proper data about glycemic control and HRR in our population which is a limitation of this study. Patients in Group C and D could not to attain ≥ 85% age predicted heart rate, i.e. chronotropic incompetence which is considered as an independent predictor of MACE and overall mortality [17]. The common reasons for chronotropic incompetence are drugs (beta blocker, calcium blocker, and amiodarone), sick sinus syndrome, AV block, heart failure or CAD [18]. In our studied cohort, drugs like beta or calcium blockers are assumed to be the sentinel reason (although patients were asked to stop 24-48 hours prior the test) as none of studied patients has had history of SA nodal or AV block and normal GMPI

essentially rules out significant CAD and heart failure.

Follow up data shows no fatal or non-fatal MI in patients who did achieve ≥ 7 METS (NPV 100% with annualized event rate 0%) while incidence of non-fatal MI was seen only in patients in whom functional capacity was <7METS irrespective of chronotropic competence or incompetence (NPV 97.9% and 97.6% and annualized event rate 2.07% and 2.35% in Group B and D respectively). This shows an excellent prognosis (100% NPV) of patients who have normal GMPI with good functional capacity (≥ 7 METS) as compared to those who have normal GMPI but low functional capacity (<7 METS). The relatively lower NPV in patients with normal GMPI at <7 METS is comparable to our previous study [19] and no event rate (100% NPV) in patients with normal GMPI at ≥ 7 METS supports synergistic effect of two predictors. These findings are similar to data published by Kodama et al which revealed substantially lower event rate in patients achieving ≥ 7.9 METS than those attaining <7.9 METS [20]. These findings are also consistent with most of the published studies upon western population [21-23]. However most of these studies have used a cut of ≥ 10 METS instead of ≥ 7 METS as used in this study. But we would like to mention that the mean METS achieved in Group A and C were 9.6 ±1.9 and 8.8 ±1.5 METS respectively which is still lower than the published studies upon western population and the reason may be an overall lower functional capacity in local population. The other possible explanation could be the negative impact of diabetes which was more prevalent in our studied and unfortunately we do not have authentic record of glycemic control which is a limitation indeed. Another important limitation of this prospective study is a relatively shorter follow up period and it is possible that more events would have occurred with longer follow-up. However, the data categorically shows an excellent short term prognosis in these patients. It is important to acknowledge that each 1-METs increment in workload achieved is associated with 14% reduction in MACE in younger and 18% in individuals >65 years of age [21, 22]. The correlation between good functional capacity (≥ 10 METS) and lower event rate is also valid for exercise echocardiography as revealed by Bhat et al [24]. Another important finding of this study is lower predictive value of MAPHR ≥ 85% than ≥ 7 METS (i.e. chronotropic competence or incompetence) as no cardiac death was noted in any group and no non-fatal MI was observed in patients who did achieve ≥ 7 METS but <85% MAPHR (i.e. Group C). This finding in concordance with a study upon 1056 patients which revealed direct correlation between ischemic burden and lower functional capacity even though ≥ 85% MAPHR was achieved [25]. However, studies have also shown that chronotropic incompetence (failure to achieve <85% MAPHR) is an independent predictor of major cardiac fatal and non-fatal events [17].

The higher negative predictive value of good functional capacity for MACE in this study raises a valid question "what is the added benefit of performing GMPI in individuals who attain ≥ 7 METS whether achieved or not achieved 85% MAPHR during exercise stress testing?" As omitting GMPI in patients who have achieved higher METS (≥ 7 METS in our study, ≥ 7.9 METS [20] or ≥ 10 METS [12, 25] in western studies) in absence of chest pain or significant ECG changes during treadmill exercise, would not only be cost effective but also avoids unjustified radiation exposure. This approach would be in accordance to the drive of various societies to minimize radiation exposure from nuclear medicine procedures which accounts 25% of medical radiation burden in Americans (MPI only is responsible for 75% of this burden) [26]. There is no doubt that this strategy could result in missing patients with an abnormal GMPI. However, recent studies have clearly shown very low prevalence of significant ischemia (≥10% of left ventricular myocardium) in patients who achieved ≥ 10 METS (< 0.4% [25] and <0.6% [12]) with only one cardiac death out of 473 patients [25]. These facts support the notion of not injecting radiopharmaceutical in patients who achieved higher METS (≥7 METS in our study or ≥7.9 METS [20] or ≥10 METS [12, 25] in western studies) without chest pain or significant ST changes as it would be not only cost effective but also avoid significant radiation exposure. Small number of patients who develop chest pain or significant ECG changes in recovery period after a high workload negative exercise test would require a redo exercise with GMPI. On the basis of these data, a large prospective study in patients with low to intermediate risk for CAD is deemed important to address the issue of cost and radiation exposure incurred by performing an unjustified GMPI. However this would certainly require a standardized protocol with exercise first and injecting radiopharmaceutical only in those who failed to achieve ≥ 7 METS / chest pain or significant ECG changes during exercise or recovery period and omit radiotracer injection in those who achieve higher METs with no chest pain or associated ECG abnormalities.

CONCLUSION

We conclude that (1) patients with higher functional capacity (≥ 7 METS irrespective of MAPHR) with a normal GMPI had 100% NPV for fatal and non-fatal MIs; (2) patients with lower functional capacity (<7

METS irrespective of MAPHR) with a normal GMPI had a NPV of about 98% for non-fatal and 100% for fatal MIs; (3) Omitting GMPI in patients with higher functional capacity (≥7 METS irrespective of MAPHR) would be cost effective and avoid unjustified radiation exposure.

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