EXERCISE TOLERANCE TEST (ETT) OR MYOCARDIAL PERFUSION SCAN (MPS) – WHAT TO CHOOSE IN PATIENTS OF ISCHAEMIC HEART DISEASE (IHD)?

Tariq Mahmood Mirza, Mehdi Raza, Zehra Naz*, Umer-i-Farooq, Mohsin Saeed Shaikh**

Armed Forces Institute of Pathology, Rawalpindi, *Islamic International Medical College, Rawalpindi, **Armed Forces Institute of Cardiology, Rawalpindi

ABSTRACT

Objective: To evaluate the validity of exercise tolerance test (ETT) with treadmill exercise in the diagnosis and follow-up of ischaemic heart disease (IHD), taking myocardial perfusion scan (MPS) as standard.

Study Design: Retrospective, validation study.

Place and Duration of Study: Nuclear Medical Centre (NMC) Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan, from 1 January to 31 December 2009.

Patients and Methods: One hundred and nineteen patients (88 males, 31 females), referred for MPS; were selected through non-probability, consecutive sampling. Patients of all ages and gender, fit to undertake treadmill exercise, were included. Patients with contraindications to ETT, like unstable angina, conduction abnormalities, etc., or those who had taken a beta blocker within the preceding 24 hours, were excluded. ETT through treadmill exercise was done, followed by MPS with single photon emission computed tomography (SPECT) technique, using Thallium-201 or Technetium-99 m 2-methoxy-isobutyl-isonitrile (MIBI). ETT was interpreted as positive or negative for ischaemia, with borderline changes considered positive. MPS was interpreted as positive or negative for ischaemia. Validity of ETT was evaluated in terms of sensitivity (Sn), specificity (Sp), and positive and negative predictive value (PPV and NPV), taking MPS as standard.

Results: Sensitivity of ETT was found to be 77.5% and specificity was 43.6%. PPV was 73.8% and NPV was 48.6%. Out of a total (n) of 119 patients, true positive (TP) cases were 62, true negative (TN) 17, false positive (FP) 22 and false negative (FN) 18.

Conclusions: ETT is an acceptably sensitive but non-specific test for evaluating myocardial ischaemia, with adequate PPV but low NPV, when validating it against MPS. Replacing the MPS with ETT, in the diagnosis and follow-up of IHD, is thus, not prudent. ETT can be useful as a screening test.

Keywords: Exercise test, Myocardial perfusion imaging, Myocardial ischaemia, Sensitivity and specificity, Validity.

INTRODUCTION

Both ETT and MPS are safe and well-accepted tests for the diagnosis and follow-up of IHD. As these have been available to the clinicians for decades and ample data and reliable, evidence-based practice guidelines are available for their judicious use, individual physician's preference often determines the choice of either, in diagnosis and follow-up of IHD.

It is well-known that the terms IHD and coronary artery disease (CAD) are independent entities, with significant CAD often being a common cause of IHD. Hence, diagnostic tests available to assess cases of IHD or to follow-up a patient, depending on the individual circumstances, also need to be different from those that ascertain luminal status of the coronary vessels only, and/or assess new or follow-up patients of larger vessel CAD.

Both ETT and MPS are non-invasive techniques used for the diagnosis and follow-up of patients of IHD, both in CAD and non-CAD patients. ETT is based on exercise induced membrane potential changes, depicted on electrocardiography during calibrated exercise, following standard protocols; while MPS is based on the delivery of a radiotracer (Thallium-201 or Technetium-99 m labelled radiopharmaceuticals) to a metabolically active substrate (myocardium), through an intact vascular system.

Correspondence: Col Tariq Mehmood Mirza, AFIP, Rawalpindi.
Email: uzmirza@yahoo.com
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Insufficient myocardial perfusion leads to myocardial ischaemia and positron emission tomography (PET) remains the present day gold standard for estimation of myocardial perfusion, hence its use in patients of IHD. It is followed–in sensitivity and specificity–by scintigraphic techniques (single photon computed tomography (SPECT) and planar myocardial perfusion imaging)[1]. ETT (employing standard 12-lead electrocardiography (ECG) trace) being another popular, non-invasive modality for determination of myocardial perfusion status, but with still less sensitivity and specificity values[2].

In the cardiac care environment in Pakistan, perhaps like the rest of the world, MPS appears to be underutilised, with more emphasis by the cardiac physicians on ETT. CT and conventional coronary angiography are also preferred, where they are readily available; despite a higher radiation and financial burden on the patient and the health care system, and adverse effects involved in their preference. As PET is only available in 02 centres in Pakistan, this study attempted to validate ETT against MPS (taken as gold standard for this study), to determine if ETT can serve as an alternative to MPS and if the results of the two modalities are comparable in our setting.

PATIENTS AND METHODS

This retrospective, validation study was conducted at Nuclear Medical Centre (NMC) and Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan for 12 months (from 1 January to 31 December 2009).

Operational definitions

Myocardial Perfusion Scan (MPS)

Myocardial perfusion SPECT scan was done using metastable Technetium 99 (Tc-99m) 2-methoxy-isobutyl-isonitrile (MIBI) or Thallium 201 (Tl-201) – thallous chloride. Scanning was done in two phases, stress and rest, which were conducted according to the standard protocol for each radiopharmaceutical.

Exercise Tolerance Test (ETT)

Exercise tolerance test was conducted by making the patient walk on a motor driven treadmill, employing Bruce protocol. The test was interpreted as positive or negative for myocardial ischaemia as per standard interpretation protocols, with equivocal results interpreted as positive.

Validityof ETT for the diagnosis and follow-up of ischaemic heart disease (IHD), was evaluated in terms of sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), taking MPS as the available gold standard for myocardial ischaemia.

One hundred and ninteen patients were included in the study (n = 119), which comprised 88 male and 31 female subjects. Patients who were referred to the department for MPS were selected through non-probability, consecutive sampling. Indoor / outdoor patients of all ages and gender, who were physically fit to undertake treadmill exercise were included in the study. Patients with unstable angina pectoris, implanted pacemaker device, atrioventricular (AV) blocks, left bundle branch block (LBBB), uncontrolled hypertension or asthma, or those who had taken a beta adrenergic blocking drug within the preceding 24 hours were excluded from the study.

The study was approved by the institutional ethics committee at AFIP, Rawalpindi. Informed consent was not obtained, as available departmental record was utilised for the study, and it was not possible to contact the patients and seek consent at this later stage. The researchers gathered the results of the tests only and omitted all personal and other details that could lead to individual patient identification. ETT was conducted through graduated exercise on a treadmill and was immediately followed by MPS, using Tl-201 or Tc-99 m MIBI, according to standard protocols. The following apparatus, radiopharmaceuticals, technique and acquisition and processing protocols were used: Quinton Q-Stress ® cardiac stress system with integrated computer and TM 65 treadmill, employing software version 3.51.6, was used for ETT. Siemens e-cam ® single headed Gamma Camera

System, employing e-soft ® software, fitted with a low energy all purpose (LEAP) parallel hole collimator was used for MPS image acquisition and subsequent processing of acquired images.

Radiopharmaceuticals

Tl-201 (in the form of Thallous chloride), 55 to 95 MBq (1.5 to 2.5 mCi) or Tc-99m MIBI, 925 to 1480 MBq (25 to 40 mCi) depending on 1-day or 2-day protocol being followed, were administered intravenously, at peak exercise, for stress phase imaging.Tc-99m MIBI, 295 to 1480 MBq (8 to 40 mCi), depending on 1-day or 2-day protocol being followed, was administered intravenously, for rest phase imaging[3].

Technique

The patients underwent a treadmill stress test / ETT, employing Bruce protocol, under the supervision of an experienced nuclear physician and were encouraged to achieve the target heart rate for their age. Beta blocking agents were discontinued, in consultation with the treating cardiologist, 12 hours prior to the exercise stress test[4]. This was immediately followed by MPS, with the radiopharmaceutical injected intravenously, through a pre-inserted cannula in the arm. Both one-day and two-day protocols for MPS with Tc-99 m MIBI were employed, depending on patient and departmental convenience, with the corresponding change in radiopharmaceutical dosage[3]. Stress and rest phase imaging followed, depending on the radiopharmaceutical and protocol being used.

Acquisition Protocol

Ungated myocardial perfusion images were acquired with the patient supine, using SPECT protocol, 64 x 64 matrix, pixel size of 6.59 mm and 20% electronic window, centred at 140 keV. Step and shoot mode in a circular orbit was used, with 180° clock-wise rotation, done in 32 steps (starting from –135° to 45°). Tl-201 injection at peak exercise, was followed by stress phase imaging within 10 minutes, with rest phase images acquired two to three hours later. For Tc-99m MIBI, injection at peak exercise was followed by a fatty meal, with the stress acquisition after 30 to 40 minutes of exercise and the rest images acquired similarly, after 1 hour of rest phase injection.

Processing Protocol

Table-1: Comparison of exercise tolerance test (ETT) with myocardial perfusion scan (MPS) in patients of ischaemic heart disease.

	MPS +ve	MPS –ve	
ETT +ve	a = 62 (TP)	b = 22 (FP)	a+b = 84 (TP+FP)
ETT –ve	c = 18 (FN)	d = 17 (TN)	c+d = 35 (FN+TN)
	a+c = 80 (TP+FN)	b+d = 39 (FP+TN)	

TP: True positive, FP: False positive, TN: True negative, FN: False negative.

System generated ETT reports were accepted as such (with default filters and settings). No special processing was done prior interpretation. MPS images, however, were reconstructed, after defining cardiac limits and apposing the corresponding slices in the American College of Cardiology / American Heart Association (ACC/AHA) myocardial perfusion SPECT orientation. Short axis, and vertical and horizontal long axis views were used for display of slices. Reconstruction of raw data was done by filtered back-projection employing a fifth-order Butterworth filter and a cut-off frequency of 0.45.

Scan interpretation

Each ETT was interpreted by an experienced physician, and MPS by an experienced nuclear physician, who were not blinded, and had access to detailed patient history and investigations. Scan interpretation involved study of the case file and comparison of stress / rest scans.

Data analysis

2 x 2 contingency table was used and Sn, Sp, PPV and NPV were computed through standard formulae. Results from patients found positive or negative for myocardial ischaemia on ETT, were compared with their results on MPS (interpreted as positive or negative for myocardial ischaemia).

RESULTS

One hundred and ninteen patients were enrolled in the study, including 88 males, with a mean age ± standard deviation (SD) of 51.85 ±

13.37 years (range = 23 to 84 years) and 31 females, with a mean age ± SD of 50.16 ± 12.53 years (range = 28 to 75 years). No adverse effects were reported.

Results of the study are tabulated in Table 1. Sensitivity of ETT was calculated as 77.5% and specificity as 43.6%. Positive predictive value (PPV) was 73.8% and negative predictive value (NPV) was 48.6%. Out of a total number (n) of 119, true positive (TP) cases were 62, true negative (TN) cases were 17, false positive (FP) cases were 22 and false negative (FN) cases were 18.

DISCUSSION

Ease of availability and low cost of ETT in a cardiology department setting, with the requirement of very limited or no preparation for the test, have made it a popular, non-invasive test[5] for diagnosis and follow-up of IHD patients. MPS, on the other hand, needs patient preparation, prior appointment, a few hours of time for the test and some more time for its interpretation and reporting, besides relatively higher cost; factors which have led to its relatively sub-optimal utilisation by treating physicians. The inability of the treating physicians to readily interpret the scan, in most cases, is also a contributing factor. This preference for ETT at the expense of MPS, however, may result in missing a fair percentage of IHD patients in initial stages of diagnosis and misdirected decisions in the management of follow-up patients.

Similarly, many patients with atypical chest pain or vague signs and symptoms – after an equivocal or borderline positive ETT, are referred for conventional or CT coronary angiography – but are found to have normal coronary vessels. This is especially true of cases of diabetes, female patients, patients of microvascular angina, cardiac syndrome X[2] and many post-revascularisation cases, with a majority of these having a stable disease status. Coronary angiography is an invasive test and involves a high radiation dose and side effects like contrast-induced hypersensitivity and nephrotoxicity and should be avoided in this setting. Multi-slice CT coronary angiography, being non-invasive, is a priority with many clinicians but is known to be poor at predicting ischaemia,[6] besides its radiation and contrast-related side effects. Use of MPS in these patients is a wiser option, specially in cases where no ETT is done or possible, or where an invasive test is advised, after an equivocal or borderline positive ETT. In this scenario, MPS may help exclude patients with mild ischaemia, residual ischaemia (in cases of partial revascularisation) and/or ischaemia in another vascular territory.

This study attempted to evaluate the validity of ETT through its comparison with MPS – a test that estimates myocardial perfusion–unlike most of previously published studies, which employ as standard, lumenographic tests, like coronary angiography or CT coronary angiography, or other techniques that cannot be used to estimate tissue perfusion or ischaemia. Following limitations in the study design or test limitations, however, can potentially influence results of this study:

Referral bias

Mostly the patients with a normal ETT are not referred for MPS, except in cases of high pretest likelihood of ischaemic heart disease, diabetes mellitus, atypical chest pain and suspected cardiac syndrome X. Similarly, patients with ETT strongly positive for myocardial ischaemia are frequently referred directly for coronary angiography. Hence it may be suggested that the spectrum of patients undergoing MPS is not normally distributed.

Sub-optimal ETT

ETT may be interpreted as negative if adequate exercise is not performed to elicit myocardial ischaemia on ECG. MPS in such cases may be positive for ischaemia. This may be specially relevant in female patients from Indo-Pakistani culture, who are mostly not used to treadmill exercise and may have anxiety related resting tachycardia.

Borderline positive ETT

Borderline positive ETT results in this study were interpreted as positive for ischaemia, which may increase the number of false positive (FP) cases, rendering the test less specific.

Scan artefacts

Scintigraphic artefacts may undermine the gold standard status of MPS for myocardial ischaemia,[7] in the absence of Positron Emission Tomography (PET). Attenuation correction software which may help in making an objective judgement in such cases, is expensive and not widely available.

Literature survey

Studies on the subject reveal conflicting observations by different investigators about the sensitivity and specificity of ETT and MPS, perhaps because it is extremely difficult to eliminate referral bias. Not all cases who undergo ETT are patients of IHD and frequently, only those with equivocal ETT results or a higher risk profile are subjected to MPS and subsequently those with normal MPS results are not generally advised invasive procedures, like coronary angiography. Another factor is the much higher cost and non-availability of PET, due to which the comparison with a non-invasive gold standard for perfusion,[8] is almost always, not realised. CT or conventional coronary angiography, or fractional flow reserve (FFR) measurement in such cases cannot give a true comparison due to the inherent difference in the nature of the tests versus ETT, MPS and PET; as the former, almost always, measure the lumen of bigger epicardial vessels or flow across stenotic lesions in resting status only and are ineffective beyond medium-sized vessels; while the latter are depicting electrical and/or metabolic changes at the tissue level, due to changes in perfusion status, both at rest and during exercise.

Studies from Pakistan

Results of our study are comparable but not similar to other studies from Pakistan. A study from Punjab Institute of Cardiology (PIC), Lahore, comparing positive ETT results in 148 patients with positive findings on coronary angiography, found a true positive (TP) rate of 85.1% and a false positive (FP) rate of 14.9%,[9] against a TP rate of 52.1% and FP rate of 18.5% seen in our study, when coronary angiography was not used for comparison and TN and FN cases were also calculated.

Of the other studies from Pakistan, one including 120 patients reported the sensitivity, specificity and accuracy of ETT at 64.6%, 66.7% and 65%, respectively;[5] while another group of investigators calculated sensitivity at 74.2% and specificity at 78.5% for ETT, against the sensitivity and specificity values of 90.9% and 70.6%, respectively, for MPS[10]. European Society of Cardiology (ESC) guidelines on stable angina pectoris reported the sensitivity and specificity of exercise scintigraphy (MPS), without excluding referral bias, depending on the meta-analysis, in the general range of 70–98% (mean range of 85–90%) and 40–90% (mean range of 70–75%), respectively[2]. Hill and Timmis mentioned a higher rate of FP ETT results in women and estimated the presence of ST segment depression, during exercise, in up to 20% of normal subjects, with the statement that an abnormal resting ECG (like in cases with preexcitation and conduction abnormalities) may even preclude an ETT or degrade its utility. In such cases, scintigraphic techniques or angiography should be resorted to[4].

International studies

The American College of Cardiology /American Heart Association (ACC/AHA) guideline update for exercise testing, in a summary of studies from chest pain centres, quotes sensitivity values of 29%, 73% and 90% and specificity values of 99.4%, 74% and 50% respectively, for exercise testing,[10] with the European Society of Cardiology (ESC) guidelines for stable angina pectoris mentioning the reported sensitivity and specificity of exercise stress testing between 23–100% (mean 68%) and 17–100% (mean 77%), respectively[2] but other studies mention low positive predictive value (PPV) of exercise testing in female patients and less likelihood of CAD in women who had a positive ETT.

Cost factor

Another pertinent factor is the cost to the patient and the health care system. Sabharwal et al. in their study involving 457 patients found no difference in cost between diagnostic approaches utilising ETT or MPS for intermediate or high likelihood patients with stable chest pain or suspected coronary artery disease (CAD). ETT was, however, found economical in low likelihood cases[12]. Other observers have also highlighted the ability of MPS to prevent downstream testing and consequently decrease costs as an advantage. Additionally, MPS may also help avoid other invasive tests, like coronary angiography[13].

Other benefits

Results from a study by Shaw et al. have supported the use of MPS (SPECT imaging) in patients at an intermediate risk for CAD and those with established CAD, including patients concomitantly suffering from diabetes mellitus, peripheral vascular disease or nephropathy[14]. Stirrup et al. have also inferred from available literature that a diagnosis of CAD or myocardial infarction (MI) may be missed in many cases who undergo ETT and that stress/rest MPS provides valuable information for diagnosis of stable CAD as well as risk stratification in IHD patients[7]. Stress-induced wall motion abnormalities are also better visualized through MPS, with relative ease compared to stress echocardiography and thus valuable information is available. A meta-analysis comparing results of MRI and MPS for detection of wall motion abnormalities demonstrated that MPS had a sensitivity of 91% and specificity of 81%[15]. Further improvement in the sensitivity and specificity values of MPS is possible through the use of SPECT, gated imaging and attenuation correction; and all these enhance its strong predictive value in estimating likelihood of future major cardiac events[16].

Current guidelines

ESC guidelines 2010, on myocardial revascularization recommend that the follow up and management strategies in post-revascularization patients should employ stress imaging (stress echo or MPS) rather than stress ECG[17]. The guidelines also recommend subsets of patients indicated for early stress testing, with imaging; including revascularized ST elevation MI patients, those in safety critical professions (pilots, drivers, etc.), diabetics (specially insulin dependent), those resuscitated from sudden death, those with incomplete or suboptimal revascularization and those with multi-vessel disease or silent ischaemia[17]. Thus, MPS is an appropriate modality for the diagnosis and follow-up of IHD, in cases of silent or overt ischaemia and is valuable in documenting the patient risk profile and choosing between medical management and surgical intervention options[18].

CONCLUSIONS

ETT was found to be an acceptably sensitive but non-specific test for evaluating myocardial ischaemia, with adequate PPV but low NPV. Replacing the MPS with ETT, in the diagnosis and follow-up of IHD, is thus, not prudent. ETT can, however, be useful as a screening test.

Competing Interests

The authors declare that they have no conflict of interest.

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Note

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