



Role of SPECT Myocardial Perfusion Imaging, in Assessment and Early Diagnosis of Asymptomatic Coronary Artery Disease; An Analytical Study Conducted in a Tertiary Care Hospital of Islamabad, Pakistan

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ABSTRACT

Exercise Tolerance Test (ETT) and Myocardial Perfusion Imaging (MPI) are known non-invasive modalities to detect coronary artery disease (CAD). Aim of this study was to find out better modality for early detection of asymptomatic CAD. Material and Methods: 25 asymptomatic individuals with one or more cardiac risk factors were enrolled. Probability of CAD was calculated, using Framingham scoring; patients classified as low, intermediate and high-risk group. Each (n=25) underwent ETT and MPI. ETT response was categorized as normal, ischemic or equivocal. MPI results as normal, mild, moderate to severe degree defects. 18 patients had follow-up angiograms. Results: Risk stratification showed 14 patients were in intermediate group, 4 had high and 7 had low risk of CAD. In intermediate group, 6 patients had ischemic ETT changes, 10 had perfusion defects on scan and all 10 patients had $\geq 70\%$ stenosis on coronary angiograms. In high-risk group; 2 subjects had positive ETTs, 3 had positive scans and all 3 showed significant vascular involvement on coronary angiogram. In low risk group 3 patients had positive ETT and MPS, 2 had mild vascular stenosis. Considering angiography as gold standard, we observed that MPI had sensitivity (86.66%) and specificity (90%), whereas ETT had 66.6% and 70% respectively. Positive and negative

predictive values of MPI were 92.8% and 81.8 % respectively. Post-test probability of MPI was i.e. 0.72-0.88; compared to ETT which was 0.55-0.78. Conclusion: MPI is a better modality than ETT for early diagnosis of occult CAD, especially in intermediate and high risk group.

Key Words: Myocardial Perfusion Imaging (MPI); Exercise Tolerance Test (ETT); Target Heart Rate (THR); Coronary Artery Disease (CAD); Ischemic Heart Disease (IHD); Framingham scoring.

INTRODUCTION

Coronary Artery Disease is leading cause of morbidity and mortality worldwide. Early diagnosis and management of the disease can reduce the probability of adverse future events. It is therefore important to identify high risk population with occult Coronary Artery Disease (CAD) so that medical therapy or revascularization can be done to enhance the survival. This can be achieved in a stepwise fashion starting from life style modification, medical treatment and finally surgical intervention. More than 95% of all coronary artery disease is due to atherosclerosis [1].

Coronary artery disease is a chronic process that begins during adolescence. There are certain risk factors that can accelerate or modify this chronic inflammatory process [2]. These risk factors are further classified into modifiable and non-modifiable. High cholesterol, diabetes, hypertension, lack of regular exercise and smoking are modifiable risk factors. Age, gender and family history are non-modifiable risk factors.

The initial diagnostic approach includes history, physical examination, ECG and baseline laboratory tests. Once the initial evaluation is done, advance diagnostic tests are performed which includes non-invasive tests like ETT, Myocardial Perfusion Imaging (MPI), Multi-Slice Computed Tomography (MSCT) and Magnetic Resonance Imaging (MRI) and Invasive modality i.e. Coronary Angiography [3-5]. Guidelines recommend non-invasive tests rather than invasive angiography when pretest probability is low [6].

A number of new approaches for quantitative analysis are being applied to gated SPECT studies obtained with Tc-99m agents to evaluate end diastole, end systole and wall thickness in region of interest [7].

In addition MPI in initial evaluation of patients with occult CAD or stable chest pain is also highly cost-effective when compared with invasive strategy i.e. direct catheterization [8-10], yielding comparable results specially when used in evaluation of females [11,12].

Framingham coronary prediction score sheet provides estimates of total CHD risk over the period of 10 years. Separate score sheets are used for men and women and the factors used to estimate risk include age, blood cholesterol (or LDL cholesterol), HDL cholesterol, blood pressure, cigarette smoking, and diabetes mellitus [13].

Studies have shown that average mortality rate in low risk group was less than 1%. In intermediate risk group the mortality rate due to CAD was 1-3% and 3% in high-risk group [9]. Risk increases multifold with even one cardiac risk factor and single abnormal ECG [14].

Studies have shown that diagnostic accuracy of Myocardial Perfusion Imaging (MPI) i.e Sensitivity came out to be 85% for single vessel disease and 95% for triple vessel disease [15].

MATERIALS AND METHODS

This analytical study was conducted for a period of 06 months, in Nuclear Cardiology Department of Federal Government Polyclinic Hospital, Islamabad, Pakistan.

25 asymptomatic patients (19 males, 6 females), with one or more major cardiac risk factors were referred from cardiology OPD, Risk factors considered were Hypertension, Diabetes mellitus, Hyperlipidemia, Smoking and positive Family history of CAD. Age range was between 32-60 (mean 45 ± 8) years.

The control group included 10 normal volunteers. All asymptomatic with no documented cardiac risk factor. Male to female ratio was 3: 1, having ages between 32-55 years (mean $43.5 \pm$ SD years).

Patients with active cardiac complaints (chest pain, angina or history of Myocardial Infarction), age greater than 60 yrs and those with conduction abnormalities like Left Bundle Branch Block (LBBB) and Right Bundle Branch Block (RBBB) were not included in the study.

Data Collection Procedure

After initial history and physical examination, patients were advised to bring fresh ECG, at the time of imaging. Fasting sugar and lipid profile of the selected patients were taken. Each patient was asked to come next day in fasting state, withholding all cardiac medicines

Categorization of the Patients

Probability for CAD was calculated using the Framingham scoring using parameters; age, total cholesterol, and HDL level, blood pressure, diabetes and smoking [13].

For all the patients relative risk was calculated and they were categorized into three groups on the basis of Framingham scoring.

- Low Risk (1-1.5)
- Intermediate Risk (1.6-3)
- High Risk (>3)

Acquisition Protocol

Siemens E-CAM double-headed camera was used for acquisition. Each patient was injected with 20 mCi (740MBq) of Tc-99m labeled Methyl Isobutyl Isonitrile (MIBI). stress / rest studies on two separate days.

Data Interpretation

Interpretation was done by 02 independent observers. Semi-quantitative interpretation using 17 segments scoring was used in each study with 0-4 point scale [97]. 0= normal perfusion, 1= equivocal, 2= moderate decrease, 3= severely decreased in radiotracer uptake, 4=absence tracer uptake.

Three variables were applied in this model; Summed Stress Score (SSS), Summed Rest Score (SRS) and Summed Difference Score (SDS). SSS less than 4 was normal, between 4-8 mildly abnormal and greater than 8 severely abnormal. SDS less than 2 was normal, between 2-4 mildly abnormal and greater than 4 showed moderate to severe perfusion defect.

In Coronary Angiogram vascular occlusion greater than 70% was considered as significant.

Statistical Analysis

Pre-test and post-test probabilities were calculated for each group, Sensitivity and specificity, positive and negative predictive values of ETT & Myocardial perfusion imaging were calculated considering angiography as gold standard.

RESULTS

Baseline Data showing Risk Factors and Framingham Scoring

For all 25 patients (mean age 45 ± 8 years), risk factors of the patients were assessed and probability of CAD over ten years was calculated using Framingham scoring, as shown in table 1.

Table 1: Risk Factors and Pretest Likelihood of CAD in Study Subjects

Sr.no	Age in years	Gender	Risk Factors	No. of Risk Factors	Framingham Score
1	55	F	H, D, F, C	4	2.8
2	60	M	H, D, S, C, F	5	4.2
3	42	M	H, D, C	3	3.25
4	59	M	H, F.	2	1.4
5	55	M	H, F.	2	1.4
6	59	F	H, D, C, S	4	3
7	60	M	D, S	2	2.7
8	49	M	H, C	2	1.5
9	60	M	H, C	2	2.3
10	60	M	S	1	1.5
11	59	M	H, D, S, F.	4	4.4
12	60	M	H, F, S	3	2.2
13	45	M	D, S, C	3	3.0
14	50	M	H, F, S	3	2.8
15	53	F	H, D, F	3	2.5
16	40	M	F	1	1.5
17	53	M	H, D, C, S	4	2.6
18	53	M	D	1	1.6
19	46	F	D, F	2	2.2
20	59	F	H, F, D	3	3
21	60	M	H, D, S, F	4	1.5
22	60	M	H, S, D, F	4	3.8
23	60	M	S, F	2	3
24	32	M	H, F	2	1.1
25	35	F	H, F	2	2

H = Hypertension; S = Smoking; D = Diabetes; C= Cholesterol; F = Family History; M = Male; F = Female; Y= years.

It was observed that 36% of study subjects had two cardiac risk factors, 24% had 3, another 24% had 4 risk factors positive, whereas only 1 out of 25 (4 %) had all the five risk factors present in them. Presence of risk factors was directly linked with Framingham score i.e. Increasing the number of risk factors increases the score.

Classification of Subjects according to Framingham Scoring

Patients were categorized into three groups on the basis of Framingham scoring risk stratification along with age association, is shown in Table 2.

Table 2: Risk Stratification of Study Subjects (Cases)

Risk	Framingham Scoring	No of Patients (%age)	Age Range (in years)	Mean Age (years)	SD
Low Risk	1-1.5	7 (28%)	32-60	45	±11
Intermediate Risk	1.6-3	14 (56%)	35-60	46	±7
High Risk	>3	4 (16%)	42-60	51	±9

Exercise Tolerance Test (ETT) Response of Patients

Exercise Tolerance Test (ETT) response was categorized on the basis of ECG changes and clinical symptoms (with angina and without angina). Results are shown in table 3.

Table 3: ETT Response of Study Subjects

ECG Changes				
Non-ischemic/	Ischemic/ positive		Equivocal / Borderline	
Normal	With Angina	Without Angina	With Angina	Without Angina
14	3	6	0	2
n= 14 (56%)	n= 9 (36%)		n= 2 (12%)	

Results of Myocardial Perfusion Imaging (MPI)

It was observed that 16 out of 25 subjects i.e. 64%, had perfusion defects on MPI and 9 i.e. 36% had normal scans.

Semi-quantitative analysis was done with the help of 17 segments scoring system. Variables used were Summed Stress Score (SSS), Summed Rest Score (SRD) and Summed Difference Score (SDS).

Results were categorized into three groups: *normal*, *mild* and *moderate to severe* degree perfusion defects. Half of the study subjects i.e. 48% had moderate to severe perfusion defects on nuclear scan [table 4].

Table 4: Results of SSS and SDS based on 17 segment scoring system

Perfusion Defect	SSS Patient no. (%age)	SDS Patient no. (%age)
Normal	10 (40%)	9 (36%)
Mild	4 (16%)	4 (16%)
Moderate to Severe	11 (44%)	12 (48%)
Total Patients	25	25

SSS=Summed Stress Score; SDS=Summed Difference Score, no. = number, % age = percentage.

Coronary Angiographic findings

Eighteen patients (72%) in this study had angiographic follow-up. Out of which 3 (17%) had normal angiograms, 8 (44%) patients had critical single vessel disease (SVD). 5 patients (28%) had triple vessel disease (TVD) and 2 (11%) had double vessel coronary artery disease (DVD) on Coronary Angiogram, shown in figure 1.

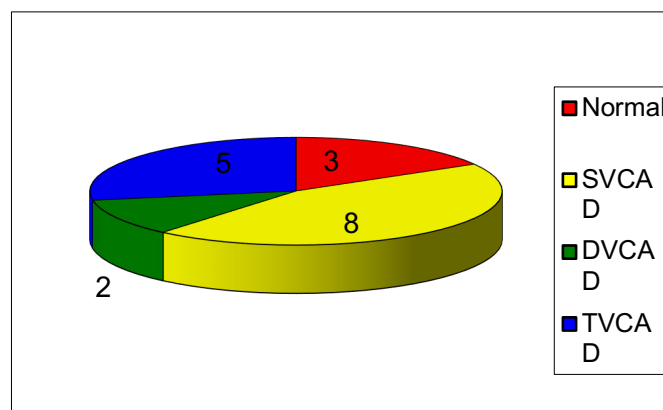


Figure 1: Coronary Angiographic findings of the Study Subjects.

SVCAD: Single vessel coronary artery disease; DVCAD: Double vessel coronary artery disease; TVCAD: Triple vessel coronary artery disease.

Relationship between Framingham Scoring and Results of Diagnostic Modalities

Results from different diagnostic modalities were compared to evaluate modality of choice for detection of occult disease in each risk group. It was observed that MPI and angiography had comparable results in intermediate and high risk group, Figure 2.

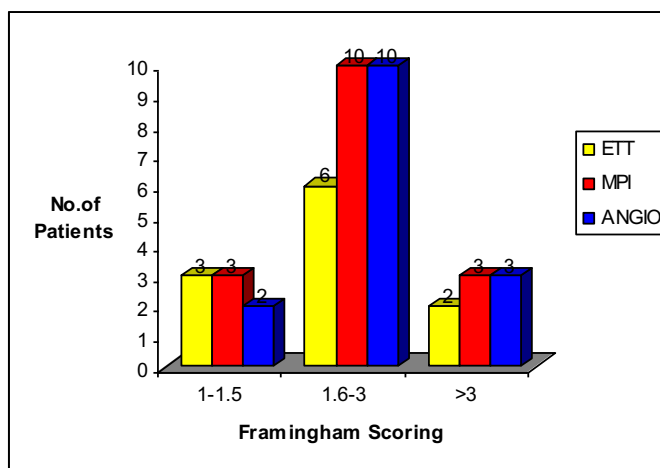


Figure 2: Comparison of ETT and MPI with Coronary angiogram to diagnose occult CAD in different risk groups.

Control Group Results

In control group, out of 10 individuals, 3 had positive ischemic response on ETT and one had mild perfusion defect on nuclear scan. Angiography was not performed in this group.

Optimization of the Results

Optimization of the results was done, considering Coronary Angiography as a gold standard, to find out which non-invasive diagnostic modality is better for detection of the occult disease CAD; Table 5.

Table 5: Optimization of the Results

Total Number.	ETT		MPI Scan		C. Angiogram	
	Normal	Positive/ borderline positive	Normal	Ischemic changes	Non- significant	Stenosis ≥ 70%
Cases (18)	8	10	5	13	3	15
Control (10)	7	3	9	1	0	0

ETT=Exercise Tolerance Test; MPI=Myocardial Perfusion Imaging.

Statistics Analysis of Modalities used in Detection of Occult CAD:

2x2 tables were used for calculation of sensitivity, specificity, positive and negative predictive values of ETT and MPS respectively.

It was observed that Sensitivity of ETT came out to be 66.66%, Specificity 70%, Positive predictive value (PPV) 77%, whereas Negative predictive value (NPV) was 58.33%.

For myocardial perfusion imaging (MPI); Sensitivity came out to be 86.66%, Specificity 90%, Positive predictive value (PPV) was 92.8% and Negative predictive value (NPV) came out to be 81.8%; in Figure 3.

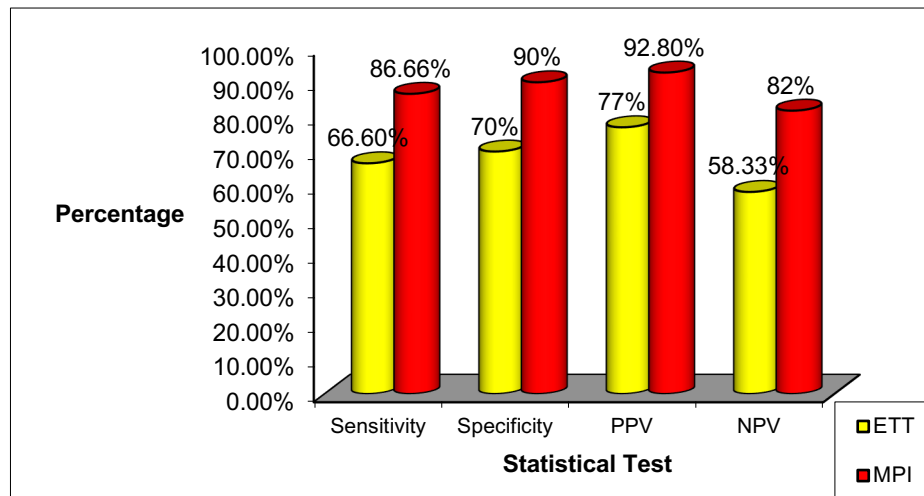


Figure 3: Graphical presentation of statistical Analysis.

Probabilities Scoring Comparison of the Diagnostic Modalities

Likelihood of the occult disease in the study patients was analyzed by comparing the post-test probability of the two non- invasive modalities with pre-test probability as shown in Table 6.

Table 6: Probability scoring of non-invasive diagnostic modalities for detection of Occult CAD

Framingham scoring.	Pre-Test probability of CAD	Post-test Probability			
		ETT		MIBI	
		Positive/ borderline	normal	Ischemic changes	normal
1-1.5	0.55	0.55	0.52	0.72	0.21
1.6-3	0.67	0.68	0.66	0.81	0.40
>3	0.77	0.78	0.75	0.88	0.44

Probability scoring for intermediate group showed that there was 68% probability of disease after patient had positive ischemic response on ETT. The probability of disease rose to 81%, after the patient had positive myocardial perfusion scan and it decreased to 40% once the scan was negative.

In high risk group probability of disease was 78% for ETT positive patients and it raised to 88% in scan positive cases, Figure: 4.

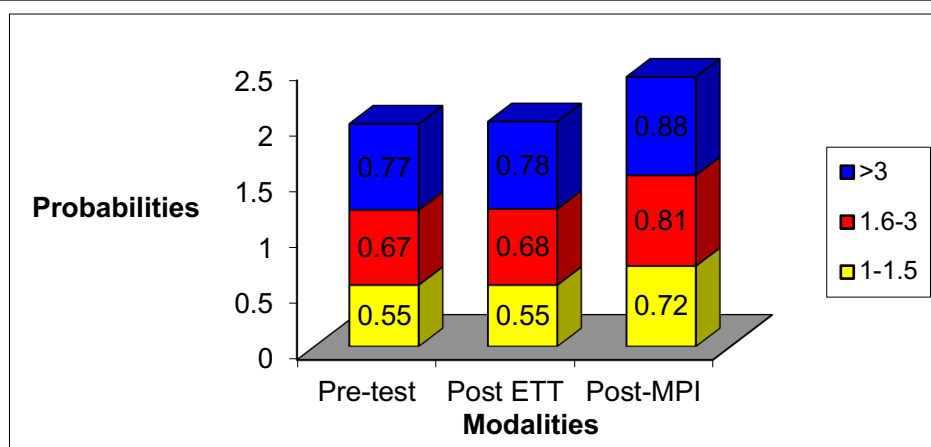


Figure 4: Comparison of Pre and Post-test probabilities in 2 non-invasive Cardiac Diagnostic Modalities

DISCUSSION

Coronary Artery Disease (CAD) having very high mortality and morbidity is an occult process in most of the high risk patients. Risk factors are only clinical presentation in these patients. It is quite difficult and expensive to modify entire high risk population so early detection is a better choice than risk modification of entire group [1].

Famous Inter-Heart study showed a significant association between risk factors, occurrence of myocardial infarction and CAD [17, 18]. Sunita D. et al. showed that in urban population of Pakistan, the most prevailing risk factors for CAD were hypertension, smoking and lack of physical activity [19].

In this study our aim was to find out better non-invasive modality for early detection of occult CAD, in asymptomatic, high risk individuals. It was a case control study; in which 25 cases and 10 controls were enrolled.

Cases had one or more cardiac risk factors present, where controls were normal volunteers. All of them were asymptomatic at time of presentation. It was observed that hypertension and positive family history of CAD were the most common risk factors among the patients. 18 out of 25 patients (72%) were hypertensive, where 17 out of 25 (68%) had positive family history of coronary artery disease, Table 1.

Probability scoring of all the patients was done, at the time of initial assessment by Framingham scoring, which detects probability of coronary artery disease over next 10 years [16].

The parameters used in this scoring were age, total cholesterol, HDL, blood pressure, diabetes and smoking. Scoring showed that probability of disease increased with increasing number of risk factors, highest score was seen in patient with all the 5 risk factors; Table 1.

On risk stratification it was observed that maximum number of patients i.e. 14 (56%) had intermediate risk of CAD, four (16%) had high risk and seven individuals (28%) were categorized as low risk group: Table 2.

In this study, all the patients underwent Exercise Tolerance Test (ETT); 9 patients (36%) had ETT positive for ischemia. Out of these 9 patients, 3 (12%) developed symptoms of angina during exercise, 2 patients had equivocal response and 14 (56%) had normal ETTs, Table 3.

Studies have shown that asymptomatic patients, with negative Exercise Tolerance Test (ETT) had only 1-11% chance of myocardial infarction in next ten years, so ETT is a useful modality to differentiate low and high risk population [20-22]. In duke treadmill study, 54% of the patients were in the intermediate group after the completion of ETT and they suggested that this group of patients required further evaluation and risk stratification [3].

We did myocardial perfusion imaging in all the study subjects; data was analyzed visually by two independent observers. After visual assessment, semi-quantitative analysis of nuclear scans was done, using 17-segment scoring system. Three variables were used in quantitative SPECT i.e. Summed Stress Score (SSS), Summed Rest Score (SRS), and Summed Difference Score (SDS) and assessment of the scans was primarily based upon the results of SDS. SDS showed that 4 (16%) patients had mild perfusion defects, 12 patients (48 %) had moderate to severe perfusion defects on scan, where 09 patients (36 %) had normal myocardial perfusion scans; Table 4.

Iskander et al showed that annual incidence of myocardial infarction in patients with normal myocardial perfusion scan was only 0.6 % [23]. Hachamovitch et al. found that if patient had mild perfusion defect on nuclear scan, chance of myocardial infarction per year was only 0.8 % [24].

When results of Myocardial Perfusion Images (MPI) were compared with Exercise Tolerance Test (ETT), it was observed that most of the patients with positive ischemic response on ETT had moderate to severe degree perfusion defect on scan [Table 5].

18 out of total 25 patients had angiographic follow up. As most of the patients had positive scans prior to the angiogram, probably this was the reason that very small percentage i.e. only 3 patients (16%) had normal angiograms, rest 15 showed vascular involvement. Eight patients (44%) had single vessel CAD, 2 (11%) had double vessel CAD and 5 patients (28%) had triple vessel disease; figure 1. When results of angiography were compared with myocardial perfusion scan, sensitivity of MPI was highest in case of triple vessel disease (TVD) and it was less when the vascular stenosis was non-critical (< 70%); figure 2.

Statistical analysis showed that sensitivity (86.66%) and specificity (90%) of Myocardial Perfusion Imaging were much better than sensitivity (66.6%) and specificity (70%) of Exercise Tolerance Test. MPI had high Positive Predictive Value (PPV) of 92.8 % and Negative Predictive Value (NPV) 82% which was again much better than ETT [Figure 3].

A meta-analysis done to detect sensitivity and specificity of ETT for Occult Coronary Artery Disease didn't show encouraging results, whereas comparable studies for MPI showed much better results, in asymptomatic CAD [8]

In our study, when comparison of the modalities was done, it was observed that for low risk group, the detection efficiency of the two modalities i.e. ETT and MPI was comparable. Seven

patients were included in low risk group; 3 patients (42%) were picked up by both the modalities. And 2 out of these 3 patients (50%) showed single vessel CAD on angiogram, figure 2.

In the intermediate risk group, out of 14 patients, 6 patients (42%) had ETT positive for ischemia, where 10 patients had positive scans, showing that 4 patients which were previously missed by ETT were picked up by MPI, one of these cases is shown in figure 5. All those 10 patients having positive scans; had vascular involvement on angiograms, (figure 2), supporting the fact that MPI is a better modality for initial assessment of patients, in intermediate risk group.

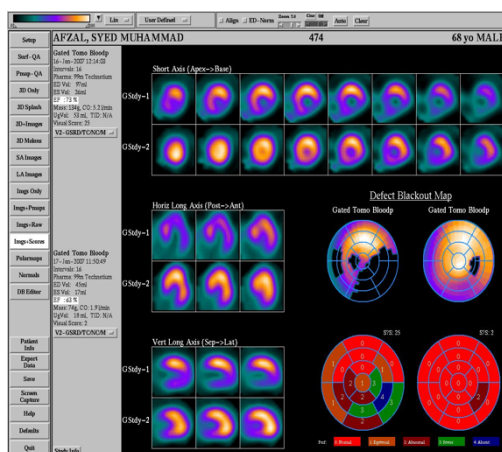


Figure 5: 60 years old smoker, hypertensive male, having Framingham score 2.4, had normal ETT. MPI showed reversible perfusion defect in inferior and inferolateral wall and mid to basal septum of left ventricle, along with T1D. Coronary angiogram showed triple vessel coronary artery disease (TVCAD).

Sensitivity of MPI for picking occult CAD was quite high, in high risk group. Out of 4 high risk patients, 3 had positive scans; only 2 patients had ischemic ECG response at THR, during ETT. All those 3 patients, picked up by MPS, had critical vascular stenosis ($\geq 70\%$), on coronary angiograms [figure 2]. Again a very strong correlation between findings of MPI and Coronary angiogram was observed.

Studies have shown that the prognostic value of MPI in risk stratification and impact on patient management in high risk asymptomatic patients is very high and observed to be more than ninety percent (90 %) before further intervention [24].

Third group in our study was low risk group (Framingham scoring less than 1.5). It was observed that in this group role of Myocardial Perfusion Imaging (MPI) was limited. Most of the low risk patients had either normal scans or mild degree perfusion defects and sensitivity of both the modalities i.e. ETT and MPI was almost the same (figure 2), so ETT being simpler and most widely used modality should be used for initial assessment in this group of patients.

Here we also want to mention control group of our study, which included 10 normal volunteers. We observed that 3 out of 10 normal individuals had positive ETTs, one had mild degree

perfusion defect on MPI. Three individuals with positive ETT had follow-up angiograms and all 03 angiograms came out to be normal.

Pre-test and Post-test probabilities of the two non-invasive modalities, used in this study were compared and it was found that probability of CAD was quite low when the patient had negative ETT, almost 52% in low risk group. Probability further decreased to 20% when patient had normal scan, on the other hand the probability raised to 72%, when patient had reversible perfusion defects on MPS [Table 6].

Intermediate risk group had pretest probability of 67%. Post-ETT probability was nearly equal to pre-test probability that was 68%, showing that ETT did not add much information to prior information. In case of Myocardial Perfusion Imaging the probability of disease raised to 81% when the scan was positive, while probability decreased to 40%, once the scan was normal.

High risk group had almost 90% post MPI probability of having CAD in positive cases (figure 4), which was at least 10% higher than post ETT probability; such patients must under-go coronary intervention.

In the study it was observed that even when ETT was strongly positive; it was not the true indicator of occult coronary artery disease. A female patient had normal perfusion scan; her ETT showed ECG changes suggestive of ischemia, where on angiography there was no definite vascular lesion; figure 6. There are multiple factors in females that can lead to false positive ETTs [8].

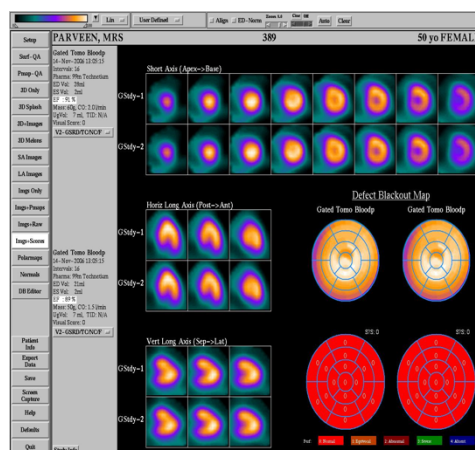


Figure 6: 50 years old hypertensive female with positive family history of CAD, had Framingham score 2.0, ETT was positive, where MPI and angiogram both were normal

Diabetes is a very common and extremely important risk factor for CAD, in this study 14 subject (56%) i.e. more than 50% study population had diabetes mellitus. Previous studies have shown that role of MPI in low risk groups especially considering diabetes as a risk factor was limited; specially in diabetics without any clinical or ECG related positive findings [25-28].

Largest group in this study was intermediate risk group i.e. 14 out of 25 (56% of study population) Table: 2. 10 out of 14 subjects in this group had positive nuclear scans and all of them had significant vascular stenosis on Coronary angiograms. This direct correlation

supports usefulness of MPI as initial diagnostic modality prior to invasive procedure like angiogram.

Even in this study where the sample size was not that big; at least 1/3rd of the intermediate risk population (4 out of 14) could be prevented from unnecessary intervention, saving a lot of money, without compromising quality of medical care.

CONCLUSION

It was observed that MPI was much superior modality than ETT for early diagnosis of asymptomatic / occult CAD, especially in intermediate and high risk group. So this non-invasive diagnostic modality can be used as a “gatekeeper” for invasive procedure like coronary angiograms.

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