Prognostic Value of $^{99m}$Tc – Sestamibi Stress Myocardial Perfusion Single Photon Emission Computed Tomography (SPECT) in Ischemic Heart Disease

Sunita Rao, V Lele, RD Lele

Abstract

Aim: To study prognostic value of $^{99m}$Tc – Sestamibi stress Myocardial Perfusion Single Photon Emission Computed Tomography (SPECT) in suspected or diagnosed ischemic heart disease, in an urban Indian population.

Methods: Eight hundred and eighty one patients with clinically suspected or diagnosed ischemic heart disease who underwent $^{99m}$Tc – MIBI stress – rest Myocardial Perfusion SPECT (MPS) between 1st February 2001 to October 2002 were followed up for 14 ± 2 months after the scan by questionnaire and telephonic interview with queries about cardiac death, myocardial infarct (hard events) and admission for unstable angina, CABG and PTCA (soft events). Patients were classified into pre-test: low, intermediate or high risk subsets based on clinical risk factors and ECG criteria. They were then reclassified based on MPS scan into post-test: high, intermediate and low risk subsets. Subsequent cardiac event rate was compared in the three subsets. A 12-lead ECG was an integral component of the stress MPS evaluation.

Results: MPS changed (1) the pre – test low risk category in 114 out of 613 patients to intermediate and 102 to high risk; (2) pre-test intermediate risk in 110 patients out of 163 to low risk and 19 patients to high risk (3) pre – test high risk category in 56 patients out of 105 to low risk and 28 to intermediate risk (total change 429 out of 881 patients). The hard cardiac event rate at one year was less than 0.5% in low risk, 2.3% in intermediate risk and 4.2% in high risk group.

Conclusions: $^{99m}$Tc – Sestamibi stress SPECT MPS thus provided incremental information for prognostic evaluation of patients with suspected or diagnosed coronary artery disease by assessing the effect of ischemic burden on LV function. This incremental information is crucial since coronary arteriography alone is not enough for prognosis and management decisions.

Patients with a normal or low risk MPS have generally a benign prognosis with a low annual hard cardiac event rate of 0.5%. Future challenge is to identify high risk subsets within this group, with CT coronary calcium score $> 100$ and inflammation markers such as high hsCRP so that more aggressive secondary preventive measures can be instituted to prevent future hard cardiac events.

INTRODUCTION

Eugene Braunwald, eminent-cardiologist has stated in 2005: “mechanical revascularization (CABG/PTCA) is probably being employed too often in United States. The mere presence of angina pectoris and / or the demonstration of critical coronary arterial narrowing at angiography should not reflexly evoke a decision to treat the patient by revascularization. Instead, this approach should be limited to those patients with ischemic heart disease whose angina has not responded adequately to medical treatment, or in whom revascularization has been shown to improve the natural history (e.g. acute coronary syndrome, or multi-vessel coronary artery disease with left ventricular dysfunction).”

ECG-gated exercise radionuclide Ventriculography (RNV) practised in the 1970’s and 1980’s clearly demonstrated the crucial importance of left ventricular function information for prognosis, risk stratification and management decisions. A five year Duke university follow-up study of 850 patients with angiographically proven significant triple vessel disease who were advised CABG but refused the same, showed no hard cardiac events in those with exercise LVEF $> 50$%.
whereas there were 30% hard events in those with ex-
LVEF less than 30%. All the benefits of CABG have been
clearly shown in the high risk groups whereas a lot of
CABG / PTCA is being done in low-risk patients as
observed by Braunwald, due to too much reliance on
angiography alone. Positive predictive value of coronary
arteriography for hard cardiac events during long term
follow-up is low even in high risk groups.3

Dobutamine stress echocardiography and stress
myocardial perfusion SPECT (MPS) provide the crucial
assessment of ventricular function in IHD. Many studies
have been published comparing these two modalities.4-
7 Echocardiography is more readily available than MPS,
but even in expert hands 25% of patients have technical
problem of window access (obesity, COPD) and
quantification is not yet possible.

An important strength of stress MPS is the ability to
quantify image pattern. The size of the myocardial
perfusion defect can be expressed as a percentage of the
left ventricle. Further, gated SPECT provides LVEF, EDV,
ESV as well as wall motion and wall thickening
information. Transient LV dilatation, increased lung
uptake and right ventricular uptake add incremental
prognostic information. Adenosine stress MPS is useful
for risk stratification and for detection of residual
ischemia following acute myocardial infarction.8-10 Rest
MPS was found to be useful in the emergency room to
Triage chest pain.11-14

The prognostic value of Tc-99m Sestamibi stress
myocardial perfusion SPECT (MPS) in an urban Indian
population with suspected ischemic heart disease is
assessed in this prospective study.

**Material And Methods**

This study was conducted in the Department of
Nuclear Medicine at the Jaslok Hospital and Research
Centre, Mumbai, India

Study Population consisted of all patients of
suspected or diagnosed ischemic heart disease. One
thousand patients were studied who underwent stress
MIBI MPS between 1st February 2001 to October 2002.
One hundred and nineteen patient were lost to follow
up therefore the effective study population was of 881
patients. The average follow up of all the patients was
14 ± 2 months (Range : 12 – 16 months) after MPS. A 12
lead ECG was an integral component of the stress MPS
evaluation. Follow-up questionnaire included queries
about admission for unstable angina, myocardial
infarction, CABG or PTCA or cardiac death.

**Inclusion criteria**

Inclusion criteria were independent of age, gender,
symptoms, status, whether patients were referred for :

- Diagnosing CAD (Coronary artery disease) or
- Prior CABG (Coronary artery bypass grafting) if
symptomatic or asymptomatic but after 5 years of
arterial grafts or 1 year of venous graft.

- Prior PTCA (Percutaneous transluminal coronary
angioplasty) done more than 3 months back or less
than 3 months if the patient is symptomatic.

Also included were patients for pre operative cardiac
evaluation for major non-cardiac surgery.

A consent form was provided to all 1000 patients who
underwent the stress MPS. Patients were included in
the follow-up study only after voluntarily signing the
consent form in the presence of a witness.

Out of 881 patients followed up for over one year, 644
(73%) were males and 237 (27%) were females. 836
(94.9%) were more than 40 years of age; only 45 (5.1%)
were less than 40 years.

**Stress protocol**

Physical stress : Beta-blocker drugs and calcium
channel antagonists were discontinued 48 hours before
the test and nitrate compounds were discontinued
atleast 6 hours before test.

Physical stress was performed using a bicycle
ergometer using a 12 lead ECG monitoring. Stress was
started at 25 W with an increment of 25 W every 3 min.
BP and heart rate was monitored at rest and the end of
every stage.

**End-Points**

1. More than 85%-Target heart rate (THR)
2. Symptoms : Angina, physical exhaustion
3. High BP more than 220 / 110 mm Hg, exertional
hypotension or failure of BP to rise
4. ECG changes :
   - ST depression more than 2 mm, horizontal, up
     sloping or down sloping.
   - Unsustained ventricular tachycardia
   - Hemodynamically significant supra ventricular
     tachycardia.

ECG was also categorized as

1. Non-ischemic (no significant changes)
2. Ischemic (significant ST segment elevation or
   depression)
3. Equivocal (borderline ECG changes)
   Patients were injected with 8 mCi of 99mTc – Sestamibi
   at peak exercise and then continued to be stressed for 1
   min after the injection. Exercise stress test was carried
   out in 708 patients (80%) and pharmacological stress in
   157 patients (19%). Rest study alone was done in 16
   patients.

**Pharmacological stress**

Pharmacological stress was performed on patients
who were unable to perform physical stress (eg.
orthopedic problems), had low ejection fraction (EF)
less than 30%, recent myocardial infarction, unstable angina,
left main coronary artery disease or triple vessel disease on angiogram. Patients were instructed not to consume tea, coffee, or caffeine containing product 24 hours before the test (being antagonist to adenosine).

After baseline ECG, heart rate and BP were monitored, adenosine was infused at a rate of 140 microgram / kg of body weight / min for 6 min. At the end of 3rd min of infusion 8 mCi of $^{99m}$Tc – Sestamibi was injected I. V. Significant ST depression during adenosine stress test was defined as more than 1 mm horizontal or down-sloping or more than 1.5 mm up-sloping ST depression. Imaging was begun 1 hour after the tracer injection.

Resting studies in all patients was done by giving about 20 – 30 mCi $^{99m}$Tc – Sestamibi I. V. at rest and imaging was done 1 hour later. 5 mg sublingual nitroglycerine was given before that injection to patients in whom perfusion defects were seen on the stress MIBI study.

**Imaging parameters**

SPECT Imaging was done using Triple Head Gamma Camera (PICKER, PRISM 3000 XP). Each head underwent 120° rotation with 6 angle step and 30 second per step. LEHR collimator was used. The study was processed with supplied software and semi-quantitative analysis was performed.

Same parameters were used for rest and stress studies.

Stress imaging was performed 1/2 hour after physical stress and 1 hour after pharmacological stress.

Rest imaging was done after 1 hour of $^{99m}$Tc – MIBI injection.

Pre–MPS probability of IHD was assessed on the basis of clinical risk factors and ECG criteria (Hilton et al 1996) (Table 1). Coronary risk factors considered were: diabetes mellitus, hypertension, smoking, abdominal obesity, high LDL and TG, low HDL, family history of premature IHD.

Myocardial perfusion imaging studies were assessed using visual and semi quantitative analysis and results were classified into post-test probability as low, intermediate and high risk subsets using Wintergreen Panel III 1999 Criteria15 – (Table 2).

Post MPS changes in pre-test risk stratification are shown in Table 3

Table 3 shows that most of our patients (613) were in the pretest low risk group. (69.1%).

Out of these, a majority i.e. 403 patients (64.5%) remained in posttest low risk group, while 110 patients (18.7%) changed to posttest intermediate group and 100 patients (16.7%) changed to posttest high risk group. Thus MPS changed the low risk category in 210 patients out of 613.

Out of 163 patients (18.5%) in the pretest intermediate risk group, 110 patients (67.4%) changed to the posttest low risk group, 34 patients (20.8%) remained in the intermediate risk group while 19 patients (11.6%) changed to the post-test high risk subset. Thus MPS changed risk category in 129 patients out of 163.

Out of 105 patients (11.9%) in the pretest high risk group, 56 patients (53.3%) changed to the posttest low risk group, 28 patients (26.6%) changed to postest intermediate risk group and 21 patients (20.0%) remained in the posttest high risk subset. Thus MPS changed risk category in 84 patients out of 105.

Total risk category change was in 423 out of 881 patients.

<table>
<thead>
<tr>
<th>Table 1 : Clinical risk categories based on coronary risk factors and electrocardiographic results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td><strong>Intermediate risk</strong></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 : Classification into risk subsets based on MPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

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Patients follow up

Patient’s follow up was performed by scripted telephone interview from the patient himself or people who had knowledge of patient’s health status (patient’s spouse or relative or referring physician).

Events were defined as:
- Hard cardiac event if there was a cardiac death or a non fatal myocardial infarction (documented by appropriate ECG and cardiac enzyme changes).
- Soft cardiac events were repeated admission for unstable angina and if patients underwent CABG or PTCA
- If a patient was found to have had 2 cardiac events the more serious event was considered.

Patients were followed up for atleast 1 year after the test, the average follow up of all patients was 14 ± 2 months (average being 12 to 16 months).

Data analysis

Statistical analysis: In this observational and follow up study group. We measured frequency and percentage for each parameter.

Chi – square test was used for significance whenever necessary. Statistical analysis was also done using Student t test.

A master chart consisting of all the variables as per our program was performed using Excel package.

RESULTS

Results of follow up of over one year are summarized in Table 4.

Summary of cardiac event rates in 3 risk categories is given in Table 5.

Table 4 shows that in the low risk category, out of 569 patients, 541 patients (95.1%) had no cardiac events, 25 patients (4.4%) had soft cardiac events while three patients (0.50%) had hard cardiac events.

In the intermediate risk category, out of 172 patients, 137 patients (79.6%) had no cardiac events, 31 patients (18.1%) had soft cardiac events while four patients (2.33%) had hard cardiac events.

In the high risk group, out of 140 patients 89 patients (63.6%) had no cardiac events, 45 patients (32.2%) had soft cardiac events while six patients (4.2%) had hard cardiac events.

The summary of cardiac event rate is give in Table 5. It is clear from Table 5 that maximum percentage of patients in the high risk category had hard cardiac events (4.2%) and had undergone some coronary intervention while least number of hard cardiac events (0.5%) were seen in patients of low risk category with majority of them being symptom free.

The percentage of hard cardiac events in patients of intermediate group were in between the low and high risk category:

Table 3 : Post-MPS test change in risk stratification on pretest risk classification

<table>
<thead>
<tr>
<th>Pre-MPS risk category</th>
<th>No. of patients</th>
<th>%</th>
<th>Post-MPS risk category</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest low 613</td>
<td>Low</td>
<td>403</td>
<td>64.5%</td>
<td>Intermediate</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>(69.1%)</td>
<td>High</td>
<td>100</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Pretest intermediate 163</td>
<td>Low</td>
<td>110</td>
<td>67.4%</td>
<td>Intermediate</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>(18.5%)</td>
<td>High</td>
<td>19</td>
<td>11.6%</td>
<td></td>
</tr>
<tr>
<td>Pretest high 105</td>
<td>Low</td>
<td>56</td>
<td>53.3%</td>
<td>Intermediate</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>(11.9%)</td>
<td>High</td>
<td>21</td>
<td>20.0%</td>
<td></td>
</tr>
<tr>
<td>Total 881</td>
<td>Total 881</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 : Summary of cardiac event rate

<table>
<thead>
<tr>
<th>Post-MPS risk stratification</th>
<th>Hard cardiac event rate</th>
<th>Soft cardiac event rate</th>
<th>No cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0.5%</td>
<td>4.4</td>
<td>95.1%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>2.3%</td>
<td>18.1%</td>
<td>79.6%</td>
</tr>
<tr>
<td>High risk</td>
<td>4.2%</td>
<td>32.2%</td>
<td>63.6%</td>
</tr>
</tbody>
</table>

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significant (p<0.001) from a Chi square test indicating that as the post test risk increases from to low to high, the cardiac event rate increase proportionately.

Therefore we can safely mention that low risk group patients are at a smaller risk for future cardiac events while patients in the high risk group are at greater risk for the same at (p < 0.05).

The comparative annual cardiac event rate in various published studies in the literature is summarized in Table 7

Thus the Cardiac event rate for normal and low risk studies was less than 1% according to the available world literature and the event rate increased as the risk stratification increased. Patients with diabetes mellitus have significantly poorer outcome than non-diabetics.

According to our study, the hard cardiac event rate was 0.5% for low risk MPS, 2.3% for intermediate risk group and 4.2% for high risk group which compares well with the previously done studies.

**DISCUSSION**

**Prognostic implication of stress myocardial perfusion SPECT**

The major goal of noninvasive MPS risk stratification in patients with chest pain on presentation, or who have known CAD, is the identification of subsets at high risk of cardiac death or nonfatal myocardial infarction. The identification of such patients enables prompt referral for cardiac catheterization with a view toward invasive strategies for revascularization. An extensive body of literature has demonstrated that the degree of abnormalities in myocardial perfusion and function are correlated with the extent of anatomical disease and most importantly, with clinical outcome. Patients with normal stress MPS are at low risk (< 0.5% / yr) for cardiac death or myocardial infarction. Patients with mildly abnormal stress MPS have low rates for cardiac death (0.7%/yr) but higher rates of myocardial infarction (2.6%/yr).19

Early detection of asymptomatic IHD in type 2 Diabetes mellitus by stress MPS is particularly important since it accounts for about 80% of morbidity and mortality. The DIAD study has shown the high prevalence of silent ischemia in asymptomatic patients of T2DM.24

Serial MPS imaging is useful to document and measure the effect of revascularization and to quantify the amount of salvaged myocardium. Similarly regression of amount of ischemia resulting from aggressive medical management can be monitored and quantified by MPS.

In renal transplant recipients cardiac events- free survival is much lower in those with abnormal MPS than in those with normal MPS.

Conversely, patients deemed at low risk for subsequent cardiac events based on stress MPS can be spared unnecessary referral for invasive evaluation, and unnecessary CABG/PTCA for low risk groups. Brown et al has emphasized the prognostic value of a normal MPS even in the presence of angiographically significant coronary artery disease.25

Females before menopause are generally a low risk group for coronary artery disease. Moreover, women have many false-positive ECG stress tests Adenosine- MPS is a better modality of diagnosis of CAD in this subset.

A normal stress MPS is generally taken as an indicator of good prognosis.26 However, recently available data on CT-coronary calcium score (CCS)27 and studies that have combined CT-CCS and MPS have provoked new thinking. Data on 1274 patients undergoing both MPS

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**Table 6 : Statistical analysis using student t test at 95% confidence interval (CI)**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Hard cardiac event rate</th>
<th>Confidence interval (P &lt; 0.05)</th>
<th>Soft cardiac event rate</th>
<th>Confidence interval (P&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.50%</td>
<td>(0.03 – 1.03)</td>
<td>4.4%</td>
<td>(2.98 – 5.81)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.30%</td>
<td>(0.44 – 4.22)</td>
<td>18%</td>
<td>(13.20 – 22.84)</td>
</tr>
<tr>
<td>High</td>
<td>4.20%</td>
<td>(1.47 – 7.10)</td>
<td>32%</td>
<td>(25.65 – 38.64)</td>
</tr>
</tbody>
</table>

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**Table 7 : Comparative annual cardiac event rate in published series**

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Study authors</th>
<th>No. of patients</th>
<th>Annualized cardiac event rate (% / yr) for normal / low risk studies</th>
<th>Annualized cardiac event rate (% / yr) for high risk studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Brown et al 1994</td>
<td>155</td>
<td>0.8</td>
<td>5.4</td>
</tr>
<tr>
<td>2</td>
<td>Brown et al 1996</td>
<td>3594</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Berman et al 1995</td>
<td>1702</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Hachamovitch et al</td>
<td>5183</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Machecourt et al 1996</td>
<td>715</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Iskander and Iskandrian 1998</td>
<td>12,000</td>
<td>0.6</td>
<td>7.4</td>
</tr>
<tr>
<td>7</td>
<td>Raiker et al 1994</td>
<td>208</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Nallamouthu et al 1996</td>
<td>707</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>9</td>
<td>Thompson et al 2005</td>
<td>1612</td>
<td>0.4</td>
<td>2.3</td>
</tr>
<tr>
<td>10</td>
<td>Current study</td>
<td>881</td>
<td>0.5</td>
<td>4.2</td>
</tr>
</tbody>
</table>
and CT-CCS from Cedar Sinai Medical Centre and other studies combining SPECT-CT imaging have indicated that unless the CCS is more than 400, it is uncommon for MPS to elicit ischemia. The more provocative finding noted in these studies is the high prevalence of coronary artery calcification in patients with normal MPS. Out of 1119 patients with normal MPS, 56% had CCS ≥ 100, 20% had CCS of 400 – 999, and 11% had CCS ≥ 1000. Even in the non-ischemic MPS group, annual hard cardiac event rate is 0.4% for CCS 11-100, 1% for CCA 101-400 and 1.9% for CCS > 400. The important message is to check the low risk subset (with 0.5% hard cardiac events), for CCS ≥ 100 and inflammatory markers such as hsCRP so that aggressive secondary medical prevention can be instituted. The PET-CT facility newly installed in several centres in India including our own, will provide a unique opportunity to test prospectively this concept of aggressive medical secondary prevention to avoid hard cardiac events in the large Indian population with ischaemic heart disease.

CONCLUSION

Statistically significant and clinically relevant risk stratification is achieved by stress MPS, which should form the basis of management decisions in IHD. Patients with normal and low risk Technetium – 99m Sestamibi stress MPS have a benign prognosis with a low annual hard cardiac event rate of 0.5%. Future challenge is to identify, within this group, a vulnerable subset with coronary calcium score ≥ 100 and hsCRP > 5, in whom aggressive secondary medical preventive measures can be instituted. This includes every newly diagnosed Type 2 DM patient.

Patients with abnormal Technetium – 99m Sestamibi stress myocardial perfusion images (intermediate and high risk subset) have a 10-fold increase in number of cardiac events.

In the intermediate and high risk category, the annual hard cardiac event rate was 2.3% and 4.8 respectively. It is in high risk group that the beneficial effects of CABG / PTCA have been clearly established. Prompt referral for cardiac catheterization with a view toward invasive strategies for revascularization is required in patients with high risk, even if they are asymptomatic. Using stress MPS as a gatekeeper, it is possible to avoid unnecessary further coronary intervention in patients with low risk and they can be spared unnecessary referral for invasive evaluation.

Intermediate risk group is still the gray zone wherein each case will have to be dealt with individually with regard to the clinical variables, and quantification of ventricular function.

REFERENCES

4. Brown KA. Prognostic value of cardiac imaging in patients with known or suspected coronary artery disease: Comparison of myocardial perfusion imaging, stress echocardiography, and position emission tomography. Am J Cardiol 1995;75:35D-41D.
17. Brown KA. Prognostic value of myocardial perfusion


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**Announcement**

Third Madras Diabetes Research Foundation (MDRF) - American Diabetes Association (ADA) Postgraduate Course on Diabetes, at Chennai, India, September 2006.

The Third MDRF-ADA Postgraduate Course on Diabetes will be held from 29th September to 1st October 2006 at Chennai, India.

The meeting will be hosted by the Madras Diabetes Research Foundation, Chennai.

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