Treadmill ECG Test Combined with Myocardial Perfusion Imaging for Evaluation of Coronary Artery Disease: Analysis of 340 Cases

Vidya Suratkal***, M Shirke**, RD Lele*

Abstract

Aim: Using Coronary arteriogram as the gold standard, stress ECG (Treadmill Test - TMT) has a sensitivity of 68% and specificity (77%) for the detection of coronary artery disease (CAD). Stress myocardial perfusion imaging (MPI) with Tc-99m Sestamibi gated SPECT has a sensitivity of 85% and specificity of 90%. The aim of the study was to ascertain if the combined use of the two physiologic tests will raise the predictive value for the presence or absence of physiologically significant CAD to 100%.

Methods and Material: Three hundred and forty patients (200 with suspected and 140 proved CAD) were studied with the same day rest and stress protocol. A rest MPI image was acquired with 8 mCi Tc-99m Sestamibi, followed by TMT; at the peak exercise 20 mCi tracer was injected and post-stress MPI image was acquired after 1 hour. 12-lead ECG at rest and during stress and recovery period was analyzed.

Results: Out of 200 patients with a prior probability of CAD 40 - 50% (151 with pain in chest, 81 with shortness of breath on exertion and 68 asymptomatic high risk for CAD - more than 5/9 risk factors), a normal stress MPI result in 150 patients excluded the probability of physiologically significant CAD. Fifty patients with abnormal stress MPI were referred for coronary arteriography. Stress ECG had 17% “false negative” and 23% “false positive” compared to stress MPI. In this group out of 140 known CAD, (56 post-infarct, 52 post-CABG and 32 post-PTCA), all sent for evaluation of ischemic symptoms, MPI documented 101 infarcts (fixed defects with no wall motion and thickening), 20 of them were “silent” (with no history of previous infarct) ECG did not help in picking them up. 58/101 infarcts had only fixed defects while 43/101 were accompanied by reversible ischaemia in same or other vascular territories. Thirty nine patients showed only reversible ischaemia without any infarct. Risk stratification was possible based on the extent and severity of the perfusion defects and number of territories in which defects were seen, rest LVEF, size of LV and transient dilation.

Conclusions: Combined stress ECG and stress MPI perform “gate keeper” function for referral for angiography, as well as for risk stratification of those who already have coronary angiograms. Decisions for revascularization should be based on combined evaluation - a shift from stenosis-based to ischaemic-based evaluation. Success or failure of revascularization was also documented by this evaluation.

INTRODUCTION

Treadmill ECG test (TMT) is routinely performed in patients of suspected or confirmed coronary artery disease (CAD). Using coronary arteriography as a gold standard this test has low sensitivity (68%) and specificity (77%) and a low positive or negative predictive value (Gianrossi et al 1989).1 The predictive value is even lower in women.

Stress myocardial perfusion imaging (MPI) with Tc-99m Sestamibi gated SPECT has a sensitivity of 85% and similar specificity for detection CAD using coronary arteriogram as the gold standard. The limitations of visual assessment of coronary angiogram to determine the physiological significance of anatomic stenosis are increasingly recognized,
hence rather than use the words “false positive” or “false negative” one should use the words concordance and discordance between anatomic and physiologic tests or two physiologic tests, and try to understand the underlying reasons.

Aim of study

It was decided to study simultaneously TMT with a 12-lead ECG and MPI in 340 patients of suspected or proved CAD to ascertain if the combination of the two tests will raise the predictive value for the presence or absence of physiologically significant CAD to 100%.

Material and Methods

During the year 2000, 340 patients were studied at the Lilavati Hospital and Research Centre. The male female ratio and age distribution are given in Table 1. The categories of patients studied are shown in Table 2. The risk factor evaluation is shown in Table 3.

Table 1 : 340 - Rest and stress myocardial perfusion and function studies, combined with stress ECG

<table>
<thead>
<tr>
<th>Males</th>
<th>270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>70</td>
</tr>
<tr>
<td>Above 40 years</td>
<td>314</td>
</tr>
<tr>
<td>Below 40 years</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 2 : Categories of patients

<table>
<thead>
<tr>
<th>Asymptomatic high risk for CAD</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>151</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>81</td>
</tr>
<tr>
<td>Post-myocardial infarct</td>
<td>56</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>52</td>
</tr>
<tr>
<td>Post-PTCA</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 3 : Risk factor evaluation (340 cases)

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>117 (34.41%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>69 (20.29%)</td>
</tr>
<tr>
<td>Family history</td>
<td>69 (20.29%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (05.59%)</td>
</tr>
</tbody>
</table>

The same day rest and stress protocol was used for all the patients. After IV injection of 8 mCi Tc-99m Sestamibi a rest image was obtained after one hour (time allowed to clear the liver activity which would interfere with inferior wall image). The patient then went on a treadmill for exercise; at peak exercise a second injection 20 mCi Tc-Sestamibi was given and patient continued to exercise for another minute. One hour later the post-stress image was acquired with a rotating gamma camera. Apart from giving images of perfusion in the short axis, and horizontal and vertical long axis, a Bull’s eye projection is also given showing comparison of all vascular territories. Gated SPECT additionally gives information about LV function - wall motion, wall thickening and LVEF at rest.

A 12 lead ECG was evaluated by the cardiologist. Duration of exercise, HR / BP double product, early onset of angina, ischaemic ST depression and fall in BP at low level exercise, profound ST depression, ischaemic changes in more that 5 ECG leads and persistence of the changes late in recovery - all those factors were taken into consideration and incorporated in the assessment of the test results.

Results

Comparison of MPI and stress ECG is given in Table 4 which also lists the abnormal MPI results. The concordance and discordance patterns is given in Table 5.

Table 4 : Comparison of MPI and stress ECG

<table>
<thead>
<tr>
<th>Stress ECG</th>
<th>MPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>134</td>
</tr>
<tr>
<td>Abnormal</td>
<td>206</td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
</tr>
</tbody>
</table>

Table 5 : Discordance pattern

| ECG false negative % | 17% |
| ECG false positive %  | 22% |

Analysis of MPI results

One hundred and fifty normal studies : Out of 200 patients who had apriori probability of 40-50% for the presence of CAD (151 with pain in the chest, 81 with shortness of breath on exertion, and 65 asymptomatic high risk for CAD), 150 were normal on stress MPI. A normal result is given only after ensuring that 85% of MPHR and HR/BP double product are achieved, 50 patients with abnormal MPI were referred for coronary arteriography. Stress ECG had 17% “false negative” and 23% “false positive” result in those 200 patients, compared to MPI.

Analysis of 190 abnormal MPI results

One hundred and one infarcts - Fixed perfusion defects with no wall motion and thickening on gated SPECT 56 were known to have previous AMI; 24 had previous CABG, 20 previous PTCA but out of these 44, previous history of AMI present in only 25 thus 20 infarcts were “silent”. Rest or stress ECGs did not help in picking up silent infarcts.

58/101 infarcts showed no additional reversible ischaemia.
43/101 infarct showed additional reversible ischaemia in the same or other vascular territories indicating a risk for future coronary events. Eight of them had prior CABG and 11 had prior PTCA.

Eighty nine patients had only reversible ischamia, no infarcts. It was possible to give risk stratification based on the extent and severity of the perfusion defect, number of territories in which defects were seen, LVEF, size of the left ventricle and presence of transient LV dilation.

For example out of 56 prior myocardial infarct patients 18
had only fixed defects and LVEF > 50% indicating low risk for future events; 34 had additional reversible ischemia in other territories indicating high risk for future events. Coronary angiograms were available in 52 post-CABG and 32 post-PTCA patients. By comparing the anatomic data and the stress MPI data it was possible to assess the success of revascularization in 20 CABG and 20 PTCA patients. In the remaining 32 CABG and 12 PTCA presence of reversible ischemia indicated the failure of previous revascularization or the need for fresh revascularization in other territories.

**DISCUSSION**

Exercise is a common physiological stress used to elicit cardiovascular abnormalities not present at rest, and to determine adequacy of cardiac function. Exercise ECG is the most frequently employed non-invasive modality used to assess patients with suspected or proven CAD. ACC / AHA guidelines are available for exercise testing (Schlant RC et al 1992, Gibbons RJ et al 1997). Using coronary arteriogram as the gold standard EX-ECG has a low sensitivity and specificity for detection of CAD (Gianrossi R et al 1989). In women the sensitivity (61%) and specificity (69%) are even lower than men, in particular the occurrence of 1 mm ST segment depression or greater. In testing pre-menopausal women with chest pain or established CAD, exercise testing should be avoided in a woman's mid cycle during which estrogen levels are highest. Women incapable of performing a minimum of 5 Mets of exercise should be candidates for vasodilation stress testing. Combining MPI with exercise ECG will have substantial incremental value in women.

The recognition of microvascular angina with normal epicardial vessels seen in women with diabetes or hypertension raises the question - if exercise ECG shows significant ST depression and the angiogram is normal, is the ECG false positive or is the angiogram false negative for ischemia? It is a good attitude to try to understand the reasons for discordance between different testing modalities.

The ECG-Gated SPECT Myocardial Perfusion Imaging (MPI) additionally allows quantitative evaluation of both global (ejection fraction, EDV and ESV) and regional (myocardial wall motion and wall thickening) cardiac function. Gating leads to greater specificity for the attenuation artifacts common on Thallium Imaging - (e.g. breast-anterior wall, diaphragm and liver - inferior wall). Stress-induced LV cavity dilatation, detected by this technique adds incremental prognostic value to the test since it is a specific marker of multivessel disease. This is the counterpart of the increased lung activity seen during Stress Thallium Imaging as an indication of LV failure. ECG-Gated SPECT MPI is unique in comparison with other forms of non-invasive imaging in providing objective and quantitative measurement of myocardial perfusion and function. Considering that a 12-lead ECG is an integral part of the test (and its findings are incorporated in the evaluation), this is indeed a ‘3 in 1’ test. By comparison no other cardiac imaging modality (including contrast echocardiography, EBCT and MRI) is currently capable of routine quantitative evaluation of Stress LV perfusion and function at comparable cost. Part of the prognostic potential of Stress MPI results from the assessment of endothelium-dependent coronary microcirculation function as proved by intracoronary infusion of acetylcholine during coronary angiography. The perfusion defects are seen in territories of angiographically abnormal as well as normal vessels and L-arginine administration is associated with reversal of these perfusion defects.

A normal stress MPI result in patients with significant triple vessel disease must mean that adequate collateral blood flow has been restored not only sufficient for resting requirements but also during increased demand. Ischaeemia is a stimulur for collateral vessel formation. The ability to form new blood vessels (angiogenesis) may be genetically determined and individuals vary in their ability to form collaterals. In canine models, occlusion of coronary arteries a identical anatomic locations produced markedly varied degrees of myocardial necrosis from 10% to over 50% due to the existence of significant epicardial collateral circulation. Porcine hearts have scant collateral which are primarily located in the mid-myocardium and subendocardium. Most coronary angiogram reports make absolutely no mention about collaterals. Evidently the technique is not sensitive to detect. Collaters Evidently the technique is not sensitive to detect collaterals smaller than 200µ. In angiogenesis trials quantitative flow estimation with PET is useful to measure the consequences of angiogenesis therapy. SPECT is not sensitive enough for this purpose. One study has shown that a difference of over 10% between two consecutive SPECT studies can be used to assess success of angionesis therapy.

Patients with normal stress MPI have an excellent prognosis even if angiographic CAD is documented (Brown and Rowan 1993) whereas patients with abnormal scans have an increased rate of non-fatal myocardial infarct as well as cardiac death during follow-up. The greater the extent of stress-induced hypoperfusion and reversibility, the greater is the probability of a cardiac event. For any extent of hypoperfusion, transit LV dilation during stress (equivalent to increased lung activity in the thallium scan) increases the event rate.

The major prognostic variables on stress MPI are: large defect size (>20 of LV); defect in more than one coronary territory; defect reversibility in multiple myocardial segments; resting LVEF < 40% and transient or persistent LV dilation.

when clinical, stress ECG and stress MPI variables are known, little incremental prognostic information is gained by coronary angiographic variables such as the number of vessels with significant stenosis. Stress MPI variables are even superior to mere knowledge of coronary anatomical variables for assessing prognosis. Infact patients with 3 vessel disease on angiography can be further risk-stratified by MPI performed after catheterization into low, intermediate and high risk groups.

In interventional cardiology great concern exists about the large number of patients undergoing PTCA without prior
objective evidence of ischemia at exercise MPI or exercise echocardiography. Since the prevalence of coronary artery stenosis in an arbitrary population of asymptomatic 60 year-old men is 20% it is not unlikely that in a number of patients with normal non-invasive tests but accepted for PTCA on angiographic anatomic basis alone, the angiographic lesion is cosmetic. Hence it should be mandatory that exercise MPI or dobutamine echocardiography should be a pre-requisite for decision for angioplasty.

Coronary arteriography is unsuitable as a gold standard to assess the prognostic value of stress MPI. The positive predictive value of coronary arteriography for hard events during long-term follow-up is low even in high risk groups. The gold standard to assess the prognostic value of stress MPI is complete long term follow-up which we are doing by annual personal or telephonic contact. Experience so far indicates that the "warranty period" of a normal stress MPI cum stress ECG is two years.

Hence this test can perform as a “gate keeper” function for management decisions based on risk stratification. Stress MPI applied to individuals with high risk factors will identify those “asymptomatic” patients who already have significant CAD and silent ischaemia as they may be benefited from intensive anti-ischaemic medical therapy and/or coronary revascularization. MPI can also monitor course of disease under therapy. In acute myocardial infarct, infarct size can be reduced through primary angioplasty or thrombolysis. How effectively this has been achieved can be documented by MPI, using Tc-99m MIBI or Tetrophosmin SPECT. Following recovery from acute myocardial infarction, the risk of future cardiac events is related to the site of the infarct (anterior Vs inferior), extent of damage (number of fixed perfusion defects and LVEF), the occurrence of remodeling (LV dilatation, aneurysm formation), extent of stress-induced ischaemia within and outside the infarct, or jeopardised viable myocardium (JVM).

The selection of patients for revascularization should be based on the evaluation of stress MPI which documents and quantitates all the above powerful determinants of prognosis.

Wherever facilities are available, a routine post-discharge stress MPI should be recommended instead of the routine coronary angiography or stress ECG testing, for better assessment of JVM.

Even when angiographic findings are known MPI provides incremental information for identifying high risk subgroups which need urgent revascularization. Conversely patients with normal stress MPI have low probability of future coronary events (less than 0.6%) regardless of the angiographic findings.

By combining the anatomic information of coronary angiography and physiological information of stress MPI, proper risk stratification and optimal decision-making can be achieved. Thereby “cosmetic” angioplasties and CABG on low-risk patients can be avoided. On the other hand many more asymptomatic high risk patients will be detected who need aggressive therapy.

**REFERENCES**


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