# Assessment of hibernating myocardium with Tc-99m sestamibi Spect: Effect of nitroglycerine and trimetazidine administration

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**Myocardial perfusion imaging with Thallium-201 has been established as non-invasive method for assessment of myocardial viability in-patients with ischaemic left ventricular dysfunction. Technetium agents, owing to their better imaging characteristics and ease of availability, are now increasingly used for this purpose. Results with Tc-99m Sestamibi are quite encouraging and show good agreement with those of thallium-201 imaging. Use of nitrates in conjunction with Tc-99m Sestamibi has been shown to enhance the sensitivity for detection myocardial viability. This study was designed to observe the effect of a new agent, trimetazidine, on the diagnostic yield of Tc-99m Sestamibi myocardial perfusion SPECT in comparison with baseline and post nitroglycerine studies. 25 patients (19 males, 6 females) aged 46±3.9 years with established coronary artery disease and left ventricular dysfunction were included in the study. All patients underwent a baseline study, a post nitroglycerine study and a post trimetazidine study on three separate days using the same dose of Tc-99m Sestamibi and imaging protocol. The data were reconstructed in trans axial slices and then reoriented into short, vertical long and horizontal slices. The images were split into 20-segment model and were qualitatively and quantitatively analyzed by three independent observers. Each segment was assigned a score ranging from 0 to 4 depending upon its perfusion status. Segments having score ≤ 1 were considered non-viable while segment with score ≥ 2 were considered viable. In the baseline study, 69.6% (348/500) segments were viable. This number increased to 74.4% (372/500) in post nitroglycerine study and to 74.2% (371/500) in post trimetazidine study. Concordance was observed in 94% segments in nitroglycerine and trimetazidine studies. Quantitative scores improved significantly in post nitroglycerine and post trimetazidine studies compared with those of baseline study ($p < 0.001$). Both nitroglycerine as well as trimetazidine administration improve the diagnostic yield of Tc-99m Sestamibi SPECT for assessment of myocardial viability.**
**Key words: Myocardial viability, Trimetazidine, Nitrates, Hybernating myocardium, Tc99m-MIBI**

Patients with severe coronary artery disease (CAD) and left ventricular (LV) dysfunction who solely receive medical therapy have a poor outcome, whereas patients who undergo coronary revascularisation have a better long term outcome and approximately one third will have improved LV function after revascularisation[1]. Nevertheless, because of an increased peri-operative mortality in such patients, coronary revascularisation should ideally be performed in those who are likely to benefit from the procedure[2]. It is well known that the recovery of LV function after revascularisation is more likely to occur in patients whose LV dysfunction is related to viable but hibernating myocardium rather than to irreversibly scarred myocardium.

An accurate noninvasive determination of myocardial viability is vitally important for clinical decision making. Prior results of clinical trials evaluating the efficacy of coronary bypass surgery have shown that patients with multi vessel CAD and a depressed left ventricular ejection fraction (LVEF) benefit most from revascularisation, even if symptoms of angina are minimal or absent[3]. In recent years, there has been a greater appreciation among clinicians of the phenomena of "stunned" and of "hibernating" myocardium[4]. Both these pathophysiologic states may result in profound regional LV dysfunction in the absence of necrosis. Thus, mere assessment of regional systolic function, by echocardiography, radionuclide angiography, or contrast Ventriculography, is insufficient to distinguish between irreversibly injured and viable but dysfunctional myocardium.

Both experimental and clinical data indicate that imaging of myocardial perfusion and/or metabolism provides clinically relevant information about the status of myocardial viability in the presence of regional and global myocardial systolic dysfunction. This ability to differentiate irreversibly damaged from viable but asynergic myocardium can help clinicians in identifying those patients with CAD and depressed LV function, which might benefit most from coronary bypass surgery or coronary angioplasty.

Myocardial perfusion imaging with Thallium-201 is being used for assessment of myocardial viability in patients with ischaemic left ventricular dysfunction[5,6]. However, low energy of Thallium-201 makes it a less preferred choice for myocardial perfusion imaging. Technetium agents on the other hand have good imaging characteristics and are readily available[7]. They are now increasingly used for myocardial perfusion imaging. There is increasing evidence that Tc-99m Sestamibi can be used as a myocardial viability agent. Use of nitrates in conjunction with Tc-99m Sestamibi has been shown to enhance the sensitivity for detection myocardial viability and it show good agreement with those of thallium-201 imaging[8].

Trimetazidine is a newly developed anti-ischaemic agent capable of shifting cellular metabolism in the favor of more glucose utilization by stimulating carbohydrate oxidation during ischaemia[9]. As a result it economizes oxygen to produce more ATP for contraction and ion balance. Since reduced mitochondrial oxidative metabolism is responsible for the decreased myocardial functions, trimetazidine might exploit this reserve by increasing mitochondrial oxidative metabolism[10], thus allowing increased amount of Sestamibi to concentrate in the myocardium.

**Patients and methods**

Twenty five patients (19 M, 6 F) aged 46 $\pm$ 3.9 years were included in the study. All patients had evidence of left ventricular dysfunction and proven coronary artery disease

Patients with history of myocardial infarction were studied at least three months after the event. All patients underwent a baseline study, a post nitrate study and a post trimetazidine study on three separate days.

***Baseline Study Protocol***

550 MBq of $^{99m}$Tc-MIBI was injected I/V to 5 hours empty stomach patient. Blood pressure and pulse were noted before and after the injection. Patients were asked to have a light fatty meal 15-20 minute after injection and viability scan was acquired 45 minuets after injection. Blood pressure and pulse were noted after the resting study.

***Nitrate Study Protocol***

With same preparations patients arrived in the department, their blood pressure (BP) and pulse was noted. Isosorbid dinitrate (Isordil™, Wyeth Labs. Pakistan) 5 mg was given sublingually. BP and pulse noted at 5th and 10th minute. After 10 minutes 2$^{nd}$ tablet of Isordil was given, BP and pulse was noted. Five minutes later 550MBq of $^{99m}$Tc-MIBI was injected and patients were asked to have a light fatty meal 15-20 minute after injection and viability scan was acquired 45 minuets after injection.

***Trimetazidine Study Protocol***

With three hours of empty stomach patients were advised to visit the department. After the recording of BP and Pulse, 3 tablets of Trimetazidine (Vastarel™, Servier pharma-ceuticals, Pakistan) 20 mg (total 60 mgs) were given orally with a glass of water. BP and Pulse were noted at 30, 60 and 120 minutes of trimetazidine ingestion. Two hours later 550 MBq of $^{99m}$Tc-MIBI was injected and patients were asked to have light fatty meal 15 to 20 minutes after injection. Acquisition was started 45 minuets after injection.

**Acquisition and processing:**

SPECT acquisition was performed using rotating large field of view gamma camera equipped with low energy general all-purpose parallel hole collimator connected to dedicated computer system. Total 60 frames each of 20 seconds were acquired in continuous acquisition mode over 180 degree, anteriorly circular arc, with a starting angle of 135 degree right anterior oblique position. A 15% symmetric energy window centered at 140 keV was used. A zoom of 1.6 was applied during acquisition. All projection images were stored on magnetic disc by means of 64 X 64-word matrix.

The data were processed using 180-degree filter back projection with ramp filter. A 3D Low pass post filtration with a cut off frequency of 0.24 and order of 5.6 was applied. A zoom was applied in reconstruction. Each slice was 2.2 mm thick (1 pixel), three slices were added together during reformatting into short axis, vertical long axis (VLA) and horizontal long axis (HLA), so as each slice is 6.6 mm thick.

**Data Analysis**

Three different observers perform data analysis and in case of discrepancy a consensus was reached. All the observers were unaware of the patient name and study type. For grading of perfusion defects, protocol of Iskandrian et al was followed. In this protocol, left ventricular cavity was divided into 20 segments, as shown in figure 1. Short axis was made at apical, mid ventricular and basal parts. These slices were cut in such a way that apical slice must contain ventricular cavity while basal segment should contain muscular part of interventricular septum. Each slice was divided into 6 parts and in this way 18 segments were created. Two other segments were taken from apical part of ventricular long axis. The visual analysis was scored as follows,

4 = normal uptake, 3 = mildly reduced uptake, 2 = moderately reduced uptake,

1 = markedly reduced uptake, 0 = absent tracer uptake

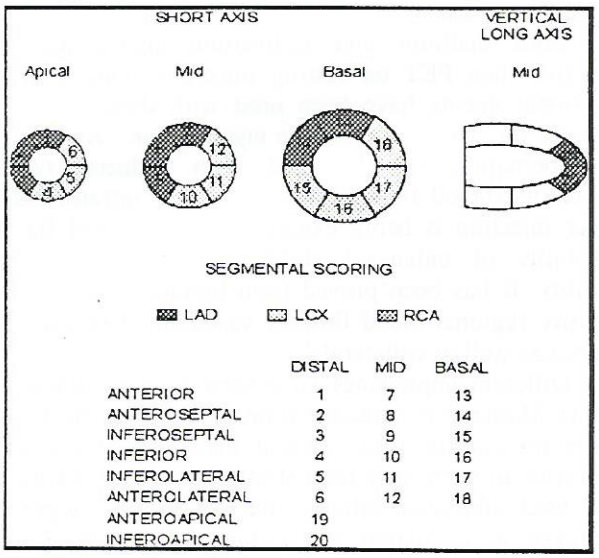


Figure 1: Segmental division of left ventricular cavity.

Myocardial segments having score of 2 or more were considered viable while segments with a score less than 2 were considered non viable.

**Results**

In the baseline study 348/500 (69.6%) myocardial segments had a score of 2 or more, thus categorized as viable, while 152/500 (30.4%) segments had a score of less than 2 and were considered non viable. In post nitrate study 372/500 (74.4) segments were considered viable and 128/500 (25.6%) segments were still non viable. In post trimetazidine study 371/500 (74.2%) segments were declared viable while remaining 128/500 (25.6%) segments were nonviable. When considering individual vessel territories there was significant improvement ($p < 0.05$) in LAD territory both with nitrate as well as trimetazidine. However, there were insignificant differences in RCA and LCX territories. Quantitative scores improved significantly in post nitroglycerine and post trimetazidine studies compared with those of baseline study ($p < 0.001$). There was good agreement between nitrate and trimetazidine. Concordance was observed in 94% segments in nitroglycerine and trimetazidine studies.

**Discussion**

In the current era of revascularization surgery and interventional cardiology, the assessment of myocardial viability is of prime importance. The distinction between viable and nonviable myocardium is clinically important in patients who are possible candidates for myocardial revascularization because these procedures are often accompanied by high operative morbidity and mortality. The detection of viable myocardium using nitrates with $^{99m}$Tc-99m-MIBI is well-established entity, while the use of trimetazidine is a relatively new concept. In this study we compare both the pharmacological agents with resting $^{99m}$Tc-99m-MIBI.

Both thallium and technetium agents are less sensitive then PET on resting injection alone, therefor additional agents have been used with these tracers to enhance the detection of viable myocardium. As the area of hibernating is associated with reduced resting myocardial blood flow, administration of nitrates before tracer injection is being extensively investigated for the possibility of enhanced ability to assess myocardial viability. It has been proved from literature that nitrates improve regional blood flow by vasodilation of coronary arteries as well as collaterals[11].

Different approaches have been used to administer nitrate. Maurea[12] et al used oral nitrates for the detection of viable myocardium and showed that 27% of segments improved after nitrate administration. Similarly Thorley[13] et al used sublingual nitrates and found 39.5% segments improved as compared to baseline, while 15% of the segments showed improvement in a study by Flotats[14] et al. From all of the mentioned studies it was cleared that pharmacological intervention of nitrates improve the detection of viable myocardium.

In our study 122 segments (24.5%), out of 500, showed improvement, 73(14.5%) segments had worsen while 305(60.9%) had remained the same. These findings were comparable to the study by Thorley[13] et al who showed improvement in 39.5% of segments while 18% of segments deteriorates after nitrate administration. The segments that showed worsening or reduced reversibility after nitrate administration may be artefactual, due to the change in attenuation between the two sets of rest images or due to the effects of nitrate on collaterals supplying the area.

We have found that trimetazidine is as effective as nitrates, in the detection of viable myocardium. In the study after administration of trimetazidine, 24.5% of segments improved, 9.7% of segments showed worsening while 65.8% segments remained as such. In a study by Ciavolella[15] et al definite improvement in uptake of tracer was noted in hibernating myocardial segments as compared to placebo. In this study, decrease in both severity and extent of defect was noted after oral administration of trimetazidine. The improvement noted in our study was comparable to study conducted by Ciavolella et al, but the cause of worsening was not clear. Another interesting point was the concordance of 94% between nitrates and trimetazidine. As the improvement by administration of nitrates is well-established entity, such a high concordance means that trimetazidine is as good pharmacological agent as nitrate for the detection of viable hibernating myocardium.

**Conclusion**

- $^{99m}$Tc-MIBI imaging with sublingual nitrate or oral trimetazidine is a good indicator for differentiating hibernating myocardium from fibrotic scar in patients with coronary artery disease and left ventricular dysfunction.
- Both the pharmacological agents have similar efficacy ($p$ = n.s.) for detection of viable myocardium.
- The uptake of tracer by the effect of pharmacological agents is more pronounced in segments with score < 2, indicating non-viable segments. Therefor it is recommended that in patients with non-viable viable segments on resting MIBI perfusion study, a repeat study using one of the pharmacological intervention must be used, as this will enhance the detection of viable myocardium

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