Original Article

A Prospective Comparative Study between 99mTc MIBI Myocardial Perfusion Single-Photon Emission Computed Tomography and Dobutamine Stress Echocardiography to Detect Viable Myocardium in Patients with Coronary Artery Disease

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Abstract

Introduction: The objective of this study was to compare 99mTc MIBI myocardial perfusion SPECT and Dobutamine Stress Echocardiography (DSE) in detecting viable myocardium in patients with Coronary Artery Disease. **Materials and Methods:** Total of 50 patients who with CAD and poor LV function were idenitifed on 2D Echo using 16 segment cardiac model. These patients underwent 99mTc MIBI myocardial perfusion SPECT and Dobutamine Stress Echocardiography and the results were compared with the gold standard 18F-FDG PET-CT findings. **Results:** A Total of 550 dysfunctional segments were identified in datasets of 50 patients on 2D echo. No significant difference was noted between the pairwise positive outcome of viable segment between MIBI SPECT and DSE (p=0.875). MIBI SPECT showed a sensitivity of 86.5% and specificity of 90.0% when compared with 18F-FDG PET-CT which was comparable with DSE having a sensitivity of 87.6% and specificity of 90.7%. **Conclusion:** 99mTc MIBI SPECT is an effective good alternative for evaluation of viable myocardial segments in patients with dysfunctional myocardium and can be considered especially in elderly or obese patients and patients with lung disease having poor echocardiographic imaging window due to lack of an optimal acoustic window.

Keywords: *18F-fluorodeoxyglucose positron emission tomography–computed tomography, cardiac viability, dobutamine stress echocardiography, MIBI, myocardial perfusion imaging*

Introduction

According to the global burden of disease age-standardized estimate 2010, nearly a quarter (24.8%) of all deaths in India are attributable to cardiovascular disease (CVD).[1] The age-standardized CVD death rate of 272/100,000 population in India is higher than the global average of 235/100,000 population. Ischemic heart disease (IHD) and stroke constitute the majority of CVD mortality in India (83%), with IHD being a predominant cause of mortality.[1] Because of the high mortality rate and increasing prevalence of heart failure alone with the need to tailor therapy to the etiology and stage of the condition, evaluation of patients with IHD by noninvasive methods has become increasingly common. Among the various parameters studied, the distinction between reversible and irreversible ventricular dysfunction has important clinical implications as the dysfunctional but viable myocardium resumes contraction following revascularization.

For a long time, dysfunctional myocardium was synonymous with myocardial necrosis. However, studies showing histological evidence of the presence of viable myocytes in dysfunctional segments as compared to areas of scarred myocardium and clinical improvement of left ventricular (LV) function post revascularization opened the path of myocardial salvage through viability assessment.[2,3] Several imaging techniques have been utilized for this purpose namely echocardiography, cardiac magnetic resonance imaging, nuclear imaging with single-photon emission tomography, and positron emission tomography imaging.[4,5] These assess several attributes, including cell membrane integrity, intact mitochondria, preserved glucose metabolism, preserved fatty acid

How to cite this article: Jha DK, Mahato A, Jain A, Bohra V, Tiwari A. A prospective comparative study between 99mTc MIBI myocardial perfusion single-photon emission computed tomography and dobutamine stress echocardiography to detect viable myocardium in patients with coronary artery disease. Indian J Nucl Med 2023;38:224-30.

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Received: 24-05-2022
Revised: 16-09-2022
Accepted: 22-09-2022
Published: 10-10-2023

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.ijnm_91_22

Quick Response Code:

metabolism, intact resting perfusion, and inotropic reserve of a viable myocardium.

Presently among these, positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) is the accepted gold standard for differentiating viable myocardial tissue from scar tissue.[6,7] However, PET assessment of viability is limited to its availability, requires a complimentary perfusion scan, and can have limited sensitivity in diabetics. On the other side, single-photon emission computed tomography (SPECT) and dobutamine stress echocardiography (DSE) are widely available; however, the situation is changing quickly. The aim of this study was to compare the accuracy of 99mTc Methoxy-Iso-Butyl-Isonitrile (MIBI) myocardial perfusion SPECT and DSE in detecting viable myocardium in CAD patients and assess the concordance and discordance between the two methods in detecting viable myocardium when compared to the gold standard 18F-FDG PET.

Materials and Methods

The study was a prospective study comparing the accuracy of resting MPI and DSE in diagnosing viable myocardium of CAD patients. The patients were also followed up with 18-FDG PET-CT which was taken as the gold standard. The study included patients of all age groups and gender with CAD who had severely impaired LV function and had been referred for a viability study. Fifty consecutive patients were enrolled in the study as per the inclusion and exclusion criteria mentioned below.

Inclusion criteria

Patients of coronary artery disease with significant LV dysfunction (LV ejection fraction [LVEF] <35%) with the following features:

a. Normal sinus rhythm
b. Willingness for coronary revascularization (by either Percutaneous coronary Intervention/ Coronary Artery bypass graft (PCI/CABG))
c. Patients willing to give consent for undergoing a radioactive procedure.

Exclusion criteria

a. Patients with history of arrhythmias
b. Unwilling for revascularization
c. Claustrophobic patients
d. Pregnant ladies
e. Patients who did not consent for undergoing a radioactive procedure
f. Patients unable to lie supine for the procedures involved (stress echo, SPECT-CT, or FDG-PET)

Patient characteristics were recorded as per the pro forma attached [Appendix B]. The selected patients underwent DSE and resting MPI with 99mTc MIBI on two separate occasions within the time period of 1 week. 18F-FDG cardiac PET was also carried out subsequently.

Viability on MPI was defined as a mean segmental 99mTc MIBI uptake equal to or more than 50% of the maximum uptake on 10-segment spectrum LUT (look up table) on Cedars Sinai QPS/QGS software. Viable myocardium on DSE was defined as hypokinetic areas with at least 1 point improvement in the wall motion score. As the stress echocardiography used a 16-segment model for the analysis of wall motion excluding the apex (17th segment in 17-segment model), hence the same was used for MPI as well as for 18F-FDG PET to avoid any bias.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD). Normality of data was tested by Kolmogorov–Smirnov test. Student's paired *t*-test was applied to test the difference between the outcomes of resting 99mTc MIBI and dobutamine stress echo. Sensitivity, specificity, PPV, and NPV values of the two modalities were calculated. The statistical software SPSS 20.0 version was used in the analysis of the data.

Results

Baseline myocardial contractile function of the patients

In our study, 50 patients of known coronary artery disease with severely compromised LVEF were enrolled. Forty-four patients were male and six were female [Table 1]. The mean ± SD of BMI of the enrolled patients was 20.8 ± 2.81 Kg/m^2. The baseline mean and standard deviation of heart rate was 74.4 ± 8.7/min.

For analysis, a total of 800 myocardial segments from the 50 patients were evaluated (16-segment model). Regional contractile function, as assessed by resting two-dimensional echocardiography examination, demonstrated normal contraction in 250 (31.2%) segments and abnormal contraction in 550 (68.8%) segments. The normal 250 segments were

Table 1: Patient characteristics

Patient profile	Frequency (%)
Gender	
Male	44 (88)
Female	8 (12)
Age (years)	
≤50	2 (4)
51-60	17 (34)
61-70	26 (52)
>70	5 (10)
Comorbidities	
HTN	15 (30)
DM-2	12 (24)
CKD	2 (0.04)
Others	3 (0.06)
Nil	29 (58)

HTN: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease

excluded from our evaluation. Of the 550 dysfunctional segments, 409 (48.1% of total segment) were hypokinetic at rest, 139 (16.4% of total segments) were akinetic, and 2 (0.23% of total segments) were dyskinetic at rest.

On segmental analysis with 99mTc MIBI, 413 (75%) out of the 550 dysfunctional segments were viable and 137 (25%) of the total 550 dysfunctional segments were labeled nonviable. On low-dose DSE (5-10mcg/kg/min), 41 (82%) patients out of the total 50 patients showed improvement in contractile functions in the dysfunctional myocardium. On segmental analysis, 407 (74%) of the 550 dysfunctional segments were viable and 143 (26%) of the total 550 dysfunctional segments were labeled nonviable. Both of the two dyskinetic segments were nonviable on low-dose DSE [Table 2].

On 18F-FDG PET, 46 (92%) patients showed viable myocardium out of the total 50 patients with dysfunctional myocardium. On segmental analysis, viable dysfunctional segments with perfusion-metabolism mismatch were seen in 453 segments (82.4%) out of 550 segments. Ninety-seven segments (17.6%) out of 550 segments were nonviable.

Table 2: Results of the viability evaluation by the three modalities

	Number of segments, *n* (%)
99m-Tc MIBI	
Viable segments	413 (75)
Nonviable segments	137 (25)
Total dysfunctional segments	550 (100)
DSE	
Viable segments	407 (76)
Nonviable segments	143 (24)
Total dysfunctional segments	550 (100)
18F-FDG	
Viable segments	453 (82.4)
Nonviable segments	97 (17.6)
Total dysfunctional segments	550 (100)

DSE: Dobutamine stress echocardiography, 18F-FDG: 18F-fluorodeoxyglucose, 99m-Tc MIBI: 99m-Tc Methoxy-Iso-Butyl-Isonitrile

Comparative segmental analysis

After all the three-test data were obtained, comparison between rest 99mTc MIBI and DSE with 18F-FDG PET was performed as depicted in Table 3. The total number of dysfunctional segments considered viable on PET (453 of 550 segments) was highest among the three modalities. The difference was significant compared to the total number of segments which were viable with DSE (407 of 550 segments, $P = 0.001$) and total segments found viable according to the preset criteria on resting 99mTc MIBI (413 out of 550 segments, $P = 0.003$).

Alternatively, if we compare pairwise number of positive outcomes (viable segments) in the patient group ($n = 50$) by the different modalities with the use of paired *t*-test. The average number of positive outcomes differs significantly in case of rest MIBI with FDG PET ($P = 0.034$) and between DSE with FDG PET ($P = 0.023$). No significant difference was noted between DSE and MIBI results ($P = 0.875$).

Comparison of segments (segmental analysis) with viable and nonviable segments by resting 99mTc MIBI and 18F-fluorodeoxyglucose positron emission tomography

Overall correspondence between the segmental grading of resting 99mTc MIBI and 18F-FDG PET was 88.7% (488 of 550 segments), 398 segments identified as viable and 90 segments identified as nonviable by both modalities as shown in Table 4. This yielded a positive predictive value of 97.5% of resting 99mTc MIBI. A segmental discordance by PET and resting MIBI viability criteria was found in 72 segments (13.0%) of all 550 segments. Sixty-two segments were viable by PET but nonviable on MIBI and 10 segments were nonviable on PET but were shown to be viable on MIBI. This yielded a negative predictive value of 59.2% of resting 99mTc MIBI. On considering 18F-FDG-PET as a gold standard for detection of viable myocardial segments, resting MIBI has shown a sensitivity of 86.5% and specificity of 90.0%. The overall accuracy of MIBI was 87.1% in our study.

Table 3: Comparative segmental analysis

	Mean	*n*	SD	Mean difference	*t*	*P*
Pair 1						
MIBI viable segments	8.16	50	5.38	0.040	0.158	0.875
Stress eco-viable segments	8.14	50	5.06			
Pair 2						
Stress eco-viable segments	8.14	50	5.06	0.920	2.34	0.023
FDG viable segments	9.06	50	5.60			
Pair 3						
MIBI viable segments	8.16	50	5.38	−0.800	2.186	0.034
FDG viable segments	9.06	50	5.60			

SD: Standard deviation, FDG: Fluorodeoxyglucose, MIBI: Methoxy-Iso-Butyl-Isonitrile

Table 4: Overall performance of the segmental analysis of the three modalities

	MIBI viable	MIBI nonviable	DSE viable	DSE nonviable
18F-FDG viable	398	62	397	56
18F-FDG nonviable	10	90	9	88
Sensitivity (%)	86.5		87.6	
Specificity (%)	90.0		90.7	
PPV (%)	97.5		97.8	
NPV (%)	59.2		61.1	
Accuracy (%)	87.1		88.2	

DSE: Dobutamine stress echocardiography, PPV: Positive predictive value, NPV: Negative predictive value, 18F-FDG: 18F-fluorodeoxyglucose, MIBI: Methoxy-Iso-Butyl-Isonitrile

Comparison of segments (segmental analysis) with viable and nonviable segments by dobutamine stress echocardiography and 18-fluorodeoxyglucose Positron emission tomography

As depicted in Table 4 Overall correspondence between the segmental grading of DSE and positron emission tomography was 88.1% (485 of 550 segments), 397 segments identified as viable and 88 segments identified as nonviable by both modalities. This yielded a positive predictive value of 97.8% of DSE. A segmental discordance by PET and DSE viability criteria was found in 65 segments (11.9%) of all 550 segments. Fifty-six segments were viable by positron emission tomography but nonviable on DSE and 9 segments were nonviable on positron emission tomography but were shown to be viable on DSE. This yielded a negative predictive value of 61.1% of DSE. On considering 18F-FDG-PET a gold standard for detection of viable myocardial segments, DSE has shown a sensitivity of 87.6% and specificity of 90.7%. The overall accuracy of DSE was 88.2% in our study.

Discussion

The Current American College of Cardiology (ACC)-published guidelines on heart failure (ACC-focused update 2009 of 2005 guidelines) assign a IIa recommendation to viability assessment in patients with heart failure, known CAD, and the absence of angina. Additionally, they suggest that further studies are needed to determine the usefulness of routine myocardial viability assessment in patients with ischemic-LV dysfunction in the absence of angina. However, the Canadian Cardiovascular Society (CCS guidelines 2006) states as a class I indication that patients with large areas of viability should be evaluated for revascularization.[8,9] The joint appropriateness criteria published by the ACCF/ASNC/ACR/ASE/SCCT/SCMR/SNM in 2009 assign an appropriate use score of 9 (highest indication) for assessment of myocardial viability in ischemic cardiomyopathy patients with reduced LV function.[10]

18FDG PET-CT is currently the best available modality for prospectively identifying such viability before revascularization.[11-13] However, positron emission tomographic facilities are not widely available for general use because of their high operating costs. In addition, using FDG PET in diabetic and glucose-intolerant patients may present some difficulties. Strong experimental arguments indicate that sestamibi can be an accurate marker of viability as it has been shown that sarcolemmal integrity and maintenance of a negative mitochondrial charge gradient are necessary for its intracellular accumulation and retention.[14]

On analysis of patients with viable myocardium in our study, there were more patients with viable dysfunctional myocardium identified on PET (46 of 50 patients) than patients on 99mTc MIBI scan (43 of 50, $P = 0.337$) and those with dysfunctional myocardium that demonstrated contractile reserve on DSE (41 of 50, $P = 0.123$); however, this number was not statistically significant. Thus, our study showed comparable results of resting MIBI with positron emission tomography and stress echocardiography in detection of patients with viable myocardium.

Similar findings were observed by Maes *et al*. Althoefer *et al*. and showing good correlation of MIBI uptake in areas with PET-assessed myocardial viability.[3,15] The positive response to dobutamine was significantly lower than those with technetium uptake in the study by Sadeghian *et al*.[16] These differences can be attributed to criteria for evaluation of viability and the subjective nature of the evaluation.

Alternatively, on comparing pairwise number of positive outcomes (viable segments) in each patient by the different modalities with the use of paired *t*-test, the average number of positive outcome differs significantly in case of rest MIBI with FDG PET ($P = 0.034$ and between DSE and FDG PET ($P = 0.023$). The difference was not significant between DSE and rest MIBI ($P = 0.875$). The likely explanation for this is that since 99mTc MIBI uptake depends both on perfusion and passive diffusion through an intact or viable mitochondrial membrane, hence in segments with severely compromised blood flow, viability is underestimated in areas with reduced perfusion at rest. In such cases, oral administration of sublingual nitrates may help in improving the resting MIBI uptake by dilating the stenotic coronaries and can lead to improved sensitivities.

Sciagra *et al*.[17] studied 35 patients with baseline and nitrate augmented MIBI scan and concluded that nitrate activity in the viable territories was significantly higher than that of baseline Tc-99m MIBI. However, this intervention was not used in our study.

Overall correspondence between the segmental grading of resting 99mTc MIBI and positron emission tomography was 88.7%. The positive predictive value was 97.5% and negative predictive value was 59.2%.

The performance of MIBI was better than the results observed by Mayes *et al*.[18] in a similar study. The positive predictive value of resting 99mTc MIBI was found to be 82% and the negative predictive value at 78% using similar criteria for viability assessment. The difference in values in our studies may be attributed to better equipment, software, and the different prognostic markers suggesting viability in these studies.

If we consider 18F-FDG-PET as a gold standard for detection of viability, our results have shown a sensitivity of 86% and specificity of 90% for resting MIBI. Corresponding values for stress echocardiography has a sensitivity of 87.6% and specificity of 90.4% respectively. These findings are comparable to other studies of similar nature.[18]

Hence, our study has suggested rest 99mTc MIBI as a good option for evaluation of viable myocardial segments in patients with dysfunctional myocardium. A high positive predictive value (PPV) of 97.5% of MIBI in detecting viable myocardium suggests it as an effective alternative to DSE (PPV of 97.8% in our study) in detection of viable myocardial segments in patients with dysfunctional myocardium, especially in obese or elderly patients with lung disease who have poor echocardiographic imaging due to lack of an optimal acoustic window. Thus, MIBI can be a suitable replacement for these patients undergoing viability studies. Furthermore, there is a high degree of inter-observer variability during the interpretation of stress echocardiography as compared to evaluation of a MIBI scan. Furthermore, in diabetic patients with uncontrolled sugar levels, FDG PET can be unreliable and is difficult to perform without an adequate control. In this patient group, resting MIBI is a suitable alternative to 18F-FDG PET.

One limitation of the study was that nitrate augmentation was not carried out in our patients. Alternatively, a CMR was also not included in our study. Both the above intervention can help in decreasing the overestimation of myocardial scar by MPI. Another limitation of the study is the fact that the recovery of myocardial function is the absolute standard for viability which entails following up the patients with echocardiography after 3–6 months which was not done in this study.

Conclusion

1. Our study showed comparable results of resting 99mTc MIBI with DSE in detection of patients with viable myocardium. However, 18F-FDG PET has detected more number of viable segments than both studies (resting MIBI and DSE)
2. In patients with moderate-to-severe ischemic LV dysfunction, resting MIBI is a useful and safe tool for detection of viable myocardium where facility for DSE is not available or where contraindications to the test exist, e.g., in very obese patients or those with very high blood pressure not controlled on antihypertensives or patients with lung disease
3. However, resting MIBI overestimates scar tissue and thus the negative results of viability on resting MIBI can be performed with nitrate augmentation or further evaluated by 18F-FDG PET for confirmation of viability.

Recommendations

1. Resting MIBI can be used as an excellent noninvasive modality for preoperative myocardial viability detection in patients with severe LV dysfunction undergoing revascularization. Further, there is a considerable increase in risk of stroke and death in patients with severe LV dysfunction undergoing revascularization (postcoronary artery bypass surgery outcome in 30 days: stroke ~3%, death ~5%).[19-22] Hence, MIBI's role in viability detection as an important selection criterion is emphasized
2. Since the study sample was small (50 patients), thus the results can't be extrapolated to the general population on a whole, hence it is recommended that a larger population can be studied using both these modalities to see if the results are similar
3. In our study, we could not carry out long-term follow-up of the patients with postoperative LVEF or cardiac event/survival data which is the most important marker for viability. Hence, future studies can be made more robust by including the same.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix B

Patient Proforma

Date:

Name	Age/Sex
Occupation	Mob No
Address	

Diagnosis:

Co-morbidities:

ECG:

Baseline 2D Echocardiography:

LVEF

LVIDs/d

RWMA: No of segment

Segment

Grade

Valves

Pericardial effusion/Clot/ PAH

Coronary Angiography:

1. Left Main Coronary
2. LAD
3. LCX
4. RCA

Dobutamine stress echo:

	Baseline	At 2.5 mcg/ kg/min	At 5.0 mcg/ kg/min	At 7.5 mcg/ kg/min	At peak dose
Heart rate					
Blood pressure					
RWMA					
At basal level					
Anterior					
Lateral					
Posterior					
Inferior					
Septal					
Ant-septal					
At middle level					
Anterior					
Lateral					
Posterior					
Inferior					
Septal					
Ant-septal					
At apical level					
Ant apex					
Ant lateral					
Inf apex					
Ant medial					
LVEF					
Mitral regurgitation					
Any symptom					
ECG changes					

***99mTc-MIBI myocardial perfusion SPECT* findings**

	Uptake abnormality
At basal level	
Anterior	
Lateral	
Posterior	
Inferior	
Septal	
Ant-septal	
At middle level	
Anterior	
Lateral	
Posterior	
Inferior	
Septal	
Ant-septal	
At apical level	
Ant apex	
Ant lateral	
Inf apex	
Ant medial	