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Role of PET-CT in the assessment of myocardial viability in patients with left ventricular dysfunction

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ABSTRACT

Aim: Role of PET-CT in assessment of myocardial viability in patients with LV dysfunction.
Methods: This prospective study included 120 patients with LV dysfunction who underwent 99mTechnetium-Sestamibi myocardial perfusion SPECT-CT and 18FFDG cardiac PET-CT. They also underwent serial echocardiography and coronary angiography along with myocardial perfusion and FDG PET study.
Results: Thirty-three patients had single vessel disease, 48 had triple vessel disease, and rest had double vessel disease. Among 786 segments, matched defects were seen in 432 (55%) and mismatched defects in 354 (45%) segments. 78 patients were surgically managed, and 42 were medically managed. The change in LVEF after surgical management was statistically significant compared to medical management.
Conclusion: Viability assessment should be performed in patients who present after 12 h of acute myocardial infarction or with LV dysfunction due to ischemic heart disease to decide upon appropriate surgical management.

1. Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in India and worldwide. In India, CAD occurs 5–10 years earlier than in western countries affecting the working population mainly between 35 and 65 years of age.[1] Various factors such as sedentary lifestyle, dietary indiscipline, and increase in prevalence of diabetes mellitus (DM) have worsened the situation. Majority of the patients, who present with features of left ventricular (LV) dysfunction have ischemic CAD.[2] Though our knowledge about the pathophysiology of CAD has tremendously improved in past years, still the prognosis remains grave with annual mortality around 10–15%.[3] Since the time Braunwald[4] described the myocardial ischemic process after brief coronary occlusion as "hit, run and stun" and Rahimtoola[5] described hibernating myocardium, the viability assessment plays an important role

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in the management of CAD patients. In patients who have viable myocardium, timely coronary reperfusion limits the progression of myocardial damage and loss of regional contraction, thereby decreasing morbidity and mortality.

In the present study, F-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography-Computed Tomography scan (PET-CT) which is one of the commonly used investigation for accurate assessment of viable myocardium was used. There are conflicting results regarding viability assessment for determining whether a particular patient would benefit from coronary revascularization process or not. The aim of the present study is to find out whether treatment planning based on viability assessment really benefitted the patients.

2. Materials and methods

The present prospective study was performed at a tertiary referral hospital in Chennai from Jan 2011 to Dec 2013. All patients were referred by the cardiologists for viability assessment. Informed consent was obtained from all the patients, and ethics committee approval was obtained. Adult patients, who presented with features of LV dysfunction with symptoms of shortness of breath, proven myocardial infarction (MI) but presenting 12 h after onset of symptoms and those with prior history of MI presenting with new onset of symptoms related to myocardial ischemia were included in the study. Patients of MI presenting within 12 h after onset of symptoms and those with left main CAD by coronary angiography were excluded from the study.

A total of 120 patients were included in this prospective study for analysis; of which, 107 were males and 13 were female, and their average age was 56.8 ± 10.9 years. DM was present in 71 patients, while hypertension (HTN) in 64 and 40 patients had both DM and HTN. Twenty-five patients did not have either of it. ST segment elevation MI (STEMI) was present in 107 patients, which was proven by either electrocardiography (ECG), biochemical parameters or by echocardiography. Rest 13 patients had evidence of non-STEMI. All patients underwent echocardiography at the time of presentation and at 3 months follow-up after PET study. The demographic parameters are shown in Table 1.

All the patients underwent Technetium-99m Sestamibi (Tc-99 m MIBI) myocardial SPECT-CT study and F-18 FDG PET-CT study for myocardial viability apart from echocardiographic testing after informed consent. Matched defects in both the studies were considered as scarred tissue. Defects in Tc-99m MIBI SPECT-CT with mismatched 18F-FDG uptake were regarded as hibernating but viable myocardium.

2.1. 99mTc-MIBI myocardial SPECT-CT study

Patients presented for SPECT CT study within 2 h fasting and 10 millicurie (mCi) of 99mTc-MIBI was administered intravenously at rest after which patients were asked to have fatty meal. They were scanned on dual head Siemens Symbia T6 SPECT-CT gamma camera using IQ.SPECT technology after 45–60 min of injection. The images were acquired in 17 projections per detector in 208° acquisition arc with 59° as starting angle using smartzoom collimators and cardio-centric orbit

Table 1 – Patients characteristics (age-wise distribution).

Age (years)	<50	51–65	>66
Age (n = 120)	33	60	27
Sex			
Male (n = 107)	29	54	2
Female (n = 13)	4	7	2
Diabetes mellitus (n = 71)			
Male	17	36	13
Female	3	1	1
Hypertension (n = 64)			
Male	12	33	11
Female	2	4	2
Both DM and HTN (n = 40)			
Male	8	24	5
Female	2	0	1
History of MI (n = 107)			
Male	30	44	21
Female	4	6	2

with 14 s per projection (total 4 min) coupled with ECG gating. Smartzoom collimators are special type of collimators that center on the heart, collecting up to 4 times more counts than parallel hole collimators. Reconstruction was done using IQ. SPECT reconstruction algorithm. Quantitative processing was done on Emory cardiac toolbox.

2.2. 18F-FDG cardiac PET-CT study

The following day after 6 h of fasting, these patients underwent F-18 FDG cardiac PET-CT study. Depending on blood glucose level, glucose load or intravenous insulin as per sliding scale was administered according to standard protocol.[6] They were injected with 5–8 mCi of F-18 FDG when the blood glucose level was <140 mg/ml. Patients, whose blood glucose level was more than >140 mg/ml, were rescheduled for subsequent days after control of blood glucose. Patients were imaged on Philips Gemini TF64 PET-CT scanner with ECG gating using standard cardiac protocol after 1 h. The images were reconstructed using RAMLA reconstruction technique. A cutoff level for FDG uptake of 50% or greater was considered as positive for viability as shown by Slart et al.[7]

2.3. Image analysis

Both SPECT and PET images were loaded on a single Extended Brilliance Workstation (EBW) platform and analyzed in the Emory cardiac toolbox by making side-to-side comparison. Generally '17-segment' model is used for analysis of cardiac segments in PET and SPECT images. However for simplicity, we had used 5-segment cardiac model. Accordingly the LV myocardium was divided into apex, septum, anterior, inferior, and lateral walls in both the studies. The defect and its extent were analyzed. Defects in both the studies (matched) were considered as scars. Defects at Tc-99 m MIBI SPECT, but with 18F-FDG uptake (mismatched), were regarded as hibernating but viable myocardium. D'Egadio et al.[8] showed that when myocardial viability is more than 7% of LV myocardium, then patient benefitted with revascularization. A similar criterion was followed in our study. All patients having myocardial viability more than 7% underwent revascularization, while

those having less than 7% viability or nonviable myocardium underwent medical management.

2.4. Echocardiography

Patients underwent echocardiography at the time of PET scans and 3 months after starting treatment during follow-up, whether medical or surgical. Echocardiographic images were obtained in the standard parasternal long, short axes and apical 4- and 2-chamber views utilizing digital Vivid 7 ultrasound equipment with a combined tissue imaging 2.5–4.0 MHz transducer. At least three cardiac cycles were monitored at the LV base, midpapillary muscle level, and apex for wall motion assessment. Two-dimensional (2D) ventricular volumes and LV ejection fraction (LVEF) were measured from the 4- and 2-chamber views using the modified Simpson's formula.[9] Regional wall motion abnormality (RWMA) was recorded as normokinesia, hypokinesia, akinesia or dyskinesia. Patients were considered responding to treatment if there was either increase or no change in LVEF on follow-up echocardiograms as reported earlier.[10,11]

2.5. Coronary angiography

All patients had undergone invasive coronary angiography. Twenty-nine patients had angiography done elsewhere and were referred for viability study to our hospital. Rest 91 underwent coronary angiography either before or within one week of myocardial perfusion and FDG PET study. The stenosis in left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) were noted. The stenosis in their respective branches were categorized under main artery for analysis purpose.

2.6. Statistical analysis

Continuous variables were expressed as mean ± SD, and all categorical variables were expressed as percentages. A paired 't' test was used for intra group comparison and unpaired 't' test for comparison between two groups. Differences were considered significant at p value <0.05. Pearson's correlation was used to find the relationship between two variables to assess how strongly they were related to each other. Confidence intervals (C.I.) were calculated at 95% interval levels.

3. Results

On analysis of coronary artery stenosis distribution, 33 patients had single vessel disease (SVD) and 48 patients had triple vessel disease (TVD). Rest of the patients had double vessel disease (DVD). Most commonly involved artery and its branches in our study was LAD in 113 patients (94%) followed by RCA in 71 patients (59%) while LCx was involved in 72 patients (60%).

A total of 786 segments of LV myocardium showed reduced perfusion on 99mTc-MIBI study, most commonly in apex (224), followed by septum (207), anterior (179), inferior (94) and lateral walls (82). Matched perfusion defects were seen in 432 segments (55%) and mismatched perfusion defects were noted in 354 (45%) segments (Table 2). Patients having DM, HTN or both showed

Table 2 – Region wise distribution of matched and mismatched segments.

Walls	Study		
	99mTc MIBI Study	F-18FDG PET Study	
		Mismatched	Matched
Apex	224	99	125
Anterior	179	74	105
Septum	207	108	99
Lateral	82	39	43
Inferior	94	34	60
Total	786	354	432

more number of matched segments (scarred myocardium) than mismatched segments (viable myocardium); however, this difference was statistically significant in hypertensive patients ($p = 0.0005$) and also in patients having both co-morbidities ($p = 0.0043$) but not in those with diabetes alone ($p = 0.0685$). Patients who did not have any co-morbidities showed more number of mismatched segments than matched segments, however this observation was not statistically significant ($p = 0.2590$) (Table 3).

Echocardiographically, there were 376 hypokinetic, 343 akinetic and 5 dyskinetic segments. In some segments the echocardiography showed RWMA but the perfusion was normal and vice versa was also observed. In 33 patients PET and SPECT study showed myocardial changes in 62 wall segments whereas echocardiography showed no RWMA. Of these, 19 patients showed mismatched defects in 29 wall segments and 14 patients showed matched defects in 33 wall segments. Similarly in 50 patients, echocardiography showed RWMA in 67 wall segments with normal perfusion and the details are as shown in Table 4.

These patients underwent either revascularization or medical management depending on the findings on viability assessment as described previously. Revascularization included either stenting or coronary artery bypass graft (CABG) surgery. Seventy-eight patients with myocardial viability of more than 7% underwent revascularization and 42 patients were managed medically as they showed either less than 7% myocardial viability or non-viable segments.

There was either increase or no change in LVEF in 106 patients (88%) after treatment; of which 73 patients managed

Table 3 – Segmental involvement and comorbidities.

	Matched segments	Mismatched segments	p value
Diabetes mellitus ($n = 71$)	262	210	0.0685
Hypertension ($n = 64$)	270	162	0.0005
Both ($n = 40$)	171	101	0.0043
None ($n = 25$)	70	84	0.2590

Table depicts distribution of matched and mismatched segments in patients with diabetes mellitus and hypertension, having both co-morbidities or having none of it. As depicted, patients with hypertension or having both co-morbidities, had statistically significantly more matched segments than mismatched segments.

Table 4 – Territory wise viability in various segments compared to echocardiographic observation.

Territory	Mismatched defects hibernating myocardium	Matched defects scarred myocardium	p-Value
LAD			
Dyskinetic	0	3	0.128
Akinetic	132	165	0.505
Hypokinetic	135	142	0.617
LCx			
Dyskinetic	0	0	N.A.
Akinetic	8	4	0.177
Hypokinetic	29	23	0.111
RCA			
Dyskinetic	0	2	N.A.
Akinetic	13	21	0.79
Hypokinetic	18	29	0.525

surgically, while 33 were managed medically. In 106 patients, 32 patients had both diabetes and HTN, while 25 patients did not have either of it and rest had either diabetes or HTN alone. Fourteen patients (12%) showed reduction in LVEF, and all them had either diabetes or HTN or both. The decrease in EF was not dependant on the number of blood vessels involved as assessed by coronary angiograms. Of the fourteen patients (5 managed surgically and 9 managed medically) who showed reduction in LVEF, six had SVD, four had DVD and four had TVD.

When comparing surgically managed patients (78 patients) with medically managed patients (42 patients), the change in LVEF after management was 3.46 ± 4.5 (C.I. = 2.46–4.46) in surgical group and 0.71 ± 5.0 (C.I. = −0.79 to 2.21) in medical group. The increase in LVEF was statistically significant for surgically managed patients ($p = 0.002$). Only 5 (6.4%) patients managed surgically showed fall in LVEF while 9 patients (21.4%) patients managed medically showed fall in LVEF. There was a weak negative correlation between changes in LVEF and patients having number of matched segments; however, this difference was not statistically significant ($r = -0.268$; $p = 0.08$). Similarly, there was positive correlation between difference in LVEF and patients having number of mismatched segments, which was also not statistically significant ($r = 0.333$; $p = 0.39$). The change in LVEF after treatment in patients, who did not have DM or HTN ($n = 25$) was 5.0 ± 4.78, which was statistically significant, when compared to patients with DM alone (1.7 ± 4.92), HTN alone (1.5 ± 4.68) or having both (1.0 ± 4.83). None of the patients without DM or HTN showed fall in LVEF

(Table 5). Figs. 1 and 2 represent 2 of our patients. Fig. 1 is an example of a 60-year-old male with severe LV dysfunction, LAD territory was found viable on PET-CT scan. After LAD stenting LVEF improved by 10% during 3 months follow-up. Fig. 2 is an example of two-vessel disease. PET assessment revealed viability only in LAD territory. Hence CABG was deferred and only LAD stenting was done. No reduction in LVEF was noted at 3 months follow-up.

4. Discussion

Viability assessment has become an important investigation in the management of patients with LV dysfunction, who present late after MI. This can be done by many imaging techniques such as ^{18}F-FDG PET-CT, Cardiac MRI, SPECT-CT imaging, and dobutamine stress echocardiography.[12–16] In general, nuclear imaging techniques have a high sensitivity for the detection of viability, whereas techniques evaluating contractile reserve have somewhat lower sensitivity and a higher specificity.[16] Many potential end points have been described to measure outcomes after revascularization in viability studies including improvement in regional LV function, global LV function, improvement of symptoms, improvement in exercise capacity and long term prognosis.[17] We used global LVEF for follow-up of our patients. Studies have shown that in patients with ischemic cardiomyopathy with viable myocardium, LVEF does not always improve after revascularization,[10,11] hence even no change in EF was considered favorable outcome in our study.

DM and HTN are important independent risk factors in the development of ischemic CAD. In our study, 79% ($n = 95$) had either DM or HTN or both and 21% ($n = 25$) did not have either of it. Peterson et al.[18] showed that when CAD occurs in diabetics, it is associated with worse outcomes than in non-diabetics. Similarly Treasure et al.[19] showed that in long standing HTN, the hypertrophied heart muscle results in impaired vasodilator stimuli and inadequate angiogenesis leading to reduced number of collaterals, hence more number of scarred segments. Our study showed similar results, that in patients having DM or HTN or both, showed less increase in LVEF as compared to patients who did not have either of it. Patients with HTN had statistically more number of scarred segments than viable segments.

Patients of CAD and LV dysfunction showing mismatch segments on PET study showed poor annual survival with medical therapy but revascularization in these patients was associated with improvement in LVEF.[20,21] In our study, all

Table 5 – Change in LVEF in different groups.

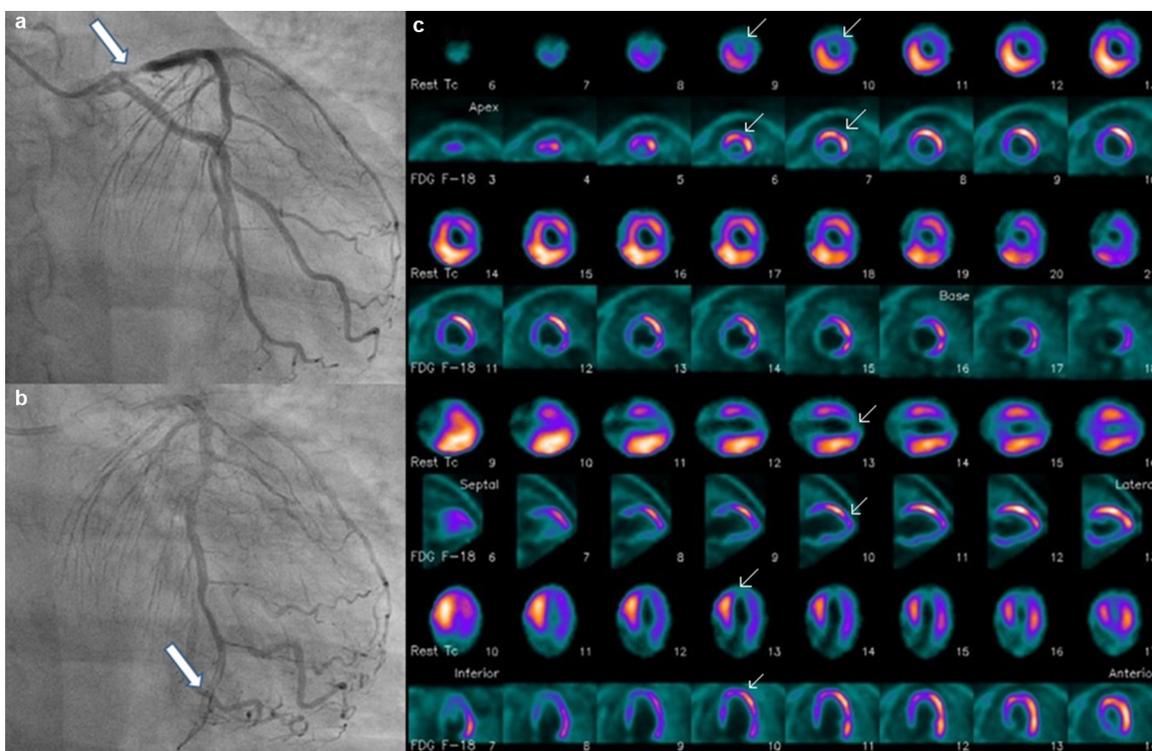|	Mean LVEF (p value compared to none group)	Change in LVEF		
		Decrease	Increase	No change
Diabetes mellitus ($n = 71$)	1.7 ± 4.92 (0.004)	12 (16.9%)	26 (36.6%)	33 (46.5%)
Hypertension ($n = 64$)	1.5 ± 4.68 (0.002)	11 (17.1%)	20 (31.3%)	33 (51.6%)
Both ($n = 40$)	1.0 ± 4.83 (0.001)	8 (20.2%)	11 (27.5%)	21 (52.5%)
None ($n = 25$)	5.0 ± 4.78	0 (0%)	15 (60%)	10 (40%)

Fig. 1 – A 60-year hypertensive male, LVEF 35%. (a) Coronary angiography shows 80% stenosis in proximal LAD. (b) Thrombus in the distal segment of LAD. (c) Viability assessment showed >95% viability in LAD territory (White arrows). The patient underwent LAD stenting. His LVEF increased by 10% at 3 months follow-up.
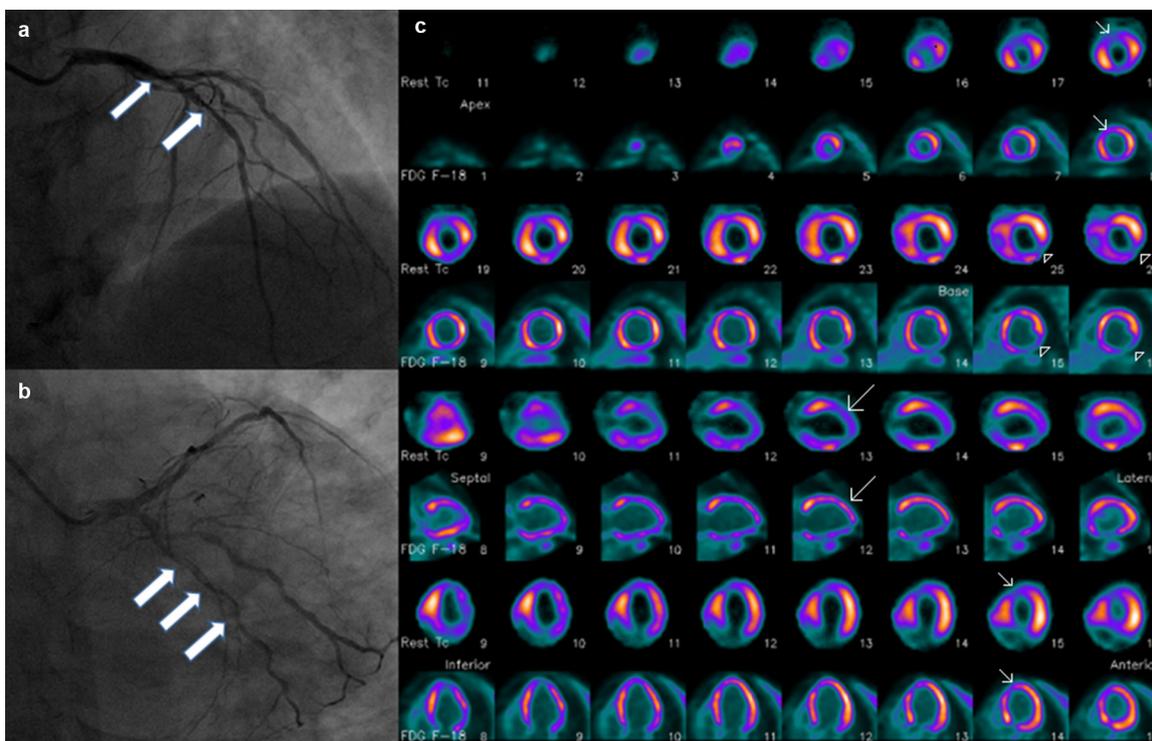

Fig. 2 – A 57-year diabetic and hypertensive male. (a) Coronary angiography shows 80% stenosis in proximal LAD before bifurcation and 80% stenosis after bifurcation. (b) A long diseased segment in the LCX. (c) Viability assessment showed viable myocardium in LAD territory (White arrows) while distal LCX showed scarred tissue (White arrowhead). Rest of the LCX territory showed normal perfusion with no mismatch viability. Hence CABG was deferred and patient underwent LAD stenting alone and no reduction in LVEF was noted at 3 months follow-up.

patients who had myocardial viability on PET underwent surgical management and of these only 6.4% of patients showed fall in LVEF as compared to 21.8% of patients who were managed medically.

The STICH trial[22] showed that patients with viable myocardium had lower overall rates of death than those without viable myocardium ($p = 0.003$), however after adjustment for other baseline prognostic variables in a multivariate model, the pre-specified viability status was not statistically significant ($p = 0.21$), thereby concluding that as regards mortality, viability assessment did not have survival advantage in patients undergoing CABG surgery compared to medical therapy. However, this study had many drawbacks such as using SPECT alone for viability assessment, asymptomatic subjects accounted for 40% of patients enrolled and only 49% of patients underwent careful functional evaluation pre-randomization. Our study differs from STICH trial in methodology, use of ^{18}F-FDG PET-CT in viability assessment and use of LVEF as end point assessment. In our study, we did not take symptoms or survival as endpoints, and this explains why our study found viability assessment useful in deciding management in 40% of our patients.

Haas et al.[23] showed that not performing a viability study before surgical management, resulted in too many high-risk patients without viability being subjected to surgery resulting in worse outcomes. To some extent we avoided this situation as only those patients who showed myocardial viability underwent revascularization and our result showed that 93.6% showed no decrease in post-revascularization LVEF. Similarly Dreyfus et al.[24] reported that viability assessment should be part of selection process in patients with low LVEF for surgical revascularization. We are in agreement with their views that proper selection of patients based on viability assessment helps in reducing peri-operative and post-operative mortality and also improves outcomes.

5.   Conclusion

Our study has shown that evidence based viability study can be used to individualize the management. It helped in deciding , whether patient should receive surgical or medical treatment based on viability assessment. This also helped in preventing unnecessary economic loss to the patient apart from reducing morbidity. In our opinion the viability study should be performed in all patients who present 12 h after acute MI and also in those who present with LV dysfunction due to ischemic heart disease.

Conflicts of interest

The authors have none to declare.

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