Original Article

Evaluating cardiac hypoxia in hibernating myocardium: Comparison of ^{99m}Tc-MIBI/^{18}F-fluorodeoxyglucose and ^{18}F-fluoromisonidazole positron emission tomography-computed tomography in relation to normal, hibernating, and infarct myocardium

ABSTRACT

The aim of this prospective study was to explore the feasibility of ^{18}F-fluoromisonidazole (^{18}F-FMISO) cardiac positron emission tomography/computed tomography (PET/CT) in the detection of cardiac hypoxia in patients of ischemic heart disease (IHD) and to compare the uptake pattern with that of ^{99m}Tc-MIBI and ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Twenty-six patients suffering from IHD were evaluated in this study. The patients initially underwent ^{99m}Tc-MIBI rest/stress myocardial perfusion imaging and ^{18}F-FDG cardiac PET/CT as a part of their routine cardiac imaging. Patients with hibernating myocardium on these scans further underwent ^{18}F-FMISO Cardiac PET/CT. Controls were also considered in the form of patients with scarred and normal myocardium. On visual assessment, increased ^{18}F-FMISO uptake was noted in the hibernating myocardium compared to scarred or normal myocardium. On semiquantification analysis, there was overlap in the uptake values with a range of maximum standardized uptake value (SUV_{max}) in hibernating, scarred, and normal myocardium being 0.8–2.2 g/dl, 0.7–1.8 g/dl, and 0.7–1.6 g/dl, respectively. On individual patient-specific comparison in subjects harboring both hibernating and scarred myocardium, it was observed that SUV_{max} of ^{18}F-FMISO in hibernating myocardium was highest, followed by scarred myocardium and normal myocardium, respectively. The ratio of ^{18}F-FMISO SUV_{max} of hibernating to the normal myocardium in these subjects was always more than 1, and never less than the ratio of SUV_{max} of scarred to normal myocardium. Thus, in this mixed population study, it was observed that on an individual patient basis, hypoxic myocardium consistently showed higher ^{18}F-FMISO uptake than surrounding scarred and normal myocardium. The ratio of ^{18}F-FMISO SUV_{max} of hibernating to normal myocardium was higher than the ratio of scarred to the normal myocardium in all patients. On overall basis, however, there was considerable overlap in the SUV values among hibernating, scarred, and normal myocardium resulting in difficulty in differentiation of these entities with FMISO cardiac PET.^{18}F-FDG cardiac PET/CT remains the standard and superior method to determine hibernating myocardium in patients of IHD due to its superior contrast. The limitation of FMISO is poor signal to noise ratio because of high background uptake from the blood pool. Cardiac PET/CT with superior hypoxia tracers needs to be further examined for imaging cardiac hypoxia.

Keywords: ^{18}F-FMISO, cardiac hypoxia, hibernating myocardium, normal myocardium, scarred myocardium

INTRODUCTION

Hypoxia is defined as the disparity between supply and demand for blood flow/oxygen, that has a pathophysiological consequence.[1] Cardiac hypoxia, i.e., ischemic heart disease (IHD) is a cause of significant morbidity and mortality in the developed as well as the developing countries.

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The majority of the current cardiac imaging techniques used clinically targets to measure blood flow/perfusion, wall motion, or cellular energy metabolism at rest and stress. Hypoxia-specific molecular imaging is of interest as a useful additional technique for identifying and characterizing acute and relatively severe hypoxia.[1,2]

^{18}F-fluoromisonidazole (^{18}F-FMISO) has been used for investigating hypoxia with positron emission tomography (PET). It is an azomycin-based hypoxic-cell tracer that has a nearly ideal partition coefficient and when reduced by hypoxia, binds covalently to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration. In the presence of molecular oxygen, it is rapidly re-oxidized back to its uncharged form, which is then able to diffuse back out of the cell.[3]

While ^{18}F-FMISO has been extensively studied in imaging and treatment of tumor hypoxia, its potential for assessing cardiac hypoxia has not been investigated widely. The current gold standard of assessing myocardial viability is by imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) cardiac PET/computed tomography (PET/CT).[4] ^{18}F-FMISO cardiac imaging is a positive hypoxic imaging which can provide an assessment of the degree of myocardial hypoxia during stress imaging and/or hibernating myocardium, and is less dependent on factors such as perfusion or cardiac wall motion. It could be therefore a valuable tool for the cardiologist to make decisions regarding the benefit of intervention for the revival of hibernating but viable myocardium.

MATERIALS AND METHODS

The prospective study was approved by the Medical Ethics Committee of the Institute. In the present study, referred patients of IHD first underwent the conventional stress-rest myocardial perfusion imaging (MPI). Subsequently, ^{18}F-FDG cardiac PET/CT for assessing myocardial viability. A comparative ^{18}F-FMISO Cardiac PET/CT was undertaken within 1 week of characterization of the myocardium through aforementioned studies.

The following two groups of patients were the primary target population and eligible for inclusion in the study (a) those who showed viable myocardium on rest MPI/FDG-PET study and (b) those who showed reversible ischemia in the stress/rest MPI. The exclusion criteria were pregnancy/lactation and patients with known tumors.

The scan analysis and classification of the patients were undertaken based on the type of myocardium were as follows: (i) Patients with scarred and normal myocardium: These patients formed the first control group of analysis, with evaluation of rest MPI, ^{18}F-FDG cardiac PET/CT, ^{18}F-FMISO cardiac PET/CT. (ii) Patients with normal myocardium only: These patients were the second control group. They underwent Rest MPI, ^{18}F-FDG Cardiac PET/CT, ^{18}F-FMISO Cardiac PET/CT. (iii) Patients with hibernating and normal myocardium: These patients underwent Rest MPI, ^{18}F-FDG Cardiac PET/CT, ^{18}F-FMISO Cardiac PET/CT. (iv) Patients with Hibernating, Scarred and Normal Myocardium: These patients underwent rest MPI, ^{18}F-FDG Cardiac PET/CT, ^{18}F-FMISO Cardiac PET/CT.

Study protocols

^{99m}Tc-MIBI MPI and ^{18}F-FDG cardiac PET-CT scans were undertaken following standardized protocol.[4-6] For, ^{99m}Tc-MIBI MPI, patients were injected with 10–12 mCi of ^{99m}Tc-MIBI as per Rest/Stress MPI protocol. Cardiac single-photon emission CT imaging is done after 30–45 min to allow for background clearance. Dual headed gamma camera with detectors aligned at 76° to each other was used. Acquisitions were done with a low energy all-purpose collimator in a 64 matrix × 64 matrix, using 17 projections (40 s per projection) over 102° (starting from the right anterior oblique position). The patient was in supine position. Reconstruction was done by filtered back projection using a Butterworth filter. Vertical, horizontal, and short axes were reconstructed for analysis.

For those patients who underwent stress-rest MPI, the studies were undertaken on two different days.

For FDG-PET/CT, the patients were injected with approximately 5 mCi of ^{18}F-FDG. Glucose load was given to overnight fasting patients for ^{18}F-FDG PET 2 h before the injection. Imaging was carried out 2 h for ^{18}F-FDG injection. Time of flight PET scanner with an LYSO detector was used to detect annihilation photons in coincidence. The patient was in supine position. Data were reconstructed using iterative reconstruction. ^{18}F-FMISO Cardiac PET was undertaken with the following protocol: (a) patient was not required to be fasting for this procedure; (b) patients were injected with 3.7 MBq/kg (0.1 mCi/kg) intravenously of ^{18}F-FMISO with maximum 370 MBq (10 mCi); and (c) cardiac imaging was undertaken after 2–2.5 h to allow for background clearance and providing adequate target-to-background ratio.

Quantification analysis

The semi-quantitative analysis of the tracer uptake on the PET/CT studies were undertaken as follows: (a) Regions of interest was drawn around the hibernating, scarred and

normal myocardium of each patient separately in each of the scans done. (b) The maximum standardized uptake value (SUV_{max}) values of the above-mentioned regions were determined separately and were determined for each scan. (c) Ratio of SUV_{max} of hibernating to normal and scarred to normal myocardium was calculated for each patient. (d) The calculated ratios were compared in each individual patient and were compared.

RESULTS

Twenty-six patients of either sex were included in this prospective study. The patients were referred by various physicians for the evaluation of known or suspected IHD. Among these, the subgroups of patient population was as follows: (a) patients had both scarred and normal Myocardium ($n = 4$), (b) patients with only normal myocardium ($n = 5$), (c) patients had only hibernating myocardium ($n = 2$), and (d) patients had both hibernating and scarred myocardium in addition to normal myocardium ($n = 15$).

The uptake values in SUV_{max} following the ^{18}F-FMISO Cardiac PET/CT scans are tabulated in the Tables 1-4 with representative examples [Figures 1-4].

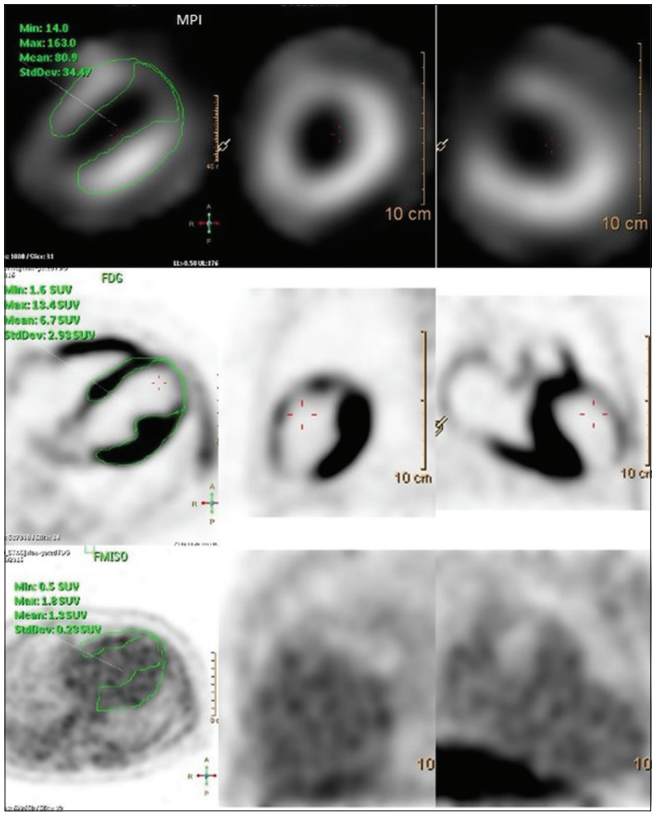

Figure 1: ^{99m}Tc-MIBI (uppermost row), ^{18}F-fluorodeoxyglucose (middle row) and fluoromisonidazole cardiac positron emission tomography (lowermost row) images in patients showing scarred and normal myocardium

DISCUSSION

The present study was an endeavor to determine if ^{18}F-FMISO cardiac PET could image cardiac hypoxia and could be clinically as efficient as ^{18}F-FDG Cardiac PET to study cardiac hypoxia. Rest MPI and ^{18}F-FDG Cardiac PET were done to determine the areas of scarred, hibernating and normal myocardium in the patients included in the study. ^{18}F-FMISO Cardiac PET was then undertaken in the same patients to determine its behavior pattern in different areas, with a focus on hibernating myocardium.

To the best of our knowledge, the above study was one of the first of the kind that attempted to study cardiac hypoxia in a single scan. It is a novel concept that utilizes the well-established tumor hypoxia agent ^{18}F-FMISO to study cardiac hypoxia. Previous animal studies have been done in

Table 1: Maximum standardized uptake values on ^{18}F-fluoromisonidazole cardiac positron emission tomography in the subgroup of patients with scarred and normal myocardium

Patient number	SUV_{max} in scarred myocardium (g/dl)	SUV_{max} in normal myocardium (g/dl)	Ratio of scarred/normal myocardium
1	1.8	1.8	1
2	1.2	1.1	1.09
3	1.4	1.4	1
4	1.8	1.8	1
Mean	1.466	1.433	

Observed range of SUV_{max} in scarred myocardium: 1.2–1.8 g/dl; range of SUV_{max} in normal myocardium: 1.1–1.8 g/dl. SUV_{max}: Maximum standardized uptake value

Table 2: Maximum standardized uptake values on ^{18}F-fluoromisonidazole cardiac positron emission tomography in the subgroup of patients with only normal myocardium

Patient number	SUV_{max} in normal myocardium (g/dl)
1	2.1
2	1.7
3	1.3
4	1.9
5	1.7
Mean	1.74

Range of SUV_{max} in normal myocardium: 1.3–2.1 g/dl. SUV_{max}: Maximum standardized uptake value

Table 3: Maximum standardized uptake values on ^{18}F-fluoromisonidazole cardiac positron emission tomography in the subgroup of patients with only hibernating myocardium

Patient number	SUV_{max} in hibernating myocardium (g/dl)	SUV_{max} in normal myocardium (g/dl)	Ratio of hibernating/normal myocardium
1	2.1	1.8	1.16
2	1.6	1.4	1.14
Mean			1.15

Range of SUV_{max} in hibernating myocardium: 1.6–2.1 g/dl; range of SUV_{max} in normal myocardium: 1.4–1.8 g/dl. SUV_{max}: Maximum standardized uptake value

Table 4: Maximum standardized uptake values on ^{18}F-fluoromisonidazole cardiac positron emission tomography in the subgroup of patients with hibernating, scarred, and normal myocardium

Patient number	SUV_{max} in hibernating myocardium (g/dl)	SUV_{max} in scarred myocardium (g/dl)	SUV_{max} in normal myocardium (g/dl)	Ratio of hibernating/normal myocardium	Ratio of scarred/normal myocardium
1	2.1	1.7	1.4	1.5	1.21
2	1.9	1.6	1.6	1.18	1.0
3	1.9	1.7	1.6	1.18	1.06
4	2.6	1.5	1.4	1.8	1.07
5	1.5	1.4	1.2	1.25	1.16
6	1.5	1.1	1.0	1.5	1.1
7	1.2	1.0	0.9	1.3	1.1
8	1.8	1.5	1.3	1.38	1.15
9	0.8	0.7	0.7	1.14	1.0
10	1.7	1.3	1.4	1.21	0.93
11	1.8	1.4	1.4	1.28	1.0
12	1.6	1.4	1.4	1.14	1.0
13	1.9	1.3	1.5	1.26	0.86
14	2.0	1.5	1.6	1.25	0.93
15	2.2	1.8	1.3	1.69	1.38
Mean				1.33	1.06

Observed range of SUV_{max} in hibernating myocardium: 0.8–2.2 g/dl; range of SUV_{max} in scarred myocardium: 0.7–1.8 g/dl; range of SUV_{max} in normal myocardium: 0.7–1.6 g/dl. SUV_{max}: Maximum standardized uptake value

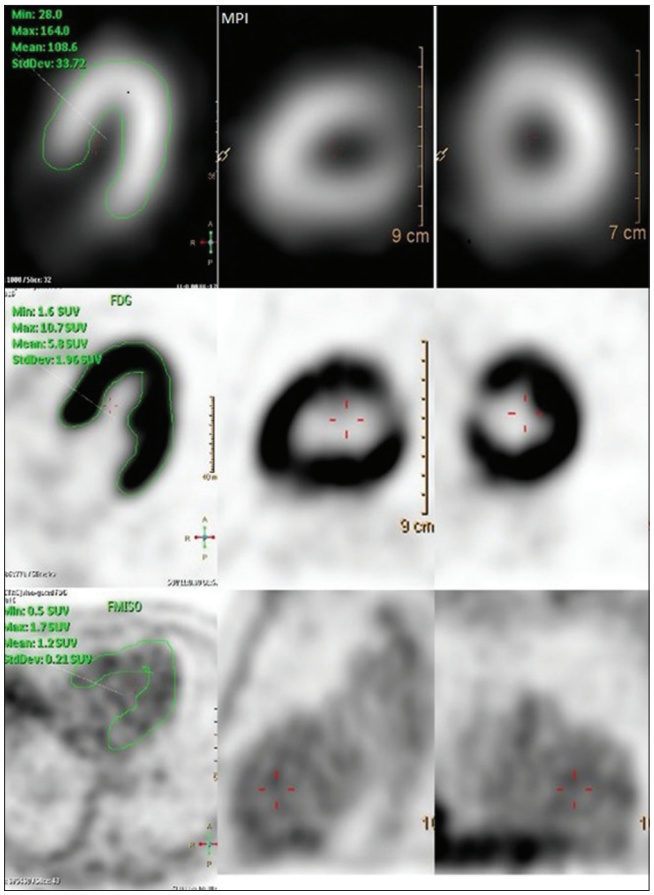

Figure 2: ^{99m}Tc-MIBI (uppermost row), ^{18}F-fluorodeoxyglucose (middle row) and fluoromisonidazole cardiac positron emission tomography (lowermost row) images in patients showing normal myocardium

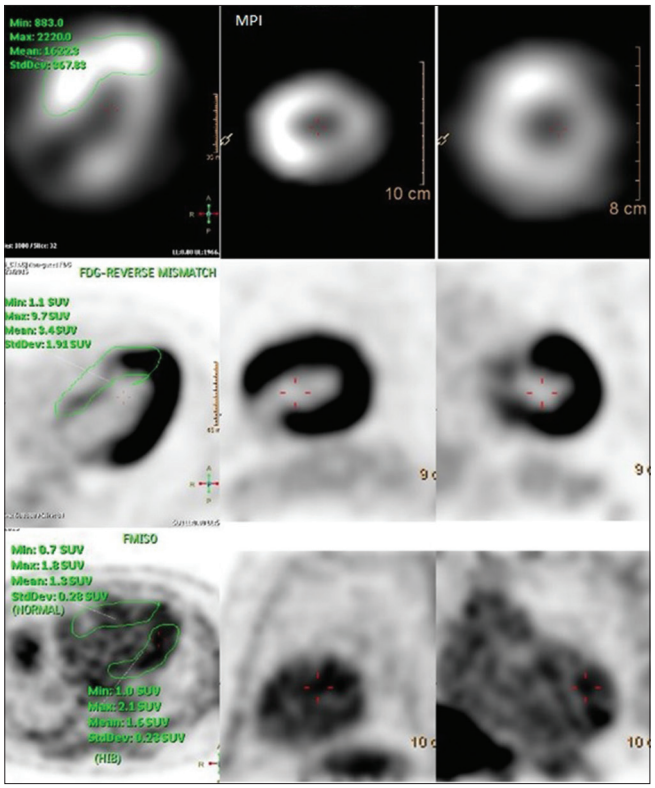

Figure 3: ^{99m}Tc-MIBI (uppermost row), ^{18}F-fluorodeoxyglucose (middle row) and fluoromisonidazole cardiac positron emission tomography (lowermost row) images in patients showing hibernating myocardium

controlled settings, but this was the first clinical study that compared ^{18}F-FMISO Cardiac PET to ^{18}F-FDG Cardiac PET. It is a mixed population study which included patients of either sex referred for evaluating the status of myocardium.

In the present study, we had four groups: (a) Group consisting of patients with scarred and normal myocardium: This group

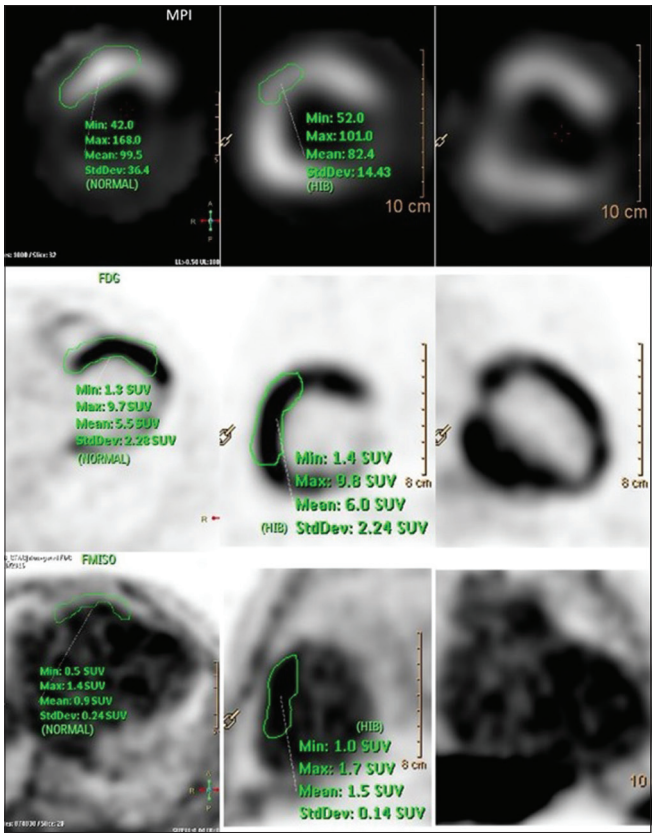

Figure 4: ^{99m}Tc-MIBI (uppermost row), ^{18}F-fluorodeoxyglucose (middle row) and fluoromisonidazole cardiac positron emission tomography (lowermost row) images in patients showing hibernating, scarred, and normal myocardium

consisted of four patients who had the presence of scarred and normal myocardium on ^{18}F-FDG Cardiac PET scans. They served as the first control group. There was no significant ^{18}F-FMISO uptake seen in both the scarred as well as normal myocardium. However, the uptake of ^{18}F-FMISO in the scarred myocardium was found to be greater than that in the normal myocardium on an individual patient comparison. The range of SUV_{max} in the scarred myocardium was 1.2–1.8 g/dl, while that of normal myocardium was 1.1–1.8 g/dl.

In the Group B consisting of patients with only normal myocardium, there was a total of 5 patients who had normally functioning myocardium. They functioned as the second control group. There was no significant uptake of ^{18}F-FMISO seen in the myocardium. The range of SUV_{max} in normal myocardium was 1.3–2.1 g/dl.

The Group C consisted of patients with both hibernating and normal myocardium; there were a total of two patients who had areas of hibernating myocardium amidst normal myocardium on ^{18}F-FDG Cardiac PET/CT scan. The normal myocardium did not show significant ^{18}F-FMISO uptake. There was increased ^{18}F-FMISO uptake seen in hibernating myocardium as compared to the normal myocardium. The range of SUV_{max} in hibernating myocardium was 1.6–2.1 g/dl while that of normal myocardium was 1.4–1.8 g/dl.

In the last group, i.e., Group D, consisting of patients with hibernating, scarred and normal myocardium as seen on ^{18}F-FDG cardiac PET/CT. The areas of hibernating myocardium had the maximum ^{18}F-FMISO uptake, followed by areas of scarred myocardium-normal myocardium had the least ^{18}F-FMISO uptake on an individual patient comparison though there was overlap in the uptake values. The range of SUV_{max} in hibernating myocardium was 0.8–2.2 g/dl that of scarred myocardium being 0.7–1.8 g/dl and the range in normal myocardium was between 0.7 g/dl and 1.6 g/dl.

The above values show that, in all groups, hibernating myocardium has the higher SUV_{max} values and range of ^{18}F-FMISO uptake, followed by that of scarred myocardium and normal myocardium. The ratio of ^{18}F-FMISO SUV_{max} of hibernating to normal myocardium, and scarred to normal myocardium was also estimated for each individual patient (as applicable). It was found that ratio of hibernating to normal myocardium was always more than 1, and was higher than the ratio of scarred to normal myocardium in all patients of all the groups.

In our study, the SUV_{max} was taken for the whole of the normal myocardium instead of just taking the value at the highest point (in both ^{18}F-FDG and ^{18}F-FMISO Cardiac PET/CT). This ensured that all the regions of normal myocardium were evaluated and duly used for calculation of the above-mentioned ratios.

On visual assessment, it was observed that areas of hibernating myocardium showed increased uptake of ^{18}F-FMISO as compared to the surrounding blood pool. This makes it a feasible tool for evaluation of tissue hypoxia visually. Based on the observations made during the study, it was found that ^{18}F-FMISO PET needs to be explored further to serve as a useful tool to detect cardiac hypoxia. However, currently, it has limited clinical utility in view of its slow clearance from the blood pool leading to poor target to background ratio.

However, we must mention that ^{18}F-FDG Cardiac PET/CT is still superior to ^{18}F-FMISO Cardiac PET/CT in the detection of hibernating myocardium, which is possible on visual assessment. It has a superior target-to-background ratio that has been consistent in detecting the extent and frequency of hibernating and scarred myocardium.

CONCLUSION

Thus, in this mixed population study, it was found that on an individual patient basis, hypoxic myocardium consistently showed higher ^{18}F-FMISO uptake than surrounding scarred and normal myocardium. The ratio of ^{18}F-FMISO SUV_{max} of hibernating to normal myocardium was higher than the ratio of scarred to normal myocardium in all patients. ^{18}F-FDG Cardiac PET/CT remains the superior method to determine hibernating myocardium in patients of IHD in view of its superior contrast. However, on overall basis, there was considerable overlap in the SUV values among hibernating, scarred and normal myocardium resulting in difficulty in differentiation of these entities with FMISO. The limitation of FMISO is poor signal to noise ratio because of high background uptake from the blood pool. Cardiac PET/CT with superior hypoxia tracers could become a useful procedure for imaging cardiac hypoxia. However, more studies need to be conducted to establish the same.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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