

Original Article

Assessing oral glucose and intravenous insulin loading protocol in ^{18}F -fluorodeoxyglucose positron emission tomography cardiac viability studies

ABSTRACT

Oral glucose and intravenous insulin (G/I) loading protocols are commonly used in ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) cardiac viability studies. Although the amount of insulin to be given per blood glucose range has been well described in guidelines, the amount of glucose to be given is not detailed well. In this retrospective study, we aimed to assess if certain parameters, particularly the amount of glucose and insulin given, may affect ^{18}F -FDG uptake in the hibernating myocardium and also determine the problems with this protocol. ^{18}F -FDG PET cardiac viability study with G/I loading protocols was performed in 49 patients. Fasting blood glucose (FBG), amount of glucose given, blood glucose level after glucose load, amount of insulin given, and blood glucose level at the time of ^{18}F -FDG injection were recorded. Statistical analysis was performed to determine if there is any difference in the above values in PET viable and PET nonviable groups and also in subgroups assessing ^{18}F -FDG uptake also in normal myocardium. For G/I loading, we used our local protocol in 43 patients, and other protocols in six. ^{18}F -FDG PET showed viability in 31 patients, and it was negative for viability in 18. In 22 patients, mainly in PET viable group, there was varying degree of reduced ^{18}F -FDG uptake in normal myocardium. There was no significant difference in FBG, amount of glucose given, blood glucose level after glucose load, amount of insulin given, and blood glucose level at the time of ^{18}F -FDG injection in PET viable and PET nonviable groups and also in subgroups. The problems with G/I loading protocol included deciding on the amounts of glucose and insulin given, maximum amount of insulin to be given, handling diabetics, optimal time to measure blood glucose after insulin administration, and interpretation of findings in cases with diffusely reduced ^{18}F -FDG uptake. Further improvements in current guidelines are necessary to obtain images in optimal conditions for accurate results.

Keywords: ^{18}F -fluorodeoxyglucose positron emission tomography, myocardial viability, oral glucose and intravenous insulin loading

INTRODUCTION

^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) cardiac imaging is commonly used to assess myocardial viability. Various protocols have been utilized to increase ^{18}F -FDG uptake in the hibernating myocardium including fasting, oral glucose loading, low-carbohydrate diet, intravenous (IV) or oral glucose and IV insulin loading, acimipox administration to reduce myocardial fatty acid metabolism, and euglycemic hyperinsulinemic clamp.^[1-7] Although euglycemic hyperinsulinemic clamp is considered as the best way to improve ^{18}F -FDG uptake in the hibernating myocardium, in routine practice oral glucose and IV insulin


loading is commonly adopted.^[1,4,8] The goal is to provide euglycemia and hyperinsulinemia at the time of ^{18}F -FDG injection as insulin increases glucose uptake in ischemic

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tissues. In oral glucose and IV insulin loading protocols, based on the fasting blood glucose (FBG) level, oral glucose is administered which is followed by IV insulin administration based on blood glucose level. Various versions of oral glucose and IV insulin loading protocols are used in hospitals.

A fasting of at least 6 h is recommended before the study to induce an endogenous insulin response.^[4] The temporary increase in plasma glucose levels stimulates pancreatic insulin production, which in turn reduces plasma fatty acid levels through its lipogenic effects of adipocytes and also normalizes plasma glucose levels.^[4] However, some believe that FDG studies performed after overnight fasting shifts normal myocardium to fatty acid metabolism thereby reducing FDG uptake in the normal myocardium that then resembling scar thereby failing to identify viable myocardium. They recommend high carbohydrate meals up to 4 h before FDG imaging to shift myocardial metabolism to glucose and FDG uptake.

In the current protocol published by the American Society of Nuclear Cardiology (ASNC) and Society of Nuclear Medicine and Molecular Imaging (SNMMI), oral glucose is given when the FBG level ≤ 13.9 mmol/L (250 mg/dl) as compared to their previous protocol which recommended administering oral glucose when FBG was < 6.11 mmol/L (110 mg/dl).^[4,8] In these protocols, the amount of glucose to be given is recommended as 25–100 g; however, glucose dosage table for FBG levels is not provided. Physicians performing the study decide on the amount of oral glucose based on FBG level, but the amount given may vary among physicians. Handling diabetic patients is also not well described in guidelines. Certain parameters can affect the viability results. High FBG level may saturate myocardial (normal and hibernating) glucose uptake and also compete with ¹⁸F-FDG. Acute oral glucose administration increases endogenous insulin which facilitates FDG uptake in normal and hibernating myocardium, but it may also compete with ¹⁸F-FDG for myocardial uptake. Amount of insulin given is also important as it facilitates myocardial ¹⁸F-FDG uptake. In this study, we aimed to investigate if certain parameters, such as FBG level, amount of glucose given, amount of insulin given, blood glucose level after glucose load, and blood glucose level at the time of ¹⁸F-FDG injection can affect the ¹⁸F-FDG uptake in hibernating and normal myocardium. We also wanted to determine and outline the common problems we come across with ¹⁸F-FDG PET cardiac viability imaging using oral glucose and IV insulin loading protocol.

MATERIALS AND METHODS

In this retrospective study, patients who had ¹⁸F-FDG PET cardiac viability and myocardial perfusion single photon

emission computed tomography (SPECT) studies were selected for further analysis. This retrospective study was approved by Kuwait Ministry of Health.

¹⁸F-FDG PET cardiac viability studies were performed after overnight fasting. The following oral glucose and IV insulin loading protocol was used in 43 patients in our hospital. First, the patient's FBG level was measured. In nondiabetic patients, 50 g oral glucose was administered if FBG was 8.32 mmol/L (150 mg/dl) and below, and 25 g glucose if FBG level was 8.38–13.87 mmol/L (151–250 mg/dl). In diabetic patients, 25 g glucose was administered if FBG was 8.32 mmol/L (150 mg/dl) and below, and 12.5 g glucose for FBG of 8.38–13.87 mmol/L (151–250 mg/dl). No glucose was administered if FBG was > 13.87 mmol/L (250 mg/dl). Blood glucose was measured 15–30 min after glucose loading. Regular insulin was administered IV in patients with FBG > 250 mg/dl and glucose loaded patients. The physician was notified if blood glucose was > 300 mg/dl. The IV insulin doses for blood glucose levels of 7.82–8.88 mmol/L (141–160 mg/dl), 8.93–9.99 mmol/L (161–180 mg/dl), 10.04–11.1 mmol/L (181–200 mg/dl), 11.15–12.21 mmol/L (201–220 mg/dl), 12.26–13.31 mmol/L (221–240 mg/dl), 13.37–14.43 mmol/L (241–260 mg/dl), 14.48–15.54 mmol/L (261–280 mg/dl), and 15.59–16.65 mmol/L (281–300 mg/dl) were 1, 2, 3, 4, 5, 6, 7, and 8 U, respectively. Blood glucose level was measured 15–30 min after insulin administration. If the blood glucose level was < 7.76 mmol/L (140 mg/dl), ¹⁸F-FDG was injected intravenously. If the blood glucose level was still high, repeat insulin was administered, and blood glucose was measured. This was repeated until blood glucose level is < 7.76 mmol/L (140 mg/dl). Blood glucose was checked every 15–30 min until the patient leaves the department to monitor for hypoglycemia.

In our two patients former SNMMI/ASNC/SCCT and in four patients current ASNC/SNMMI oral glucose IV insulin protocols were used.^[4,8]

For PET imaging, 185–370 MBq (5–10 mCi) of ¹⁸F-FDG was administered intravenously. The patients were asked to eat a light meal 15 min after ¹⁸F-FDG injection. PET images were obtained 60–90 min after ¹⁸F-FDG injection using Phillips Gemini time of flight 64 PET/CT camera (Philips Medical Systems, Best, Netherlands). The duration of PET acquisition was 15–20 min following a low-dose CT scan for attenuation correction. In some cases with high-blood pool activity, delayed PET images were also obtained.

Stress and rest myocardial perfusion SPECT images were obtained using 2 days' protocol following IV injection of 740 MBq (20 mCi) Tc-99 m tetrofosmin.

SPECT and PET images were evaluated visually by two readers. SPECT and PET images were evaluated using short axis, horizontal and vertical long axis images as well as bullseye polar maps. The size of fixed perfusion defects, size and severity of reversible or fixed perfusion defects as well as left ventricular ejection fraction, wall motion, wall thickening, and cavity size were assessed on SPECT images. SPECT findings included normal perfusion (normal perfusion at rest and stress), reversible defect/ischemia (normal perfusion at rest with reduced or absent perfusion at stress), fixed defect/infarct or hibernating myocardium (perfusion defect at rest and stress), and mild reversible perfusion defect surrounding fixed defect/peri-infarct ischemia.

On PET images, distribution of ^{18}F -FDG in areas of fixed perfusion defect as well as in normally perfused segments was assessed. Myocardial viability was assessed with visual analysis (mild, moderate, and significant). Viability was considered mild if it involved less than one-third of the area of perfusion defect, moderate if between one-third and two-thirds, and significant if more than two-thirds of the perfusion defect area. Visual evaluation and segmented bullseye polar maps were used to compare the size of the perfusion defect and the viable area.

Based on the SPECT and PET findings, patients were divided into two main groups and four subgroups. Group 1 included PET viable studies and Group 2 included PET-nonviable studies. Subgroups included PET viable with normal ^{18}F -FDG uptake in normal myocardium, PET viable with reduced ^{18}F -FDG uptake in normal myocardium, PET nonviable with normal ^{18}F -FDG uptake in normal myocardium, and PET nonviable with reduced ^{18}F -FDG uptake in normal myocardium.

FBG level, amount of oral glucose given, blood glucose level after glucose load, amount of IV insulin given, and blood glucose level at the time of ^{18}F -FDG injection values were recorded.

Statistical analysis was used to see if there is any difference in above values in two main groups (nonparametric Mann–Whitney U-test for two independent samples) and also in subgroups (nonparametric Kruskal–Wallis test for k independent samples) to determine if these parameters affect ^{18}F -FDG uptake in the hibernating and normal myocardium. $P < 0.05$ was statistically significant.

RESULTS

Our study included 49 patients (11 females and 38 males) with mean age of 63.1 years, ranging from 23 to 87 years. All patients had one or more risk factors including diabetes mellitus, hypertension, hyperlipidemia, obesity, and angina.

All the patients had fixed perfusion defects in one or more segments with wall motion abnormality. Six patients also had mild peri-infarct ischemia, and seven had varying degree of stress-induced ischemia in other walls on myocardial perfusion SPECT study.

PET showed varying degree of viability (mild, moderate, or significant) in 31 of 49 patients (63.2%) [Figures 1 and 2]. PET was nonviable in 18 patients (36.7%). In 18 of PET viable and 4 of PET nonviable studies, there was absent or decreased ^{18}F -FDG uptake in one or more normally perfused segments.

The mean \pm standard deviation values of FBG level, amount of oral glucose given, blood glucose level after glucose loading, amount of IV insulin given, and blood glucose level before ^{18}F -FDG injection in PET viable and PET nonviable patients are shown in Table 1.

Mean amount of glucose given was lower in PET viable patients as compared to PET nonviable patients, but it did not reach a statistical significance ($P = 0.065$) [Table 1].

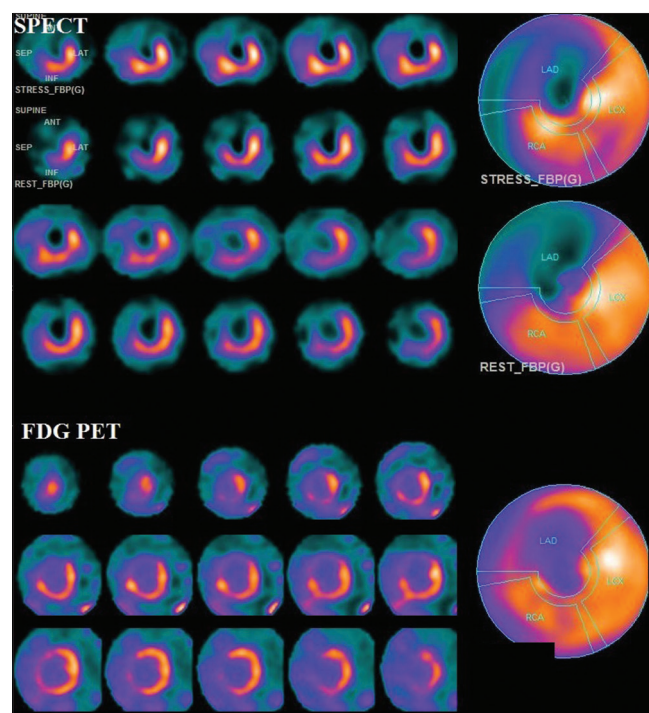


Figure 1: Myocardial perfusion single-photon emission computed tomography and ^{18}F -fluorodeoxyglucose positron emission tomography images of a patient with fasting blood glucose level of 3.9 mmol/L (70.2 mg/dl) who received 50 g oral glucose and 4 unit insulin. Blood glucose at the time of ^{18}F -fluorodeoxyglucose injection was 8.3 mmol/L (149.4 mg/dl). Single photon emission computed tomography images demonstrate moderate size fixed perfusion defect involving apex, anterior, and anteroseptal walls with mild possible ischemia in inferior wall. ^{18}F -fluorodeoxyglucose positron emission tomography images demonstrate small area of viability in the anterior and anteroseptal base. ^{18}F -fluorodeoxyglucose uptake in the rest of the myocardium is near normal with only mild reduction in the inferior wall

Mean amount of insulin given was higher in PET viable than PET nonviable patients, but it was significant ($P = 0.280$) [Table 1].

There was no significant difference in other values (FBG, blood glucose after glucose loading, and blood glucose

Table 1: Mean \pm standard deviation values of fasting blood glucose level, amount of glucose given, blood glucose after glucose loading, amount of insulin given, blood glucose before ^{18}F -fluorodeoxyglucose injection and P values of nonparametric Mann-Whitney U-test for two independent samples

	<i>n</i>	Mean \pm SD	<i>P</i>
FBG (mmol/L)			
PET viable	31	8.4226 \pm 2.30806	0.108
PET non-V	18	7.6389 \pm 3.12808	
Glucose (g)			
PET viable	29	27.586 \pm 19.8710	0.065
PET non-V	17	33.824 \pm 14.4999	
BG after glucose (mmol/L)			
PET viable	27	11.3667 \pm 2.13686	0.402
PET non-V	13	10.8769 \pm 2.38961	
Insulin (U)			
PET viable	31	8.419 \pm 4.6656	0.280
PET non-V	18	6.667 \pm 3.8995	
BG before FDG injection (mmol/L)			
PET viable	31	6.7065 \pm 1.22446	0.827
PET non-V	18	6.8944 \pm 1.29682	

FBG: Fasting blood glucose; BG: Blood glucose; U: Unit; Non-V: Nonviable; *n*: Number of patients; SD: Standard deviation; FDG: Fluorodeoxyglucose; PET: Positron emission tomography

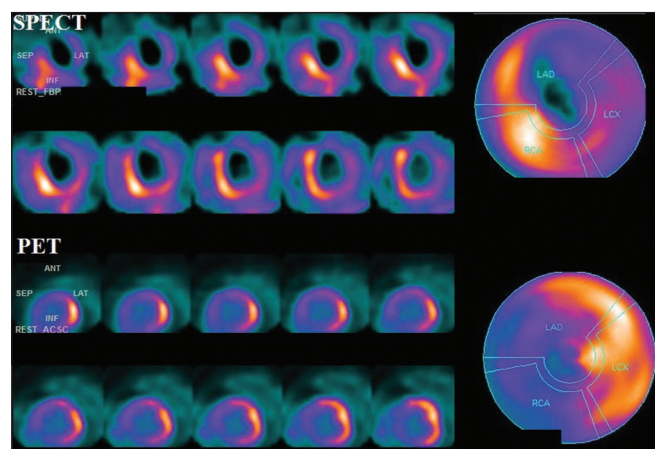


Figure 2: Rest myocardial perfusion single photon emission computed tomography and ^{18}F -fluorodeoxyglucose positron emission tomography short axis and bullseye images of a patient with fasting blood glucose of 7.7 mmol/L (138.6 mg/dl). No oral glucose was given in this patient. One unit insulin was given intravenously. Blood glucose at the time of ^{18}F -fluorodeoxyglucose injection was 5.5 mmol/L (99 mg/dl). Single photon emission computed tomography images demonstrate a large area of significantly reduced perfusion involving the apex, anterior, and lateral walls and inferolateral region. ^{18}F -fluorodeoxyglucose positron emission tomography images demonstrate significant viability in these regions but significantly reduced ^{18}F -fluorodeoxyglucose uptake in normal myocardium (flip-flop pattern)

at the time of ^{18}F -FDG injection) in PET viable and PET nonviable patients [Table 1]. There was also no significant difference in all values in subgroups.

In three patients, no oral glucose was given due to very high blood glucose level in one patient and due to diabetic status in two.

Blood glucose levels after glucose loading were not available in our records in nine patients.

Blood glucose level at the time of ^{18}F -FDG injection was below 7.76 mmol (140 mg/dl) in all patients, except in five.

Blood pool activity was high in comparison to myocardial wall uptake in four diabetic patients. Delayed imaging helped in two patients but not in other two [Figure 3].

In two patients, there was diffusely reduced uptake in the myocardium including the area of fixed perfusion defect and also the normally perfused myocardium.

Majority of our patients were diabetic (32 patients). Patients' diabetic status was determined based on referring physicians' notes or patients' history.

The problems we encountered when performing our viability studies included deciding on the amount of glucose to be given, particularly when using ASNC/SNMMI

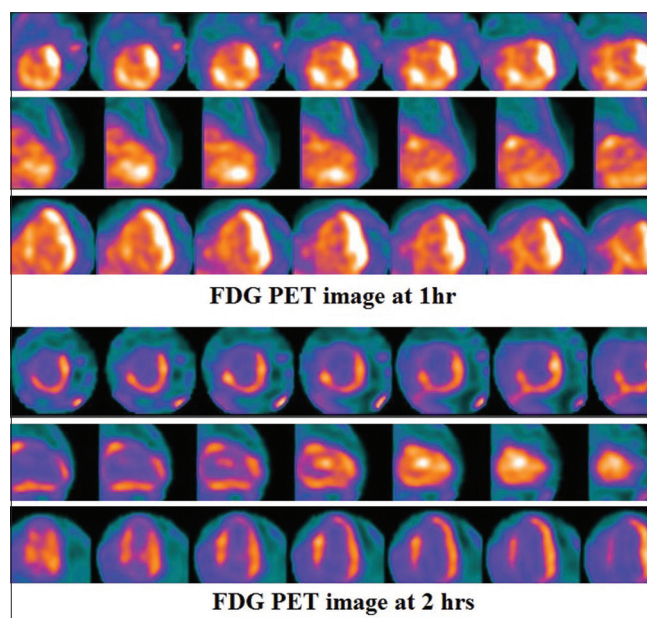


Figure 3: ^{18}F -fluorodeoxyglucose 1 h and 2 h cardiac images in short axis (top row), vertical long axis (middle row), and horizontal long axis (bottom row) slices in a patient with diabetes. Note the high blood pool activity on early imaging which significantly reduces with delayed imaging

protocol, amount of divided and maximum doses of insulin to be given, handling diabetic patients, time of measuring blood glucose after insulin administration and interpretation of findings in cases with diffusely or heterogeneously reduced ^{18}F -FDG uptake in the myocardium.

The protocol we use in our hospital details the amounts of glucose and insulin to be given per blood glucose range, but only in few of our cases our physicians did not strictly follow this protocol and in six patients old and current ASNC/SNMMI protocols were used.

In some of, our cases blood glucose gradually decreased, in some, it did not change, and in some, it further increased after insulin administration. Multiple doses of insulin were given until blood glucose level is below 7.76 mmol/L (140 mg/dl). Guidelines did not provide detail about the maximum dose of insulin to be given. The maximum amount of insulin given in our cases ranged from 1 to 21 units.

In diabetic patients, we gave a reduced amount of oral glucose based on blood glucose level and then IV insulin using our protocol. ASNC/SNMMI protocol did not guide on handling diabetics with low-blood glucose level in whom administration of insulin can further reduces blood glucose to a critical level. In those cases, we called the referring physician to ask permission to give oral glucose and also ask about the dosage.

DISCUSSION

Normal cardiac metabolism is primarily aerobic, and most of the chemical energy (adenosine triphosphate [ATP]) is supplied through oxidative phosphorylation.^[9] In the normal myocardium fatty acids, carbohydrates, and ketone bodies are used for the synthesis of ATP. Fatty acids are the predominant substrate used in the heart and generate the most ATP.^[9] Glucose is the preferred energy source in the postprandial state whereas free fatty acids and ketone bodies in the fasting state. Glucose is also the main source of energy for the ischemic/hibernating myocardium.

^{18}F -FDG is a radiolabeled glucose analog which is commonly utilized to detect viable myocardium using PET camera. ^{18}F -FDG enters myocytes by means of insulin-sensitive glucose transporters. In the cell, ^{18}F -FDG is phosphorylated into ^{18}F -FDG-6-phosphate by hexokinase enzyme. ^{18}F -FDG-6-phosphate does not undergo subsequent metabolism (glycogen synthesis or aerobic glycolysis) but only minimal dephosphorylation.^[1] ^{18}F -FDG PET imaging has

been reported to have a high sensitivity in detecting viable hibernating myocardium.^[10-13]

When the insulin level is low during fasting, there is an increase in lipolysis in peripheral tissue and increased plasma-free fatty acids levels. In fasting, there is reduced ^{18}F -FDG uptake in normal myocardium due to low glucose and insulin levels and high free fatty acids levels. After glucose loading, increase in plasma glucose stimulates the release of endogenous insulin, which decreases the plasma-free fatty acids levels, and increases glucose transporters and facilitates the transport and utilization of ^{18}F -FDG by the normal and hibernating myocardium.^[4,14]

^{18}F -FDG uptake in the normal and hibernating myocardium may be affected by various factors including but not limited to the duration of fasting, patient's regular diet (fat, carbohydrates, or protein dominant diet vs normal diet), patient's glucose levels at fasting and at the time of ^{18}F -FDG injection, viability protocol used, amount of glucose loaded, amount of injected insulin, blood insulin level at the time of ^{18}F -FDG injection, insulin resistance due to diabetes or other reasons, blood-free fatty acids levels at the time of ^{18}F -FDG injection, utilization of substrates other than glucose, or suboptimal patient preparation.

In our recently published study, we found that reduced ^{18}F -FDG uptake in normal myocardium was more common in PET viable than PET nonviable studies.^[15] In PET viable studies, ^{18}F -FDG uptake in the perfusion defect area and reduced ^{18}F -FDG uptake in normally perfused myocardium (flip-flop pattern) could be due to higher glucose avidity/need of hibernating myocardium than normal myocardium, preferential use of fatty acids in normal myocardium, or various other factors [Figure 4].^[15,16] In cases with diffusely reduced ^{18}F -FDG uptake in normal myocardium, the absence of ^{18}F -FDG uptake in fixed perfusion defect area may not always indicate nonviability as it could be due to various other factors affecting ^{18}F -FDG uptake both in normal and hibernating myocardium, such as suboptimal study, inadequacy of the current glucose and insulin loading protocols, or various other patient-related causes such as insulin resistance.^[17,18]

In our current study, we did not find statistical significance in FBG level, amounts of glucose and insulin given, blood glucose after glucose loading and blood glucose at the time of ^{18}F -FDG injection in PET viable and PET nonviable cases as well in cases with normal and reduced ^{18}F -FDG uptake in normal myocardium. Mean amount of glucose given was

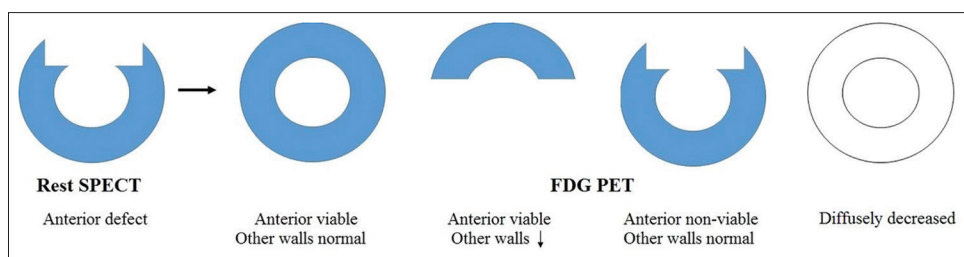


Figure 4: Illustration of ^{18}F -fluorodeoxyglucose uptake patterns in fixed perfusion defect and normal myocardium

slightly lower and mean amount of insulin given was slightly higher in PET viable than PET nonviable cases, but it was not significant statistically.

Insulin promotes the ^{18}F -FDG uptake into normal and hibernating myocardium. The amount of insulin to be injected per blood glucose range is well detailed in guidelines. Some institutes calculate the insulin dose using formulas which is different for diabetics and nondiabetics and limit the maximum dose of insulin to 8 units in nondiabetics. However, this is not well detailed for the amount of oral glucose load in guidelines. Current ASNC/SNMMI protocol recommends loading oral glucose (25–100 g) when FBG is <250 mg/dl in nondiabetic patients.^[4] The amount of oral glucose to be given is decided based on the FBG level, but some physicians prefer giving higher and some lower glucose which may affect the test result. In our hospital, amount of glucose given is 25–50 g in nondiabetics and 12.5–25 g in diabetics based on blood glucose level. In some other institutes, amount of oral glucose given in nondiabetics is lower which is 12.5–25 g. There is a need for oral or IV glucose loading dose table per FBG range in guidelines. It is well known that oral glucose loading increases endogenous insulin and then subsequent administration of IV insulin promote ^{18}F -FDG uptake in hibernating myocardium. In routine oncologic studies, high blood glucose is avoided as it reduces ^{18}F -FDG uptake in tumors due to competition. Whether high oral glucose loading can prevent subsequent ^{18}F -FDG uptake in hibernating myocardium due to saturation or competition is a question to be answered.

Coronary artery disease is common in patients with diabetes.^[19] In our study, 65.3% of cases were diabetic. Handling diabetic patients is challenging. Diabetic patients have limited ability to produce endogenous insulin, and their cells are less able to respond to insulin stimulation.^[4] In ASNC/SNMMI and some local guidelines, oral glucose loading is not recommended in diabetics, and only IV insulin is given based on FBG level.^[4] However, there is no recommendation on handling diabetic patients with low-FBG level in this

guidelines. The prevalence of insulin resistance is also high in patients with diabetes, and diabetic patients have impaired myocardial glucose metabolism which together may limit the efficiency of ^{18}F -FDG PET cardiac viability study in diabetics.^[17,18,20,21]

Emotional stress increases blood glucose, particularly in diabetics through adrenal glands triggering the release of glucose stored in various organs.^[22] In some of our cases, blood glucose further increased after insulin administration which required multiple IV insulin administration and significantly extended the duration of the study. In guidelines, there is no detail about the maximum amount of insulin to be given as well as handling emotional stress in patients.

^{18}F -FDG should be injected when blood glucose is <7.76 mmol/L (140 mg/dl). However, due to rapid changes in blood glucose, blood glucose measurement should be repeated in 10 min to confirm 7.76 mmol/L (140 mg/dl).

We monitored blood glucose every 15–30 min. Optimum time to measure blood glucose after insulin administration should be determined in guidelines.

A main limitation our study is relatively low number of patients to provide an accurate statistical result, particularly for subgroups as well as using mainly 1 protocol and therefore lacking to compare various protocols for various amounts of glucose loading. However, it is comparing the cases of the same protocol in regard to lower (25 g) and higher (50 g) amount of glucose given in nondiabetics and half of the glucose in diabetics. Another limitation of our study in regard to comparing various parameters in PET viable and PET nonviable cases include lack of confirmation of false-negative and true-negative PET nonviable cases. The other limitation of our study at comparing the values in subgroups (based on ^{18}F -FDG uptake status in normal myocardium) is the lack of confirmation of perfusion status of normal myocardium. In our study, normal perfusion status of myocardium was defined based on rest and stress myocardial

SPECT findings. As it is well known, normal myocardial perfusion on rest and stress SPECT does not always indicate the lack of coronary artery disease. Various reasons such as low-level coronary artery stenosis, inadequate exercise or inadequate/suboptimal pharmacologic stress, or balanced ischemia can cause normal SPECT although there is coronary artery disease.^[23,24]

CONCLUSION

Oral glucose and IV insulin loading protocols are commonly used in ¹⁸F-FDG PET cardiac viability studies with variations in the protocols in various institutes on the duration of fasting before the study, amount of glucose and insulin given and handling diabetic patients which may affect the result of the study. Further improvements in current guidelines are necessary to obtain images in optimal conditions for accurate results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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