# Effect of duration of fasting and diet on the myocardial uptake of F-18-2-fluoro-2-deoxyglucose (F-18 FDG) at rest

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Context: Patterns of myocardial fluoro-2-deoxyglucose (FDG) uptake with respect to duration of fasting and dietary ABSTRACT modifications. Aim: We observed the effect of duration of fasting and diet on the myocardial uptake pattern of F-18 FDG in patients routinely referred for oncological evaluation and no previous history of Coronary Artery Disease (CAD). Settings and Design: Prospective study. Subjects and Methods: A total of 153 patients (M: 81, F: 72; mean age: 47  $\pm$  15 years; mean blood glucose level (mBG) 105  $\pm$  23 mg/dl) were randomly divided in three groups. Group A: 4-6 h fasting; Group B: Overnight fasting (12–14 h); Group C: Low carbohydrate and fat rich diet for 2 days coupled with overnight fasting prior to the positron emission tomography (PET) scan. FDG uptake was classified as following: 1) homogeneous uptake, 2) heterogeneous uptake, and 3) 'no uptake' in the left ventricular (LV) myocardium. FDG PET study was performed as standard protocol for oncological conditions. Statistical Analysis Used: Descriptive statistics, Chi-square test or Fisher's exact test, and Spearman's rank correlation tests were applied. Results: We observed the 'no uptake' pattern in five (10%), 28 (55%), and 39 (77%), 'heterogeneous' pattern in 20 (39%), 14 (28%), and seven (14%), and 'homogeneous' pattern in 26 (51%), nine (18%), and five (10%) patients in Group A, B, and C, respectively. There was statistically significant difference of myocardial uptake pattern between group A and B (P < 0.0001), between group A and C (P < 0.0001), and between Group B and C (P = 0.023). The mBG was 102, 105, and 111 mg/dl in 'no uptake', heterogeneous, and homogeneous uptake pattern, respectively, (P = 0.103). Also, within each group the mBG was not related to the uptake pattern. **Conclusion:** Both restricted diet and duration of fasting play an important role in determining the pattern and suppression of myocardial F-18 FDG uptake. Overnight fasting and restricted diet together suppress myocardial FDG uptake more than overnight fasting alone, which suppresses uptake more than 4-h fasting.

Keywords: Fasting, fat-rich diet, fluoro-2-deoxyglucose, low carbohydrate, myocardial uptake, no uptake

# INTRODUCTION

F-18-2-fluoro-2-deoxyglucose (F-18 FDG) is a glucose analog positron emission tomography (PET) radiotracer that is routinely used in cardiology for the assessment of myocardial viability in conjunction with perfusion tracer. F-18 FDG is transported within the myocytes and undergoes phosphorylation to FDG-6-phosphate where no further metabolism occurs.

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In normal myocardium, oxidative metabolism is primary source of energy and utilizes free fatty acids, glucose, and lactate as substrates. In fasting state, free fatty acid becomes substrate of choice as the plasma insulin levels fall that results in lesser transport of glucose into the myocytes and an increase in the availability of free fatty acids secondary to increased lipolysis in peripheral adipose tissue. After feeding, plasma insulin levels rise, glucose becomes the primary substrate for oxidative metabolism as lipolysis within adipose tissue is inhibited, and arterial fatty acid content decreases.<sup>[1,2]</sup> Because FDG uptake reflects the glucose metabolism, then in fasting state there should be negligible FDG uptake in the myocardium. However, variable uptake of FDG is noted in the myocardium in fasting state.<sup>[3]</sup> Even in the post-glucose load protocol, if patient preparation is not adequate, a heterogeneous F-18 FDG uptake is noted in the myocardium making the interpretation of the scan difficult.

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Therefore, we have designed this study to observe the variable patterns of myocardial FDG uptake in fasting state for a short interval of 4 h, longer duration of overnight fasting (>12 h), and overnight fasting with a low carbohydrate and fat-rich diet for 2 days prior to the study.

# SUBJECTS AND METHODS

## **Study population**

A total of 153 patients referred for FDG PET scan for routine oncological evaluation to our department were enrolled in the study. The patients were recruited after obtaining ethical clearance from ethics committee of the institute. Patients with any previous investigation suggestive of coronary artery disease, with past history of myocardial infarction, past history of revascularization, and uncontrolled diabetes were excluded from the study. Also patients with history of chemotherapy or radiotherapy within 8 weeks, age below 12 years, and mediastinal radiation were excluded. The recruited patients were randomized in blocks of three subjects in three groups.

Patients in each group were advised to follow instructions as part of preparation prior to PET scan. Group A patients were advised to fast for at least 4 h, and Group B patients were advised to fast overnight so as to have fasting period of at least 12 h (range 12-14 h). Group C patients in addition to fasting overnight were requested to follow low carbohydrate and fat-rich diet for period of 2 days before the scan. Group C patients were explained and a dietary chart of permitted and non-permitted foods was given based on dietary habits, and all the patients who complied and followed the diet chart were considered. We did not follow a fixed standard diet so as to have a better patient compliance. Also, it was not logistically possible to provide a special diet to each patient in the department before the FDG injection. These patients were requested to avoid carbohydrate-rich diet like rice, potato, and sweet potatoes and fruits like grape, banana, and litchi and sweets like chocolate, honey, and jam. Depending upon dietary habits, they were asked to consume protein-rich diet like pulses, cottage cheese, green vegetables, and egg and high fat-rich diet like butter, cheese, chicken, meat, and fried food.

Before the FDG study, we confirmed compliance of each patient for the instructions given. Blood glucose level was checked for each patient using glucometer. Ten-15 mCi (370-555 MBq) of F-18 FDG was injected into the patient through an intravenous catheter. A whole body PET scan was acquired 40-60 min after injection on dedicated PET-computed tomography (CT) scanner (Biograph 2, Siemens, Erlangen, Germany). In the PET-CT system, CT acquisition was performed on spiral dual slice CT with a Kv of 130, mAs of 60, slice thickness of 4 mm, and a pitch of 1. Image was acquired using a matrix of  $512 \times 512$  pixels and pixel size of 1 mm. After CT, three-dimensional (3D) PET acquisition was done for 2-3 min per bed position. PET data were acquired using matrix of  $128 \times 128$  pixels with a slice thickness of 1.5 mm. CT-based attenuation correction of the emission images was used. PET images were reconstructed by iterative method ordered subset expectation maximization (OSEM; two iterations and eight subsets). After CT acquisition, PET acquisition of the same axial range was done with the patient in the same position. After completion of PET acquisition, the reconstructed attenuation-corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and sagittal planes, as well as in maximum intensity projections (MIP), and 3D cine mode. Attenuation-corrected PET images focussing the heart were reoriented from the transaxial slices to generate the conventional cardiac short axis and vertical and horizontal long axis. Two nuclear medicine physicians reported the PET studies that were blinded to patient group.

#### Image interpretation

All the studies were viewed in MIP and in 3D cine mode for initial assessment of cardiac and extracardiac FDG uptake. Patients with abnormal FDG uptake in mediastinum were excluded from further analysis. F-18 FDG PET cardiac images were analyzed for myocardial uptake in conventional cardiac format as short axis vertical and horizontal long axis. To observe the variable pattern of FDG uptake in the left ventricular (LV) myocardium, we classified the uptake as follows: 1) homogeneous uptake in the entire LV myocardium, 2) heterogeneous uptake in the LV myocardium. This regional uptake was assigned to conventional anatomical walls of the LV myocardium based on 20 segment model using Emory Cardiac Toolbox (ECTbox; Emory University, Atlanta, Georgia (GA), United States of America (USA)). The regions were identified irrespective of the intensity of the uptake, provided they could be delineated separately from the blood pool activity in the LV cavity and the surrounding background. 3) No uptake or negligible uptake in the LV myocardium.

#### Statistical analysis

Descriptive statistics was used for reporting the demographics of patient data. Findings of the three groups of uptake patterns were compared with Spearman's rank correlation test. Chi-square test or Fisher's exact test was applied to assess relationship between categorical variables within group. P < 0.05 was taken as significant. The statistical package used in the study was International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) Statistics 19.0.0.

#### RESULTS

# **Demographic profile**

Among 153 patients in our study, 81 (53%) were male, whereas remaining 72 (47%) were female. Mean age of the patients included in the study was 47  $\pm$  15 years (median age: 48 years, range: 16-84 years). Mean blood glucose level (mBG) was 105  $\pm$  23 mg/dl (median: 102 mg/dl, range: 62-200 mg/dl). Among 153 patients, 30 (20%) were smokers, 26 (17%) had diabetes well controlled by medication, 20 (13%) had controlled hypertension, and 62 (41%) patients had history of chemotherapy. All the three groups were matching for confounding factors like sex, age, diabetes, smoking, hypertension, and chemotherapy [Table 1]. There was statistically significant difference in the mBG between group A and B (P=0.0001) and between group A and C (P=0.0001), but the difference in mBG between group B and C was statistically insignificant (P=0.425). Groupwise mBG distribution is depicted in Figure 1. The mBG of patients in Group A was 117 ± 21, Group B was 101 ± 17, and Group C was 98 ± 26 mg/dl.

#### Distribution of myocardial FDG uptake pattern

We analyzed all the 153 studies to observe the pattern of FDG uptake in the myocardium classified as homogenous, heterogeneous, and 'no uptake' pattern.

We observed the 'no uptake' pattern in five (10%), 28 (55%), and 39 (77%), 'heterogeneous' pattern of FDG uptake in 20 (39%), 14 (28%), and seven (14%), and 'homogeneous' pattern in 26 (51%), nine (18%), and five (10%) patients in Group A, B, and C, respectively [Figure 2].

On overall groupwise comparison between Group A, Group B, and Group C, there was statistically significant difference of myocardial uptake pattern between the three groups (P < 0.0001). There was also significant difference of myocardial uptake pattern between group A and B (P < 0.0001), between group A and C (P = 0.023).

A total of 41 patients showed heterogeneous pattern, of which 20 (39%) were noted in Group A, 14 (28%) in Group B, and seven (14%) in Group C. We could identify seven different patterns involving the ventricular walls [Table 2]. The most common regions that showed myocardial FDG uptake were lateral wall (90%), followed by base of the heart (88%), inferior wall (56%), and distal anteroapical region (46%).

The mBGs were calculated and analyzed for effect of blood glucose on myocardial uptake pattern. We observed that in 'no uptake' pattern the mBG was lowest  $102 \pm 25$  mg/dl and it was highest in 'homogeneous' uptake pattern  $111 \pm 24$  mg/dl and  $105 \pm 17$  mg/dl in heterogenous pattern. However, there was



Figure 1: Bar plot with error bars showing mean  $\pm$  SD of blood glucose level in three groups. SD = Standard deviation

no statistically significant difference in the mBG in between the three patterns (P = 0.103) [Figure 3].

We observed the effect of mBG on myocardial uptake pattern in each group. Within each group the mBG was not related to the uptake pattern. Groupwise mBG and myocardial FDG uptake pattern distribution results are shown below Table 3.

Table 1: Matching of confounding variables in three groups							
Total number of		Р					
patients=153	А	В	С				
Age	46±16	47±15	47±13	0.904			
Sex							
Male	28 (35)	27 (33)	26 (32)	0.930			
Female	23 (32)	24 (33)	25 (35)				
Smoking	10 (33)	6 (20)	14 (47)	0.137			
Diabetes	9 (35)	7 (27)	10 (38)	0.723			
Hypertension	3 (15)	9 (45)	8 (40)	0.168			
Chemotherapy	30 (33)	30 (33)	32 (34)	0.897			

Age presented as mean $\pm$ SD. Values in brackets represent percentages, P<0.05 was considered significant, SD: Standard deviation

# Table 2: Regional distribution of heterogeneous uptake pattern

Patternsn (%)Basal uptake4 (10)Basal, distal anteroapical region, lateral and inferior wall14 (34)Basal, distal anteroapical region, and lateral wall5 (12)Basal and lateral wall6 (15)Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	•	
Basal uptake4 (10)Basal, distal anteroapical region, lateral and inferior wall14 (34)Basal, distal anteroapical region, and lateral wall5 (12)Basal and lateral wall6 (15)Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	Patterns	n (%)
Basal, distal anteroapical region, lateral and inferior wall14 (34)Basal, distal anteroapical region, and lateral wall5 (12)Basal and lateral wall6 (15)Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	Basal uptake	4 (10)
Basal, distal anteroapical region, and lateral wall5 (12)Basal and lateral wall6 (15)Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	Basal, distal anteroapical region, lateral and inferior wall	14 (34)
Basal and lateral wall6 (15)Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	Basal, distal anteroapical region, and lateral wall	5 (12)
Basal, lateral, and inferior wall7 (17)Lateral and inferior wall2 (5)Lateral only3 (7)	Basal and lateral wall	6 (15)
Lateral and inferior wall2 (5)Lateral only3 (7)	Basal, lateral, and inferior wall	7 (17)
Lateral only 3 (7)	Lateral and inferior wall	2 (5)
	Lateral only	3 (7)

# **Table 3:** mBG and myocardial FDG uptake pattern distribution in three groups

Group	No uptake		Heterogeneous		Homogeneous		Р
	п	Mean	n	Mean	п	Mean	
А	5	130±28	20	113±17	26	118±23	0.245
В	28	103±18	14	100±17	9	98±17	0.727
С	39	99±28	7	96±12	5	93±27	0.737

Value presented as mean±SD, mBG: Mean blood glucose level, FDG: Fluoro-2-deoxyglucose, SD: Standard deviation



Figure 2: Myocardial uptake pattern distribution between the three groups



Figure 3: Bar plot with error bars showing mean  $\pm$  SD of blood glucose level with respect to uptake pattern. SD = standard deviation

We observed and analyzed the myocardial uptake pattern in patients with controlled diabetes. A total of 26 diabetics were present in the study population. Overall, no significant difference was noted between the uptake pattern in the diabetics and the nondiabetic patients (P = 0.475).

We also analyzed the effect of chemotherapy on the myocardial uptake pattern. There was no significant relation between the uptake pattern noted between the patients who received chemotherapy (n = 61) and those who need not receive any chemotherapy (P = 0.747).

# DISCUSSION

Unlike a perfusion tracer that is solely flow-dependent and any heterogeneity reflects abnormal myocardial perfusion, FDG uptake is dependent on many factors and produces a variable uptake in myocardium depending on the substrate available for oxidative metabolism and the hormonal status. PET scans routinely performed for oncological evaluation have shown a variable spectrum of FDG uptake in myocardium even in fasting state. This variable uptake poses difficulty in interpretation when suppression of FDG uptake in normal myocardium is desired, e.g., in detection of ischemic myocardium,<sup>[4-7]</sup> in oncological evaluation of thorax and upper abdominal area,<sup>[8]</sup> and when a low myocardial uptake is required in plaque imaging of the coronary vessels.<sup>[9]</sup> Even in the post-glucose load studies for assessment of viability, often a heterogeneous F-18 FDG uptake is noted in the myocardium making the interpretation difficult. Therefore, we designed this study to observe the influence of duration of fasting and dietary modifications on myocardial FDG uptake.

In our study, we evaluated a total of 153 patients who were divided into three groups, Group A: Patients with 4-h fasting (range 4-6 h), Group B: Patients with 12-h overnight fasting (range 12-14 h), and Group C: Patients with overnight fasting and on low carbohydrate and fat-rich diet for 2 days prior to the study.

To observe the variable pattern of FDG uptake in the LV myocardium, we visually classified the uptake into homogeneous uptake, heterogeneous uptake, and 'no uptake' in the LV myocardium. Some authors have compared the myocardial FDG uptake with background or other organs like liver by visually grading the uptake or using standardized uptake value (SUV).<sup>[10,11]</sup> In our study, we did not take into consideration myocardial SUV values or compared the ratio of myocardial uptake with background or other organs. These parameters routinely are not taken into consideration when reporting cardiac study. The focus of our study was to observe and identify the pattern of FDG myocardial uptake in relation to duration of fasting and diet so as to bePnefit the interpretation of cardiac PET studies in day to day practice. Although all the studies were viewed in the 3D cine format, the final analysis of all the studies was done in conventional cardiac format as short axis and vertical and horizontal long axis, like any routine cardiac study.

In our study, we observed the 'no uptake' pattern in 10, 55, and 77%, 'heterogeneous' pattern of FDG uptake in 39, 28, and 14%, and 'homogeneous' pattern in 51, 18, and 10% patients in Group A, B, and C, respectively. These results showed that Group C protocol of overnight fasting and restricted diet (2 days of low carbohydrate and fat-rich diet) before F-18 FDG administration suppresses myocardial F-18 FDG uptake more than Group B that suppresses the uptake more than Group A. Our results suggest that myocardial uptake suppression is better with combination of controlled diet and fasting than fasting alone.

Several authors have studied the role of diet and fasting on myocardial FDG uptake.<sup>[10,12-14]</sup> De Groot et al.,<sup>[12]</sup> had concluded that age, fasting period, and blood glucose levels did not influence physiological uptake of FDG in myocardium. This study suggests that carbohydrate-restricted fat-rich diet may be more effective than fasting to suppress myocardial FDG uptake. Balink et al.,<sup>[10]</sup> in their study described the effect of a 1-day fat-allowed carbohydrate-restricted diet on myocardial F-18 FDG uptake in fasting protocol for PET oncology study. They found that after a carbohydrate-restricted diet, 68% of patients had a homogeneously low myocardial uptake of F-18 FDG. Therefore, we designed the 2-day protocol of carbohydrate-restricted fat-rich diet in order to achieve better myocardial FDG suppression and also compare the findings with prolonged fasting period. In our study, myocardial suppression was higher (77%) in patients who fasted overnight and were put on a controlled diet for 2 days.

In a recent study, Harisankar *et al.*,<sup>[13]</sup> evaluated the feasibility to consistently suppress myocardial FDG uptake with a low carbohydrate high fat protein permitted (LCHFPP) diet. In their study, they compared 50 patients (>12-h fasting) and 60 patients on special LCHFPP diet, which the patients were advised to consume on previous night and also at 4 h before the test. After exclusion of noncompliant patients in LCHFPP group, 84% of subjects demonstrated significant FDG suppression. The authors observed better myocardial FDG uptake suppression using LCHFPP diet compared with prolonged (>12 h) fasting protocol. We analyzed the relation of blood glucose level on the myocardial uptake pattern. The mBG was lowest in 'no uptake' pattern calculated to be  $102 \pm 25$  mg/dl, which was comparable with  $111 \pm 24$  mg/dl in homogeneous pattern. Also within each group, no relationship could be established between mBG and the uptake pattern. These results suggest that mBG does not determine the uptake of FDG in the myocardium. Other factors like insulin level, free fatty acid concentration, glucagon level, and influx rate constants of FDG may also play role in myocardial FDG uptake as suggested by Choi *et al.*<sup>[15]</sup> Similarly, de Groot *et al.*,<sup>[12]</sup> in their study on patients who underwent repeated PET scans for oncological evaluation suggested that the variable uptake in the myocardium is not influenced by the blood glucose level.

We further evaluated the heterogeneous uptake pattern in relation to the regions in the ventricular wall. The regions were identified irrespective of the intensity of the uptake, provided they could be delineated separately from the blood pool activity in the LV cavity and the surrounding background. A total of 41 patients showed heterogeneous pattern, of which 20 (39%) were noted in Group A, 14 (28%) in Group B, and least seven (14%) in Group C. We could identify seven different patterns involving the ventricular walls. Region wise the most common regions that showed myocardial FDG uptake were lateral wall (90%), followed by base of the heart (88%), inferior wall (56%), and distal anteroapical region (46%). The regions with negligible or absent FDG uptake were septum, mid anterior wall, and inferoapical region. Similar findings of regional heterogeneity of FDG uptake in the myocardium have been described in previous studies.<sup>[2,15-18]</sup> Gropler et al.,<sup>[2]</sup> reported that myocardial accumulation of FDG in the septum and anterior wall averaged 80% of that in the lateral and posterior walls in the subjects with regional uptake. The regional heterogeneity of FDG uptake could be attributed to preferential substrate utilization by different regions of the myocardium in the fasting state. Hicks et al.,<sup>[17]</sup> studied normal variation in regional myocardial substrate metabolism and quantitatively evaluated myocardial oxidative metabolism with carbon-11 acetate and glucose metabolism using F-18 FDG. They observed that the glucose utilization was 13% lower in the septum compared with the lateral wall. This could not be explained by decreased metabolic demand because C-11 clearance constants were marginally higher in the septum than in the lateral wall in both studies. The authors suggested that relatively decreased septal glucose utilization could reflect regional variation in substrate use and possible preferential free fatty acid utilization by the septum.

In our study, we studied the effect of diabetes on the myocardial FDG uptake. On overall analysis, we found no relation between uptake pattern and presence of diabetes. Previous studies have assessed the role of diabetes on myocardial FDG uptake and suggested that in diabetics, myocardium shows preference for fatty acid as substrate compared with glucose.<sup>[19-21]</sup> But the same tendency was not noted in our study population. However, due to small numbers of diabetic patients in our study population

and still lesser number in each group, a definite conclusion cannot be made.

In our study, we also assessed whether chemotherapy can affect the myocardial uptake pattern. Overall, we found no relation between uptake patterns in patients who received chemotherapy when compared with patients who had not received chemotherapy.

In summary, the results of our study show that Group C protocol of overnight fasting and restricted diet (low carbohydrate and fat-rich diet) for 2 days before F-18 FDG study suppresses myocardial F-18 FDG uptake more than Group B protocol of overnight fasting alone that suppresses uptake more than Group A protocol of 4-h fasting. Blood glucose, diabetes, and chemotherapy do not influence myocardial FDG uptake. Therefore, our results suggest that both restricted diet and duration of fasting play an important role in suppression of myocardial FDG uptake.

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