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# $^{18}$F-FDG Positron Emission Tomography in Myocardial Viability Assessment: A Practical and Time Efficient Protocol

Joyce Mhlanga, MD;[1] Paul Derenoncourt, MD;[1] Adeel Haq, MD; [1] Anita Bhandiwad, MD;[2]

Richard Laforest, PhD; [1] Barry A. Siegel, MD; [1] Farrokh Dehdashti, MD;[1]

Robert J Gropler, MD;[1,2] Thomas H. Schindler, MD, PhD[1,2]

[1] Mallinckrodt Institute of Radiology, Division of Nuclear Medicine, Washington University School of Medicine, St. Louis, Missouri, USA. [2] Cardiovascular Division, John T. Milliken Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, USA.

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**Address for correspondence:**
Thomas Hellmut Schindler, M.D., PhD.
*ORCID: https://orcid.org/0000-0002-2141-7716*
Mallinckrodt Institute of Radiology, Division of Nuclear Medicine,
Washington University School of Medicine, 510 S. Kingshighway Blvd., St. Louis, MO 63110.
E-mail: thschindler@wustl.edu

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**ABSTRACT**

We assessed image quality using a practical and time-efficient protocol for intravenous glucose loading and insulin injection prior to administration of $^{18}$F-fluorodeoxyglucose ($^{18}$F -FDG) for PET myocardial viability evaluation in patients with ischemic cardiomyopathy, with and without type 2 diabetes mellitus.

**Methods:** Metabolic preparation period (MPP) or optimal cardiac $^{18}$F-FDG uptake was determined from the time of intravenous infusion of 12.5 or 25 gram of 50% dextrose to the time of $^{18}$F-FDG injection. Cardiac $^{18}$F-FDG image quality was evaluated according to a 5-point scoring system (5=excellent to 1=non-diagnostic) by two independent observers. In cases of disagreement, consensus was achieved in a joint reading. Fifteen patients with ischemic cardiomyopathy, who underwent oral glucose loading and i.v. insulin administration, served as reference for MPP comparisons.

**Results:** 59 consecutive patients (age: 63±10yrs, men n=48 and women n=11) underwent rest $^{99m}$Tc-tetrofosmin SPECT/CT and $^{18}$F-FDG PET/CT for the evaluation of myocardial viability. FDG image quality was scored as excellent in 42%, very good in 36%, good in 17%, fair in 3%, and non-diagnostic in 2%. Comparing diabetic and non-diabetic patients, the quality scores were excellent in 29% vs. 76% , very good in 41% vs. 18%, good in 24% vs. 6%, fair in 4% vs. 0% , and non-diagnostic in 2% vs. 0%. The mean (±SD) quality score was 4.12±0.95 and overall it was better in non-diabetic than in diabetic patients (4.71±0.59 vs 3.88±0.96; $p<0.0001$). Notably, the average MPP was significantly less with i.v. glucose loading when compared to oral glucose loading (51±15 vs. 132±29 min; $p<0.0001$), paralleled by higher insulin doses (6.3 ± 2.2 vs. 2.0 ± 1.69 U; $p<0.001$).

**Conclusions:** Using a practical and time efficient protocol for i.v. glucose loading and insulin administration prior to $^{18}$F-FDG injection reduces the MPP by 61% as compared to oral glucose challenge that affords good-to-excellent image quality in 95% of ischemic cardiomyopathy patients.

**Keywords:** coronary artery disease**,** $^{18}$F-fluorodeoxyglucose, hibernation, myocardial perfusion, myocardial viability, SPECT, PET

## INTRODUCTION

Numerous clinical investigations (1) have documented that, in patients with ischemic cardiomyopathy (ICM), timely coronary revascularization to restore myocardial perfusion of ischemic, jeopardized viable myocardium improves heart failure symptoms and prognosis. Positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose ($^{18}$F- FDG) and $^{99m}$Tc single-photon emission computed tomography (SPECT) afford a high diagnostic accuracy for the detection and characterization of a perfusion-metabolism mismatch (2,3). Myocardium exhibiting this pattern in conjunction with segmental severe hypokinesis/akinesis, is commonly referred to as hibernating myocardium, and has a high probability of regaining myocardial contractility with timely revascularization (1,3,4). Accurate assessment of the extent and severity of the perfusion-metabolism mismatch is critical for patients with ICM to define those in whom early restoration of coronary blood flow will improve left ventricular function and cardiovascular outcome (5,6).

Although $^{18}$F- FDG PET is the most sensitive imaging method for detecting viable, hibernating myocardium, the procedure commonly necessitates a tedious, time-consuming glucose loading and insulin administration protocol to achieve adequate myocardial $^{18}$F-FDG uptake required for optimal diagnostic accuracy (7). In particular in diabetic patients, frequent blood glucose monitoring and supplemental insulin administration may lead to a significant delay in PET image acquisition and, thus, logistical problems in a busy clinical PET facility (7). Several protocols of glucose loading with insulin administration have been proposed for $^{18}$F-FDG PET myocardial viability assessment in routine clinical practice (7). In this study, we evaluated a practical and time-efficient intravenous (i.v.) glucose loading and insulin administration protocol and assessed the quality of cardiac $^{18}$F-FDG PET images for viability assessment in diabetic and non-diabetic patients with ICM.

## MATERIAL AND METHODS

### Study population

The study population consisted of 59 patients with ischemic cardiomyopathy (ICM) who underwent $^{99m}$Tc-tetrofosmin SPECT/CT, followed by i.v. glucose loading and insulin injection before $^{18}$F-FDG PET/CT who were referred for the evaluation of myocardial viability between September, 2018 and July, 2020 (Table 1). In addition, a group of fifteen consecutive patients with ICM (56±8yrs of age, men n=12 and women n=3, diabetes n=13 and non-diabetes n=2) underwent the same imaging protocol but with oral glucose loading and i.v. insulin administration (7), between March, 2016 and September 2018. The Washington University institutional review board approved this retrospective study and waived the requirement for informed consent.

**Cardiac SPECT/CT and PET/CT** are described in detail in the Online Appendix.

### Metabolic Preparation Protocol

Patients on oral antidiabetic medication and/or insulin regimen were classified as patients with known and treated diabetes mellitus (n=39), while three patients without antidiabetic medication but with elevated fasting blood glucose levels (≥125mg/dL) at the time of the PET study were also assigned to the diabetic group (Table 1). The metabolic preparation period (MPP) was defined as the period between intravenous infusion of 12.5 or 25g of 50% dextrose in 50mL water and $^{18}$F-FDG injection. All patients were studied after an overnight fast. The metabolic preparation protocol was performed by a highly skilled nurse in a dedicated preparation room, and patients were moved and positioned in the PET/CT scanner about 10 min before starting the scan. However, blood glucose levels were measured at baseline at the start of the MPP (Figure 1). With baseline

serum glucose levels <125mg/dL, 25g of 50% dextrose in 50mL water was slowly infused intravenously, whereas with baseline serum glucose ≥125mg/dL – 140mg/dL, only 12.5g of 50% dextrose in 50mL water was slowly infused intravenously. Post-challenge serum glucose levels were measured after a 20 min interval to capture the peak of the serum glucose increase for optimal dosing of insulin administration. If the serum glucose after the glucose challenge was between 140-180mg/dL, insulin was administered i.v. according to the insulin protocol shown in Table 2, and followed immediately by i.v. injection of ≈370 MBq $^{18}$F-FDG. In this lower range of post-challenge serum glucose levels, sufficient insulin sensitivity can be assumed so that insulin administration commonly leads to a marked decrease in serum glucose levels and effectively drives the $^{18}$F-FDG into the myocardium. In rare cases of patients without an appropriate decline in serum glucose by ≥20 mg/dL, an additional 1-2 U insulin were injected i.v. to stimulate an appropriate drop in serum glucose and, thus, cardiac $^{18}$F-FDG uptake (Figure 1).

If the serum glucose after glucose challenge was ≥180mg/dL (Figure 1), insulin was administered i.v. according to the insulin protocol (Table 2) and serum glucose was remeasured 10 min later. The short 10-min interval was chosen, as the aim was to verify that insulin had effectively initiated reduction of the post-challenge serum glucose levels and, thus, the effectiveness for driving the $^{18}$F-FDG into the myocardium. If the serum glucose declined ≥20 mg/dL, ≈370 MBq $^{18}$F-FDG were injected immediately. If the decline in serum glucose was not ≥20mg/dL, another 2-3 U of insulin were administered and serum glucose was measured again after another 10min. If serum glucose had then declined by ≥ 20mg/dL, ≈370 MBq $^{18}$F-FDG were injected. In diabetic patients arriving with baseline serum glucose ≥150 mg/dL (Figure 1), no glucose challenge was performed and intravenous insulin was administered according to the insulin protocol (Table 2). If after 10min, the serum glucose had then declined by ≥ 20mg/dl, then ≈10mCi $^{18}$F-FDG were injected.

If the decline in serum glucose was not ≥20mg/dL, another 3 U of insulin were administered i.v. and serum glucose measured again after another 10min. If serum glucose had then declined by ≥ 20mg/dl, then ≈370 MBq $^{18}$F-FDG were injected. After $^{18}$F-FDG injection, serum glucose was monitored every 15-20 minutes, and before and after the 10-min PET/CT image acquisition. If a patient developed symptomatic or asymptomatic hypoglycemia (serum glucose <70mg/dL) after insulin, the protocol allowed for administration of 2-3 ounces of orange juice orally to maintain normal blood glucose levels. However, if symptomatic or asymptomatic hypoglycemia developed, necessitating the supplementation with orange juice to maintain normal blood glucose levels, within 30 min of the $^{18}$F-FDG cardiac uptake period, the study was discontinued since it was expected that $^{18}$F-FDG PET images would be suboptimal. Patients on oral antidiabetic medication were instructed not to take their oral antidiabetic medication in the morning. Patients with insulin-dependent diabetes mellitus were asked to adhere to their regular diet and baseline insulin regimen the day before the study, but to fast after midnight and to withhold insulin until the metabolic preparation of the $^{18}$F-FDG PET study was begun. If a diabetic patient developed symptomatic or asymptomatic hypoglycemia, despite fasting state, appropriate food or juice intake at the discretion of the patient was allowed; however, this was followed by a 6-hour fasting period before starting the metabolic preparation or glucose challenge for the FDG-PET examination.

**Evaluation of SPECT and PET Images**

On the reoriented short- and long-axis myocardial images and the corresponding polar maps, the relative distributions of $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG uptake were evaluated quantitatively, using the standard American Heart Association recommended 17-segment model and the Corridor 4DM software. As described previously and consistent with guidelines by the American Society

of Nuclear Cardiology (7), myocardium with the highest $^{99m}$Tc-tetrofosmin uptake on the rest perfusion images (5 % of the sectors with the highest activity) was defined as 100% and served as reference for normalization of regional $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG activity concentrations. Regional $^{99m}$Tc-tetrofosmin activity concentrations on the rest images in the patients were compared to a normal reference database (Corridor 4DM). Corresponding $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG images were automatically scored quantitatively in all 17 segments by Corridor 4DM software. A 5-point scoring system was used to indicate segmental $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG uptake: 0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, and 4 = absent. Myocardium was defined as normal (and, therefore, viable) when the $^{99m}$Tc-tetrofosmin uptake on SPECT images yielded a score of 0, regardless of the $^{18}$F-FDG uptake on PET. A concordant reduction in $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG activity scores was classified as a perfusion-metabolism match, indicating non-viable myocardium. A reduction in $^{99m}$Tc-tetrofosmin uptake more severe than the reduction in $^{18}$F-FDG uptake by ≥1 point was defined as a perfusion-metabolism mismatch, indicating viable myocardium. The total myocardial extent of match or mismatch patterns was determined as N/17, where N was the number of segments exhibiting match or mismatch, respectively (2).

**Cardiac FDG-PET Image Quality Analysis**

The quality of $^{18}$F-FDG PET images was assessed visually by two independent experienced nuclear medicine physicians (T.H.S. and J.M.). Nine instances of minor disagreement were settled by a joint consensus reading. Cardiac $^{18}$F-FDG image quality was evaluated according to a 5-point scoring system (5=excellent, 4=very good, 3=good, 2=fair, and 1=non-diagnostic) (Figure 2).

As resting ischemia may cause a disproportionate increase in $^{18}$F–FDG uptake in jeopardized but viable myocardium, likely related to an increase in Glut-4 receptors and other yet unknown factors, the $^{18}$F–FDG uptake in the ischemic region may exceed that in the remote and normally perfused myocardium. In addition, this ischemic region with high $^{18}$F–FDG uptake, then defines the 100% uptake that again leads to a relative downscaling of FDG signal in the remote non-ischemic myocardium. Apart from the intensity of the homogenous or heterogenous myocardial $^{18}$F–FDG uptake, the residual $^{18}$F–FDG blood activity served as a second evaluation criterion. Accordingly, excellent image quality (score 5) was defined as homogenous/heterogenous $^{18}$F-FDG signal and no blood pool activity; very good image quality (score 4) as homogenous/heterogenous $^{18}$F-FDG-signal and mild blood pool activity; good image quality (score 3) as homogenous/heterogenous $^{18}$F-FDG-signal and moderate blood pool activity; fair image quality (score 2) as homogenous/heterogenous moderate $^{18}$F-FDG-signal and high blood pool activity; and non-diagnostic image quality (score 1) with low homogenous/heterogenous or no $^{18}$F- FDG-signal and high blood pool activity, respectively. In addition, the absolute counts of the left ventricular $^{18}$F-FDG uptake were automatically displayed for the LAD, LCx and RCA distributions on the polar map analysis, and the averaged value of the left ventricle was calculated.

**Statistical Analysis**

Data are presented as mean ± SD for quantitative and absolute frequencies for qualitative variables. The appropriate Wilcoxon rank test for independent or paired samples was used. Comparison between the different groups was performed by one-way analysis of variance (ANOVA), followed by Scheffe's multiple comparison tests. Statistical significance was assumed

if a null hypothesis could be rejected at $p<0.05$. All statistical analyses were performed with SPSS 22.0 for Windows.

## RESULTS

### Clinical and Study Characteristics

The characteristics of the study population are given in Table 1. Coronary angiography performed in all patients revealed coronary lesions, as defined as ≥50% epicardial arterial narrowing of a one vessel in 9 (15%), two in 15 (25%), and three in 43 (73%). Serum glucose levels at baseline and the dosage of insulin were significantly higher in diabetic than in non-diabetic patients, while serum glucose levels after intravenous glucose challenge did not differ significantly among groups (Table 1). Interestingly, when compared to the group with oral glucose loading, the baseline serum glucose levels did not differ significantly between both groups and subgroups of diabetic and non-diabetic patients ($p=0.06$), while peak serum glucose levels after glucose challenge were significantly less with oral versus i.v. glucose loading, and also in both subgroups ($p\leq0.05$, respectively) (Table 1). Accordingly, the dose of i.v. insulin was also significantly less in the group with oral versus i.v. glucose loading ($p<0.0001$) (Table 1). For the whole study group with i.v glucose loading, the MPP averaged 51±15 min, and did not differ between diabetic and non-diabetic patients (51±16 and 50±14 min) (Table 1). However, in the group with oral glucose loading, the mean MMP was significantly longer than in the i.v. glucose loading group (132±29 vs. 51±15 min, $p<0.0001$) and also for the subgroups of diabetic and non-diabetic patients (141 ± 31 vs. 51±16 min and 122 ± 28 vs. 50±14 min; $p<0.0001$, respectively).

With the i.v. glucose protocol, administration of a small amount of orange juice was necessary in 11 patients (19%) whose serum glucose levels decreased below <70mg/dL (Table 3), while this

was not necessary for the oral glucose loading group. Nine of the patients in the i.v. glucose cohort developed hypoglycemia that did not become symptomatic likely because of timely administration of 2-3 ounces of orange juice orally to restore normal blood glucose levels. Two patients had hypoglycemia with minor symptoms, such as dizziness, headache or sweating, that were resolved immediately by administration of 2-3 ounces of orange juice orally (Table 3).

**Imaging Results and Quality Assessment**

Combined $^{99m}$Tc-SPECT/$^{18}$F-FDG PET demonstrated ischemic, compromised but predominantly viable, myocardium in the majority of patients of 75% (n=44) with ICM (Figure 3-4 and supplemental Figure I-II with quantitative polar map display). Of the 59 patients who were studied, standard quantitative polar map analysis 44 (75%) showed perfusion-metabolic mismatches (viable myocardium), and 15 (25%) had perfusion metabolic matches (non-viable myocardium). Both, mismatches and matches coexisted in 26 patients (44%). For the whole study population, the total mismatch score in viable myocardium was 17±9. When evaluated in relation to arterial territory, the regional mismatch score was 8±5 for the LAD, 5±4 for the LCX, and 4±3 for the RCA distributions, respectively. Regarding myocardial $^{18}$F-FDG image quality assessment, the mean quality score in the study population was 4.12±0.95, and overall it was better in non-diabetic than in diabetic patients (4.71±0.59 vs 3.88±0.96; $p \leq 0.0001$). Myocardial $^{18}$F- FDG PET images were scored for the total study population as excellent in 42% (n=25), very good in 36% (n=21), good in 17% (n=10), fair in 3% (n=2), and non-diagnostic in 2% (n=1) (Figure 5). Comparing diabetic and non-diabetic patients, the quality scores were excellent in 29% (n=12) vs. 76% (n=13), very good in 41% (n=17) vs. 18% (n=3), good in 24% (n=10) vs. 6% (n=1), fair in 4% (n=2) vs. 0% (n=0), and non-diagnostic in 2% (n=1) vs. 0% (n=0) (Figure 4b). Thus, the majority of

diagnostic FDG image quality in diabetic patients was very good with 41% and in non-diabetic patients, it was predominantly excellent with 76%. Notably, there was a significant and progressive decrease of the left ventricular absolute count statistics of $^{18}$F- FDG uptake on polar map analysis from excellent, very good, good to fair and non-diagnostic $^{18}$F- FDG uptake scores (score 5: 21,671±7,802, score 4: 13,652±7,430, score 3: 7,281±2,734, to score 2: 3,847±56 and score 1: 2,121 counts, respectively ($p<0.0001$ by ANOVA).

## DISCUSSION

The current study is unique in demonstrating a practical and time-efficient protocol for i.v. glucose loading and insulin injection prior to i.v. $^{18}$F-FDG injection that affords good-to-excellent image quality in 95% of patients with ICM. Notably, the $^{18}$F-FDG image quality with our protocol is in keeping with the findings of previous studies (2,5,6,8,9), and is maintained despite our shortened metabolic preparation protocol, even in diabetic patients, as compared to oral glucose loading.

Although myocardial $^{18}$F-FDG PET may be considered as the reference standard among cardiac imaging modalities for the detection of viability in dysfunctional myocardium (3,4,10), the metabolic preparation protocol for this test needed to achieve optimal myocardial $^{18}$F-FDG uptake and, thus, image quality is commonly quite complex and time consuming (7). It is well known that, in fasting nondiabetic subjects, 40%–60% of myocardial $^{18}$F-FDG PET scans may be uninterpretable because of low radiotracer uptake and significant regional heterogeneity, reflecting predominant reliance of the heart on free fatty acids as source of energy (7,11), In this respect, oral or intravenous glucose loading has been used to stimulate endogenous insulin release in order to enhance the myocardial uptake of glucose and, thus, of $^{18}$F- FDG. Standard protocols have typically involved oral administration of 50-100g dextrose solution to fasted patients followed by intravenous injection of $^{18}$F-FDG intravenously 60-90 minute later (7). However, oral glucose administration without insulin injection yielded poor cardiac image quality in 2% to 33% of patients, including non-diabetic patients (12,13). With i.v. administration of insulin for elevated serum glucose levels after oral glucose loading, the rate of poor image quality could be substantially reduced to 8% to 15% (14,15). One important limitation of oral glucose loading is the long MPP owing to a large proportion of patients with undiagnosed impaired glucose tolerance or insulin resistance as well as a variability in the rate of intestinal glucose absorption (7,15). The

MPP of oral glucose loading with insulin administration may therefore be 120-160 min. The current approach with i.v. glucose loading and insulin administration had an average MPP of only ≈ 51 min as compared to ≈132 min when we used oral glucose loading with subsequent insulin administration. The substantially shorter MPP with i.v. glucose loading likely is related to a markedly higher serum glucose peak with subsequently higher insulin dose administration as compared to oral glucose loading commonly associated with delayed and variable intestinal glucose absorption and a substantially lower glucose peak necessitating lower insulin doses. It is also important to note that higher peak glucose levels with i.v. glucose loading necessitates not only a substantially higher dose of insulin but also stimulates more endogenous release of insulin from pancreatic β-cells. Thus, the blood insulin levels can be assumed to be much higher than those achieved with oral glucose loading; this, in turn, will lead to greater myocardial $^{18}$F- FDG-uptake resulting in good-to-excellent image quality in most patients. Further, the metabolic preparation time did not differ between diabetic and non-diabetic patients with intravenous glucose loading likely related to the significantly higher insulin doses applied in diabetic patients after glucose challenge.

This practical and time-efficient MPP offers the advantage that the injection and myocardial uptake of $^{18}$F-FDG are occurring when the effect of insulin likely is maximal. Similar protocols have recommended delaying $^{18}$F-FDG injection until the serum glucose level decreases below 125-140mg/dL after insulin injection (7). This, however, necessitates repeat assessments of serum glucose and it carries the risk of missing the maximal insulin effect required to drive the FDG into the myocardium resulting in suboptimal image quality. When compared to protocols using oral glucose loading, the advantage of the proposed protocol with an average MPP of 51 min is the ability to better plan timing of the PET scan, while maintaining diagnostic image quality even in

diabetic patients. After FDG-injection, we typically aimed for 60min and 90min cardiac uptake periods in non-diabetic and in diabetic patients, respectively. The average $^{18}$F-FDG uptake period in the whole study population was 82 min (86 min in diabetic and 74 min in non-diabetic patients). The difference from our planned goals reflect the scanner availability in routine clinical practice.

It is important to note that our protocol allowed administering about 2-3 ounces of orange juice orally after an $^{18}$F-FDG uptake period of at least 30min, if serum glucose levels decreased below 70mg/dL after insulin administration. This was necessary in 11 (19%) of our patients and 2 of these had symptoms, which were mild and resolved immediately after ingestion of orange juice. None of the patients had severe side effects; this emphasizes the safety profile of the proposed protocol despite administration of higher insulin doses than with oral glucose challenge.

## CONCLUSIONS

A clinically practical and time-efficient protocol for intravenous glucose loading and insulin injection prior to $^{18}$F-FDG injection reduces the MPP by 61% as compared to oral glucose challenge that is safe and affords good-to-excellent diagnostic image quality in 95% of patients with ICM. This protocol holds promise to improve the application and efficacy of $^{18}$F-FDG PET-determined myocardial viability in routine clinical practice.

## DISCLOSURE

All authors declare that they have no conflict of interest pertaining to the contents and presentation of the current study.


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## KEY POINTS

**Question:** Is it feasible to apply a practical and time-efficient protocol for intravenous glucose loading and insulin injection prior to $^{18}$F-FDG injection, while maintaining safety and diagnostic image quality of myocardial $^{18}$F-FDG PET images?

**Pertinent findings:** In this retrospective analysis, we found that the shortened metabolic preparation protocol with intravenous glucose loading, insulin injection, and $^{18}$F-FDG injection consistently yields good-to-excellent diagnostic image quality even in diabetic patients with ICM

**Implications for patient care:** The suggested protocol is safe, practical, and should enhance the clinical application and cost-effectiveness of $^{18}$F-FDG PET for the detection and characterization of viable myocardium.

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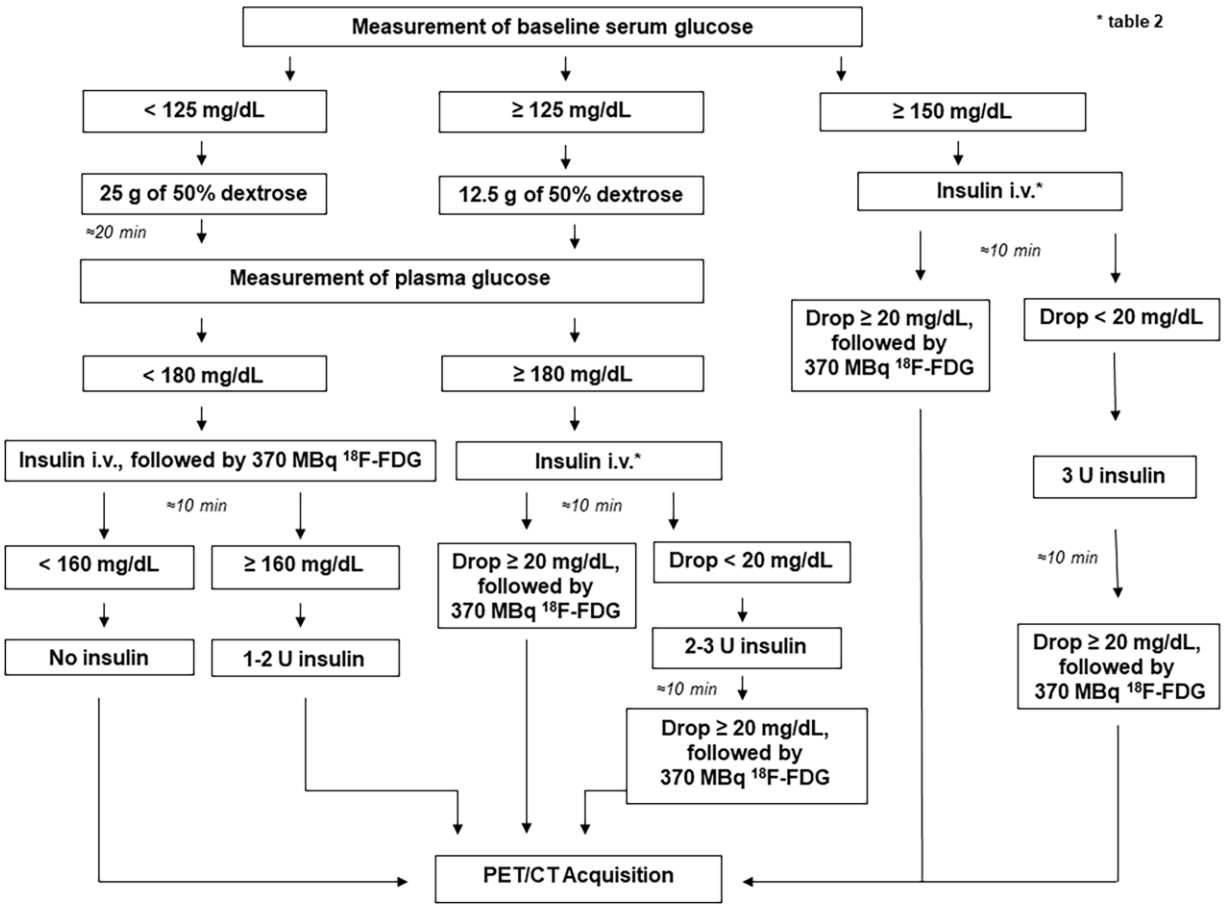


**Figure 1.** Schematic illustration of the metabolic preparation protocol based on initial serum glucose levels.

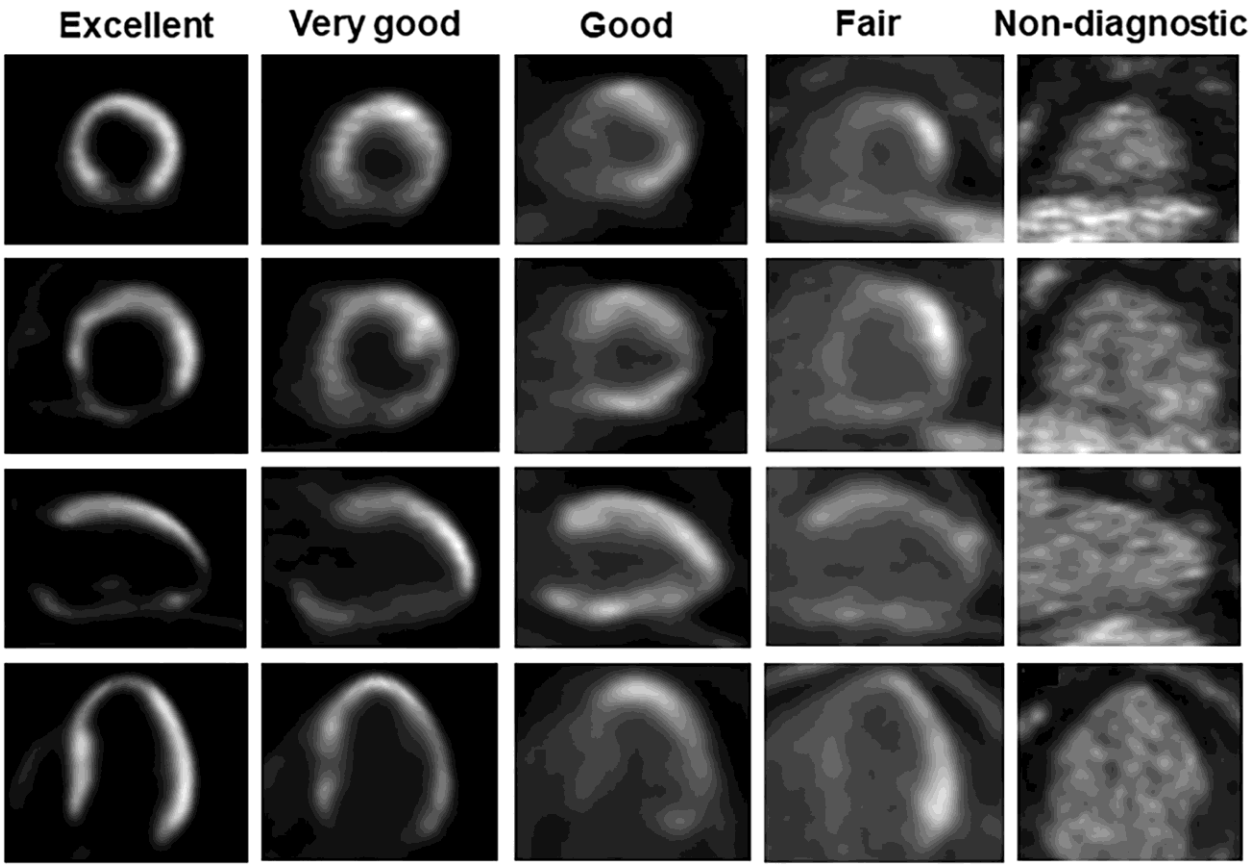


**Figure 2.** Myocardial $^{18}$F-FDG image quality was evaluated according to a 5 point score system.

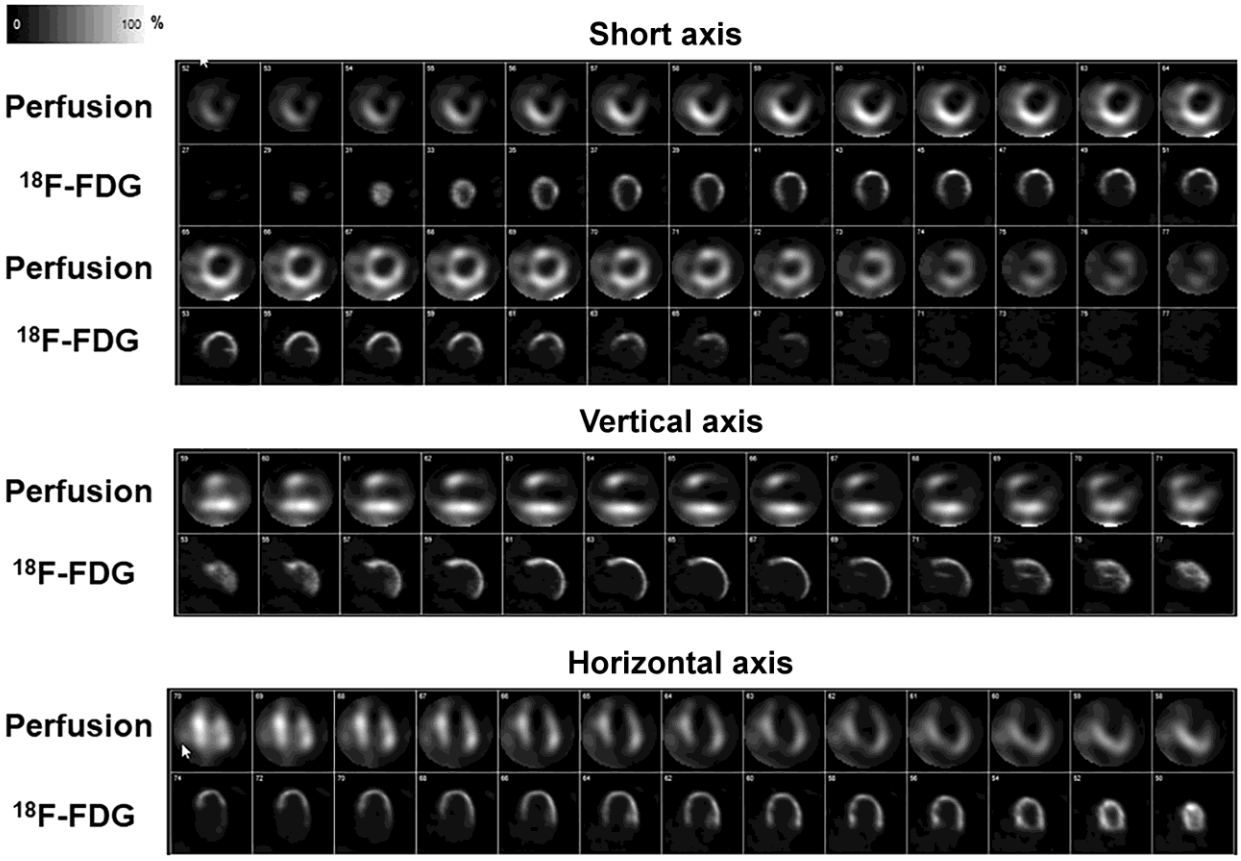


**Figure 3.** Rest myocardial perfusion with SPECT/CT images with $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG PET/CT in a patient with dilated ischemic cardiomyopathy, demonstrating a *"mismatch"*.

$^{99m}$Tc-SPECT/CT rest perfusion with short, vertical, and horizontal long axis images demonstrates a severe perfusion defect in the predominantly akinetic antero-septo-apical, apical, and anterolateral walls that is accompanied by normal or upregulated $^{18}$F-FDG-uptake on the PET images, consistent with hibernating-stunned myocardium. Given the disproportionately high FDG-uptake in the *"mismatch"* regions (reflecting 100% reference for signal normalization), some of the remaining myocardium demonstrates mildly lower or no $^{18}$F-FDG signal (e.g., inferoseptal and inferior wall segments, respectively) associated with normal rest perfusion ("reverse mismatch") indicating viability in these segments.

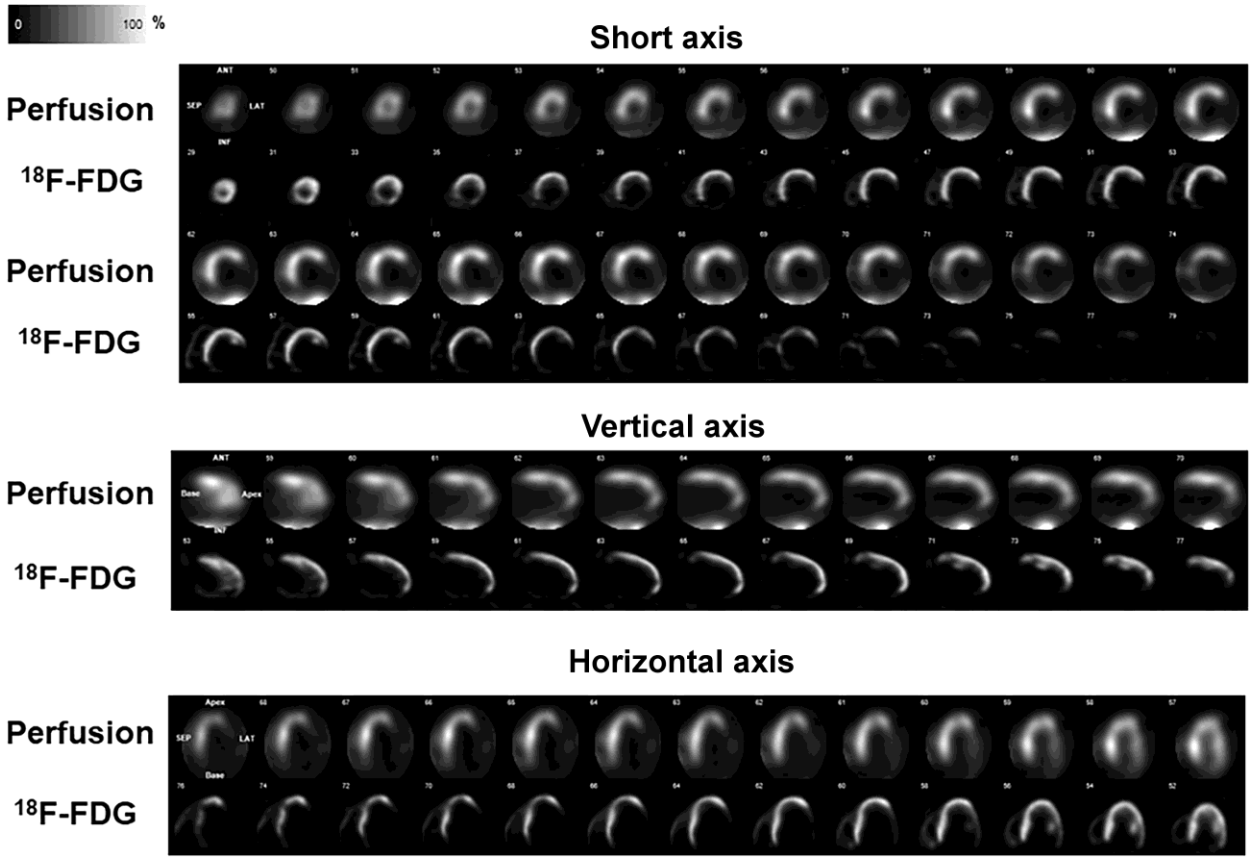


**Figure 4.** Rest myocardial perfusion SPECT/CT images with $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG-PET/CT images in a patient with ischemic cardiomyopathy, demonstrating a *"match".*

$^{99m}$Tc-SPECT/CT rest perfusion with short, vertical, and horizontal long axis images demonstrate a severe perfusion defect in the inferior and inferolateral walls with mild extension inferoseptally and laterally that is associated with predominant absence of $^{18}$F-FDG-uptake on the PET images. Thus, there is widely a "match" finding with concordant absence of perfusion and viability to signify predominant transmural necrosis in LCx and RCA distribution.

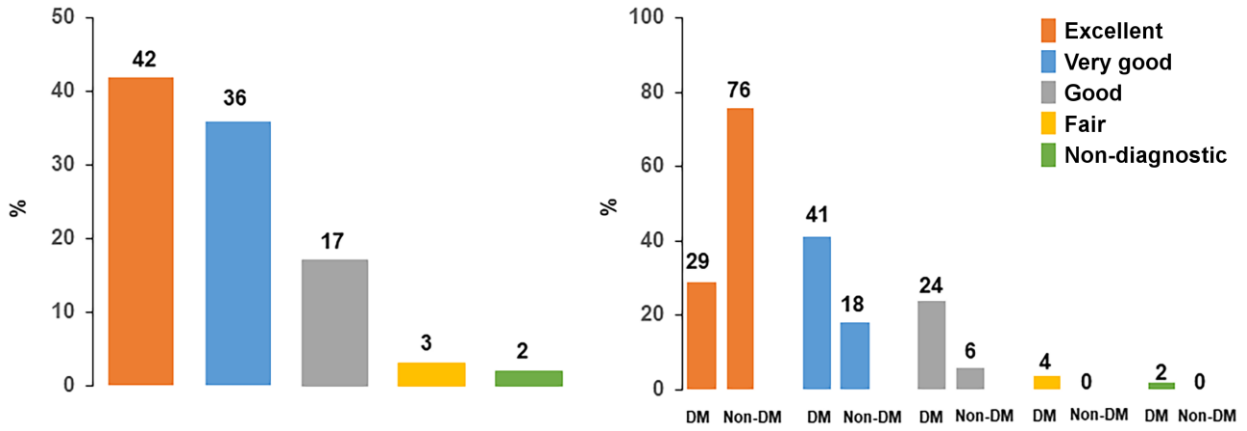


**Figure 5.** Myocardial $^{18}$F-FDG image quality score distribution (%) in the whole study population (right panel) and when sub-grouped and compared among those with diabetes mellitus (DM) and those without (non-DM) (left panel).

## Graphical Abstract

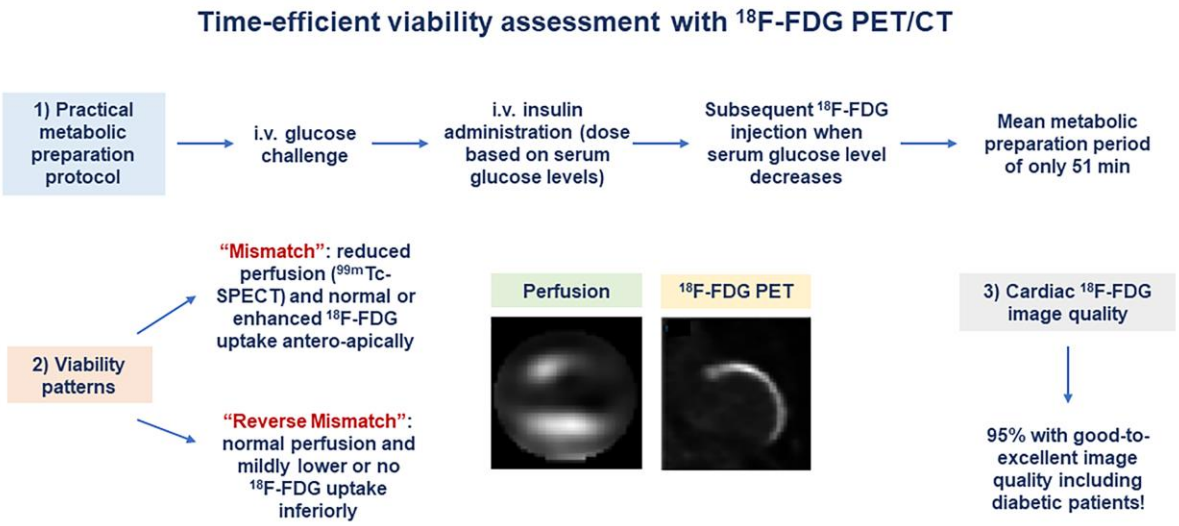

**Table 1:** Patients and study characteristics.

| | **All** | **Diabetic** | **Non-Diabetic** |
|---|---|---|---|
| ***Patients characteristics*** | | | |
| N | 59 | 42 | 17 |
| Age (yrs) | 62 ± 10 | 63 ± 11 | 62 ± 11 |
| Male/female | 48/11 | 32/10 | 16/1 |
| Ejection fraction (%) | 29 ± 10 | 30 ± 9 | 27 ± 9 |
| Prior CABG/PTCA | 4/5 | 3/3 | 1/2 |
| Prior MI | 43 (73%) | 27 (64%) | 16 (94%) |
| Hypertension | 57 (96%) | 25 (60%) | 16 (94%) |
| Smoking | 39 (66%) | 28 (67%) | 11 (65%) |
| Dyslipidemia | 53 (90%) | 38 (90%) | 15 (88%) |
| Diabetes mellitus | 42 (71%) | 42 (100%) | 0 (0%) |
| ***Study characteristics with i.v. glucose load*** | | | |
| Glucose baseline (mg/dL) | 121 ± 32 (70,214) | 131 ± 33 (70,214) | 97 ± 11* (83,122) |
| Glucose peak after challenge (mg/dL) | 184 ± 31 (124,304) | 188 ± 33 (126,304) | 175 ± 24 (124,203) |
| Glucose before imaging (mg/dL) | 101 ±25 (62,166) | 108 ± 24 (63,166) | 87 ±20* (62,146) |
| Insulin (U) | 6.3 ± 2.2 (2,11) | 6.8 ± 2.3 (2,11) | 4.9 ± 1.3* (3,8) |
| MPP (min) | 51 ± 15 (25,89) | 51 ± 16 (25,85) | 50 ± 14 (30,89) |
| FDG-uptake period (min) | 82 ± 19 (52,122) | 86 ± 19 (52,122) | 74 ± 17* (54,115) |
| Preparation period (min) | 133 ± 26 (83/190) | 137 ± 25 (83,190) | 124 ± 25 (92,184) |
| ***Study characteristics with oral glucose load*** | | | |
| Glucose baseline (mg/dL) | 99 ± 9 (84,112) | 105 ± 5 (101,112) | 91 ± 7* (84,99) |
| Glucose peak after challenge (mg/dL) | 158 ± 26 (123,187) | 171 ± 11 (164,187) | 146 ± 32* (116,185) |
| Glucose before imaging (mg/dL) | 105 ± 23 (76,144) | 101 ± 23 (76, 129) | 108 ± 28 (82,144) |
| Insulin U) | 2.0 ± 1.69 (0,5) | 3.0 ± 1.63 (1,5) | 1.0 ± 1.16* (0,2) |
| MPP (min) | 132 ± 29 (90,180) | 141 ± 31 (110,180) | 122 ± 28* (90,158) |
| FDG-uptake period (min) | 72 ± 15 (57,98) | 64 ± 11 (57,80) | 80 ± 17*(62,98) |
| Preparation period (min) | 203 ± 25 (167,237) | 205 ± 33 (167,237) | 201 ± 19 (187,228) |

*≤0.05 vs diabetic group; values are mean ± SD or n (%); range (lowest, highest value); CABG: coronary artery bypass surgery; PTCA: percutaneous transluminal coronary angioplasty; MI: myocardial infarction; min: minutes; MPP: metabolic preparation period. FDG-uptake period: time from FDG-injection and start of imaging; preparation period: time from start of MPP and start of imaging.

**Table 2:** Insulin dosage in response to glucose challenge after intravenous infusion of 25g or 12.5g of 50% dextrose in 50mL water in non-diabetic and diabetic patients, respectively.

Abbreviations: i.v. = intravenous; mg=milligram; dL=deciliter; and U=unit

| | Non-Diabetic | Diabetic |
|---|---|---|
| Serum Glucose (mg/dL) | i.v. Insulin Dose (Regular Insulin, U) | i.v. Insulin Dose (Regular Insulin, U) |
| 130-140 | 1 | 2 |
| >140-150 | 2 | 3 |
| >150-160 | 3 | 4 |
| >160-170 | 4 | 5 |
| >170-180 | 5 | 6 |
| >180-200 | 6 | 7 |
| >200 | 7 | 8 |

**Table 3:** Hypoglycemia and adverse side effects of i.v. insulin administration in response to i.v. glucose challenge in non-diabetic and diabetic patients, respectively.

| | Non-Diabetic | Diabetic |
|---|---|---|
| Hypoglycemia without symptoms | 4 | 5 |
| Hypoglycemia with symptoms | 1 | 1 |
| Dizziness or light-headedness | 1 | 0 |
| Headache | 0 | 1 |
| Shakiness | 0 | 1 |
| Irritability | 0 | 0 |
| Sweating | 1 | 0 |
| Blurred vision | 0 | 0 |
| Fast heart rate | 0 | 0 |
| Mood change | 0 | 0 |
| Confusion | 0 | 0 |
| Slurred speech | 0 | 0 |
| Anxiety | 0 | 0 |
| Hunger | 0 | 0 |
| Allergic reactions | 0 | 0 |
| Rash | 0 | 0 |

Hypoglycemia defined as serum glucose <70mg/dL

**Supplemental Materials and Methods:**

# $^{18}$F-FDG Positron Emission Tomography in Myocardial Viability Assessment:

# A Practical and Time Efficient Protocol

Joyce Mhlanga, MD;[1] Paul Derenoncourt, MD;[1] Adeel Haq, MD; [1] Anita Bhandiwad, MD;[2]

Richard Laforest, PhD; [1] Barry A. Siegel, MD; [1] Farrokh Dehdashti, MD;[1]

Robert J Gropler, MD;[1,2] Thomas H. Schindler, MD, PhD[1,2]

[1] Mallinckrodt Institute of Radiology, Division of Nuclear Medicine, Washington University School of Medicine, St. Louis, Missouri, USA. [2] Cardiovascular Division, John T. Milliken Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, USA.

**Short Running Title:** FDG-PET and Myocardial Viability

**Address for correspondence:**
Thomas Hellmut Schindler, M.D., PhD.
*ORCID: https://orcid.org/0000-0002-2141-7716*
Mallinckrodt Institute of Radiology, Division of Nuclear Medicine,
Washington University School of Medicine, 510 S. Kingshighway Blvd., St. Louis, MO 63110.
E-mail: thschindler@wustl.edu

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## MATERIAL AND METHODS

### Study population

All patients had ICM documented angiographically with coronary artery stenosis defined as ≥50% narrowing in the left main and/or proximal epicardial coronary arteries or their major branches; reduced left ventricular ejection fraction, regional resting perfusion deficit on $^{99m}$Tc-SPECT/CT; and/or a history of myocardial infarction. Left ventricular wall motion and ejection fraction (LVEF) were evaluated by standard 2-dimensional echocardiography

### SPECT Perfusion Imaging

For myocardial perfusion assessment, patients underwent $^{99m}$Tc-tetrofosmin SPECT/CT at rest either the day before or on the same day before the scheduled $^{18}$F-FDG PET/CT study. $^{99m}$Tc-tetrofosmin (20 mCi) was administered intravenously (1). Forty minutes later, each patient was positioned supine under a SPECT/CT camera (Discovery NM/CT 670CZT or 670 Pro; or Optima NM/CT 640; or GE Healthcare, Chicago, IL) and standard parameters were used. Using SPECT/CT for myocardial perfusion imaging allowed optimal attenuation correction, minimizing attenuation artifacts that could have led to false perfusion-metabolism mismatch interpretations. The projection data were then reconstructed with 2D-ordered-subset expectation maximization (2D-OSEM) with 4 iterations 6 subsets into transaxial views by applying a Butterworth filter with a cutoff frequency of 0.4/cm with order of 5.0. Subsequently, transaxial views were transferred to the HERMES software for analysis with $^{18}$F-FDG PET data using Corridor 4DM (INVIA Medical Imaging Solutions, Ann Arbor, MI, USA).

**$^{18}$F-FDG PET Scan**

$^{18}$F-FDG was used as radiotracer of myocardial glucose consumption to identify the viability state. PET/CT (either Biograph TruePoint/TrueView or Biograph mCT, Siemens, Knoxville, TN), which acquires 109 transaxial images simultaneously in one bed position of 21.6cm, was used to determine cardiac $^{18}$F-FDG uptake. Images were reconstructed with and without attenuation correction with the 3D-ordered-subset expectation maximization (3D-OSEM 2 iterations – 21 subsets) algorithm with resolution recovery (PSF) and time of flight (TOF on mCT) in a 168x168 matrix (TrueoPoint/TrueView) or 200x200 matrix (mCT) with a zoom of 1 and a 1-mm Gaussian post-reconstruction filter. Following the metabolic preparation protocol, 10mCi of $^{18}$F-FDG were injected i.v. and after an uptake period of at least ≈ 60 min in all patients and up to 90 min in diabetic patients, if PET scheduling allowed, a 10-min PET acquisition was performed. The CT for attenuation correction was performed with an effective tube current of 50 mAs, voltage of 120 kVp, 0.80 pitch, and 28.8mm collimation.

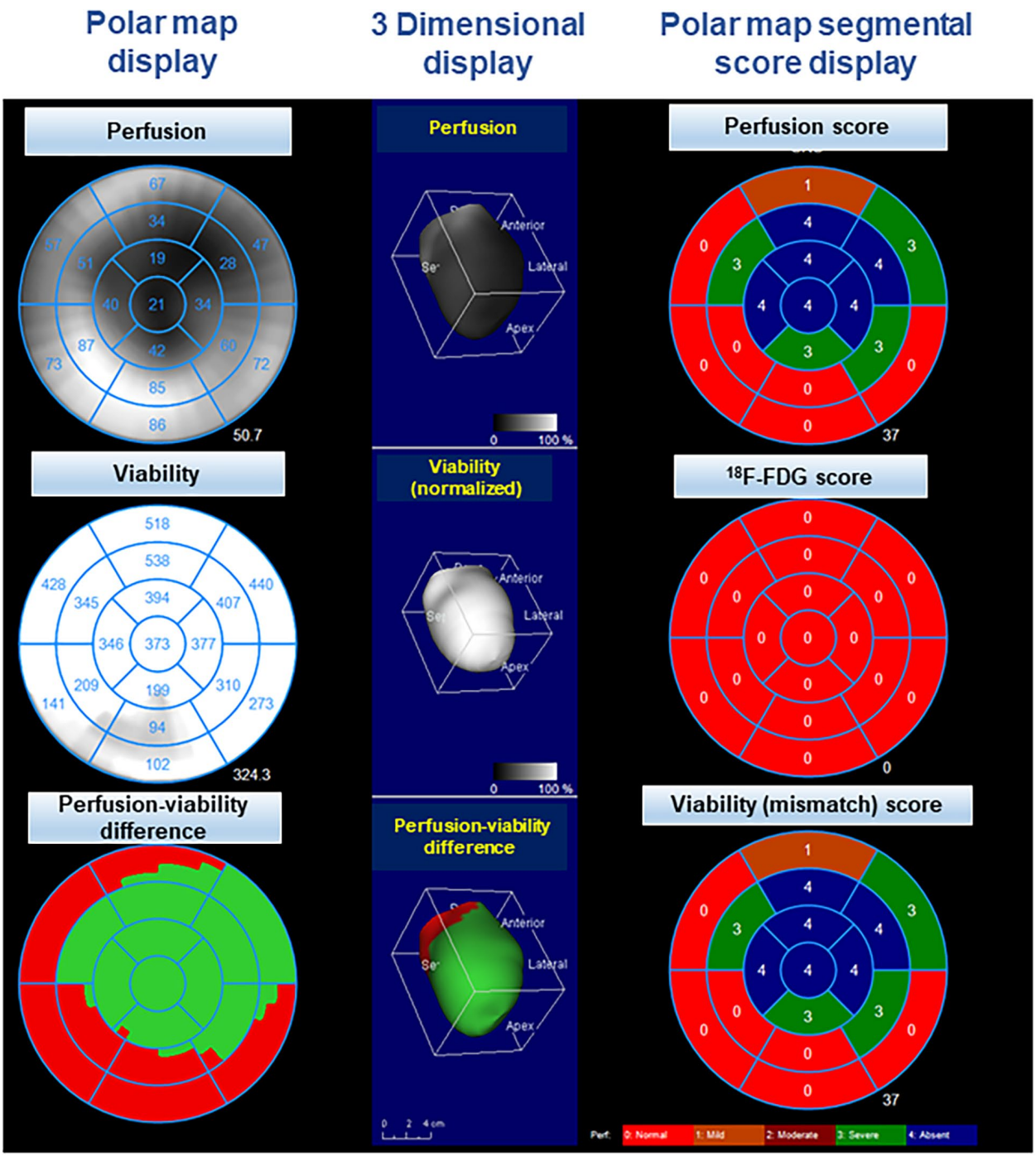


**Figure I.** Corresponding to the images shown in Figure 3, the polar map and three-dimensional display of the rest myocardial perfusion SPECT/CT images with $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG PET/CT images in a patient with dilated ischemic cardiomyopathy, demonstrate a *"mismatch"*.

As can be appreciated, quantification of rest perfusion with $^{99m}$Tc-tetrofosmin demonstrates a large (11- segments) and severe perfusion defect (summed rest score: 37) in the predominantly akinetic antero-septo-apical, apical, and anterolateral walls *(upper panel)* associated with normal or upregulated $^{18}$F-FDG-uptake (score: 0) *(middle panel)* that signifies a large area of "mismatch" indicative of hibernating-stunned myocardium *(lower panel)*. The quantitative evaluation approach with the normalization of the $^{18}$F-FDG-uptake to myocardial perfusion and the "mismatch" quantification affords an accurate evaluation of the extent and severity of ischemic compromised but viable myocardium likely to benefit from restoration of coronary flow both functionally and prognostically.

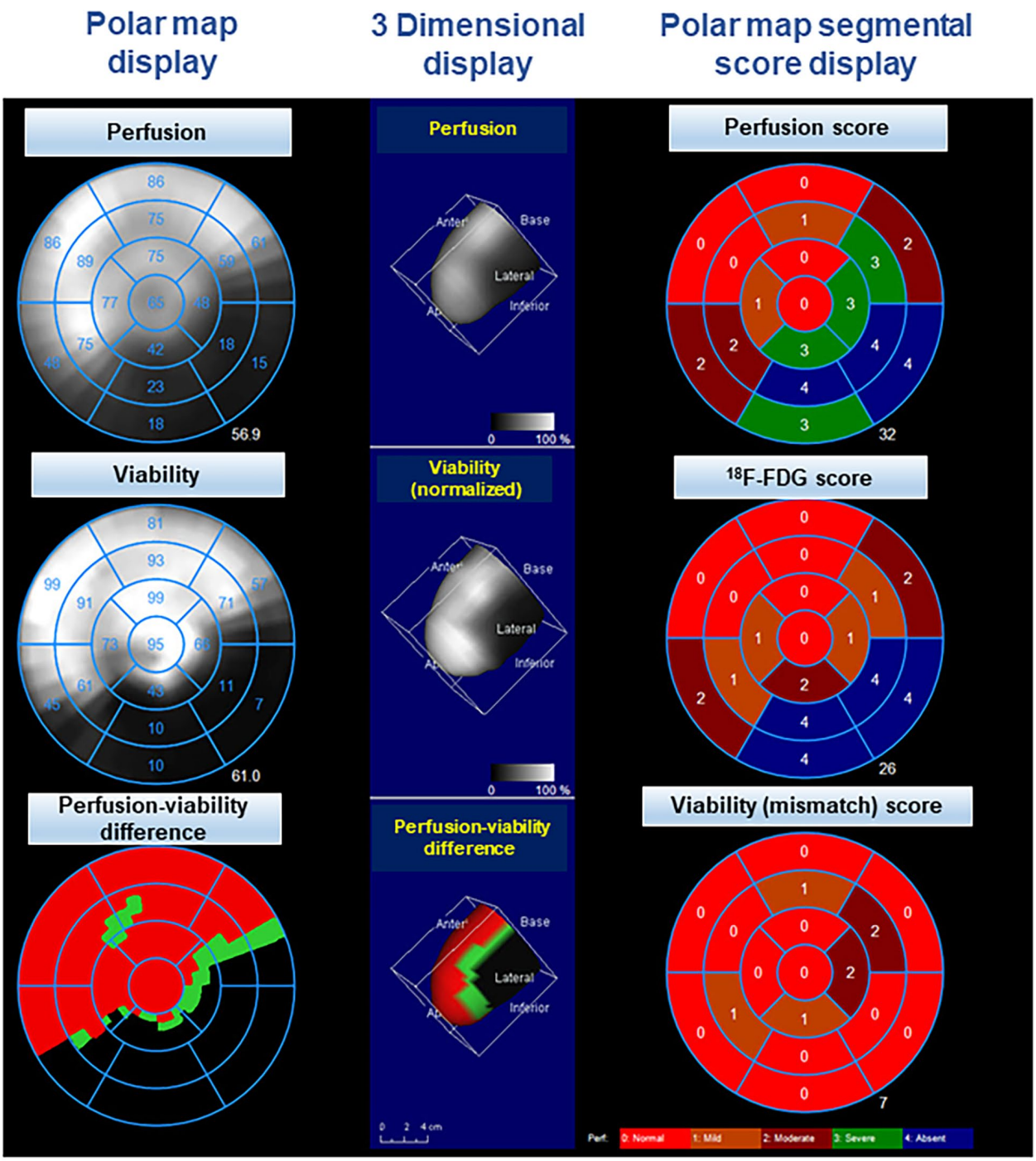


**Figure II.** Corresponding to the images shown in Figure 4, the polar map and three-dimensional display of the rest myocardial perfusion SPECT/CT images with $^{99m}$Tc-tetrofosmin and $^{18}$F-FDG-PET/CT images in a patient with ischemic cardiomyopathy, demonstrate a predominant *"match"*.

Quantification of rest perfusion with $^{99m}$Tc-tetrofosmin demonstrates a large (12-segments) and severe perfusion defect (summed rest score: 32) in the predominantly akinetic inferior and inferolateral walls with mild extension inferoseptally and laterally *(upper panel).* This is paralleled by predominant absence of $^{18}$F-FDG-uptake (score 26) *(middle panel)* that denotes a large area of "match" reflecting predominantly transmural necrosis (low residual mismatch score: 7) *(lower panel),* unlikely to benefit from coronary revascularization.