

Detection of Viable Myocardium by FDG SPECT Predicts Major Adverse Cardiac Events in Patients with Coronary Artery Disease and Left Ventricular Dysfunction

Vijayakumar V, Ali S, Briscoe EG, Bertolino P, Rahman A

Nuclear Medicine Section, Department of Radiology, UTMB, Galveston, TX, USA

Abstract

Positron Emission Tomography (PET) imaging with F-18 Fluorodeoxyglucose (FDG) is considered the gold standard for detection of myocardial viability. However, accessibility to PET is limited and, Single Photon Emission Computed Tomography (SPECT) imaging with FDG has been proposed as a viable alternative. SPECT imaging using Thallium-201 (Tl-201), on the other hand, though more widely available, has lower specificity compared to PET imaging. We retrospectively reviewed patients with known coronary artery disease (CAD) who underwent myocardial perfusion imaging (MPI) using Tc-99m Sestamibi (MIBI), Tl-201 and FDG as well as coronary angiograms. SPECT imaging using FDG, Tl-201 and MIBI, as well as coronary angiograms in 72 patients (age $60 \pm SD$ 14 years; 55 male, 17 females) with known CAD (37 pts with ≥ 3 vessels, 35 patients with ≤ 2 vessels) and left ventricular (LV) dysfunction (mean LVEF $24\% \pm 14$) were performed. Results of fifty seven patients who fulfilled the criteria for analyses, were analyzed in order to evaluate the predictability of major adverse cardiac events (MACE) during the 48 months period following the above cited four studies. MACE included fatal and nonfatal MI, requiring coronary artery bypass graft (CABG), further deterioration of heart failure and hospitalization with angina. It was observed that FDG SPECT has similar sensitivity but a better specificity for detecting myocardial viability in patients with known CAD and LV dysfunction. Based on this retrospective study it was concluded that detection of viable myocardium ($>5\%$ of total myocardium) on the FDG SPECT predicts major adverse cardiac events better compared to conventional imaging with Thallium-201.

Key Words: Viable Myocardium, F-18 FDG, Thallium-201, MACE, CAD

Correspondence

Atiar Rahman, M.D., Ph.D.
Director of Nuclear Medicine
University Of Texas MDACC
1515 Holcombe Blvd, Box 449
Houston, TX 77039
USA

Email: amrahman@mdanderson.org

World J Nucl Med 2006;5:74-78

Introduction

Myocardial perfusion imaging (MPI) plays a very important role in the detection of reversible left ventricular dysfunction, since coronary revascularization results in improvement in left ventricular contractility, ejection fraction, functional class and prognosis in patients with viable myocardium (1-10). Reversible dysfunction is mostly secondary to viable myocardium that is either 'stunned', 'hibernating' or both. 'Stunned' myocardium refers to severe left ventricular dysfunction following an episode of ischemic event like acute myocardial infarction while 'hibernating' myocardium is a chronic ischemic state believed to result from reduction of myocardial flow and metabolism. Revascularization of stunned or hibernating myocardium leads to improved function, where as no such improvement is noted in any of the above mentioned parameters from revascularization of nonviable myocardium. Therefore, identification of patients who would benefit most from revascularization is very important, and nuclear imaging is often used in addressing myocardial viability and thus in patient management (3). Several methods have been used to identify viable ischemic myocardium including positron emission tomography (PET) to measure blood flow and metabolism; and SPECT imaging for perfusion (1-3). Since uptake of radiotracers requires intact cell membrane, the status of viability may be qualitatively identified from the uptake of radiotracers in the myocardium at risk. However, the diagnostic accuracy of some of the techniques is limited and standard protocols for detecting viable myocardium are often modified to improve the diagnostic capability. Of these the following imaging techniques are often used: a) Rest-redistribution Thallium-201 (Tl-201); b) Stress-redistribution-reinjection Tl-201; c) Rest Tc-99m MIBI imaging (with gating and quantification); d) Dual isotope imaging and e) Metabolic imaging using F-18 Fluorodeoxyglucose (FDG). The aim of this communication is to evaluate the role of FDG-SPECT in assessing the viable myocardium and compare its usefulness to other techniques. Historically FDG PET is the gold standard for the assessment of myocardial viability.

Materials and Methods

A clinical protocol was written in 1995 to compare Tl-201, MIBI and FDG SPECT in their ability to assess myocardial perfusion and metabolism. The clinical study was approved by the Institutional Review Board (IRB) and patient accrual was carried out during 1995-2001. This is a post ad-hoc analysis. A preliminary report was published in an abstract form in 1996 and here we present the final analysis of the data. There were a total of 72 patients with known coronary artery disease (CAD). There were 55 males and 17 females with an average age of 68 years. The average body weight of the patient group was 100kgs. No exclusions to participate in the study were based on left ventricular ejection fraction (LVEF). Patient characteristics are as shown in Table 1. The images were interpreted independently by three board certified nuclear medicine physicians. Thirty seven patients had more than three vessel disease and 35 patients had two or less than two vessel disease. The mean LVEF of the entire patient population was 24%. All the patients underwent coronary angiograms. The following protocols were used for various radionuclide procedures:

Resting Thallium study

For resting redistribution thallium study, patients received 3 mCi of Tl-201 intravenously followed by SPECT of the chest 10 minutes later. 4 hrs later 1.5 mCi intravenous Tl-201 was re-injected followed by SPECT of the chest.

Stress and Rest MIBI study:

For rest and stress MIBI study, 8 mCi of MIBI was injected intravenously for rest study and 25 mCi intravenously at peak exercise or pharmacological stress followed by SPECT 1 hr later.

FDG SPECT study:

FDG was used as a non PET site in 1996-97. FDG was obtained from Positron Diagnostic Research Center at UT Houston. Additional license was obtained at the Cyclotron facility and at UTMB. FDG was produced around 8am in Houston and delivered to our institution UTMB at around 10 am. Signed informed consents were obtained from patients. Baseline glucose determination was done. Diabetics with a fasting glucose level of >120 mg/dl

received 10U of regular insulin. 50 grams of glucose intravenously over 15 minutes was administered followed by 10 -20 mCi FDG intravenously. About 45 to 60 minutes later SPECT of the chest using Dual head gamma camera with ultra high energy collimator with a 20% energy window centered at the 511 keV. The collimators were designed to handle 511 keV in the single mode with 8% septal penetration. The resolution of the system was 10mm FWHM at 10cms. The sensitivity of the collimators was 38% compared to collimators used for Tl-201 and Tc-99m Sestamibi.

Image Acquisition and processing:

SPECT acquisition was done for all radiopharmaceuticals using time per azimuth 20-30sec, 180 degree rotation, and 32 azimuths with dual head gamma camera FDG SPECT total acquisition time was 35 minutes with 2 minutes per step for 32 steps. The total number of counts ranged between four to six million. Decay correction was used accounting FDG half-life of 109 minutes. SPECT reconstruction was performed using Butterworth filter with frequency cutoff 0.35 and order of 7 Y-axis filters on. Oblique orientation was done with two pixel slice thickness.

Results

Results of a total of 57 patient out of the 72 studied were included here for the analysis. Results from fifteen patients were excluded due to incomplete data. Of the eligible 57 patients, 14 patients had all three studies and 43 had two studies (12 patients had Tl-201 and FDG SPECT; 31 patients had Sestamibi and FDG SPECT).

Our results can be summarized as follows: (a) none of the patients had larger defects on FDG SPECT compared to Tl-201 or Sestamibi SPECT; (b) twenty one patients had larger defects on Sestamibi SPECT compared to FDG SPECT; (c) five patients had larger defects on Tl-201 SPECT compared to FDG SPECT; (d) defect of similar sizes were reported in 8 patients with Sestamibi and FDG SPECT and in 6 patients with Tl-201 and FDG SPECT and (f) seventeen patients who had larger defects on MIBI and Tl-201 studies than FDG SPECT were obese (weight more than 80 kg)

Patients Characteristics	Range or number	Mean
Age	33-91 Years	68 Years
Sex:	M:55 F:17	N/A
Weight	53- 162 kg	100 kg
LVEF	15 65%	24%
CAD		
3 Vessel Involvement	37	N/A
≤ 2 Vessel Involvement	35	N/A
Old CABG	19	N/A
Old PCI	3	N/A

Table 1. Demographic profile of patients

The results of the three radio isotope studies were compared with the results of the coronary angiograms. It was observed that the perfusion defects seen in territories of the three major coronary arteries were not significantly different from one another, and that the results of both FDG SPECT and Thallium SPECT correlated well with those of coronary angiography. Attenuation artifacts on Thallium SPECT occurred more frequently and were not confined to easily identifiable subgroups of patients such as obese patients and women with large breasts.

The average specificity for Thallium SPECT was lower compared to FDG SPECT. In subgroup analysis, 19 patients underwent CABG of which 4 (21%) patients had no difference between FDG and Thallium /MIBI images, while 7 (36%) patients showed significantly larger viable areas on FDG images. Furthermore, 22 out of 49 patients (44%) with MACE had larger areas of perfusion defects with significant amount of viable myocardium (>5% of total myocardium) on the FDG SPECT images. Six patients had cardiac death, all showing multiple coronary territory and large defects on FDG and MIBI/Thallium imaging and all had LVEF <40%. Fifty two patients were hospitalized one to three times subsequent to the performance of the study. The MACE for hospitalization includes CHF, cardiac arrest, arrhythmias and chest pain.

Discussion

Detection of dysfunctional viable myocardium is an important aspect of metabolic imaging (8). There are several patterns of perfusion and functional abnormalities described in relation to viable myocardium. Viable myocardium exhibits three patterns including a) normal flow and glucose metabolism or b) good perfusion, reduced glucose metabolism or c) reduced flow, and normal glucose metabolism (flow- metabolism mismatch). Reduced flow and glucose metabolism (matched flow- metabolism defect) is characteristic of myocardial scar. Identification of viable myocardial tissue is important for further interventions. Viable myocardium demonstrates functional recovery after reversible dysfunction where as non viable myocardium demonstrates irreversible dysfunction. Stunned myocardium after acute ischemia and successful reperfusion has reversible and prolonged mechanical functional abnormalities. Hibernating myocardium is chronically hypoperfused. It is important to know whether low LVEF is associated with stunned or hibernating myocardium as improvement in LVEF is noted after recovery of perfusion.

The link between the improvement in LVEF and myocardial viability is well established. Furthermore, revascularization in the high risk patients with low LVEF and viable myocardium will decrease the incidence of cardiac death, future hospitalizations and improve symptoms (10).

Several radiopharmaceuticals and imaging modalities are

available to assess the myocardial viability (1-30). Tl-201 is the most commonly used radiopharmaceutical to assess myocardial viability. Myocardial uptake of Tl-201 is proportional to the blood flow and viable myocardium. About 4% of injected dose of Tl-201 is extracted by the resting myocardium. The rate of myocardial washout of Tl-201 is determined by the initial myocardial and blood concentration as well as myocardial blood flow. Viable myocardium demonstrates redistribution of Thallium at 4 to 24 hours after injection. However, Tl-201 is not ideal for gamma camera imaging due to its long half life and low energy. Attenuation artifacts are more common due to the low energy. In addition Tl-201 is cyclotron produced and needs deliveries from out side pharmacy. Finally the maximum dose given is limited due to the significant radiation dose to the target organ. Due to these reasons, other technetium radiopharmaceuticals were looked into to assess the myocardial viability. Technetium agents have better spatial resolution due to higher energy and short half life allowing administration of higher doses. The myocardial uptake is mediated by the mitochondria with no redistribution property. However using this procedure it is possible to assess perfusion and ventricular function at the same time. Tc-99m Sestamibi gated SPECT myocardial perfusion and wall motion assessments have been used successfully in the determination of myocardial viability.

In patients with known CAD and fixed defects on perfusion scan, it is important to distinguish viable from non-viable myocardium because of therapeutic intervention and prognostic value (1). In the evaluation of myocardial viability, Tl-201 is the radionuclide of choice due to its redistribution property (2, 3). There are several imaging protocols with Thallium; namely stress and 4 hour rest; or Stress, 4 hour rest and re-injection; or Stress, 4 hour rest and 24 hour rest or early and 4 or 24 hour delay with re-injection (2,3). The commonly used protocol is early rest and 24 hour delay with re-injection. It has been shown that in a significant percent of patients fixed defects noted on the Thallium images at 4 hours improve after re-injection and imaging at 24 hours (2, 3, and 6). In up to a third of patients who do not show redistribution of Thallium, improvement in perfusion is noted after re-vascularization. This phenomenon has been attributed to decrease sensitivity of Thallium in diagnosing severe chronically ischemic (hibernating) myocardium (1-4)

In spite of the wide use of Tl-201 in myocardial viability imaging, it lacks the characteristic ideal gamma imaging qualities because of its low energy, long half life and off-site cyclotron production. Technetium agents were tried as an alternative for the assessment of myocardial viability because of their high photon flux and better imaging quality, short half life and easy on-site availability. However, technetium agents lack the redistribution capability limiting their use. Subsequently with the introduction of gated SPECT several investigators have documented good correlation of myocardial contractility

and viability. Tc-99m agents have been used for this purpose either alone or in combination with Tl-201.

With the introduction of FDG-18, another alternative for the assessment of myocardial viability became available (12). FDG is a glucose analog taken up by myocardial cells through plasma membrane receptors and remains trapped in the cell. Ischemic and viable myocardium accumulate glucose and hence FDG is an ideal agent to assess the viability. However, F-18 FDG is a positron emitter with high energy requiring PET scanner. Due to the lack of wide availability of PET scanners, several other methods have been used for metabolic imaging, e.g., SPECT imaging with FDG to assess myocardial viability. We utilized this SPECT imaging with FDG to assess viable myocardium and compared its sensitivity and specificity with those of Thallium and Technetium based agents. We also looked into the outcome in patients with various degrees of ischemic defects noted on these different techniques.

Myocardial viability assessment is valuable in patients with known CAD and severe LV dysfunction or following myocardial infarction. To predict the recovery of regional function and improvement in global LV function after revascularization of the viable segment is an important aspect of myocardial viability testing. The clinical outcome in terms of major cardiac adverse events (fatal and nonfatal MI, progression to heart failure and angina) are less in patients with viable myocardium after revascularization. The LVEF and residual viable myocardial tissue after MI are prognostic factors.

With the availability of PET, F-18 FDG myocardial metabolism assessment has become the gold standard for the detection of viable myocardium. However, in 1996-97 due to limited PET availability, FDG SPECT was used for the first time as an alternative for myocardial viability assessment. There are several studies performed using FDG SPECT to establish the effectiveness in assessing myocardial viability (12, 15-19). The results were compared to FDG-PET, Tl-201 SPECT and Tc-99m Sestamibi SPECT. A study by Mabuchi et al (12) demonstrated attenuation artifacts in the inferior wall with FDG SPECT. Nevertheless the detection of myocardial viability has been shown to be better with FDG SPECT compared to Tl-201 SPECT and gated Sestamibi (20). Several of the studies demonstrated improvement in LV function after revascularization (10, 13, 22, 23). FDG SPECT with 511 keV collimation is less expensive and the technique is simpler. FDG SPECT showed sufficient sensitivity and resolution to detect myocardial viability (16-29).

Dobutamine echocardiography and MRI (24, 31-34) are the other imaging modalities that are being evaluated in the assessment of myocardial viability. Dobutamine stress echo has been shown to demonstrate improved sensitivity in predicting recovery of function after revascularization. Contrast enhanced MRI demonstrated lack of improvement in regional and LV global function with hyper enhancement

corresponding to the non-viable tissue.

Conclusion

FDG SPECT is an alternative modality where dedicated PET is not available in the assessment of myocardial viability. In comparison to Tl-201 and Tc-99m Sestamibi Gated SPECT, FDG SPECT has similar sensitivity but better specificity in detecting and defining perfusion defects for myocardial viability in patients with known CAD and low LVEF. Detection of viable myocardium (more than 5% of total myocardium) on FDG SPECT predicts major adverse cardiac events better compared to the rest re-injection Thallium myocardium perfusion study. Attenuation artifacts are less with FDG SPECT compared to the Thallium SPECT.

References

1. Abdel Fattah A, Kamal AM, Pancholy S, Iskandrian AS. Prognostic implications of normal exercise tomographic thallium images in patients with angiographic evidence of significant coronary artery disease. *Am J Cardiol* 1994; 74:769-71.
2. Hakki AH, Nestico PF, Heo J, Unwala AA, Iskandrian AS. Relative prognostic value of rest thallium-201 imaging, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring after acute myocardial infarction. *J Am Coll Cardiol* 1987; 10:25-32.
3. Iskandrian AS, Hakki AH, Kane SA, et al. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary arterial bypass grafting. *Am J Cardiol* 1983; 51:312-6.
4. Zaret BL, Rigo P, Wackers FJ, Iskandrian AS, et al. Myocardial perfusion imaging with Tc-99m tetrofosmin. Comparison to Tl-201 and coronary angiography in a phase III multicenter trial. Tetrofosmin International Trial Study Group. *Circulation* 1995; 91:313-9.
5. Villanueva-Meyer J, Ali S, Cesani F, et al. Implementing F18 deoxyglucose imaging in a hospital without a cyclotron. *Clinical Nuc Med*. 1996; 21:172.
6. Gonzalez P, Massardo T, Coll C, et al. The predictive value of Tl-201 rest-redistribution and 18F-fluorodeoxyglucose SPECT for wall motion recovery after recent reperfused myocardial infarction. *Ann Nucl Med*. 2004; 18:97-103.
7. Schindler TH, Nitzsche EU, Magosaki N, et al. Myocardial viability in patients with ischemic cardiomyopathy-evaluation by 3-D integration of myocardial Scintigraphic data-and coronary angiographic data. *Mol Imaging Biol*. 2004; 6:160-171.
8. Udelson JE, Bonow RO, Dilsizian V. The historical and

- conceptual evolution of radionuclide assessment of myocardial viability. *J Nucl Cardiol.* 2004; 11:318-34.
9. Go V, Bhatt MR, Hendel RC. The diagnostic and prognostic value of ECG-gated SPECT myocardial perfusion imaging. *J Nucl Med.* 2004; 45:912-21.
 10. Liao L, Cabell CH, Jollils JG, et al. Usefulness of myocardial viability or ischemia in predicting long term survival for patients with severe left ventricular dysfunction undergoing revascularization. *Am J Cardiol.* 2004; 93:1275-9.
 11. De Boer J, Slart RH, Blanksma PK, et al. Comparison of ^{99m}Tc-sestamibi single photon emission computed tomography for the assessment of myocardial viability. *Nucl Med Commun.* 2003; 24:251-7.
 12. Mabuchi M, Kubo N, Moriat K, et al. Value and limitation of myocardial fluorodeoxyglucose single photon emission computed tomography using ultra-high energy collimators for assessing myocardial viability. *Nucl Med Commun.* 2002; 23:879-85.
 13. Schinkel AF, Bax JJ, Sozzi FB, et al. Prevalence of myocardial viability assessed by single photon emission computed tomography in patients with chronic ischemic left ventricular dysfunction. *Heart.* 2002; 88:125-30.
 14. Kaltoft A, Bottcher M, Sand NP, et al. Tc-99m Sestamibi SPECT is a useful technique for viability detection: results of a comparison with NH₃/FDG PET. *Scand Cardiovasc J.* 2001; 35:245-51.
 15. Di Bella EV, Kadrmas DJ, Christian PE. Feasibility of dual-isotope coincidence/single-photon imaging of the myocardium. *J Nucl Med.* 2001; 42:944-50.
 16. Kerrou K, Toussaint JF, Froissart M, et al. Myocardial viability assessment with FDG imaging: comparison of PET, SPECT, and gamma-camera coincidence detection. *J Nucl Med.* 2000; 41:2099.
 17. Thorley PJ, Beacock DJ, Trickett CA, et al. ¹⁸F-FDG SPECT to assess myocardial viability: initial experience a hospital remote from a cyclotron. *Nucl Med Commun.* 2000; 21:715-8.
 18. Kukuchi K, Katafuchi T, Fukushima K, et al. Estimation of myocardial perfusion and viability using simultaneous ^{99m}Tc-tetrofosmin/FDG collimated SPECT. *J Nucl Med.* 2000; 41:1318-23.
 19. Hasegawa S, Uehara T, Yamaguchi H, et al. Validity of ¹⁸F-fluorodeoxyglucose imaging with a dual-head coincidence gamma camera for detection of myocardial viability. *J Nucl Med.* 1999; 40:1884-92.
 20. DePuey EG, Ghesani M, Schwartz M, et al. Comparative performance of gated perfusion SPECT wall thickening, delayed thallium uptake, and F-18 fluorodeoxyglucose SPECT in detecting myocardial viability. *J Nucl Cardiol.* 1999; 6:418-28.
 21. Schraml FV, Driver DR, Randolph R, et al. PET versus SPECT for determining myocardial tissue viability using fluorine-18-fluorodeoxyglucose. *J Nucl Med Technol.* 1997; 25:272-4.
 22. Bax JJ, Cornel JH, Visser FC, et al. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularization by fluorine-18 fluorodeoxyglucose single-photon emission computer tomography. *J Am Coll Cardiol.* 1997; 30:377-83.
 23. Bax JJ, Cornel JH, Visser FC, et al. F-18-fluorodeoxyglucose single-photon emission computed tomography predicts functional outcome of dysenteric myocardium after surgical revascularization. *J Nucl Cardiol.* 1997; 4:302-8.
 24. Bax JJ, Valkema R, Visser FC, et al. FDG SPECT in the assessment of myocardial viability. Comparison with Dobutamine echo. *Eur Heart J.* 1998; 18:124-9.
 25. Chen EQ, MacIntyre WJ, Go RT, et al. Myocardial viability studies using fluorine-18-FDG SPECT: a comparison with fluorine-18-FDG PET. *J Nucl Med.* 1997; 38:582-6.
 26. Bax JJ, Visser FC, Raymakers PG, et al. Caridac F-18 FDG SPET studies in patients with non-insulin-dependent diabetes mellitus during hyperinsulinemic euglycaemic clamping. *Nucl Med Commun.* 1997; 18:200-6.
 27. Martin WH, Delbeke D, Patton, JA, et al. FDG-SPECT: correlation with FDG-PET. *J Nucl Med.* 1995; 36:988-95.
 28. Burt RW, Perkins OW, Oppenheim BE, et al. Direct comparison of fluorine-18-FDG SPECT, fluorine-18-FDG PET and rest thallium-201 SPECT for detection of myocardial viability. *J Nucl Med.* 1995; 36:176-9.
 29. Drane WE, Abbott FD, Nicole MW, et al. Technology for FDG SPECT with a relatively inexpensive gamma camera. Work in progress. *Radiology.* 1994; 191:461-5.
 30. Yoshinaga K, Katoh C, Noriyasu, K, et al. Low-dose Dobutamine stress gated SPET for identification of viable myocardium: comparison with stress-rest perfusion SPET and PET. *Eur J Nucl Med Mol Imaging.* 2002; 29:882-90.
 31. Lund GK, Freyhoff J, Schwaiger M, et al. Prediction of left ventricular functional recovery by Dobutamine echocardiography, F-18 deoxyglucose or ^{99m}Tc sestamibi nuclear imaging in patients with chronic myocardial infarction. *Cardiology.* 2002; 98:202-9.
 32. Underwood SR, Bax JJ, vom Dahl J, et al. Imaging techniques for the assessment of myocardial hibernation Report of a Study Group of the European Society of Cardiology. *Eur Heart J.* 2002; 25:815-36.
 33. Thomason LE, Kim RJ, Judd RM. Magnetic resonance imaging for the assessment of myocardial viability. *J Magn Reson Imaging.* 2004; 19:771-88.
 34. Ingkanisorn WP, Rhoads KL, Aletras AH, et al. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol.* 2004; 43:2253-9