

Role of F-18 FDG Positron Emission Tomography (PET) in the Assessment of Myocardial Viability

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Positron emission tomography (PET) is a functional imaging technique with important clinical applications in cardiology, oncology, and neurology. In cardiac imaging, its role has been extensively evaluated in the noninvasive diagnosis of coronary artery disease and in the determination of prognosis. Additionally, cardiac PET with F-18 fluorodeoxyglucose (FDG) is very helpful in selection of patients with coronary artery disease and left ventricular dysfunction who would benefit from coronary artery revascularization. Cardiac PET is arguably considered by many as a gold standard in this particular application. F-18, unlike other positron emitters, has a reasonably long physical half-life, which permits its distribution through commercial radiopharmacies. This is further facilitated by increasing popularity of FDG PET in oncology, which makes cardiac FDG PET a practical option for hospitals and outpatient centers equipped with PET scanners. In addition, gamma camera single photon emission computed tomography (SPECT) systems, routinely used in nuclear medicine departments, can be equipped with coincidence circuit or high-energy 511 KeV collimators, providing a cost-effective means of FDG cardiac imaging. Myocardial utilization of glucose as a substrate is variable, depending, among other factors, on serum levels of glucose and insulin. Therefore, patient preparation is important in obtaining good-quality images and in turn allowing for accurate interpretation of myocardial viability. There are various protocols to choose from that provide diagnostic image quality in both diabetic and nondiabetic patients. Mismatch between blood flow and FDG metabolism, an indicator of viable, jeopardized myocardium, can predict postrevascularization improvement in left ventricular function, symptomatic relief, and long-term survival. (ECHOCARDIOGRAPHY, Volume 22, February 2005)

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Heart failure may be a consequence of either nonischemic or ischemic cardiomyopathy. Bonow et al.¹ pooled 13 randomized multicenter heart failure trials and observed that coronary artery disease was present in approximately 70% of > 20,000 enrolled patients. Coronary disease may result in repetitively stunned and/or hibernating myocardium, both potentially reversible causes of heart failure. Whereas patients with heart failure due to noncoronary etiologies may best benefit from medical therapy or heart transplantation, coronary revascularization has the potential to improve ventricular function, symptomatology, and long-term survival in those patients with heart failure at-

tributable to repetitive stunning and/or hibernation.

Viable myocardium may be characterized by several attributes, including cell membrane integrity, intact mitochondria, preserved glucose metabolism, preserved fatty acid metabolism, intact resting perfusion, and inotropic reserve.²⁻⁵ Not all of these are present in every viable myocardial segment. Therefore, a combination of techniques evaluating several of these parameters is generally used clinically in considering if repetitively stunned or hibernating myocardium exists as a cause of reversible left ventricular dysfunction, warranting coronary revascularization. Cell membrane integrity can be evaluated by assessing delayed thallium-201 uptake^{1,6} or the exclusion of MRI contrast in delayed images⁷⁻⁹ (absence of delayed hyperenhancement). Tc-99m sestamibi and tetrofosmin are radiotracers whose uptake is related to the

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presence of intact mitochondria.^{10–12} F-18 fluorodeoxyglucose PET and SPECT assess glucose metabolism.^{13–23} Free fatty acid metabolism can be evaluated with I-123 IPPA²⁴ and I-123 BMIPP. Resting perfusion can be evaluated by a variety of methods including Tc-99m sestamibi and Tc-99m tetrofosmin uptake, immediate thallium-201 uptake, as well as the transit of echocardiographic, MRI, and radiographic contrast material. Coronary flow reserve may be estimated by comparison of nitrate enhanced Tc-99m sestamibi uptake to baseline uptake. Inotropic reserve can be determined echocardiographically as an increase in regional left ventricular function after low-dose dobutamine infusion.²⁵

Positron emission tomography (PET) is being increasingly recognized as a noninvasive imaging technique with clinical applications in cardiology, oncology, and neurology. Positron emitters, such as O-15, C-11, F-18, Rb-82, and N-13, are short-lived radioisotopes, which require a cyclotron for their production and have proven to be very valuable in depicting physiology and metabolism. This is in part due to the fact that many positron emitters are radioisotopes of naturally occurring elements in the body. PET imaging has been extensively studied in the diagnosis of coronary artery disease, as well as determination of prognosis and assessment of myocardial viability in patients known to have coronary artery disease. The principal radiopharmaceuticals used in cardiac applications include Rb-82 or N-13 ammonia for myocardial perfusion imaging and F-18 fluorodeoxyglucose (FDG) for myocardial viability.

Following intravenous (IV) injection of positron-emitting radiopharmaceuticals and a variable amount injection-to-imaging delay (called “the uptake period”), tomographic images are acquired. The positrons, once emitted from the nucleus, interact with electrons within a few millimeters in the tissue, resulting in emission of two simultaneous high-energy photons, 180° apart from each other. Imaging of these high-energy photons is best achieved with multicrystal complete or partial ring detector systems, called “dedicated PET systems.” Crystal materials used in these systems, such as BGO, LSO, and GSO, possess variable degree of efficiency in absorbing these high-energy photons and converting them to light and provide high spatial and temporal resolution. In addition, gamma camera SPECT systems, routinely used in Nuclear Medicine departments, can

be equipped with coincidence circuit or high-energy 511 KeV collimators, providing a cost-effective means of imaging positron-emitting radiopharmaceuticals. In general, higher image resolution is more critical for oncological PET imaging than for cardiac PET imaging. Therefore, relatively poor image resolution of gamma camera SPECT systems is not a significant limitation in cardiac PET imaging.

Methods

There are a number of available positron emitters available to assess different markers of myocardial viability with cardiac PET.^{13–23,26–32} These include assessment of coronary arterial blood flow with Rb-82, O-15 water or N-13 ammonia; glucose metabolism as a marker of viability with F-18 FDG (Fig. 1 and Fig. 2); oxidative metabolism with C-11 acetate or O-15 oxygen; and integrity of membrane function with Rb-82. With the exception of F-18 FDG, however, all other methods utilize very short half-life positron emitters, requiring an on-site cyclotron, which is costly and available in a small number of mostly academic institutions. In contrast, due to increasing applications of F-18 FDG PET in clinical oncology, combined with its relatively longer half-life (approximately 120 min) when compared to other positron emitters, F-18 FDG is now widely available through a rapidly expanding network of commercial cyclotrons.

Patient Preparation

F-18 FDG is an analog of glucose allowing noninvasive evaluation of glucose metabolism. Glucose metabolism is an ATP-dependent process, requiring viable myocardial cells. Since myocardial cells utilize both fatty acids and glucose to meet their energy needs, FDG uptake in the myocardium will indicate viable myocardium, but since myocardium may also alternatively utilize fatty acids as a substrate lack of glucose uptake may not be necessarily indicative of nonviable tissue. Therefore, one needs to ensure predominantly glucose metabolism in the myocardium at the time of tracer injection and subsequent uptake period in order to achieve an accurate assessment of myocardial viability. Fasting the patient for 6–12 hours, and then administering a standardized glucose load, either orally or intravenously, results in rising plasma glucose and insulin levels, thereby making glucose the preferred

fuel substrate for myocardial metabolism. The following method, with either oral or IV glucose loading, is acceptable while evaluating myocardial viability with FDG in nondiabetic patients.^{33–35}

The fasting blood glucose is first checked. If it is less than 110 mg/dL, 100-gm glucose is administered orally followed by a repeat blood glucose measurement 30–45 minutes later. If it is less than 140 mg/dL, FDG is administered. If it is >140 mg/dL, IV boluses of regular insulin are administered in an effort to lower blood glucose below 140 mg/dL, and FDG is injected at that time. The IV glucose loading protocol involves 8 units of regular insulin and 10-gm dextrose IV bolus, followed by an infusion of insulin (1.7 μ /kg/min) and dextrose (10 mg/kg/min) for 60 minutes. Blood glucose is checked every 10 minutes. If, it is between 100 and 200 mg/dL at 20 minutes, FDG is administered. If it is >200 mg/dL, small IV boluses of regular insulin are given until the value is <200 mg/dL. FDG is administered at that time. To prevent hypoglycemia, 20% dextrose infusion is started (2–3 mg/kg/hour) at 60 minutes and continued during image acquisition.

The methods described above provide suboptimal image quality in most diabetic patients. Since coronary artery disease can frequently be a complication of diabetes, the critical question of myocardial viability in these patients requires modification of the protocol to optimize myocardial glucose metabolism.^{36–40} Even though some improvement in myocardial FDG uptake can be achieved by a longer injection-to-imaging time interval, optimal uptake can be accomplished with a euglycemic hyperinsulinemic clamp, a rigorous and time consuming procedure, allowing regulation of metabolic substrates and insulin levels. This method provides diagnostic image quality in most patients.^{36–38}

Injection and Imaging

Whereas the patient preparation for cardiac FDG metabolism component of imaging is generally the same regardless of the detector systems, the dose of FDG and the imaging protocol varies considerably depending on whether a standard gamma camera or dedicated PET scanner is used for imaging. In case of dedicated PET imaging systems, the dose injected further depends on whether two-dimensional (2D) (septa in) or three-dimensional (3D) (septa out) acquisition is employed. A 3D imaging protocol

is more applicable for PET scanners equipped with LSO or GSO crystals and newer BGO scanners with high-speed electronics and modified coupling of photomultiplier tubes and crystals. The following are general guidelines for imaging with a dedicated PET scanner.

For comparison of glucose metabolism with myocardial perfusion in order to assess myocardial viability, there are several available options, depending on the resources, availability of radioisotopes, and user preference. These include, positron emitters such as N-13 ammonia and Rb-82 for myocardial perfusion PET and thallium-201 or technetium-99m-based radiotracers for myocardial perfusion SPECT.⁴¹

At an optimal time (determined by one of the protocols described above), approximately 185–555 megabecquerel (MBq) [5–15 millicurie (mCi)] F-18 FDG are injected in a peripheral vein. After a delay of at least 45 minutes, imaging is performed. In patients with diabetes or elevated fasting blood glucose, imaging can be delayed for 90 minutes to achieve better blood pool clearance and uptake. Since glucose (and therefore, FDG) uptake is time dependent, this interval should be kept constant in patients who require comparison of baseline and follow-up scans. Imaging is generally performed for 10–30 minutes, depending on the PET detector sensitivity, and attenuation correction is routinely performed by means of a transmission scan using built-in rods made up of positron-emitting isotopes. For PET imaging, attenuation correction is critical to compensate for the differential soft tissue attenuation of the 511 keV photons emitted in 180° opposed directions.⁴² In case of newer PET/CT imaging systems, a CT scan can be used for attenuation correction. Ongoing research in this field will help address additional factors such as the effect of respiration that degrade image quality. For reconstruction of acquired data, filtered back projection (FBP) and newer iterative methods (such as OSEM-ordered subset expectation maximization) are available options, depending on the type of the scanner, computer systems available, and the user preference. Iterative methods, due to their clear advantage in improving noise characteristics in oncologic applications, are becoming increasingly popular. However, since OSEM methods do not improve noise characteristics in high uptake structures, such as the heart, the choice of reconstruction method used depends on the type of the scanner, the computer systems available, and the user preference.

Image Interpretation

Myocardial metabolism imaging with PET identifies preserved metabolic activity in dysfunctional and hypoperfused myocardial regions. As such, assessment of myocardial viability is accomplished by comparing FDG uptake to the regional distribution of myocardial perfusion, determined either by PET or SPECT. There are three possible combinations of blood flow and metabolism.

1. Normal blood flow and glucose utilization.
2. Regionally increased ^{18}F -FDG-uptake relative to regional myocardial blood flow (perfusion-metabolism mismatch) suggests myocardial viability and predicts reversibility of contractile dysfunction following revascularization (Fig. 2). Consideration should be given to the fact that such a mismatch does not always predict complete recovering of contractile function because scar and viable myocardium may coexist in such regions.
3. Regionally reduced ^{18}F -deoxyglucose uptake in proportion to regionally reduced myocardial perfusion (perfusion-metabolism match) suggests irreversibility of contractile dysfunction (i.e., absence of myocardial viability) (Fig. 1).

While evaluating the images for perfusion-metabolism match or mismatch, an important factor to remember is that relative FDG uptake should be normalized to areas with normal flow and not to segments with maximal FDG uptake. In addition, interpretation of F-18 FDG PET images and comparison with myocardial perfusion imaging should be meticulous, taking into account both technical and clinical factors.^{14,43,44}

Technical sources of errors include, but are not limited to patient motion, reconstruction artifacts, and poor count density. Patient motion is easier to identify on SPECT, due to sequential nature of imaging, which allows easy detection of vertical patient motion by evaluation of projection images displayed in endless-loop cine format. In contrast, due to simultaneous acquisitions of all projections in PET, motion affects all projections similarly and is therefore more difficult to identify. Due to the relatively short half-life of the PET radiotracers, repeat imaging is not an option. In addition, motion correction algorithms for PET imaging are not available yet. For all these reasons, every effort should be made to avoid

patient motion. This can be achieved by explaining the procedure to the patient beforehand, careful and comfortable positioning of the patient, and rigorous monitoring of image acquisition.

Reconstruction artifacts may occur if intense extracardiac activity is present adjacent to the myocardium. Due to physiological differences between F-18 FDG and Tc-99m-based myocardial perfusion SPECT tracers, the reconstruction artifacts are less likely with F-18 FDG PET when compared to myocardial perfusion SPECT. The likelihood of these artifacts is further reduced if an iterative reconstruction algorithm is used instead of filtered back projection. Therefore, when using myocardial perfusion SPECT imaging for comparison with FDG PET, the interpreting physician should be aware of technical and methodological differences between SPECT and PET.

Poor count density may be due to physiologic factors, such as poor myocardial utilization of glucose, particularly in diabetic patients or suboptimal patient preparation, such as inadequate glucose loading or improper timing of the FDG injection. Other factors affecting image statistics include body habitus, radionuclide dose infiltration, acquisition time, and scanner performance. Consequently, meticulous attention to the technique is essential in obtaining good quality images.

Limitations of FDG PET Myocardial Imaging

Whereas diabetes is an important risk factor in the development of coronary artery disease, and for morbidity and mortality in patients with coronary artery disease, diabetic patients pose a significant challenge in obtaining good quality FDG PET images. However, appropriate control of plasma glucose levels and the use of IV insulin provides good image quality in majority of diabetic patients. Heterogeneous FDG uptake in the myocardium may occur, more commonly in the fasting state.^{43,44} Patient groups studied in majority of reported series include those with chronic coronary artery disease. It is not clear whether the concept of flow-metabolism mismatch is as accurate in the setting of acute myocardial infarction. However, some publications emphasize the clinical use of F-18 FDG cardiac PET in early postinfarction patients.^{45,46}

Other Methods in the Assessment of Myocardial Viability

Myocardial PET with Other Tracers

Various other positron emitters have been studied for the assessment of myocardial viability.^{26,28,47-49} These include assessment of residual blood flow with Rb-82, O-15 water or N-13 ammonia; oxidative metabolism with C-11 acetate or O-15 oxygen; and the integrity of membrane function with Rb-82. Due to its high first pass extraction and metabolically inert characteristics, O-15 water is ideally suited for blood flow measurement. However, as with many short-lived isotopes, performance of O-15 (half-life: 2 min) water PET requires an on-site cyclotron. Additionally, the tracer is present in both the cardiac chambers and the myocardium, requiring subtraction of cardiac blood pool for the accurate assessment. Unlike O-15 water, N-13 ammonia localizes in the myocardium and does not persist in cardiac blood pool. This characteristic, combined with relatively longer half-life of 10 minutes, allows better quantitation of regional myocardial tracer distribution. Rb-82 is also retained by the myocardium. In addition, it is a potassium analog and therefore, a marker of disrupted integrity of the cell membrane. Even though its short half-life (75 sec) would allow repeated studies, inadequate image counting statistics usually prevents such sequential imaging. In addition, positrons emitted from the Rb-92 nucleus possess relatively higher energy, thereby traveling longer distances before interacting with electrons. This in turn compromises image resolution.

As an alternative to glucose metabolism as an indicator of viability, C-11 acetate PET that evaluates residual oxidative metabolism, has been proposed as a marker of myocardial viability.⁵⁰⁻⁵² Oxidative metabolism in dysfunctional but viable myocardium was comparable with that in normal myocardium, whereas oxidative metabolism, when compared to normal myocardium, was reduced to 66% in irreversibly dysfunctional segments.⁵¹ However, in a study involving patients with recent myocardial infarction,⁵³ there was no difference in oxidative metabolism between myocardial segments having a matched versus a mismatched pattern. Also, a relatively short half-life (20 min) makes availability of C-11 limited to the centers with cyclotrons.

Myocardial SPECT With Tc-99m Cardiac Flow Tracers

Theoretically, the volume of viable myocardium and consequently the degree of regional functional recovery should be directly related to resting myocardial perfusion. Therefore, functional recovery should be proportional to the amount of uptake of resting flow tracers such as Tc-99m sestamibi in regions of left ventricular dysfunction demonstrated by gated perfusion SPECT, echocardiography, or contrast ventriculography. Indeed, published reports^{14,54-56} have demonstrated that regional functional recovery following revascularization increases in proportion to Tc-99m sestamibi uptake. In those segments with >55% maximal uptake the likelihood of functional recovery is >70%. However, there are several drawbacks to this approach. First, factors such as normal physiological variations in tracer distribution (e.g., decreased inferior count density in men) confound this type of semiquantitative analysis. Secondly, in actual clinical practice there are many segments where viability is questioned in which relative uptake falls between 50% and 60%, rendering the results equivocal. Finally, and perhaps most importantly, there are two different conditions that may result in a mild-to-moderate decrease in uptake of radionuclide flow tracers: (i) chronically decreased blood flow in hibernating, viable myocardium, and also (ii) a nontransmural infarct supplied by either a patent or occluded proximal coronary vessel. Whereas revascularization will likely be beneficial in the former situation, it will not be likely to improve regional function in the latter.

Because of these limitations of semiquantitative analysis of a single SPECT image acquired after the injection of a radionuclide flow tracer, several investigators, particularly from Italy,^{10,11} have used improvement in the regional concentration of a flow tracer injected after IV, oral, or sublingual nitrate administration as a marker of viability. Tracer uptake should increase in the distribution of hibernating myocardium supplied by a patent coronary artery. Such enhancement in tracer uptake will not be observed in the presence of baseline perfusion abnormalities due to attenuation artifact, physiologic regional variations in tracer distribution, or nontransmural myocardial infarction.

Myocardial Viability With Tl-201

There are a number of studies evaluating the accuracy of delayed thallium uptake in predicting functional recovery. More than half of these studies employed rest-redistribution protocols wherein radionuclide imaging was performed immediately after thallium-201 injection and again at a delayed interval.^{1,6,54,57} The mean sensitivity in predicting functional recovery was 86%. However, specificity was only 59%, indicating that in 41% of patients with delayed thallium-201 uptake there was no evidence of regional functional recovery following revascularization. However, it is now known that in patients with hibernating myocardium (in contradistinction to those with only stunning), functional recovery may not occur until as long as 6 months after revascularization. Many of these published studies performed follow-up for only 3 months or less, so actual specificity may have been underestimated. Moreover, it is known that the probability of functional recovery increases with increasing amounts of jeopardized myocardium. Some studies failed to establish a threshold for the degree of defect reversibility as a predictor of recoverable function. Finally, we must keep in mind that improved outcome and long-term survival following revascularization may not only be due to functional recovery but also to the prevention of remodeling and arrhythmogenesis afforded by revascularization. However, it has yet to be demonstrated that these latter beneficial effects of revascularization can be predicted by thallium-201 viability imaging protocols. Marin-Neto et al.,⁵⁷ in a study of 44 patients with chronic coronary artery disease and left ventricular dysfunction, compared exercise thallium SPECT with 3- to 4-hour redistribution and reinjection imaging and PET with F-18 FDG and O-15-water. In the subgroup of patients with moderate-to-severe left ventricular dysfunction, information regarding regional myocardial viability provided by SPECT and PET was similar. However, in patients with severely reduced left ventricular function, there was >20% discordance of regions manifesting severe irreversible thallium defects. Because 4-hour defects often redistribute late, delayed imaging may enhance assessment of tissue viability. In a study comparing F-18 FDG PET and 24-hour Tl-201 SPECT, Brunken et al.⁵⁸ found viability as evidenced by glucose metabolic activity on PET in the majority of fixed 24-hour Tl-201 defects. Patients with very se-

vere 24-hour Tl-201 defects were less likely to exhibit metabolic activity on PET. Bonow et al.⁵⁹ performed stress-redistribution thallium imaging followed by reinjection of Thallium at rest and reacquisition of SPECT imaging. The data were compared with F-18 FDG PET. In the subgroup of segments with irreversible thallium defects and mild or moderate reduction in thallium activity, majority of the segments were considered viable on the basis of PET. In contrast, FDG uptake was present in only 51% of segments with severe reduction in irreversible thallium defects. Although Tl-201 SPECT is a widely available option for assessment of myocardial viability, there are reports of significantly higher sensitivity of FDG PET when compared to Tl-201 rest-redistribution imaging.^{60,61}

Dobutamine Stress Echocardiography

Dobutamine is a synthetic catecholamine, capable of augmenting myocardial contractility at low doses and causing increased heart rate and peripheral vasodilatation at higher doses. Dobutamine-induced increases in heart rate, LV ejection fraction, and mean arterial pressure are accompanied by decrease in pulmonary capillary wedge pressure and better contractility in the regions containing viable, jeopardized myocardium.⁶² In these regions, there is a biphasic response, low doses of dobutamine resulting in better contractility but higher doses resulting in impaired wall motion. In the evaluation of viable myocardium in patients undergoing IV thrombolysis following acute anterior wall myocardial infarction, Pierard et al.⁶³ compared echocardiography before and during dobutamine infusion with PET. Echocardiography and PET were repeated at a mean interval of 9 months. In both initial and follow-up studies, concordant interpretation of the two techniques was found in 79% of the affected segments. They concluded that echocardiography during dobutamine infusion is a promising method to unmask viable myocardium in acute myocardial infarction. Early recovery of perfusion in the area at risk was associated with a good functional outcome, whereas a high glucose to perfusion ratio suggested jeopardized myocardium that frequently lost viability. Contractile reserve can be assessed relatively easily using standard echocardiographic techniques. In 32 published studies correlating postrevascularization functional recovery

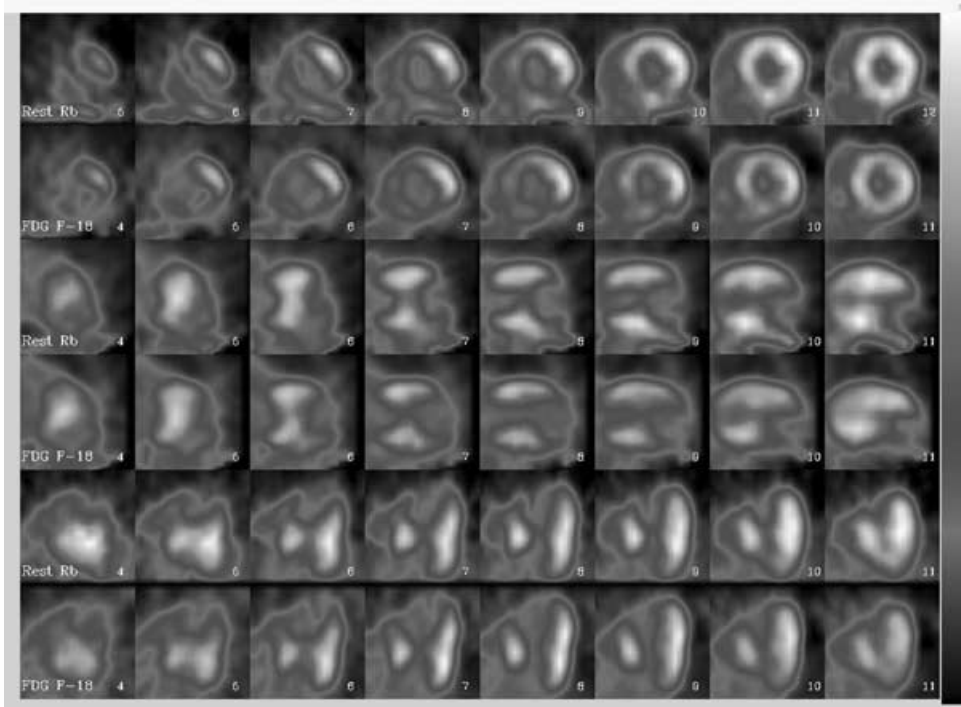


Figure 1. Resting Rb-82 and FDG PET images demonstrate a large and severe apical/inferoapical defect. This flow-metabolism match pattern is most consistent with myocardial scarring.

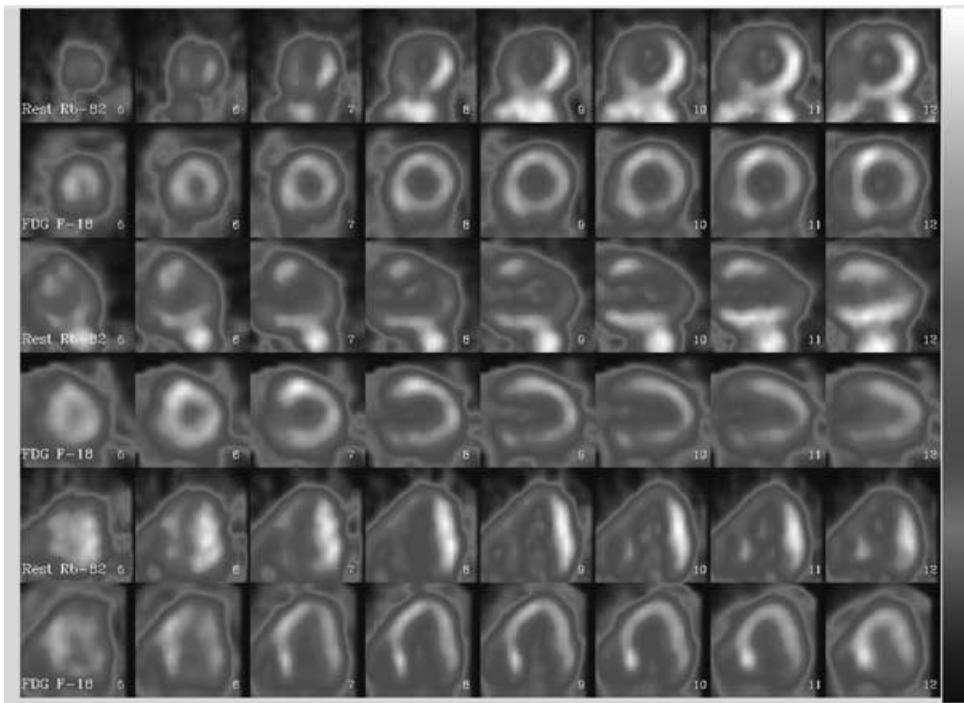


Figure 2. Resting Rb-82 PET perfusion images demonstrate apical, anterior, and septal defects. FDG PET images demonstrate normal glucose metabolism in these segments. This flow-metabolism mismatch pattern is suggestive of resting ischemia of viable, jeopardized myocardium.

with contractile reserve demonstrated following low-dose dobutamine infusion; the mean sensitivity and specificity were 82% and 79%, respectively.⁶⁴ Of note, the reported “specificity” (no evidence of contractile reserve and no subsequent evidence of functional recover after revascularization) was higher than that for either delayed thallium-201 uptake or F-18 FDG uptake. However, this is not surprising since the endpoint of all of these studies was functional recovery, and low-dose dobutamine echocardiography specifically evaluates functional improvement. It is yet to be determined if other important parameters such as the prevention of ventricular remodeling and the prevention of life-threatening arrhythmias are better predicted by radionuclide or echocardiographic techniques. In addition, recent enhancements to echocardiography, such as echo contrast, harmonic imaging, and power Doppler imaging, all of which enhance endocardial border definition, may improve echocardiography’s diagnostic accuracy in detecting contractile reserve.

Due to various factors, including variations in dobutamine protocols, differences in the patient selection criteria, and the length of follow-up, there is a wide reported range of predictive accuracy for recovery of contractile dysfunction from 77% to 95%.⁶² A comparison analysis showed higher specificity but a lower sensitivity of stress echocardiography for detection of reversible contractile dysfunction.⁶⁴

Role of MRI in the Assessment of Myocardial Viability

The spatial resolution of magnetic resonance imaging, particularly with regard to differentiating subendocardial versus transmural myocardial abnormalities, is far superior to SPECT, PET, and echocardiography. MRI techniques have been developed to detect myocardial deformity or torque during ventricular contraction. Whereas regions of viable myocardium will demonstrate deformity of “tagged” magnetic lines during systole, myocardial scars will show no such deformity. A more recent and technically less demanding MRI method to assess myocardial viability is the phenomenon of “delayed hyperenhancement.” Following MRI contrast injection, T₁- and T₂-weighted images will demonstrate decreased signal intensity both in regions of myocardial scar and also in areas of resting ischemia (i.e., hibernating myocardium). However, in repeat, delayed images,

myocardial scars will accumulate contrast (delayed hyperenhancement) whereas resting ischemia will not. It has been demonstrated that if less than 25% of the thickness of a myocardial wall demonstrates delayed hyperenhancement, wall motion will improve following revascularization. In a study of 31 patients with ischemic heart failure, Klein et al.⁶⁵ compared MRI and F-18 FDG PET. They concluded that MRI hyperenhancement as a marker of myocardial scar closely agreed with PET data. However, MRI seemed to identify scar tissue more frequently than PET, reflecting the higher spatial resolution. In a study of 35 patients with chronic coronary artery disease, myocardial infarction and regional akinesia or dyskinesia, Baer et al.⁶⁶ compared rest/dobutamine MRI and FDG-PET and found that dobutamine-induced wall thickening was a better predictor of residual metabolic activity than end-diastolic wall thickness at rest. However, when viability was defined as the presence of at least one MRI parameter, improved sensitivity without a major decrease of specificity, or positive predictive accuracy. In a recent study, Kuhl et al.⁶⁷ compared FDG PET, Tc-99m tetrofosmin SPECT, and contrast-enhanced MRI (ceMRI) for assessment of nonviable myocardium in 26 patients with chronic coronary artery disease and left ventricular dysfunction. Segmental glucose uptake on PET was inversely correlated ($r = -0.86$, $P < 0.001$) to segmental extent of hyperenhancement (SEH) on MRI. Using SEH threshold of 37%, sensitivity and specificity of ceMRI to detect nonviable myocardium as defined by PET were 96% and 84%, respectively.

Predictive and Prognostic Value of F-18 FDG PET

Tillisch et al.¹⁸ (Table I) evaluated 17 patients with 73 dysfunctional myocardial segments. Sixty-seven of these regions were revascularized adequately. At 3-month follow-up, there was improvement of wall motion in 85% of segments with normal flow and glucose metabolism or with flow-metabolism mismatches. In contrast, only 8% of segments with flow-metabolism matched defects showed functional improvement. The positive predictive value of preserved F-18 FDG uptake in predicting functional recovery was 85%, and the negative predictive value was 92%. The predictive value of F-18 FDG PET is related to the extent of mismatches and the severity of

TABLE I

Diagnostic Accuracy of Positron Emission Tomography Blood Flow-¹⁸F-2-Deoxyglucose Studies for Recovery of Regional Left Ventricular Dysfunction

Authors	Number of patients	Number segments	Number segments with WMA		Sensitivity	Specificity	PPV	NPV	Accuracy
			Improved	Not Improved					
Tillisch ¹⁸	17	67	41	26	95	80	85	93	88
Tamaki ¹⁹	22	48	23	23	78	78	78	78	78
Tamaki ⁷⁴	11	58	50	6	100	38	80	100	82
Marwick ⁷⁵	16	85	35	50	71	78	88	79	74
Lucignani ⁴¹	14	54	38	15	82	88	95	80	91
Carrel ⁷⁶	21	23	19	4	85	50	84	75	83
Gropier ^{51,52}	34	118	73	43	83	50	52	81	63
Knuuti ⁷⁷	48	90	87	13	88	79	84	84	84
Tamaki ⁷⁸	43	130	59	71	88	82	76	92	85
Maes ⁷⁹	20	20	12	8	80	80	67	75	70
Gerber ⁸⁰	39	39	24	15	75	67	78	67	71

WMA = wall motion abnormalities prior to coronary revascularization; PPV = positive predictive value; NPV = negative predictive value.

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the left ventricular dysfunction prior to revascularization.^{18,19,68} In patients with a perfusion/metabolism mismatch involving only one myocardial segment, the left ventricular ejection fraction remained unchanged. In patients with mismatches involving two or more myocardial segments, LVEF increased significantly.^{18,19} The predictive accuracy of F-18 FDG cardiac PET is also related to the severity of the left ventricular dysfunction prior to revascularization.⁶⁸ It was higher in patients with severe as opposed to mild hypokinesis. The predictive value was highest in segments with akinesis.

There are a number of studies evaluating the prognostic value of F-18 FDG cardiac

PET^{20-23,69} (Table II) with regard to future cardiac events. In patients with prior myocardial infarction but stable coronary artery disease, FDG uptake was shown to be the most important independent predictor of future cardiac events.²² Other studies have shown flow-metabolism mismatch as an indicator of cardiac death.^{20,69} Di Carli et al.²³ have shown a correlation between the extent of mismatches and subsequent improvement in cardiac failure symptoms.

With respect to the perioperative course of patients following coronary artery bypass surgery, two investigations reviewed outcomes based on conventional selection criteria with and

TABLE II

Cardiac Events Rates in Studies Addressing Prognostic Value of Pet Blood Flow-Metabolism Imaging

Authors	Number of patients	Age (year)	LVEF (%)	Follow-up (months)	PET viable		PET nonviable	
					Revascularized (%)	Medical treatment (%)	Revascularized (%)	Medical treatment (%)
Di Carli ⁶⁹	93	65 ± 4	25 ± 6	13 ± 6	3/26 (11.5)	7/17 (41.2)	1/17 (5.9)	3/33 (9.1)
Eitzman ²⁰	82	59 ± 10	35 ± 14	12	3/26 (11.5)	9/18 (50)	1/14 (7)	3/24 (12.5)
Lee ²¹	129	68 ± 12	35 ± 15	17 ± 9	8/49 (16.3)	13/21 (61)	2/19 (10.5)	7/40 (17.5)
Total	304				14/101 (10.1), P = 0.014	29/56 (52), P = 0.042	4/50 (8)	13/97 (13.4)

PET = positron emission tomography; LVEF = left ventricular ejection fraction.

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without the blood flow-metabolism mismatch information.^{70,71} Among 317 patients with coronary ischemia and left ventricular dysfunction, conventional criteria (left ventricular ejection fraction >20%, suitable coronary anatomy for bypass grafting, and lack of significant comorbidities) were applied in the subgroup of 122 patients undergoing coronary artery bypass surgery. In the second subgroup of 195 patients, the presence of a blood flow-metabolism mismatch was considered a prerequisite. In this subgroup, 145 patients showed a mismatch pattern and subsequently underwent bypass grafting. This subgroup showed fewer preoperative complications, including the need for intra-aortic balloon pump and inotropic support. The 30-day mortality rate in the latter subgroup was only 0.01%, in sharp contrast to the rate of 17.2% in conventional criteria subgroup.

Several studies have established a strong relationship between blood flow-metabolism mismatches and subsequent development of myocardial infarction or cardiac death. In these long-term studies, the combined data reveal that when there was presence of blood flow-metabolism mismatch, there was an average of 24% incidence of cardiac death in 1–2 years.⁷² When mismatch was absent, this rate dropped to 10% during the same period. These results make a strong argument for the value of blood flow-metabolism mismatch in prognostication as well as in selection of patients likely to benefit from coronary artery bypass surgery. In the patients selected on the basis of blood flow-metabolism mismatch, 1-year and 5-year survival is reported to be as high as 70–80%. In contrast, when patients were managed conservatively despite the mismatch, the survival was only 40–50%. In addition, relief of ischemia, as documented by preoperative flow-metabolism mismatch, improves symptoms of congestive heart failure and improves quality of life. However, one investigation reported similar 5-year survival rates achieved in patients with ischemic cardiomyopathy, irrespective of presence of absence of flow-metabolism mismatch,⁷³ questioning the value of cardiac FDG PET in this setting.

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