Medical Review of F-18 Fluorodeoxyglucose Positron Emission Tomography (F-18 FDG PET) for Cardiac Indications

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I. Introduction

The purpose of this review is to determine whether existing clinical data are sufficient to demonstrate the safety and efficacy of F-18 FDG PET imaging in support of an indication for cardiac use.[1] Positron emission tomography (PET) imaging with F-18 fluorodeoxyglucose (F-18 FDG) has been used in cardiology primarily to evaluate myocardial hibernation. This review summarizes and evaluates a number of literature studies in which PET imaging with F-18 FDG was used to assess myocardial hibernation in patients with coronary artery disease and left ventricular dysfunction.

F-18 FDG is an analog of glucose that contains the radionuclide Fluorine F-18. Fluorine F-18 decays by positron (β+) emission and has a physical half-life of 109.7 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (i.e., positron annihilation). As a glucose analog, F-18 FDG is transported into myocytes by the glucose transporter and can enter metabolic glucose pathways. After phosphorylation by hexokinase, F-18 FDG is not metabolized further, and the reverse reaction (dephosphorylation by glucose-6-phosphatase) is minimal. Phosphorylated F-18 FDG is therefore trapped within myocytes.

Under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids, and most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being

[1] On 21 November 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA) into law. Section 121 of FDAMA requires FDA to develop appropriate procedures for the approval of PET drugs pursuant to section 505 of the Federal Food , Drug, and Cosmetic Act (21 U.S.C. 355). As part of FDA's efforts, this review is being conducted to determine whether the medical literature supports approval of F-18 FDG, one of the more commonly used PET radiopharmaceuticals, for use in cardiac imaging.

converted into glycogen. Under these conditions, as described above, phosphorylated F-18 FDG accumulates in the cell and can be detected with PET imaging.

Myocardial hibernation is defined as chronic, reversible left ventricular dysfunction due to coronary artery disease.[i] The ability to identify hibernating myocardial tissue is potentially of great clinical significance. Hibernating myocardium with longstanding systolic dysfunction may be able to regain some, or all, of its function after successful coronary revascularization with procedures such as coronary artery bypass grafting (CABG) or coronary angioplasty. However, infarcted or scarred myocardium will not regain function after such procedures. Thus, the ability to distinguish hibernating from infarcted tissue before revascularization may be useful clinically in helping to predict the likelihood of left ventricular functional recovery after revascularization.

Because uptake and phosphorylation of F-18 FDG are active cellular processes, the localization of F-18 FDG in asynergic myocardium has been investigated as being a marker for myocardial viability. On PET imaging, increased accumulation of F-18 FDG in myocardial regions with reduced perfusion, or flow-metabolism mismatch, has been used to detect hibernating myocardium. Conversely, a matched defect, with concordant reductions in both perfusion and F-18 FDG accumulation, has been viewed as being a marker for a myocardial scar. Other imaging methods which have been used to assess myocardial hibernation include stress echocardiography with dobutamine, single-photon-emission-computed tomography (SPECT) with thallium-201, radionuclide imaging with technetium-99m sestamibi, and PET imaging with C-11 acetate. However, none of these other methods have indications for the evaluation of myocardial hibernation.

II. Evaluating the Effectiveness Data for F-18 FDG PET Imaging for Identifying Myocardium with Reversible Loss of Systolic Function in Patients with Coronary Artery Disease and Left Ventricular Dysfunction

A. Data Sources

FDA's Center for Drug Evaluation and Research (CDER) conducted a literature search of recent peer-reviewed medical journals to evaluate the F-18 FDG effectiveness data. The search criteria included the following items: studies published from January 1990 to July 1, 1998 identified as human clinical studies with F-18 FDG in PET, written in English, found by searching on-line databases of Medline (n=250), Embase (n=274), Derwent (n=38), Cochrane (n=33), Cancerlit (n=25), Biosis (n=9), and HSTAR (n=3). Of the articles generated by this search, the medical reviewer further narrowed the search by use of the search terms "viability" and "hibernation." FDA also solicited references from the PET community on the use of F-18 FDG in cardiac PET imaging from any time period published in peer-reviewed journals. Review articles on F-18 FDG PET cardiac imaging were identified, including one recent pooled analysis.[ii] To ensure completeness, the reference list of Guidelines, Scientific Statements, and Position Statements from three professional organizations were reviewed, as were the reference sections of some of the articles identified in the above searches.[iii,iv,v] One abstract was also identified because of the number of patients enrolled and because it describes a multicenter study.[vi]

For primary review, I selected ten articles of prospective studies in patients with coronary artery disease and left ventricular dysfunction in which cardiac imaging with F-18 FDG was used to assess regional myocardial hibernation. Each article allowed the results of cardiac PET F-18 FDG imaging to be compared with the functional outcome of the left ventricle ("truth"), as described in the next section. In addition, several other selected articles were reviewed in support of the potential clinical usefulness of such cardiac F-18 FDG PET evaluations. Each of the ten principal studies was considered to be well controlled, and in aggregate, the articles provide an adequate data base upon which to judge the effectiveness of F-18 FDG in identifying myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction.

B. Approach to the Review

In a dysfunctional left ventricle, hibernating myocardium may be identified operationally by determining whether myocardial regions regain systolic function after coronary revascularization. In each of the principal studies summarized in this review, the performance of PET imaging with F-18 FDG is therefore measured against a functional outcome: the recovery (or lack of recovery) of regional systolic function after myocardial revascularization with either CABG or angioplasty. Thus, in these studies, "truth" is ascertained by a functional outcome--recovery or lack of recovery--after revascularization. Truth is not ascertained by comparing the results of PET imaging with F-18 FDG to those of a "gold standard." The various technologies by which this recovery of systolic function was assessed in each of these studies (including echocardiography, radionuclide ventriculography, and contrast ventriculography) are each sufficiently valid and reliable to allow such determinations of functional outcome to be made.

Stated differently, some of the principal studies assessed myocardial hibernation by additional methods (e.g., stress echocardiography with dobutamine). Although the results of these other methods were noted in this review for completeness, these results were not used to assess the efficacy of PET imaging with F-18 FDG. That is, the efficacy of PET F-18 FDG was assessed on its own merits and by its ability to predict systolic recovery (i.e., by evaluating its predictive validity). Efficacy was not assessed by comparison of PET imaging with F-18 FDG to other modalities or to a gold standard (i.e., by evaluating its criterion validity). Efficacy was evaluated by comparing predictions of functional recovery (made with PET F-18 FDG before revascularization) with actual functional outcome after revascularization.

The studies are all of a similar design, even though different technologies may have been used to make the various assessments. Thus, enrolled patients were typically patients with coronary artery disease and left ventricular dysfunction who were scheduled for coronary revascularization. These patient entry criteria were typically documented with coronary arteriography and with either contrast or radionuclide ventriculography.

Before revascularization, except as noted, the following core parameters were assessed:

- Myocardial metabolism (by positron emission tomography with F-18 FDG).

- Myocardial perfusion (by PET with N-13 ammonia, PET with Rb-82, thallium-201 scintigraphy, SPECT with Tc-99m sestamibi, or PET with C-11 acetate, depending on the study). However, in some cases, myocardial perfusion was not assessed as part of the study.
- Ventricular function, such as segmental wall motion (by two-dimensional echocardiography, radionuclide ventriculography, contrast ventriculography, or transesophageal echocardiography, depending on the study).

After revascularization with either CABG or angioplasty, ventricular function was reassessed (with two-dimensional echocardiography, radionuclide ventriculography, contrast ventriculography, or transesophageal echocardiography, depending on the study).

The performance of PET F-18 FDG imaging has been emphasized in the results section of each study, even if the manuscript had other principal objectives. For each study, the results of F-18 FDG PET imaging as a predictor of functional recovery have been displayed in 2x2 tables as in the prototype below. Diagnostic performance measures such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, likelihood ratio(+), and likelihood ratio(-), were calculated with conventional formulas. Confidence intervals for these binomial parameters were calculated with statistical software by either the normal theory method or the exact method, as appropriate. Other results and statistical evaluations are included in this review as they were described in the manuscript.

Table 1: Prototype of 2x2 Table

	Improved Function after Revascularization (i.e., truth)	
Prediction of Functional Recovery F-18 FDG PET (i.e., test results)	Yes	No
Yes	true positive	false positive
No	false negative	true negative

Given the relatively small number of patients in each study, the performance measures from any particular study should be interpreted with caution. Because of the small sample sizes, the widths of the confidence intervals for these measures are rather broad, and these measures may not be generalizable to larger populations. Moreover, performance measures such as positive predictive value, negative predictive value, and accuracy will vary depending on prevalence and should therefore be interpreted even more carefully. Finally, the studies divided the left ventricle into different numbers of segments and divided the left ventricle in different ways. This means that a diagnostic performance measure made "by segment" in one study, including sensitivity, specificity, PPV, NPV, and accuracy, may have a somewhat different clinical meaning than the corresponding diagnostic performance measure in other studies.

As used in this review, the terms "hibernation" and "viability" are used synonymously because in the manuscripts they have been used by different authors to describe essentially the same myocardial state. For the purposes of this review, these terms refer to myocardium with reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction.

A draft of this review was shared with FDA's Medical Imaging Drugs Advisory Committee on 28 June 1999, and after consideration of the Committee's comments and recommendations, the draft review was modified as appropriate.

C. Published Literature

The published clinical studies are described below, listed in alphabetical order by the last name of the first author. These published studies allowed FDA to evaluate the effectiveness of F-18 FDG PET in the assessment of reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction. The studies shared the following design elements: 1) Each study allowed the predictive performance of F-18 FDG to be compared with "truth" in terms of a functional outcome. 2) Each study was prospective and the enrolled patients (when considered in aggregate) are sufficiently similar, though not identical, to the population in which F-18 FDG will likely be used. 3) Each study specified the methods by which F-18 FDG PET images were analyzed and the criteria used to make predictions of functional outcome (e.g., predictions of reversible vs. irreversible). 4) Each study specified the methods by which myocardial function was analyzed (e.g., by echocardiography, radionuclide ventriculography, or contrast ventriculography), the ways in which the corresponding images were interpreted, and the criteria used to determine whether functional improvement had occurred (e.g., improved myocardial function vs. unimproved myocardial function). 5) In many studies adequate procedures had been followed to minimize potential bias: for example, a) blinding the wall-motion analysis to the outcome of the PET F-18 FDG and perfusion studies; b) blinding the interpretation of the PET F-18 FDG and perfusion images, particularly when the interpretation is qualitative, to the results of the wall-motion analysis, and; c) attempts to avoid selection bias in the choice of patients or myocardial segments for inclusion in the study (e.g., evaluation of consecutive patients) or for inclusion in the analysis (e.g., not restricting the analysis to myocardial segments with obvious patterns of flow-metabolism match or mismatch).

As will be discussed in greater detail at the end of this review, other highly desirable features noted in some, but not all of these studies, include the following design elements: 1) an adequate accounting of patient disposition; 2) an adequate accounting of segment disposition; 3) a full description of the characteristics of the patients enrolled in the studies; 4) an assessment of the reproducibility of the assessments of wall motion, the PET F-18 FDG scans, and the perfusion scans (e.g., by formally evaluating reproducibility and/or by the use of multiple readers); 5) a definition of the term "blinded," (e.g., a description of the specific information to which the readers were blinded); 6) a method of evaluating the success of the

revascularization procedure; 7) a description of how alignment (e.g., segmental concordance) was ensured across imaging modalities, or even within the same imaging modality (e.g., PET imaging with N-13 ammonia to assess perfusion and F-18 FDG to assess metabolism at different times); 8) a full description of all drugs used in the study, particularly of F-18 FDG and drugs used to assess perfusion, along with the conditions of their administration (e.g., such information includes the method of preparation, radiochemical purity, radiation dose, mass dose, route of administration, frequency of administration, and glucose state of the patient); 9) full details of image acquisition; 10) full details of image analysis (e.g., quantitative, qualitative, normalization, external control group, description of myocardial segments); 11) a formal statistical description of the prospective hypotheses that were to be tested, along with a description of the originally statistical analytic plan; 12) inclusion of analyses "by patient," as well as analyses "by segment;" 13) comparison of the diagnostic performance of F-18 FDG PET with the performance of other diagnostic techniques used to assess the reversibility of left ventricular function; 14) repeat evaluation of PET FDG-18 and perfusion imaging after revascularization; 15) serial evaluations after revascularization of the reversibility of left ventricular dysfunction (e.g., to assess the time course of myocardial recovery); 16) evaluations of the functional outcomes of segments that were not successfully revascularized, 17) evaluation of endpoints that include not only regional ventricular function, but also global left ventricular function and clinical outcomes, and; 18) descriptions of how safety was monitored and of the safety results.

1. **Baer FM, Voth E, Deutsch HJ, et al. Predictive Value of Low Dose Dobutamine Transesophageal Echocardiography and Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography for Recovery of Regional Left Ventricular Function after Successful Revascularization. J Am Coll Cardiol 1996;28:60-9.**

Description of Study:

Objective: The objective of this study was to compare the predictive value of myocardial viability, as assessed by dobutamine transesophageal echocardiography and F-18 FDG positron emission tomography, for left ventricular functional recovery after revascularization in patients with chronic left ventricular dysfunction.

Design and sequence of events: This was a prospective study that enrolled consecutive patients with coronary artery disease and regional left ventricular akinesia or dyskinesia documented by angiography and ventriculography. Patients were evaluated in random sequence with a) positron emission tomography with F-18 FDG, and b) transesophageal echocardiography at rest and under stress (with low-dose dobutamine at 5 and 10 μg/kg/min). The PET and transesophageal echocardiography studies were performed within one week of each other. Myocardial perfusion was not assessed. Four to six months after CABG or angioplasty was performed, the success of revascularization was assessed by coronary angiography. In patients with successful revascularization, transesophageal echocardiography studies were repeated at rest to evaluate segmental and regional improvement in myocardial function.

Transesophageal echocardiography studies were evaluated by two blinded readers who did not know the results of left ventriculography and F-18 FDG positron emission tomography. In case of disagreement in segmental gradings, a third reader reviewed the study and the subsequent majority judgment was binding. The F-18 FDG PET scans were evaluated quantitatively. The manuscript did not specify whether these PET scans were read blindly, without knowledge of the results from the post-operative assessments of wall motion, nor did it specify the number of readers for these evaluations.

Subjects: To be included, subjects were required to have angiographically-documented coronary artery disease (at least one infarct-related major coronary artery with ≥80% diameter stenosis) and regional akinesia or dyskinesia by left ventriculography. Only patients with regional akinesia or dyskinesia that persisted for at least four months after the ischemic event were included in the study. Patients were excluded if they had global left ventricular dysfunction due to multiple myocardial infarcts, severe three vessel disease, diabetes mellitus, unstable angina, or a history of sustained ventricular tachycardia. Beta-adrenergic blocking agents were withdrawn before testing. All patients received a long-acting nitrate before the echocardiographic and tomographic studies to optimize perfusion.

F-18 FDG positron emission tomographic studies: Positron emission tomography was performed by using a whole body scanner with an axial field of view of 16.2 cm and equipped with germanium-68/gallium-68 retractable line sources for transmission scans. Each patient received a solution of 50 g of glucose one hour before the administration of F-18 FDG. Images were corrected for attenuation by using coefficients measured by a transmission scan of 30 minutes duration. Emission scans (6x5 minutes) were started 30 minutes after injection of 370 MBq (10 mCi) of F-18 FDG. The transaxial resolution was 6-mm full width at half maximum.

Image analysis: For the blinded echocardiographic segmental analysis, each left ventricle was divided into 28 segments. Segmental myocardial wall motion and systolic wall thickening were graded on a four-point ordinal scale: 1 = normal or hyperkinetic, 2 = hypokinesia (i.e., reduced but not absent systolic wall thickening and inward wall motion), 3 = akinesia (i.e., absent wall thickening and wall motion), 4 = dyskinesia (i.e., systolic outward movement of the endocardial border and absent systolic wall thickening or systolic wall thinning). Akinetic and dyskinetic segments at rest were graded viable before revascularization if dobutamine-induced wall thickening could be observed (i.e, score improvement from 3 or 4 when at rest to 1 or 2 on dobutamine).

After successful revascularization, improvement of systolic function was defined if systolic wall thickening became apparent in a segment graded akinetic or dyskinetic at rest before revascularization (score improvement from 3 or 4 before revascularization to 1 or 2 after revascularization). Infarct region-related recovery of systolic function after revascularization was based on apparent systolic wall thickening (score 1 or 2) in ≥50% of akinetic or dyskinetic segments at rest.

For PET images, F-18 FDG accumulation in the segments was assessed quantitatively. For each segment the mean F-18 accumulation was calculated in percent of the segment with the maximal F-18 FDG accumulation. This segment was required to be perfused by a coronary artery with ≤50% diameter stenosis, and to have normal wall motion. PET segments were predicted to be viable if the mean segmental F-18 FDG accumulation was ≥50% of the maximal accumulation.

Statistics: Differences of wall thickening scores at rest, during dobutamine infusion and after revascularization for patients with and without dobutamine systolic reserve were analyzed with the Student t test. Analysis of variance with Bonferroni correction was used to assess the significance level of mean segmental F-18 FDG accumulation and the mean infarct-related wall thickening score for different transesophageal echocardiographic categories based on wall thickening analysis.

Results:

Patient disposition and characteristics: Overall, 121 consecutive patients were considered for the study. Four patients were excluded: two because of diminished quality of F-18 FDG positron emission tomographic images and two because they refused to swallow the transesophageal probe. Of the remaining 117 patients, 59 underwent coronary angiography 4 to 6 months after revascularization (to assess the success of the revascularization). Of these 59 patients, 42 had a successful revascularization. The results from these 42 patients were included in the analyses.

The 42 patients (38 men, 4 women) had a mean ejection fraction of 40 ± 13% (range 18% to 55%), a mean infarct age 25 ± 47 months. Twenty (20) had undergone successful catheter-based interventional therapy, and 22 had patent bypass grafts. Eleven (11) patients had one-vessel, 18 had two-vessel, and 13 had three-vessel coronary artery disease. A totally occluded infarct-related vessel was found in 21 patients (50%), a subtotal occluded infarct-related artery (high grade stenosis and slow anterograde opacification of the vessel) was present in 10 patients. The other 11 patients had ≥80% diameter stenosis of the infarct-related coronary vessel. The ages of these 42 patients were not specified.

Segment disposition and functional outcome: These 42 patients had 1176 transesophageal echocardiographic segments (28 per patient). Of the 1176 segments 72 (6%) were excluded because of inadequate image quality for transesophageal echocardiographic wall thickening analysis, 699 (60%) were normokinetic or hypokinetic at rest, and 405 (34%) were graded akinetic or dyskinetic. Of these latter 405 segments, 371 could be assigned to successfully revascularized infarct regions, whereas the other 34 belonged to regions not revascularized or unsuccessfully revascularized. These 371 akinetic or dyskinetic segments were related to 42 individual infarct zones, and were the segments used to evaluate functional recovery. Postoperatively, 180 of these 371 segments (49%) improved, whereas the remaining 191 (51%) did not.

Imaging results: The tables below summarize the performance of F-18 FDG positron emission tomography and of low-dose dobutamine transesophageal echocardiography when these tests are used to predict whether depressed myocardial function can be reversed by coronary revascularization. Analyses were performed by-segment as well as by-patient for each imaging modality.

PET, by-segment analysis: Mean segmental F-18 FDG accumulation was significantly lower ($p<0.0001$) in dyskinetic segments (n=43, 39±14%) than in akinetic segments (n=328, 64±18%).

Among the 371 asynergic segments that had been adequately revascularized, PET imaging with F-18 FDG predicted that wall-motion abnormalities would reverse in 232 segments and would be irreversible in 139 segments. Reversibility was predicted correctly in 167 of 232 segments (PPV=72.0%). Lack of reversibility was predicted correctly in 126 of 139 segments (NPV=90.6%). These results are summarized in the two tables below.

Table 2. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to F-18 FDG Accumulation

	Improved Segmental Wall Motion		
F-18 FDG Accumulation	**Present**	**Absent**	**Total**
≥50% of maximum	**167**	**65**	**232**
<50% of maximum	**13**	**126**	**139**
Total	**180**	**191**	**371**

Table 3. Performance of PET When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments (By-Segment Analysis)

Performance Measure	**Value (no. of segments)**	**95% CI**
Sensitivity (%)	**93 (167/180)**	**(88, 96)**
Specificity (%)	**66 (126/191)**	**(59, 72)**
PPV (%)	**72 (167/232)**	**(66, 78)**
NPV (%)	**91 (126/139)**	**(84, 95)**
Accuracy (%)	**79 (293/371)**	**(75, 83)**
Likelihood ratio (+)	**2.7**	
Likelihood ratio (-)	**0.11**	

PET, by-patient analysis: Among the 42 patients with successful revascularization, left ventricular functional recovery occurred in 26 (62%) and did not occur in 16 (38%). PET imaging with F-18 FDG had predicted that regional wall motion would improve in 30 and would not improve in 12. Reversibility was predicted correctly in 25 of 30 patients (PPV=83%), and lack of reversibility was correctly predicted in 11 of 12 patients (NPV=92%). These results are summarized in the two tables below.

Table 4. Number of Patients with Improved Regional Wall Motion after Revascularization: Relation to F-18 FDG Accumulation

	Improved Regional Wall Motion		
F-18 FDG Accumulation	**Present**	**Absent**	**Total**
≥50% of maximum	**25**	**5**	**30**
<50% of maximum	**1**	**11**	**12**
Total	**26**	**16**	**42**

Table 5. Performance of PET When Used to Predict Improvement in Regional Wall Motion (By-Patient Analysis)

Performance Measure	**Value (no. of patients)**	**95% CI**
Sensitivity (%)	**96 (25/26)**	**(80, 100)**
Specificity (%)	**69 (11/16)**	**(41, 89)**
PPV (%)	**83 (25/30)**	**(65, 94)**
NPV (%)	**92 (11/12)**	**(61, 100)**
Accuracy (%)	**86 (36/42)**	**(71, 95)**
Likelihood ratio (+)	**3.1**	
Likelihood ratio (-)	**0.06**	

Dobutamine, by-segment analysis: In the 204 segments with dobutamine-induced systolic wall thickening, mean segmental F-18 FDG accumulation was significantly higher than in the remaining 167 segments that remained akinetic (73±15% vs. 48±15%, $p<0.001$). The ability of rest and stress transesophageal echocardiography to predict functional outcome after successful revascularization in myocardial segments is summarized in the two tables below:

Table 6. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to Dobutamine Transesophageal Echocardiography.

	Improved Segmental Wall Motion		
Dobutamine-induced Wall Thickening	**Present**	**Absent**	**Total**
Present	**161**	**43**	**204**
Absent	**19**	**148**	**167**
Total	**180**	**191**	**371**

Table 7. Performance of Dobutamine Transesophageal Echocardiography When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	**Value (no. of segments)**	**95% CI**
Sensitivity (%)	**89 (161/180)**	**(85, 94)**
Specificity (%)	**77 (148/191)**	**(72, 83)**
PPV (%)	**79 (161/204)**	**(73, 84)**
NPV (%)	**89 (148/167)**	**(84, 93)**
Accuracy (%)	**83 (309/371)**	**(80, 87)**
Likelihood ratio (+)	**3.9**	
Likelihood ratio (-)	**0.14**	

Dobutamine, by-patient analysis: The ability of rest and stress transesophageal echocardiography to predict functional outcome on a by-patient basis after successful revascularization is summarized in the two tables below:

Table 8. Number of Patients with Improved Regional Wall Motion after Revascularization: Relation to Dobutamine Transesophageal Echocardiography.

	Improved Regional Wall Motion		
Dobutamine-Induced Wall Thickening	**Present**	**Absent**	**Total**
Present	**24**	**2**	**26**
Absent	**2**	**14**	**16**
Total	**26**	**16**	**42**

Table 9. Performance of Dobutamine Transesophageal Echocardiography When Used to Predict Improvement in Regional Wall Motion (By-Patient Analysis)

Performance Measure	**Value (no. of patients)**	**95% CI**
Sensitivity (%)	**92 (24/26)**	**(75, 99)**
Specificity (%)	**88 (14/16)**	**(62, 98)**
PPV (%)	**92 (24/26)**	**(75, 99)**
NPV (%)	**88 (14/16)**	**(62, 98)**
Accuracy (%)	**90 (38/42)**	**(77, 97)**
Likelihood ratio (+)	**7.7**	
Likelihood ratio (-)	**0.09**	

Safety: No serious side effects or complications occurred during the low-dose dobutamine infusions. The safety of positron emission tomography with F-18 FDG was not addressed in the manuscript.

Conclusions in manuscript: Both dobutamine transesophageal echocardiography and F-18 FDG positron emission tomography were highly sensitive in predicting functional recovery of chronically akinetic or dyskinetic myocardium after successful revascularization. Dobutamine transesophageal echocardiography is a clinically valuable alternative to F-18 FDG positron emission tomography for assessing residual viability and predicting functional recovery after revascularization.

Reviewer's comments: This study had several strengths. Although none of the principal studies had more than fifty patients included in the analysis, this study was one of three with more than forty patients analyzed (n=42). Consecutive patients were prospectively studied, limiting potential selection bias during patient enrollment. The analysis of wall motion, the primary functional outcome of interest, was performed by two readers who did not know the results of the F-18 FDG PET scans. This was one of the few principal studies that performed a "by-patient" analysis of the results. The study compared different diagnostic modalities, and the predictive performance of both F-18 FDG PET and dobutamine echocardiography were evaluated with respect to the functional outcome ("truth"). Such direct head-to-head comparisons of diagnostic test performance provide information that is very useful clinically. That is, such comparisons provide health care providers facing choices among diagnostic tests with data upon which to base their selections. The study is also notable in that it had a good accounting of patients and segments, most of whom/which were included in the analyses. This allows for assessments of diagnostic performance that are closer to what might be experienced in actual use. This study was also notable in that the success of coronary revascularization was assessed with a rigorous technique (coronary arteriography).

The study had several limitations. Perfusion was not assessed, and so the diagnostic performance of perfusion-metabolism match/mismatch could not be evaluated. The manuscript did not specify whether the PET scans were analyzed blindly nor did it specify the number of readers for these evaluations. However, the PET image analysis was quantitative, which likely decreases substantially the extent of potential bias that could enter into such an unblinded analysis. The definition of wall motion improvement was based only on systolic wall thickening, and not on wall motion. Optimally, it should have been based on both. No assessments of global improvements in ventricular function or in clinical outcomes were included in the study. The evaluations of wall motion improvement after revascularization ("truth") were made with echocardiography, which was also one of the test modalities. In general, this is undesirable because findings with a modality under one setting are somewhat likely to correlate with findings with the same modality under a different setting.

2. Gerber BL, Vanoverschelde JJ, Bol A, et al. Myocardial Blood Flow, Glucose Uptake, and Recruitment of Inotropic Reserve in Chronic Left Ventricular Ischemic Dysfunction: Implications for the Pathophysiology of Chronic Myocardial Hibernation. Circulation 1996;94:651-659.

Description of Study:

Objectives: The objectives of this study were a) to delineate the flow and metabolic correlates of the reversibility of left ventricular ischemic dysfunction in patients with chronic coronary artery disease and b) to test the hypothesis that, even in unselected patients with chronic reversible dysfunction, regional contraction is disproportionately reduced compared with resting perfusion.

Design and sequence of events: This was a study consecutive patients with chronic coronary artery disease and left ventricular dysfunction undergoing coronary revascularization. The study

was designed to assess whether "match" or "mismatch" patterns on positron emission tomography with N-13 ammonia and F-18 FDG can predict wall-motion recovery of the region of the left ventricle supplied by the left anterior descending coronary artery, where disease of the left anterior descending coronary artery was identified angiographically.

At baseline, subjects underwent selective coronary arteriography and left ventriculography to evaluate coronary artery disease and left ventricular function. Positron emission tomography studies were performed with N-13 ammonia and F-18 FDG to evaluate myocardial perfusion and metabolism. Control positron emission data were obtained from six healthy volunteers. Left ventricular function was evaluated by two-dimensional echocardiography at rest and during low-dose dobutamine infusion (5-10 μg/kg/min). Postoperative angiographic follow-up to assess the adequacy of revascularization by CABG or angioplasty was requested prospectively in every patient, but could not be obtained in all. Approximately five months after revascularization, two-dimensional echocardiography (at rest) was repeated to assess changes in wall motion. The manuscript did not specify the number of readers who evaluated the two-dimensional echocardiography or PET images, or whether these readers were blinded.

Subjects: Patients with chronic coronary artery disease and left ventricular dysfunction who were undergoing coronary revascularization were considered for the study. Patients were considered eligible for inclusion in the study if they had a) severe dysfunction in the anterior wall at contrast cineventriculography, b) proximal disease of the left anterior descending coronary artery suitable for CABG or PTCA, c) revascularization of all dysfunctional segments, d) absence of perioperative or periprocedural myocardial infarction, and (e) adequate transthoracic echocardiograms to assess wall motion in every segment of the left ventricle.

F-18 FDG and N-13 ammonia positron emission tomographic studies and PET image analysis: Volunteer subjects were used as controls to measure absolute myocardial blood flow and glucose uptake. All patients and volunteers were studied during application of the hyperinsulinemic euglycemic glucose clamp technique. Glucose plasma levels were maintained between 75 and 95 mg/dl throughout the study.

N-13 ammonia (dose not specified) and F-18 FDG (dose not specified) were injected intravenously over 30 seconds with an infusion pump. One dynamic midventricular transaxial study per patient was analyzed for dynamic imaging. Three large irregular volumes of interest were assigned to each image of the left ventricular myocardium, and a circular volume of interest was assigned to the center of the left ventricular blood pool. One of the volumes of interest encompassed the interventricular septum, another the anterior wall (the primary region of interest for this study), and the remaining the lateral free wall of the left ventricle. The lateral free wall was considered to be the remote normal segment if no dysfunction was present on two-dimensional echocardiograms. Counts were corrected for spatial-volume spillover effects by use of a specially developed Monte Carlo simulation, as well as for dead-time losses. The volumes of interest drawn on the F-18 FDG study were copied onto the N-13 ammonia study. Identical placement of the volumes of interest on all dynamic studies was ascertained, and manual correction for patient movement was done if necessary.

N-13 ammonia and F-18 FDG localization: N-13 ammonia and F-18 FDG cross-sectional images were analyzed with an operator-interactive computer program using circumferential profiles. The program normalized F-18 and N-13 counts within a given myocardial cross section to maximal activity in the same ventricular slice. Each cross section of the left ventricle was divided into serial 10^{o} segments. Activity within each segment was expressed in relative terms (reported as F-18 and N-13 accumulation) as percentage of maximal activity.

Flow-metabolism match and mismatch: A pattern of flow-metabolism "match" was considered to be present when there was a concordant reduction (<70%) of F-18 FDG and N-13 ammonia activity in a given myocardial segment. A pattern of flow-metabolism "mismatch" was considered to be present in segments when the relative N-13 ammonia accumulation was lower than the minimal range of the normal volunteers (i.e., <70%) and when the ratio of F-18 FDG to N-13 ammonia activity was 1.2 or greater. For this analysis, both F-18 FDG and N-13 ammonia activity were normalized to peak N-13 ammonia activity.

Tomographic data were quantified by a published method, and regional myocardial perfusion was quantified by use of a previously validated three-compartment model. Glucose uptake, normalized glucose uptake, glucose extraction, and normalized glucose extraction were calculated.

Wall motion analysis: For purposes of assessing return of systolic function, two-dimensional echocardiograms were obtained at rest and approximately five months after revascularization. Regional function was interpreted in 16 myocardial segments (basal, midventricular, and apical levels of the septum and lateral, anterior, and inferior walls; and basal and midventricular levels of the anteroseptal and posterior walls) and was graded on a 3-point ordinal scale as normal (1), hypokinetic (2), or akinetic (3). Normal wall motion was defined as ≥5 mm of endocardial excursion and obvious systolic wall thickening. Hypokinesis was defined as <5 mm of endocardial excursion and reduced wall thickening. Akinesis was defined as near absence of endocardial excursion or thickening. A wall motion score for the segments supplied by the left anterior descending coronary artery was calculated by summing up the scores of the midanterior, lateroapical, and anteroapical segments.

Dysfunctional myocardium at baseline was considered to have improved functionally after revascularization if wall motion decreased by one full grade in any of the three segments assigned to the left anterior descending coronary artery after revascularization or to remain persistently dysfunctional if no change was noted.

Statistics: Groups were compared for categorical data by Fisher's exact test or the χ^2 test, when the minimum expected cell size was >5. A Mann-Whitney rank-sum test was used to assess differences in continuous variables between patients with and without improved wall motion. One-way ANOVA was used to compare anterior segments that improved wall motion with those that did not, with remote segments, and with segments from normal volunteers. Post hoc comparisons were made by Scheffés test. All tests were two-sided.

Results:

Patient disposition and characteristics: Thirty-nine consecutive patients were enrolled, and data from all 39 were included in the analysis. Six healthy volunteers served as control subjects for measurement of absolute myocardial blood flow and glucose uptake.

The 39 patients included 34 men and 5 women and had a mean age of 60±9 years (range 39-75 years). The patients had a mean ejection fraction of 33±10% and a mean wall motion score of 8.1±0.9. Twenty three patients had sustained a previous anterior Q-wave myocardial infarction, the most recent occurring 13 days before inclusion in the study. Thirty-two of the 39 patients were in NYHA class III and IV, and the remaining seven were in NYHA class I or II. Thirty-three of the 39 patients had two- or three-vessel coronary artery disease, and the remaining six had one-vessel disease. Seven patients had type II diabetes mellitus, of which six were treated with sulfonylurea and one with insulin. Thirty one patients underwent CABG, and eight underwent PTCA. All of the six volunteers were men and were nonsmokers. The volunteers had a mean age of 24±3 years, with a range of 21 to 28 years.

Segment disposition and functional outcome: For PET analysis, regions of the left ventricle that encompassed the anterior wall for each of the 39 patients were included in the analysis. At a mean of 5.0±1.9 months after revascularization, the anterior wall motion score improved in 24 patients (from grade 8.0±1.0 to 5.7±1.6) and did not change in the other 15 patients (from grade 8.3±0.7 to 8.4±0.6). A pattern of flow-metabolism mismatch was present in 18 of 24 dysfunctional regions that improved functionally after revascularization (sensitivity=75%) but was absent in 10 of 15 regions that remained dysfunctional revascularization (specificity=67%). These results are summarized in the two tables below.

Table 10. Number of Asynergic Anterior-Wall Myocardial Regions with Improved Segmental Wall Motion after Revascularization: Relation to PET Patterns with F-18 FDG and N-13 ammonia

	Improved Regional Wall Motion		
PET Pattern	**Present**	**Absent**	**Total**
Mismatch	**18**	**5**	**23**
Match	**6**	**10**	**16**
Total	**24**	**15**	**39**

Table 11. Performance of PET When Used to Predict Improved Wall Motion in Asynergic Anterior-Wall Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	**75 (18/24)**	**(53, 90)**
Specificity (%)	**67 (10/15)**	**(38, 88)**
PPV (%)	**78 (18/23)**	**(56, 92)**
NPV (%)	**62.5 (10/16)**	**(35, 85)**
Accuracy (%)	**72 (28/39)**	**(55, 85)**
Likelihood ratio (+)	**2.3**	
Likelihood ratio (-)	**0.37**	

Before revascularization and as assessed by PET with N-13 ammonia, absolute myocardial blood flow in anterior regions was higher in reversibly dysfunctional segments compared with persistently dysfunctional segments (84±27 versus 60±26 ml/min/100 g, p=0.007). In segments with reversible dysfunction, values of myocardial blood flow were similar to those in the remote segments of the same patients (82±22 ml/min/100 g) or in anterior segments of normal volunteers (88±22 ml/min/100 g). Only 4 of 24 dysfunctional segments that improved after revascularization had baseline levels of absolute myocardial blood flow below the lowest value of the normal volunteers, i.e., 60 ml/min/100 g).

During glucose clamp F-18 FDG uptake was higher (69±17% versus 49±18%, p <0.01) but myocardial glucose uptake was not different (38±20 versus 29±19 μmol/min/100 g, p=NS) in reversibly compared with persistently dysfunctional anterior segments. During glucose clamp, estimates of myocardial glucose uptake in remote segments reached values similar to those found in normal volunteers (47±17 versus 53±11 μmol/min/100 g, p=NS).

Other Findings: With dobutamine, wall motion improved in 17 of 24 reversibly dysfunctional segments and did not change in 13 of 15 segments with persistent dysfunction. Thus, the performance of dobutamine as a predictor of functional recovery of the anterior wall may be summarized with the following performance measures: sensitivity=71% (17 of 24 regions), specificity=87% (13 of 15 regions), PPV=89% (17 of 19 regions), NPV=65% (13 of 20 regions), accuracy=77% (30 of 39 regions), likelihood ratio(+)=5.3; likelihood ratio(-)=0.34.

Safety: The safety of positron emission tomography with F-18 FDG and N-13 ammonia was not addressed in the manuscript. However, hemodynamic consequences of infusion of dobutamine were summarized.

Conclusions in manuscript: The study indicates that chronic but reversible ischemic dysfunction is associated with almost normal resting myocardial perfusion, with maintained FDG uptake, and with recruitable inotropic reserve. These data support the contention that chronic hibernation is not the consequence of a permanent reduction of transmural myocardial perfusion at rest.

Reviewer's comments: The study had several strengths. Consecutive patients were prospectively enrolled, limiting possible selection bias during patient enrollment. Data were included from all 39 patients. Such inclusion of all patients in the study and in the analysis decreases the likelihood that potential biases might have been introduced by selective exclusion of patients from the study or the analysis. Moreover, as a consequence of only focusing on one region of the heart (i.e., the anterior wall) per patient, the segmental analysis is identical to the by-patient analysis. Such by-patient analyses facilitate assessments of clinical benefit as compared to risk. The study compared different diagnostic modalities, and the predictive performance of both F-18 FDG PET and dobutamine echocardiography were evaluated with respect to the functional outcome ("truth"). Such direct head-to-head comparisons of diagnostic test performance provide information that is very useful clinically. For the evaluation of absolute levels of regional glucose uptake and of absolute levels of myocardial blood flow, the study utilized external controls (from healthy subjects). Wall-motion assessments included evaluation of not only the excursion of the wall, but also of systolic wall thickening, increasing the specificity of these assessments.

The study also had several limitations. Doses of F-18 FDG and N-13 ammonia were not specified in the manuscript. The manuscript did not specify the number of readers who evaluated the two-dimensional echocardiograms or PET images, or whether these readers were blinded. However, because both of these readings were quantitative (particularly the analyses of the PET images with F-18 FDG and N-13 ammonia), possible biases from unblinded readings were mitigated. The study focused only on functional recovery of the anterior wall of the left ventricle, the region supplied by the left anterior descending coronary artery, and performance of PET F-18 FDG may not be similar for other ventricular regions. The adequacy of revascularization was not assessed in several patients. No assessments of global improvements in ventricular function or in clinical outcomes were included in the study.

3. Gropler RJ, Geltman EM, Sampathkumaran K, et al. Comparison of Carbon-11-Acetate with Fluorine-18-Fluorodeoxyglucose for Delineating Viable Myocardium by Positron Emission Tomography. J Am Coll Cardiol 1993;22:1587-97.

Description of Study:

Objective: The objective of this study was to determine in patients with advanced coronary disease whether prediction of recovery of mechanical function after coronary revascularization (as assessed by two-dimensional echocardiography, radionuclide ventriculography, or contrast ventriculography) could be accomplished more effectively by PET with carbon-11 acetate than by PET with F-18 FDG.

Design and sequence of events: This study enrolled patients with left ventricular wall motion abnormalities and angiographically documented coronary artery disease. At baseline, patients underwent cardiac catheterization and selective coronary angiography to document coronary artery disease and left ventricular dysfunction. Baseline assessments of regional left ventricular wall motion were performed by 2-D echocardiography, contrast ventriculography, and radionuclide ventriculography. Positron emission tomography was performed with C-11 acetate to assess myocardial oxidative metabolism and regional myocardial perfusion (in relative terms), and with F-18 FDG to assess metabolism of glucose.

After revascularization by either CABG or angioplasty, the adequacy of the revascularization was verified by review of the operative reports documenting the successful placement of bypass grafts and, in the case of coronary angioplasty, by angiographic documentation of successful balloon dilitation. After revascularization, patients had repeat assessments of regional left ventricular wall motion (by 2-D echocardiography, contrast ventriculography, and radionuclide ventriculography). Wall-motion assessments were made by two observers blinded to both PET and clinical data. The PET scans with F-18 FDG and C-11 acetate were evaluated quantitatively. The manuscript did not specify whether these PET scans were read blindly, without knowledge of the results from the post-operative assessments of wall motion, nor did it specify the number of readers for these evaluations.

Subjects: The study enrolled patients with left ventricular wall motion abnormalities secondary to angiographically documented coronary artery disease. Patients with diabetes mellitus were excluded. Healthy volunteers were evaluated to develop tomographic criteria of tissue viability and of nonviability (i.e., values for oxidative metabolism and utilization of glucose in patients were referenced to mean values obtained in these control subjects).

F-18 FDG and C-11 acetate positron emission tomographic studies and image analysis: All subjects were studied in the postprandial state after the consumption of a high carbohydrate meal 2 to 3 hours before and 75 grams of glucose 1 to 2 hours before the administration of F-18 FDG . An initial transmission scan was performed to correct subsequent emission scans for attenuation. C-11 acetate (0.25 to 0.40 mCi/kg) was then administered intravenously, followed by an 1,800-s list mode data collection performed 45 min later. To ensure that each patient was positioned consistently within the PET system for all data collections, position was checked with the use of a low energy laser and indelible marks placed on the torso.

Regional myocardial perfusion in relative terms was based on the early myocardial uptake of C-11 acetate (i.e., regional distribution of activity within the myocardium from 60 to 180 sec after the administration of C-11 acetate). Myocardial oxidative metabolism was quantified by determining the myocardial turnover rate constant of acetate (k_1). Regional myocardial utilization of glucose was assessed on the basis of composite images of relative F-18 FDG activity.

Myocardial images were reformatted from the transaxial orientation to true short-axis views, with the heart divided into 8 to 12 tomographic slices on which circumferential profiles of C-11

acetate, k1, and F-18 FDG were generated for each. The left ventricular myocardium was segmented into eight segments as for studies of wall motion.

Average values for myocardial uptake of C-11 acetate, k1, and F-18 FDG were calculated for each segment. Carbon-11 acetate myocardial localization and F-18 FDG activity were normalized to peak myocardial activity for C-11 acetate and F-18 FDG, respectively, to yield relative values for myocardial blood flow and utilization of glucose. In addition, myocardial utilization of glucose was normalized to blood flow within each segment by dividing normalized F-18 FDG activity by dividing normalized myocardial localization of C-11 acetate for the same segment.

Threshold Criteria for viability: Tomographic criteria of tissue viability and of nonviability were developed by referencing values for oxidative metabolism and utilization of glucose to mean values obtained in control subjects for each of the eight segments. *Definition of viability using C-11 acetate (oxidative metabolism)*: dysfunctional but viable myocardium was considered present when values for k_1 were within 2 SD of the mean value for a particular segment in the control group. Conversely, non-viable myocardium was considered present when values for k_1 were lower than the mean value minus 2 SD in the control group. *Definition of viability using F-18 FDG (glucose utilization)*: dysfunctional but viable myocardium was defined by values for myocardial utilization of glucose within 2 SD of the mean value in the control group. Values for myocardial utilization of glucose normalized to flow that were >2 SD above the mean value in the control group were defined as indicative of dysfunctional but still viable myocardium. Conversely, reductions in myocardial utilization of glucose (>2SD below the mean value in the control group) that were not associated with increased utilization of glucose normalized to flow were defined as indicative of nonviable myocardium. *Resected segments:* Segments that were resected (e.g., during left ventricular aneurysmectomy) were classified as nonviable.

Wall motion evaluation and image analysis: To quantify regional systolic function, the left ventricular myocardium was segmented into eight regions. With all three modalities (echocardiography, radionuclide ventriculography, and contrast left ventriculography), regional systolic function was graded as follows: 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic, and 5=aneurysmal. Wall motion analyses were performed by two observers blinded to both PET and clinical data. The average wall motion score reflecting values assigned by both observers was tabulated for each segment in each study.

As assessed by these blinded observers, improvement in wall function in initially dysfunctional segments (i.e., segments that were hypokinetic, akinetic, dyskinetic or aneurysmal before revascularization) as assessed by echocardiography or radionuclide ventriculography was defined as an improvement in wall motion score of at least one full grade after revascularization.

Statistics: Comparisons of paired frequency data were performed with a continuity-corrected McNemar test. Receiver operating characteristic curves were compared with the methods of Hanley and McNeil.

Results:

Patient disposition and characteristics: Data were obtained from 34 patients, and from 10 control patients. The 34 patients included 26 men and 8 women, and had a mean age of 60 years (range 30 to 77 years). Twenty-one patients had sustained at least one myocardial infarction from 11 days to 10 years before enrollment in the study. In 17 patients, the myocardial infarction had occurred ≥1 month before enrollment. Eight patients had angiographically defined lesions in a single vessel, 8 had lesions in two vessels, and 18 had lesions in three vessels. In 24 patients, CABG was performed, and 10 underwent PTCA.

The ten control subjects included 9 men and 1 woman, and had a mean age of 24±3 years. These subjects had no history and a low likelihood for coronary artery disease.

Segment disposition and functional outcome: The left ventricle in each of the 34 patients was divided into eight segments, yielding a total of 272 segments for possible analysis. Of these 272 possible segments, 131 had normal wall motion and 141 were dysfunctional. Of the 141 dysfunctional segments, 25 segments were excluded, leaving 116 dysfunctional segments for analysis. Of these dysfunctional segments, 46 had reversible wall motion abnormalities and 70 did not. The patients had repeated assessments of regional left ventricular wall motion (by 2-D echocardiography, contrast ventriculography, or radionuclide ventriculography) at a mean of 2.0 months (range, 0.5-7 months) after revascularization.

Using the threshold criteria described above, positron emission tomography with F-18 FDG normalized to flow correctly predicted wall motion improvement in 38 of 46 reversibly dysfunctional segments (sensitivity=83%) and correctly predicted that wall motion would not improve in 35 of 70 segments with persistent dysfunction (specificity=50%). These results are summarized in the tables below.

Table 12. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to F-18 FDG Uptake, Normalized to Flow

	Improved Segmental Wall Motion		
F-18 FDG Uptake, Normalized to Flow	**Present**	**Absent**	**Total**
Viable	**38**	**35**	**73**
Nonviable	**8**	**35**	**43**
Total	**46**	**70**	**116**

Table 13. Performance of PET F-18 FDG Uptake, Normalized to Flow, When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

	Value

Performance Measure	(no. of segments)	95% CI
Sensitivity (%)	**83 (38/46)**	**(68, 92)**
Specificity (%)	**50 (35/70)**	**(38, 62)**
PPV (%)	**52 (38/73)**	**(40, 64)**
NPV (%)	**81 (35/43)**	**(67, 92)**
Accuracy (%)	**63 (73/116)**	**(54, 72)**
Likelihood ratio (+)	**1.7**	
Likelihood ratio (-)	**0.35**	

Other results: When the threshold criteria for viability described above were applied, positron emission tomography with C-11 acetate correctly predicted wall-motion improvements in 40 of 46 reversibly dysfunctional segments and correctly predicted that wall motion would not improve in 50 of 70 segments with persistent dysfunction. Thus, the performance of positron emission tomography with C-11 acetate as a predictor of wall-motion recovery may be summarized with the following performance measures: sensitivity=87% (40 of 46 segments), specificity=71% (50 of 70 segments), PPV=67% (40 of 60 segments), NPV=89% (50 of 56 segments), accuracy=78% (90 of 116 segments), likelihood ratio(+)=3.0; likelihood ratio(-)=0.18.

Analysis of receiver operating characteristic curves indicated that estimates of oxidative metabolism (with C-11 acetate) were more robust in predicting functional recovery than were estimates of glucose metabolism ($p<0.02$). Moreover, threshold criteria with C-11 acetate exhibited superior positive and negative predictive values (67% and 89%, respectively), than did the criteria with F-18 FDG (52% and 81%, respectively), $p<0.01$. In segments with initially severe dysfunction, estimates of oxidative metabolism with C-11 acetate tended to be more robust than estimates of glucose metabolism in predicting functional recovery. Moreover, in such segments, the threshold criteria with C-11 acetate tended to exhibit superior positive and negative predictive values (85% and 87%, respectively) than did the criteria with F-18 FDG (72% and 82%, respectively), although statistical significance was not achieved.

Safety: The safety of positron emission tomography with F-18 FDG or with C-11 acetate were not addressed in the manuscript.

Conclusions in manuscript: In patients with advanced coronary artery disease, the extent to which functional recovery can be anticipated after coronary revascularization can be delineated accurately by quantification of regional oxidative metabolism by PET with C-11 acetate. The analysis of wall motion, the primary functional outcome of interest, was performed by two readers who did not know the results of the F-18 FDG PET scans. The blinding of these readers increases the validity of the estimates of F-18 FDG performance. Moreover, the use of multiple readers allows for potential assessment of interreader variability and decreases the likelihood

that the results reflect the idiosyncracies of any particular reader (i.e., the results are more likely to be generalizable to other similar readers).

Reviewer's comments: The study had several strengths. The wall-motion analysis, the primary functional outcome of interest, was performed by two readers who did not know the results of the PET scans or the clinical data. The blinding of these readers and the use of multiple readers are highly desirable characteristics. Such characteristics minimize potential bias and make possible assessments of interreader variability and increase the generalizability of the readings. The alignment of the different imaging modalities was well discussed, increasing the likelihood that the observed segmental results are valid. The authors performed ROC analysis, making full use of the generated data and allowing the performance characteristics of the tested methodologies to be assessed at different thresholds. That is, the performance of these two drugs was compared over the full spectrum of possible sensitivities and specificities by using different threshold criteria for each (as is inherent in such an ROC analysis). The study compared different diagnostic modalities, and the predictive performance of both F-18 FDG PET and C-11 acetate PET were evaluated with respect to the functional outcome ("truth"). Such direct comparisons of diagnostic test performance provide useful information. The study used healthy volunteers to establish normal values for oxidative metabolism (as assessed by C-11 acetate) and for glucose metabolism (as assessed by F-18 FDG).

The study had several limitations. The dose of F-18 FDG was not indicated. A relatively unconventional marker for perfusion was employed (PET with C-11 acetate). Moreover, C-11 acetate was also one of the test modalities, and this may confound the interpretation of the direct comparison of F-18 FDG with C-11 acetate. That is, the method of evaluating perfusion was independent of one of the test agents (F-18 FDG) but not of the other (C-11 acetate). The manuscript did not specify the number of readers who evaluated the PET images, or whether these readers were blinded. However, because the PET readings were quantitative, potential bias from an unblinded interpretation was minimized. Although the success of revascularization was documented as part of the study, analyses were not provided for segments that were not successfully revascularized (if any). Such analyses would have provided useful data on the diagnostic performance as might be expected in actual use as compared to under ideal circumstances. No assessments of global improvements in ventricular function or in clinical outcomes were included in the study.

4. Knuuti MJ, Saraste M, Nuutila P, et al. Myocardial viability: Fluorine-18-deoxyglucose positron emission tomography in prediction of wall motion recovery after revascularization. Am Heart J 1994; 127:785-96.

Description of Study:

Objectives: The objective of this study was to assess the value of positron emission tomography imaging with F-18 FDG in predicting cardiac wall motion recovery (as assessed by two-dimensional echocardiography) after revascularization. The study also compared prediction of

functional recovery by evaluation of normalized F-18 FDG uptake and of F-18 FDG uptake relative to perfusion.

Design and sequence of events: This was a study of consecutive patients with previous myocardial infarctions and wall motion abnormalities at rest. At baseline, patients underwent selective coronary angiography and angioventriculography to document coronary artery disease and left ventricular dysfunction. Baseline assessments of regional left ventricular wall motion and systolic thickening were performed with 2-D echocardiography. Positron emission tomography was performed with F-18 FDG to predict myocardial viability. Baseline myocardial perfusion was evaluated by SPECT with thallium-201 or technetium-99m-methoxy-isobutyl-isonitrile (TC99m-MIBI).

After revascularization by either CABG or angioplasty, a myocardial segment was considered to be revascularized if a corresponding major epicardial coronary artery branch had undergone a successful procedure. Myocardial scars were detected and localized visually during bypass surgery. Assessments of segmental left ventricular wall motion and systolic wall thickening after revascularization were made with 2-D echocardiography. These assessments were made 2 to 6 months after CABG or 3 to 8 weeks after angioplasty.

The 2-D echocardiograms were read blindly by an experienced physician. SPECT perfusion scans were read blindly by two experienced nuclear medicine specialists. Discordances were resolved by conjunct reanalysis. Positron emission scans with F-18 FDG were analyzed semi-quantitatively. The manuscript did not specify whether the PET scans were read blindly, without knowledge of the results from the post-operative assessments of wall motion and systolic thickening, nor did it specify the number of readers for these evaluations.

Subjects: Patients were included if they had a prior myocardial infarction that had been confirmed both by electrocardiographic and enzymatic criteria, and if they had stable, angiographically confirmed coronary artery disease. Patients with diabetes were excluded.

F-18 FDG positron emission tomographic studies and image analysis: All studies were performed after the patients had fasted for 12 hours overnight. Patients took only nitrates, if needed, for the last 24 hours before the PET study. Patients were positioned supine in a tomograph with a measured axial resolution of 6.7 mm and 6.5 mm in plane. Correction for photon attenuation was performed. The patients ingested 50 g glucose 60 minutes before the intravenous injection of 260 ± 60 MBq (7.0 ±1.5 mCi) of F-18 FDG. Imaging was continued for 60 minutes.

The myocardium was divided into eight segments (anterobasal, anterior, anteroseptal, lateral, inferoseptal, apical, inferior, and posterobasal). The mean segmental count rate measured during 30 to 60 min after tracer injection was used for further calculations. Assuming that glucose metabolism is normal in myocardial regions with noncompromised blood flow, the uptake of F-18 FDG was normalized relative to the uptake of the segment with the highest tracer uptake observed visually in resting SPECT perfusion imaging (typically an anterior or lateral segment).

In those five patients with no SPECT imaging, the noninfarcted lateral or anterior segment supplied by a normal or nonsignificantly stenosed coronary artery was used as a reference.

To calculate the range of F-18 FDG uptake in normal segments, the segments that gave normal results by all non-PET methods were identified. Recovery of systolic function was predicted by normalized F-18 FDG uptake by making the assumption that F-18 FDG uptake above the lower limit (mean-2SD) represented viable myocardium.

Perfusion studies and image analysis: Patients were administered 1 mCi of Tl-201 or 20 mCi of Tc-99m-MIBI one hour before imaging in all but one patient, who was studied at rest 4 hours after Tl-201 stress imaging (4 hour washout). Tomographic images of the heart were reconstructed in 10 mm thick transaxial slices and three perpendicular planes. The tracer uptake in the eight anatomic segments was assessed qualitatively and blindly by two experienced nuclear medicine specialists. The results from resting images were scored according to the following scale: (1) normal, (2) mild defect, (3) moderate defect, and (4) severe or complete defect. Discordances were resolved by conjunct reanalysis.

Wall motion analysis: Wall motion analyses were performed by 2-D-echocardiography. Standard long-and short-axis views were obtained and videotaped. The echocardiograms were analyzed by a blinded, experienced physician. These readings of the separate echocardiograms were verified by a paired comparison of the echocardiograms that were performed before revascularization with the echocardiograms that were performed after revascularization.

Segmental left ventricular wall motion and systolic thickening were visually scored according to the following scale: 1) normal, 2) hypokinetic wall motion with systolic thickening, 3) akinetic wall motion with no systolic thickening, and 4) dyskinetic motion with no systolic thickening. Improvement of systolic function was diagnosed if systolic thickening (corresponding to score 1 or 2) became apparent in a segment that had been akinetic or dyskinetic, or if normal motion was detected in a previously hypokinetic segment. Improvement in function was acknowledged only if it was apparent in a central area of the segment.

Statistics: Independent variables were compared by analysis of variance and Bonferoni testing when appropriate. To test different F-18 FDG uptake levels in predicting functional recovery, the discriminant analysis of SAS statistical program was used.

Results:

Patient disposition and characteristics: 48 patients were enrolled and included in the analysis of positron emission tomography with F-18 FDG. Forty-three patients also underwent SPECT perfusion imaging at rest (25 patients with thallium-201 and 18 patients with Tc-99m-MIBI).

The 48 patients included 46 men and 2 women and had a mean age of 54±7 years. The mean ejection fraction was 53±11% (n=38). The mean number of abnormal segments at rest was 2.2±1.3 (out of eight segments per patient). Thirty-four patients (71%) had a Q-wave myocardial

infarction, 25 (52%) had an anterior wall myocardial infarction, and 23 (48%) had an inferior or posterior wall myocardial infarction. Thirty-one patients (65%) had three-vessel coronary artery disease, 10 (21%) had two-vessel disease, and 7 (15%) had one-vessel disease. Considering angina, 3 patients (6%) were NYHA class I , 26 (54%) were NYHA class II, 15 (31%) were NYHA class III, and the remaining 4 (8%) were NYHA class IV. For revascularization, 37 (77%) of the patients underwent CABG, and 11 (23%) underwent angioplasty.

Segment disposition and functional outcome: The left ventricle of each of the 48 patients was divided into 8 segments, yielding a total of 384 possible segments: Of these, 264 had normal wall motion, and 106 had abnormal wall motion. Fourteen segments were excluded because of poor visualization. Of the 106 segments that had abnormal wall motion at baseline, 90 were successfully revascularized, and 16 were not. These 90 segments were used to evaluate the performance of F-18 FDG PET as a predictor of functional recovery. Of these 90 dysfunctional segments, 84 had SPECT perfusion results available. Of the 90 segments with abnormal wall motion at baseline that were successfully revascularized, 27 recovered function and 63 did not.

To calculate the normal range of F-18 FDG uptake, the segments that gave normal results by all non-PET methods were identified. One hundred fifty-eight of the 264 echocardiographically normal segments were also normal by SPECT perfusion imaging and were associated with ≤75% stenosis in the respective coronary artery.

Imaging results: When F-18 FDG uptake above the lower limit of normal (mean - 2SD) was defined as viable myocardium, the presence or absence of F-18 FDG uptake by itself, without consideration of perfusion of the segment, correctly predicted postinterventional wall motion in 67 of the 90 asynergic segments (i.e., accuracy=74%). However, only 27 (54%) of the 50 segments with preserved uptake were able to recover functionally (i.e., PPV=54%). None of the 40 revascularized segments with reduced (mean - 2SD) F-18 FDG uptake recovered (i.e., NPV=100%). These results are shown in the tables below.

The ability of F-18 FDG uptake to distinguish between segments with and without recovery was tested by discriminant analysis. When 85% to 90% of normalized F-18 FDG uptake by itself, without consideration of perfusion to the segment, was used as a threshold value (i.e., an "optimized" threshold, instead of the use of the lower limit of normal as a threshold), a sensitivity of 85% and specificity of 84% to predict functional recovery were reached simultaneously.

Table 14. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to Normal F-18 FDG Uptake

	Improved Segmental Wall Motion		
Prediction by normal F-18 FDG Uptake*	**Present**	**Absent**	**Total**
Viable: uptake > LLN	**27**	**23**	**50**

Nonviable: uptake <LLN	**0**	**40**	**40**
Total	**27**	**63**	**90**

***Normal F-18 FDG uptake defined as F-18 FDG uptake greater than the lower limit of normal (LLN), where LLN = mean - 2SD**

Table 15. Performance of PET F-18 FDG Uptake When Normal* Values are Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	**100 (27/27)**	**(87, 100)**
Specificity (%)	**63 (40/63)**	**(50, 75)**
PPV (%)	**54(27/50)**	**(39, 68)**
NPV (%)	**100 (40/40)**	**(91, 100)**
Accuracy (%)	**74 (67/90)**	**(64, 83)**
Likelihood ratio (+)	**2.7**	
Likelihood ratio (-)	**0.00**	

***Normal F-18 FDG uptake defined as F-18 FDG uptake greater than the lower limit of normal (LLN), where LLN = mean - 2SD**

F-18 FDG uptake and functional recovery: In the 158 normal segments, the value of the lower limit (i.e., mean - 2SD) of normalized F-18 FDG uptake varied by segment location: anterobasilar 70%, anteroseptal 77%, anterior 80%, lateral 90%, inferoseptal 72%, apical 61%, inferior 75%, posterobasilar 79%. The overall value of the lower limit of normal of F-18 FDG uptake was 74%.

Recovery of function occurred only in segments with the highest F-18 FDG uptake values. None of the 40 segments with reduced F-18 FDG uptake (i.e., uptake below the mean - 2SD) recovered. This pattern was reflected in the mean uptake values for F-18 FDG in different groups of segments. Thus, the mean uptake of F-18 FDG in the 158 normal segments was 95%±11% (range 58% to 127%). Similarly, the mean uptake of F-18 FDG in the 27 asynergic segments with subsequent functional recovery was 110±22%. However, the mean uptake of F-18 FDG in the 63 asynergic segments without subsequent functional recovery was 65±24% ($p<0.05$).

Contribution of resting SPECT perfusion to predictions of viability made with F-18 FDG: SPECT perfusion results were available in 84 of the 90 initially dysfunctional revascularized segments.

As shown in the table below, significantly higher mean F-18 FDG uptake values were detected in segments with functional recovery as compared to the segments without recovery in the groups of moderate or severe perfusion defects. In the segments with moderately or severely reduced perfusion at rest, the positive and negative predictive values for viability were 100%.

Table 16: Relationship of Resting SPECT Perfusion Defects, Wall Motion Recovery, and F-18 FDG Uptake in 84 Revascularized Segments with Abnormal Wall Motion*

SPECT results	Total No	Recovery	No	F-18 FDG uptake (Mean ± SD)	p value
Normal or mild defect**	**31**	**Yes**	**14**	**101±18**	**0.09**
		No	**17**	**89±19**	
Moderate defect	**17**	**Yes**	**6**	**128±28**	**0.003**
		No	**11**	**69±12**	
Severe	**36**	**Yes**	**5**	**116±13**	**0.0006**
		No	**31**	**51±20**	

*** This table was taken from the manuscript.**
****In five segments, SPECT perfusion at rest was classified as normal.**

Other findings: In the 90 asynergic segments, the mean F-18 FDG uptake was lower depending on the severity of the ventricular wall-motion abnormality. Thus, the 43 hypokinetic segments had a mean F-18 FDG uptake of 97±25%, the 38 akinetic segments had a mean uptake of 64±27%, and the 9 dyskinetic segments had a mean uptake of 52±24%.
A significant proportion of segments with preserved F-18 FDG uptake was found in each of the asynergic segment groups (i.e., hypokinetic, akinetic, and dyskinetic segment groups). However, within each group recovery occurred only in segments with the highest F-18 FDG uptake values.

Safety: The safety of positron emission tomography with F-18 FDG was not addressed in the manuscript.

Conclusions in manuscript: The results of this study show that the presence of viable tissue indicated by preserved F-18 FDG uptake does not inevitably imply functional recovery after revascularization. However, acceptable diagnostic accuracy for viability might be reached by F-18 FDG alone, providing that appropriate uptake limits are use.

The combined evaluation of F-18 FDG uptake and perfusion enables precise assessment of myocardial viability.

Reviewer's comments: The strengths of the study include the following items. Of the ten principal studies, this study had the largest sample size of evaluated patients (n=48). The wall-motion analysis, the primary functional outcome of interest, was performed blindly. The analysis of SPECT perfusion was performed blindly by two readers. Alignment of myocardial segments obtained by different methods was described. The reproducibility of wall-motion analysis by the same reader was assessed and documented. This is one of the only studies in which F-18 FDG localization in segments with normal wall motion was assessed, or in which the various factors that are correlated with the degree of F-18 FDG localization were evaluated (e.g., severity of wall motion dysfunction, diastolic wall thickness). The authors evaluated different potential thresholds for F-18 FDG localization, and therefore provided a more complete picture of the performance of PET F-18 FDG in evaluating the reversibility of myocardial dysfunction in patients with coronary artery disease and left ventricular dysfunction.

The study had several limitations. The manuscript is not specific about to what information readers were blinded (i.e., the readers who evaluated wall motion by echocardiograms and perfusion by SPECT). The manuscript did not specify whether the PET F-18 FDG images were interpreted blindly or the number of readers. However, because the image analysis was quantitative the possibility of introducing bias was decreased. The wall motion analysis was performed by a single reader. An analysis by patient was not performed.

5. Lucignani G, Paolini G, Landoni C, et al. Presurgical identification of hibernating myocardium by combined use of technetium-99m hexakis 2-methoxyisobutylisonitrile single photon emission tomography and fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in patients with coronary artery disease. Eur J Nucl Med 1992;19:874-881.

Description of study:

Objective: The objective of this study was to identify areas of hibernating myocardium by the combined assessment of perfusion, using single photon emission tomography (SPET) with Tc-99m 2-methoxyisobutylisonitrile (Tc-99m MIBI), and metabolism using positron emission tomography with F-18 FDG.

Design and sequence of events: This was a study that enrolled patients waiting to undergo CABG who had chronic coronary artery disease and left ventricular dysfunction. At baseline, coronary angiography was performed to assess coronary artery disease. First-pass radionuclide angiography (with Tc-99m MIBI) and ECG-gated planar perfusion scintigraphy (with Tc-99m MIBI) were performed to evaluate wall motion. Myocardial perfusion at rest and under stress was evaluated by SPET scintigraphy with Tc99m MIBI. Positron emission tomography with F-18 FDG was performed to assess myocardial metabolism. Patients underwent revascularization with CABG, and the imaging evaluations described above were repeated. The success of revascularization was verified by repeat coronary angiography.

SPET perfusion studies at rest and during exercise were evaluated concurrently and scored qualitatively (i.e., visually) by three independent observers, who were unaware of the results of the PET studies. The PET studies of metabolism were evaluated and scored qualitatively (i.e., visually) by three other independent observers who were unaware of the results of the SPET studies. The manuscript did not specify whether wall-motion analyses were performed blindly nor did it specify the number of readers for these evaluations.

Subjects: Enrolled subjects were waiting to undergo CABG, had stable or unstable angina, chronic multivessel coronary artery disease, and moderate left ventricular dysfunction (ejection fraction below 50%). No patient had diabetes mellitus.

F-18 FDG positron emission tomographic studies and image analysis: Patients were studied after an overnight fast of at least 16 hours. In each patient, two emission scans, lasting 10 minutes each, were carried out between 40 and 60 minutes after intravenous administration of approximately 250 MBq (6.8 mCi) of F-18 FDG. Images were corrected for attenuation. Data were reconstructed on the horizontal and vertical long axis and the short axis.

A qualitative visual analysis was carried out on the tomographic images of metabolism by dividing the left ventricle image into five segments comparable with those selected

for the wall motion analysis. The PET studies of metabolism were evaluated and visually scored by three independent observers who were unaware of the results of the SPET study. Segments were assigned a scores on a four-point ordinal scale (0=no F-18 FDG uptake, 1=low uptake, 2=moderate uptake, 3=high uptake). Myocardial viability as assessed by F-18 FDG was defined as any degree of F-18 FDG uptake based on the same scale.

Analysis of perfusion: SPET scans were performed at rest 90 minutes after the first-pass angiography study (with Tc-99m MIBI), following a standard cholecystokinetic fatty meal at 30 minutes after injection. Stress perfusion studies were performed within 72 hours following the rest study. A qualitative visual analysis was carried out on the tomographic images of perfusion by dividing the left ventricle image into five segments comparable with those selected for the wall motion analysis.

The SPET perfusion studies at rest and during exercise were evaluated concurrently and visually scored by three independent observers, who were unaware of the results of the PET study. The score ranged from 0 to 3 (0=markedly reduced or absent perfusion at rest, 1 = rest hypoperfusion worsening after stress, 2 = hyperperfusion only under stress, 3 = normal perfusion).

Evaluation of wall-motion: First-pass radionuclide angiography was performed at rest after an intravenous bolus injection of approximately 900 MBq (24 mCi) of Tc-99m MIBI. ECG-gated planar perfusion scintigraphy was performed about 60 minutes later. Segmental wall motion was assessed on a pixel by pixel basis of the RAO 30^{o} first-pass radionuclide angiography study displayed on a relative color scale in the anterior, apical and inferior wall. The analysis of these images was used for the segments in which the wall motion could not be assessed by ECG gated planar perfusion scintigraphy due to the absence of Tc 99m-MIBI uptake. Anterior and LAO 45^{o} projections were analyzed to assess the wall motion in five segments: anterior, apical, inferior, lateral, and septum.

Wall motion scores were given by three independent observers in each segment from 0 to 4 (0 = dyskinesis, 1 = akininesis, 2 = severe hypokinesis, 3 = hypokinesis, 4 = normal kinesis). Wall motion was considered to be improved when the score increased by 1 or more from before CABG to afterwards.

Statistics: Statistical analyses were carried out on the scores of perfusion, metabolism, and wall motion from the myocardial segments. One-way ANOVA was used to test interobserver variability. A stepwise multiple logistic analysis was carried out on the segments that exhibited impaired wall motion prior to the intervention to estimate the independent contribution of the preoperative perfusion and metabolism scores on wall motion improvement. The maximum likelihood method was used to assess the significance of each term in selecting the one to be removed or entered in each step. The only statistical test carried out on the 14 patients as a set of data was a two-tailed

Student's t-test to compare the mean values of the ejection fraction before and after CABG.

Results:

Patient disposition and characteristics: Data from 14 patients were included in the analysis. The 14 patients included 12 men and 2 women. The patients had a mean age of 61.2 years (range 46-70 years), and a mean ejection fraction of 37.5±4.9%. All had undergone diagnostic coronary angiography within six months of the nuclear studies. Twelve patients had three-vessel disease, one patient had two vessel disease, and one had one-vessel disease. No patient had had an acute myocardial infarction in the seven months before the study. The average time between the completion of the preoperative evaluation (including PET evaluation) and CABG was 9±4 days (mean±SD). The average time between the preoperative and postoperative evaluations was 179±40 days (mean±SD).

Segment disposition and functional outcome: The left ventricle of each of the 14 patients was divided into 5 segments, yielding 70 segments overall. Fifty-four (54) of these segments had abnormal wall motion. Wall motion improved in 40/54 (74%) segments after CABG, and it remained unchanged in 14/54 (26%) segments.

The table below shows the distribution of the 54 asynergic segments by degree of F-18 FDG uptake and degree of perfusion.

Table 17: Number of Asynergic Segments as a Function of F-18 FDG Uptake and Degree of Perfusion*

	F-18 FDG Uptake				
Perfusion	**Absent**	**Low**	**Moderate**	**High**	**Total**
Absent at rest	**4**	**2**	**3**	**2**	**11**
Rest hypoperfusion worsening after stress	**6**	**4**	**9**	**3**	**22**
Stress hypoperfusion	**5**	**7**	**3**	**5**	**20**
Normal	**0**	**1**	**0**	**0**	**1**
Total	**15**	**14**	**15**	**10**	**54**

*** This table was taken from the manuscript**

Imaging results: Of the 39 segments that were predicted to have reversible function by F-18 FDG uptake, segmental wall motion actually improved after revascularization in 37 segments (PPV=95%). Of the 15 segments that were predicted to have irreversible

loss of function, segmental wall motion did not improve in 12 (NPV=80%). The tables below summarize these results.

Table 18. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to F-18 FDG Uptake

	Improved Segmental Wall Motion		
F-18 FDG Uptake	**Present**	**Absent**	**Total**
Uptake present	**37**	**2**	**39**
Uptake absent	**3**	**12**	**15**
Total	**40**	**14**	**54**

Table 19. Performance of PET F-18 FDG Uptake When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	**Value (no. of segments)**	**95% CI**
Sensitivity (%)	**92.5 (37/40)**	**(80, 98)**
Specificity (%)	**80 (12/15)**	**(52, 96)**
PPV (%)	**95 (37/39)**	**(83, 99)**
NPV (%)	**80 (12/15)**	**(52, 96)**
Accuracy (%)	**91 (49/54)**	**(80, 97)**
Likelihood ratio (+)	**4.6**	
Likelihood ratio (-)	**0.09**	

Multiple Logistic Analysis:

Two multiple logistic analyses were performed on the scores of metabolism and perfusion. The first was to predict wall motion improvement, taking into account both perfusion and F-18 FDG uptake. The results provide estimates of wall motion recovery as a function of the preoperative scores of perfusion and F-18 FDG uptake. As shown in the table below, the highest probability of wall motion recovery was associated with the presence of high F-18 FDG uptake and absent perfusion at rest.

Table 20: Estimated Probability of Wall Motion Improvement as a Function of Preoperative F-18 FDG Uptake and Preoperative Degree of Perfusion*

	F-18 FDG Uptake			
Perfusion	**Absent**	**Low**	**Moderate**	**High**
Absent at rest	**25**	**94**	**96**	**99**
Rest hypoperfusion worsening after stress	**14**	**89**	**92**	**97**
Stress hypoperfusion	**7**	**78**	**84**	**94**
Normal	**-**	**4**	**-**	**-**

***Values in each cell indicate the estimated percentage probability of wall motion improvement. This table was taken from the manuscript.**

The second multiple logistic analysis was performed on F-18 FDG uptake data. As shown in the table below, the likelihood of wall motion improvement increased as F-18 FDG uptake increased.

Table 21: Estimated Probability of Wall Motion Improvement as a Function of Preoperative F-18 FDG Uptake*

F-18 FDG Uptake			
Absent	**Low**	**Moderate**	**High**
13	**79**	**92**	**96**

***Values in each cell indicate the estimated percentage probability of wall motion improvement This table was taken from the manuscript.**

Other Endpoints: The left ventricular ejection fraction improved in 13/14 patients and remained unchanged in one. The preoperative ejection fraction was 37.5±4.9% (mean±SD), whereas the postoperative ejection fraction was 47.9±4.1 ($p<0.001$).

Safety: The safety of positron emission tomography with F-18 FDG was not addressed in the manuscript.

Conclusions in manuscript: Despite the potential limitations due to the semiquantitative analysis of the images, the method appears to provide reliable information for the diagnostic and prognostic evaluation of patients with coronary artery disease undergoing CABG and confirm that the identification of hibernating myocardium with F-18 FDG is of paramount importance in the diagnosis of patients undergoing CABG.

Reviewer's comments: Although the analysis of this study only included data from 14 patients, the study had several strengths and relatively unique characteristics. The analyses of the F-18 FDG PET images and the SPET perfusion images were qualitative, suggesting that quantitative analyses may not be always necessary to evaluate with F-18 FDG PET whether left ventricular systolic dysfunction is reversible in patients with coronary artery disease. The readers of the F-18 FDG PET images were blinded to the SPET perfusion images, and vice versa. Three independent readers were used for these image analyses, allowing assessments of interreader variability and increasing the generalizability of the results. This was one of the few papers that evaluated stress hypoperfusion, showing that F-18 FDG PET imaging may have useful predictive value not only when analyzed in relation to resting perfusion deficits, but also in the expanded group of patients who have perfusion deficits that are apparent only during stress. The authors also evaluated probabilities of wall motion improvement for different ratios of perfusion-metabolism mismatch (see Table 20), thereby extracting additional information from the data. Localization of F-18 FDG was evaluated in all 70 segments, not just in the 54 that were asynergic.

One of the greatest limitations of the study is its small sample size, as is reflected in the wide confidence intervals for the performance measures. This also limits the generalizability of the study. The readers of the F-18 FDG PET images and the SPET perfusion images were apparently not blinded to the results of the wall-motion analysis. The manuscript did not specify the number of readers for the wall-motion analysis, or whether these readers were blinded. Analyses by patient were not performed. Although an assessment of global ventricular function was made (i.e., ejection fraction), the results were not correlated with the degree of reversible ventricular dysfunction as predicted by imaging with F-18 FDG PET and SPET (for perfusion). Clinical outcomes were not assessed.

6. Maes AF, Borgers M, Flameng W, et al. Assessment of Myocardial Viability in Chronic Coronary Artery Disease Using Technetium-99m Sestamibi SPECT: Correlation with Histologic and Positron Emission Tomographic Studies and Functional Follow-Up. J Am Coll Cardiol 1997;29:62-8.

Description of study:

Objective: The objective of this study was to evaluate the value of Tc-99m-sestamibi (2-methoxy-isobutyl isonitrile [MIBI]) as a viability tracer in patients undergoing coronary artery bypass surgery. The results of these SPECT studies were compared to the results of PET metabolism and perfusion studies.

Design and sequence of events: This was a prospective study performed in patients with known coronary artery disease and anterior wall motion abnormalities. Patients underwent coronary angiography and contrast ventriculography to identify the location and extent of coronary artery disease and to demonstrate left ventricular dysfunction. Patients with severe stenosis of the left anterior descending coronary artery (≥70%) and hypokinesia, akinesia or dyskinesia on contrast ventriculography underwent radionuclide angiography. Radionuclide angiography with Tc-99m-labeled red blood cells was performed to evaluate global and regional left ventricular function. Rest Tc-99m-MIBI SPECT studies were performed to evaluate myocardial viability, and the results were compared with results from PET studies performed with N-13 ammonia and F-18 FDG. A preoperative transmural biopsy specimen was taken from the left ventricular anterior wall, and morphometry was performed to assess percent fibrosis. Patients underwent revascularization with CABG. The manuscript did not specify whether the success of revascularization was assessed. Three months after CABG, radionuclide angiography was repeated to assess changes in myocardial function.

The analyses of the F-18 FDG PET scans, N-13 ammonia PET scans, and Tc-99m MIBI SPECT scans were limited to a portion of the anterior left ventricular wall. Analyses of these scans were quantitative. The manuscript did not specify the number of readers, nor did it specify whether the analyses of left ventricular function by SPECT were performed blinded to the results of the PET scans. Conversely, the manuscript did not specify whether the analyses of the PET scans were performed blinded to the results of the SPECT scans.

Subjects: Patients were included in the study if they had known coronary artery disease, one- or two-vessel disease, an occlusion or severe stenosis (≥70%) of the left anterior descending coronary artery, and anterior wall abnormalities. Patients with diabetes mellitus were excluded.

PET studies and image analysis: Before each study, 15-minute transmission scans were performed to correct for photon attenuation. Myocardial perfusion was evaluated by administration of 20 mCi of N-13 ammonia in 5 ml of saline followed by a 20 minute flush of saline. Acquisition started simultaneously with the injection of N-13 ammonia. In each patient, 19 dynamic frames were recorded. Total acquisition time was 10 minutes.

Regional myocardial utilization of exogenous glucose was evaluated with F-18 FDG. The metabolic studies were performed by using the euglycemic hyperinsulinemic clamp technique. A total of 10 mCi of F-18 FDG was injected 50 min after N-13 ammonia injection. In each patient, 22 dynamic frames were recorded. Acquisition time was 70 min.

The 22 frames of the metabolic studies and the 19 frames of the perfusion studies were reconstructed. The PET studies (of both N-13 ammonia and F-18 FDG) were divided into polar maps, with 33 sectors in each map. Analysis of the sectors was limited to those in the anterior wall (i.e., the average of two sectors covering the region from which the biopsy specimen was taken). After absolute flow values for this myocardial region, a flow index was calculated as the ratio of the flow in the biopsy region divided by flow in the reference sector (no stenosis or stenosis <50% in the left circumflex or right coronary artery). A metabolic index was calculated by determining the ratio of glucose utilization in the biopsy region compared to that in the reference sector. Regions were defined as PET viable with the ratio of metabolic and flow index was > 1.2.

Wall motion analysis: Regional and global myocardial function were assessed with radionuclide angiography using 20 mCi of Tc-99m labeled red blood cells. Regional and global ejection fractions were calculated. Regional function was considered to have improved if the regional ejection fraction in the anterior wall was 5% higher three months after revascularization than before revascularization.

Tc-99m MIBI SPECT studies: Tc-99m MIBI SPECT studies were performed at rest one or two days before and three months after operation. A total of 15 mCi of Tc-99m MIBI was injected at rest 60 minutes before the start of acquisition. The Tc-99m MIBI images were delineated with the same procedure applied to the PET images, and comparable polar maps were constructed. Counts in the polar maps were normalized to the maximal value of the entire map. The mean value of the two sectors that corresponded to those used in the PET analyses was used for further analysis of Tc-99m MIBI uptake.

Statistics: Differences between groups were evaluated statistically with the Student t test for paired data. For evaluation of the relation between Tc-99m sestamibi uptake or normalized PET flow and percent fibrosis, linear regression plots were used. Differences between correlation coefficients were tested by using Fisher z transformation. To calculate an optimal threshold for MIBI (100-% false positive - % false negative) was maximized.

Results:

Patient disposition and characteristics: Thirty patients were enrolled. PET studies were not performed in four patients, and global and regional ejection fraction were not followed up postoperatively with radionuclide angiography in three additional patients. Therefore, 23 patients were included in the PET analyses.

The 30 patients included 25 men and 5 women, and had a mean age of 63 ± 14 years. All had severe (≥70%) stenosis of the left anterior descending coronary artery. Coronary artery bypass surgery was scheduled for 22 of the 30 patients because of stable angina, for five because of unstable angina, and for three because of heart failure. Four patients had a previous anterior infarction. Preoperatively, the contrast ventriculogram revealed regional hypokinesia in 8, severe hypokinesia in 12, and akinesia or dyskinesia in 10 patients.

Segment disposition and functional outcome: Although the PET studies were divided into polar maps, with 33 sectors per map, analyses were limited to the anterior wall for each patient (i.e., the average of 2 sectors covering the region from which the biopsy specimen was taken). Thus, 23 anterior wall segments, one per patient, were evaluated. Twelve of these segments showed functional improvement after revascularization, and 11 did not.

PET results: The performance characteristics of F-18 FDG and N-13 ammonia in predicting functional recovery, using the PET match/mismatch criteria, are described in the tables below.

Table 22. Number of Asynergic Anterior Myocardial Segments with Improved Function after Revascularization: Relation to PET match/mismatch findings

	Improved Regional Ejection Fraction		
PET Findings	**Present**	**Absent**	**Total**
Mismatch of F-18 FDG and N-13 Ammonia Uptake	**10**	**1**	**11**
Match of F-18 FDG and N-13 Ammonia Uptake	**2**	**10**	**12**
Total	**12**	**11**	**23**

Table 23. Performance of PET F-18 FDG Uptake When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	**83 (10/12)**	**(52, 98)**
Specificity (%)	**91 (10/11)**	**(58, 100)**
PPV (%)	**91 (10/11)**	**(58, 100)**
NPV (%)	**83 (10/12)**	**(52, 98)**
Accuracy (%)	**87 (20/23)**	**(66, 97)**
Likelihood ratio (+)	**9.15**	
Likelihood ratio (-)	**0.18**	

N-13 ammonia results: Predictive values for anterior-wall functional recovery as assessed by N-13 ammonia flow were separated out from the overall PET criteria of flow and glucose uptake. An optimal threshold was calculated by maximizing (100 - % false positives - % false negatives). A threshold of 50 % flow was found, resulting in the following performance characteristics: sensitivity = 92% (11/12); specificity = 55% (6/11); PPV = 69% (11/16); NPV = 86% (6/7); accuracy = 74% (17/23); LR(+)= 2.0; LR(-)=0.16.

Tc-99m MIBI results: Predictive values for anterior-wall functional recovery as assessed by Tc-99m MIBI were also calculated by using an optimal threshold that was obtained by maximizing (100 - % false positives - % false negatives). A threshold of 50% of peak activity was found, resulting in the following performance characteristics: sensitivity = 92% (12/13); specificity = 60% (6/10); PPV = 75% (12/16); NPV = 86%; accuracy=78% (18/23); LR(+) = 2.3; LR(-)=0.13.

Other Results: Global and regional ejection fraction was followed up postoperatively with radionuclide angiography in 27 patients; in 13 global ejection fraction was improved and in 16, regional systolic function was improved.

Significantly higher Tc-99m MIBI values were found in the group with myocardial viability as assessed by PET than in the group with PET-assessed nonviability ($p<0.01$). Significantly higher MIBI values were found in the group with enhanced systolic function at three months ($76\pm13\%$ vs. $53\pm22\%$, $p<0.01$). A linear relation was found between MIBI uptake and percent fibrosis in the biopsy specimen ($r=0.78$, $p<0.00001$).

Safety: The safety of F-18 FDG and N-13 ammonia PET was not discussed in this manuscript.

Conclusions in manuscript: Tc-99m MIBI uptake was significantly higher in PET-assessed viable areas and in regions with enhanced contractility at three months. A linear relation was found between percent fibrosis and Tc-99m MIBI uptake. An optimal threshold of 50% was found for prediction of functional recovery with Tc-99m MIBI.

Reviewer's comments: Of the principal studies, this is the only study which evaluated morphological correlates of imaging studies in myocardium with reversible left ventricular function. Although the results were expressed in terms of a correlation between percent fibrosis and Tc-99m MIBI uptake, a similar relationship likely holds for F-18 FDG. Moreover, as a consequence of only focusing on one region of the heart (i.e., the anterior wall) per patient, the segmental analysis is identical to the by-patient analysis. Such by-patient analyses facilitate assessments of clinical benefit as compared to risk. Moreover, the study compared different diagnostic modalities, and the predictive performance of both F-18 FDG PET and Tc-99m MIBI SPECT were evaluated with respect to the functional outcome ("truth"). Such direct head-to-head comparisons of the performance of different imaging modalities provide data that are potentially of substantial clinical value.

One limitation of the study is the small sample size. The manuscript did not specify the number of readers for the PET or SPECT scans, or whether these images were analyzed blindly. However, this limitation is mitigated by the quantitative nature of the image analyses. The study focused only on functional recovery of the anterior wall of the left ventricle; the predictive performance of PET F-18 FDG may not be similar in other ventricular regions. Although global ejection fraction was evaluated postoperatively in many patients, these results were not correlated with the PET F-18 FDG predictions of functional recovery that were made before revascularization. Thus, the ability of PET F-18 FDG to predict global improvement in left ventricular function was not demonstrated. Clinical outcomes were not assessed.

7. Marwick TH, MacIntyre WJ, Lafont A, et al. Metabolic Responses of Hibernating and Infarcted Myocardium to Revascularization: A Follow-up Study of Regional Perfusion, Function, and Metabolism. Circulation 1992;85:1347-53.

Description of Study:

Objective: The objective of this study was to examine the metabolic response of hibernating tissue to revascularization, as assessed by PET metabolic imaging with F-18 FDG and PET perfusion imaging with Rb-82.

Design and sequence of events: This study was performed in patients with a previous myocardial infarction. At baseline, patients underwent rest and stress myocardial perfusion imaging using Rb-82 PET. Postexercise F-18 FDG positron emission tomography was performed to evaluate myocardial metabolism. Digitized two-dimensional echocardiography was performed to evaluate regional wall motion. Patients then underwent either CABG or angioplasty. Although the authors assert that "segments identified as potentially hibernating were adequately revascularized," the manuscript did not specify how the adequacy of

revascularization was assessed. After revascularization, PET imaging with Rb-82, PET imaging with F-18 FDG, and digitized 2-D echocardiography were repeated.

The evaluation of the 2-dimensional echocardiograms was performed by two blinded readers. However, the manuscript did not specify to what information these readers were blinded. Similarly, evaluation of the PET Rb-82 scans and the PET F-18 FDG scans were each performed by two blinded readers. Again, however, the manuscript did not specify to what information these readers were blinded.

Subjects: Patients with a previous myocardial infarction who were undergoing coronary revascularization were included in the study. Patients with unstable angina and asthma were excluded from the study because dipyridamole was used as a pharmacological stressor. Patients with elevated fasting blood glucose levels were excluded. No patients with extensive coronary disease (involving all three major epicardial coronary arteries) were entered into the protocol, as the definition of normal F-18 FDG uptake required the definition of a site of normal perfusion.

Perfusion studies and image analysis: Rest and stress PET imaging with Rb-82 were performed before and after surgery, and images were corrected for photon attenuation. Rb-82 was administered at a dose of 40 - 60 mCi, with the dose dependent on the generator life. Resting imaging was started 75 seconds after the conclusion of the injection and lasted for seven minutes. After resting imaging, dipyridamole handgrip stress was performed. Another 40-60 mCi was injected 8 minutes after commencement of this protocol, and stress imaging was performed over 4 minutes, acquiring 20-40 million counts.

The left ventricle was evaluated over thirteen myocardial segments by two blinded observers. Perfusion was graded as follows: (a) normal; (b) reversible perfusion defect (identified by a 20% relative reduction of Rb-82 activity after stress); (c) or a fixed perfusion defect (defined by regions with >20% fewer than maximum counts.

F-18 FDG positron emission tomographic studies and image analysis: Fasting F-18 FDG imaging was performed after perfusion imaging, and images were corrected for photon attenuation. Four to 10 mCi of F-18 FDG were injected 30 minutes after maximum symptom-limited treadmill exercise, and imaging began 40 min later. Image acquisition lasted 20 minutes.

The left ventricle was evaluated by two blinded observers over the same thirteen myocardial segments evaluated for Rb-82 . For each patient, a "reference normal" segment was determined for metabolic activity by selecting the site of maximum resting flow without significant reduction at stress perfusion imaging and subtended by a normal coronary artery. Sites other than this reference normal segment with resting perfusion within the normal range, supplied by normal coronaries and without stress-induced defects, were then combined to establish a range of normal F-18 FDG uptake measured as a percentage below or above the reference level. In each patient, the presence of F-18 FDG activity >2SD (≥30%) above the reference normal segment

was classified as abnormal (i.e., having the potential to recover myocardial function, and labeled as "hibernating").

Wall motion analysis Wall motion was assessed by digitized 2-D echocardiography (parasternal long- and short-axis and apical four and two-chamber views). The left ventricular myocardium was divided into thirteen myocardial segments. Wall motion was scored by two blinded observers on a 6-point ordinal scale (1=normal , 2=hypokinesia, 3 = akinesia, 4=dyskinesia, 5=aneurysm, 6=akinesia or dyskinesia with thinning of the myocardium). The presence of hibernation was defined by improvement ≥1 point.

Statistics: Groups were compared with regard to continuous and noncontinuous variables by the t test or χ^2 or Fisher's exact test respectively (the latter depending on sample sizes).

Results:

Patient disposition and characteristics: Sixteen patients, 14 men and two women, were enrolled and evaluated. The patients ranged from 42 to 76 years of age. All patients had previous myocardial infarction (5±11 months before the preinterventional studies). Nine patients had one-vessel disease, seven had multivessel disease, but none had disease in all three major coronary arteries. Revascularization was accomplished in nine by coronary angioplasty and in seven by CABG. Six patients had angina before revascularization.

Segment disposition and functional outcome: The left ventricle of each of the 16 patients was divided into 13 segments, yielding a total of 208 segments for potential analysis. Overall, 85 segments showed fixed perfusion defects and resting wall motion disturbances before revascularization. These 85 segments were those used for analysis. At least two months (4.9±2.6 months) after intervention, 35 (41%) of these segments (in 12 patients) demonstrated improved function. Fifty segments failed to improve at follow-up.

Preoperative perfusion and preoperative wall motion score did not distinguish between the segments that were destined to improve after revascularization and those destined not to improve. Specifically, before revascularization, the 50 segments that failed to improve at follow up had a mean perfusion score (as assessed by regional Rb-82 activity) that was 55±13% of the maximum score, and the 35 segments that did improve at follow up had a mean perfusion score that was 57±11% of the maximum (p=NS). Similarly, before revascularization, the 50 segments that failed to improve at follow up had a mean segmental wall motion score of 3.0±1.0, and the 35 segments that did improve at follow up had a mean segmental wall motion score of 2.8±0.7 (p=NS).

F-18 FDG results: Considering the 85 segments with resting wall motion disturbances, preoperative F-18 FDG activity was significantly higher in the 35 segments that demonstrated improved function after revascularization than in the 50 segments that did not (29 ±11% vs. 15±15% above reference normal, $p<0.001$). As noted in the previous section, preoperative perfusion did not distinguish between the two groups, nor did preoperative wall motion.

Of the 35 segments that improved in function after revascularization, 25 were correctly predicted to do so by F-18 FDG (sensitivity = 71%). Of the 50 segments that failed to improve in function, 38 were correctly predicted to do so by F-18 FDG (specificity = 76%). These results are summarized in the tables below:

Table 24. Number of Hypoperfused, Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to F-18 FDG Uptake

	Improved Segmental Wall Motion		
F-18 FDG Uptake	**Present**	**Absent**	**Total**
>2 SD Above Uptake in Reference Normal Segment	**25**	**12**	**37**
≤2 SD Above Uptake in Reference Normal Segment	**10**	**38**	**48**
Total	**35**	**50**	**85**

Table 25. Performance of PET F-18 FDG Uptake When Used to Predict Improved Wall Motion in Hypoperfused, Asynergic Myocardial Segments

Performance Measure	**Value (no. of segments)**	**95% CI**
Sensitivity (%)	**71 (25/35)**	**(54, 85)**
Specificity (%)	**76 (38/50)**	**(62, 87)**
PPV (%)	**28 (25/37)**	**(50, 80)**
NPV (%)	**79 (38/48)**	**(65, 89)**
Accuracy (%)	**74 (63/85)**	**(63, 83)**
Likelihood ratio (+)	**3.0**	
Likelihood ratio (-)	**0.38**	

Other Findings Somewhat paradoxically, F-18 FDG activity fell significantly after revascularization both in the segments that improved in function as well as in those that did not. Specifically, in the 35 segments that improved in function, regional F-18 FDG activity fell from 29±11% to 16±17% above the reference normal segment after revascularization ($p<0.001$). In the 50 segments that did not improve in function, a reduction of F-18 FDG activity from 15±15 to 7±19% above the reference normal segment also occurred ($p<0.001$), despite failure of regional wall motion and regional perfusion to improve after revascularization.

At follow-up (4.9 ± 2.6 months after revascularization), hibernating segments were characterized by reduction of wall motion score (from a mean segmental wall motion score of 2.8±0.7 to 1.4±0.5; $p<0.001$), improvement of perfusion (from 57±11 to 69±13 percent of maximum; $p<0.001$), and reduction of F-18 FDG activity (see previous paragraph, $p<0.001$). Of the 35 hibernating segments, however, 10 still had abnormal elevation of FDG uptake (>2 SD above normal) without differing from other hibernating segments with respect to postoperative perfusion or wall motion score. Segments with persistently abnormal metabolism were characterized before intervention by more severe malperfusion ($p<0.01$) and greater FDG activity ($p<0.01$).

Six patients had angina before revascularization, but none had ongoing angina at the time of follow-up.

Safety: The safety of PET F-18 FDG was not addressed in the manuscript.

Conclusions in manuscript: Although wall motion and perfusion improve with revascularization of hibernating tissue, myocardial metabolism remains abnormal in a significant proportion of segments. These segments are characterized by more extensive perfusion and metabolic changes before revascularization.

Reviewer's comments: Despite its small size, the study had several strengths. The analyses of the two-dimensional echocardiograms for wall motion, the PET F-18 FDG scans for metabolism, and the PET Rb-82 for perfusion were performed in a blinded fashion. Images were analyzed by two blinded readers. This was one of the few principal papers that evaluated stress hypoperfusion (and also post-exercise F-18 FDG uptake) showing that PET imaging may have useful predictive value not only when analyzed in relation to resting perfusion deficits, but also in the expanded group of patients who have perfusion deficits that are apparent only during stress. This is also one of the few papers that performed PET imaging to evaluate perfusion and F-18 FDG uptake after revascularization.

One of the greatest limitations of the study is its sample size. The manuscript did not specify the nature of the information to which the readers were blinded. A by-patient analysis was not performed. Global ventricular function was not assessed. Although the clinical outcome of angina was assessed, this outcome was not correlated with the predictive capabilities of PET findings with F-18 FDG and Rb-82.

8. Tamaki N, Yonekura Y, Yamashita K, et al. Positron Emission Tomography Using Fluorine-18 Deoxyglucose in Evaluation of Coronary Artery Bypass Grafting. Am J Cardiol 1989; 64:860-865.

Description of Study:

Objective: The objective of this study was to assess the "clinical value" of PET (i.e., perfusion imaging with N-13 ammonia, and metabolic imaging with F-18 FDG) in the evaluation of CABG.

Design and sequence of events: This study was performed in consecutive patients with coronary artery disease who were undergoing CABG. Prior to revascularization, patients underwent PET imaging with N-13 ammonia to evaluate myocardial perfusion and with F-18 FDG to evaluate myocardial metabolism. Radionuclide ventriculography was performed before CABG to assess left ventricular wall motion. After revascularization, radionuclide ventriculography (to assess wall motion) and PET imaging with N-13 ammonia and F-18 FDG were repeated. Segmental improvements in perfusion, as assessed quantitatively by N-13 ammonia, were used to assess the adequacy of revascularization.

The evaluation of wall motion was performed by three experienced observers without knowledge of other radionuclide or postoperative results. N-13 ammonia and F-18 FDG images were visually (qualitatively) evaluated by three experienced observers. The manuscript did not specify whether these latter three observers were blinded.

Subjects: The study enrolled consecutive patients who were to undergo CABG. Normal subjects served as controls for the evaluation of perfusion.

Perfusion studies and image analysis: To evaluate perfusion, 10-20 mCi of N-13 ammonia was injected at rest, and myocardial perfusion imaging was performed for 5 minutes. Immediately after the first scan, a second scan was carried out for 8 minutes in a position 8 mm caudal to the first scan. These two scans provided a total of 14 contiguous transverse slices of the myocardium with 8-mm intervals.

Perfusion scans were quantitatively analyzed by circumferential profile analysis of three transverse slices of N-13 ammonia distribution in a patient and the lower limit of a normal subject. The lower limit was determined as the mean minus 2 SD from the values of ten normal volunteers. The left ventricular myocardium was divided into five segments (anterior, septal, apical, inferior, and lateral). Segments with perfusion below the lower limits and covering at least 30^{o} of the profiles were considered hypoperfused segments. The manuscript did not specify whether this analysis of the N-13 ammonia PET images was blinded.

Perfusion was considered improved when the postoperative perfusion at rest improved ≥10% in comparison with the preoperative perfusion on the profile curves. When the postoperative

perfusion decreased ≥10% versus the preoperative perfusion on the profile curves, the perfusion was considered deteriorated.

F-18 FDG positron emission tomographic studies and image analysis: The F-18 FDG study was separately performed within a week after the N-13 ammonia study. All patients fasted for at least five hours before the study. Two to 7 mCi of F-18 FDG were injected at rest and, 60 minutes later, two emission scans were obtained every eight to ten minutes.

For evaluation of the F-18 FDG images, the left ventricle was divided into five segments that corresponded to the segments obtained with N-13 ammonia images. Three experienced observers visually interpreted the uptake on both the N-13 ammonia and F-18 FDG images. The segments with normal perfusion were defined as normal areas. Hypoperfused segments with F-18 FDG uptake definitely higher than N-13 ammonia uptake (i.e., "mismatch" pattern) were defined as ischemia. Hypoperfused segments with F-18 FDG uptake less than or similar to N-13 ammonia uptake were defined as myocardial scar (i.e., "match" pattern).

Wall motion analysis: Regional wall motion was assessed with radionuclide ventriculography (20 mCi of technetium-99m in vivo-labeled red blood cells were administered). The evaluation of wall motion on these radionuclide ventriculograms was performed by three experienced observers without knowledge of other radionuclide or postoperative results. Scores for wall motion ranged from 2 to -1 (i.e., normal, hypokinetic, akinetic, and dyskinetic). Improved wall motion was defined as an increase in the wall-motion score by ≥1 after CABG. Deteriorated wall motion was defined as a decrease in the wall motion score by ≥1. The septal segment was excluded from the wall motion analysis because of frequent postoperative paradoxical motion.

Statistics: Comparisons of proportions were performed by chi-square analysis or Fisher's exact test.

Results:

Patient disposition and characteristics: Twenty-two consecutive patients were enrolled and evaluated. Of the 22 enrolled patients, 20 were men and 2 were women. The patients had a mean age of 57 (range 36 to 68 years). Seventeen patients had a history of myocardial infarction with a duration >1 month after onset.

Segment disposition and functional outcome: The left ventricle of each of the 22 patients was divided into 5 segments, yielding 110 segments for possible evaluation. Of the 110 segments, 46 had wall motion abnormalities (in 20 of the 22 patients). These 46 segments were used to evaluate functional recovery. Considering these 46 asynergic segments, wall motion improved after CABG in 23 (50%), was unchanged in 19 (41%), and deteriorated in 4 (9%).

F-18 FDG and N-13 ammonia results: Preoperative PET F-18 FDG identified 23 segments as metabolically viable regions. Wall motion abnormality improved in 18 (78%) of these segments, whereas the remaining 5 segments did not improve postoperatively. In contrast, of 23 segments

exhibiting metabolically inactive regions, 5 (22%) improved in wall motion abnormality ($p<0.001$). These results are summarized in the tables below:

Table 26. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to PET Findings with F-18 FDG and N-13 Ammonia

	Improved Segmental Wall Motion		
PET findings	**Present**	**Absent**	**Total**
Mismatch pattern	**18**	**5**	**23**
Match pattern	**5**	**18**	**23**
Total	**23**	**23**	**46**

Table 27. Performance of PET F-18 FDG and N-13 Ammonia When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	**78 (18/23)**	**(56, 92)**
Specificity (%)	**78 (18/23)**	**(56, 92)**
PPV (%)	**78 (18/23)**	**(56, 92)**
NPV (%)	**78 (18/23)**	**(56, 92)**
Accuracy (%)	**78 (36/46)**	**(64, 89)**
Likelihood ratio (+)	**3.6**	
Likelihood ratio (-)	**0.28**	

Other Findings: Postoperative improvement in hypoperfusion was observed more often in the metabolically active segments (62%) than in the inactive segments (27%) on the preoperative PET study ($p<0.05$). As shown in the table below, of 19 asynergic segments showing increased F-18 FDG uptake before operation, the postoperative PET revealed a decrease in F-18 FDG uptake in 13 (68%) and persistent uptake in 6 (32%). The improvement in asynergy was observed in all the segments that showed a postoperative decrease in F-18 FDG uptake, but in only 50% of those with persistent uptake ($p<0.01$). On the other hand, 4 of 5 segments showing new F-18 FDG uptake after operation revealed further wall motion abnormality. Furthermore, the segments metabolically active before operation were more likely to have patent grafts (95%) than the metabolically inactive segments (70%) ($p<0.05$).

Table 28: Correlation of Changes in F-18 FDG Uptake with Wall Motion Changes in 46

Segments that were Asynergic Preoperatively**

		Postoperative Wall Motion		
F-18 FDG Change	**No. of Segments**	**Improved**	**Unchanged**	**Deteriorated**
F-18 FDG (+) →F-18 FDG (-)	**13**	**13**	**0**	**0**
F-18 FDG (+) →F-18 FDG (+)	**6 (1)***	**3**	**3 (1)**	**0**
F-18 FDG (-) →F-18 FDG (-)	**22 (5)**	**7 (1)**	**15 (4)**	**0**
F-18 FDG (-) →F-18 FDG (+)	**5 (4)**	**0**	**1 (1)**	**4 (3)**
Total	**46 (10)**	**23 (1)**	**19 (6)**	**4 (3)**

***Parentheses denote number of segments supplied with occluded grafts.**
**** This table was taken from the manuscript.**

Safety: The safety of PET F-18 FDG imaging was not addressed in the manuscript.

Conclusions in manuscript: Preoperative metabolic imaging using PET appears to be useful for predicting the response to CABG. Improvement in metabolic derangement was associated with improvement in regional function after CABG.

Reviewer's comments: A strength of the study was that the wall motion analysis was performed by several blinded readers. Another strength was that the success of revascularization was assessed quantitatively (with N-13 ammonia PET imaging). The authors specified how the N-13 ammonia scans that were obtained before revascularization were aligned with those obtained after revascularization. Similarly, the alignment of different imaging modalities (e.g., radionuclide ventriculography and positron emission tomography) was also addressed. Another relatively unique aspect of the study was that F-18 FDG PET imaging was done after patients had fasted, and without a glucose load.

Limitations of the study included the paucity of information provided about the study subjects. Such limited data make it difficult to know to whom the results may be generalizable. The manuscript did not specify whether the image analyses of match and mismatch patterns (of F-18 FDG and N-13 ammonia) were blinded. In this situation, blinding is of particular importance because these image analyses were qualitative (i.e., were performed visually).

9. Tamaki N, Kawamoto M, Tadamura E, et al. Prediction of Reversible Ischemia after Revascularization: Perfusion and Metabolic Studies with Positron Emission Tomography. Circulation 1995;91:1697-1705.

Objective: The objective of this study was to compare the value of resting perfusion studies with PET, exercise perfusion studies with PET, and metabolic studies with PET for predicting improvement in wall motion, as assessed by contrast or radionuclide ventriculography, after revascularization.

Design and sequence of events: This study was performed in consecutive patients with chronic myocardial infarction who were to undergo coronary revascularization with either CABG or angioplasty. Prior to revascularization, contrast ventriculography was performed to assess the motion of the left ventricular wall and to measure the left ventricular ejection fraction. Patients then underwent PET imaging with N-13 ammonia at rest and under stress to evaluate myocardial perfusion, and with F-18 FDG after fasting to evaluate myocardial metabolism. After either CABG or angioplasty, a follow-up angiogram was performed to assess the success of revascularization. Four to eight weeks after revascularization, regional wall motion was assessed by contrast ventriculography or radionuclide ventriculography.

Left ventricular wall motion was assessed by three blinded, experienced readers. However, the manuscript did not specify the nature of the information to which the readers were blinded. The PET images with N-13 ammonia and F-18 FDG were evaluated quantitatively. The manuscript did not specify the number of readers or indicate whether the readers were blinded.

Subjects: The study enrolled consecutive patients with chronic myocardial infarction. Patients with insulin-dependent diabetes were excluded.

F-18 FDG positron emission tomographic studies: Patients fasted for at least five hours before the F-18 FDG scan. A radiation dose of 80-300 MBq (2.2 to 8.1 mCi) of F-18 FDG was injected with the patient at rest. Approximately 60 minutes later, a scan was performed for 10 to 15 minutes.

N-13 ammonia positron emission tomographic studies: Rest and stress perfusion scans were performed separately within one week of the F-18 FDG study. Approximately 400 to 600 MBq (10.8 to 16.2 mCi) of N-13 ammonia were injected at rest, and resting perfusion scanning was started three minutes later. Two hours later, patients performed graded exercise using a supine ergometer. Another dose of N-13 ammonia was injected at peak exercise and the exercise was continued for an additional 30 to 60 seconds. The stress perfusion scan was performed 3 minutes after N-13 ammonia administration.

Image analysis: In each patient, resting and stress N-13 ammonia images were normalized to a normal reference region. The left ventricular myocardium was divided into five segments to calculate the mean regional perfusion as percent activity of the maximal counts in the normal

reference regions by using a circumferential profile analysis of four to six short-axis slices of the N-13 ammonia distribution. Stress and resting N-13 ammonia images were compared using a circumferential profile analysis based on the corresponding short-axis slices.

In each segment, F-18 FDG uptake was quantitatively measured as the percent (corrected for body weight) of the injected dose per 100 g of tissue. F-18 FDG images were shown as a parametric display as F-18 FDG uptake index (not normalized to uptake).

The images from the PET perfusion and metabolic studies were used to predict improvement in wall motion after revascularization: (a) For the F-18 FDG images, hypoperfused segments with an increase in F-18 FDG uptake above the normal range (based on an F-18 FDG uptake index--not normalization) were predicted to show functional improvement after revascularization. Those with no increase in F-18 FDG uptake were defined as PET scarring. The normal range of F-18 FDG uptake was obtained in healthy subjects. (b) For the N-13 ammonia images obtained at rest, asynergic segments were divided into two groups to compare the improvement in wall motion after revascularization: those with perfusion of more than 50% of the maximal value in the whole myocardium were considered to have reversible ischemia; those with perfusion of less than 50% of the maximal value in the whole myocardium were considered to have irreversible ischemia. (c) For the stress N-13 ammonia images, segments with stress perfusion more than 10% lower than resting perfusion were considered to have stress-induced hypoperfusion and reversible ischemia; those with lesser degrees of stress-induced hypoperfusion were considered to have irreversible ischemia.

Left ventricular wall motion was assessed by three blinded, experienced observers who used a five-point ordinal scale (normal, mild hypokinesis, severe hypokinesis, akinesis, and dyskinesis). Improved wall motion, from before revascularization to after revascularization, was defined as an increase by one or more points in the wall motion score.

Statistics: Comparisons of the predictive value of each study were performed with χ^2 analysis or Fisher's exact test. No adjustments in p values were made to correct for multiple comparisons.

Results:

Patient disposition and characteristics: Sixty one (61) consecutive patients with chronic myocardial infarction underwent myocardial perfusion and metabolic studies with PET before revascularization. Forty-three (43) of these patients had a successful revascularization and were included in the analysis. The remaining 18 subjects had inadequate revascularization and were not included in the analysis. Of these 43 patients, 24 underwent CABG and 19 underwent PTCA.

The 43 patients included 41 men and 2 women. The patients had a mean age of 58.1 years (range: 36 years to 72 years). The mean left ventricular ejection fraction was 41% (range: 21% to 64%) All patients had regional wall motion abnormalities and a history of myocardial

infarction that occurred more than 1 month before onset. Two patients had non-insulin-dependent diabetes.

Segment disposition and functional outcome: The left ventricle of each of the 43 patients was divided into 5 segments, yielding a total of 215 segments for possible evaluation. Of the 215 possible segments, 130 (60%) were asynergic before revascularization. These 130 segments were used to evaluate functional recovery. After revascularization, 51 segments (39%) showed improvement in the wall motion abnormality, whereas the remaining 79 segments did not.

PET imaging results: Among the 130 asynergic segments, an increase in F-18 FDG uptake was seen in 59 segments and no increase was seen in 71 segments. After revascularization, 45 of the 59 segments with increased F-18 FDG uptake showed improved regional wall motion (PPV=76%), whereas 65 of the 71 segments without increased F-18 FDG uptake failed to improve (NPV=92%).

Overall, the positive and negative predictive values for improvement in asynergy were 48% and 87% by the rest perfusion study, 63% (P=0.05 versus the rest value) and 87% by the rest-stress perfusion study, and 76% (P<0.01 versus the rest value) and 92% by the F-18 FDG study. The tables below summarize the PET imaging results for F-18 FDG, N-13 ammonia at rest, and N-13 ammonia under stress. These results are summarized in the tables below.

Table 29. Number of Hypoperfused, Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to F-18 FDG Uptake Index

	Improved Segmental Wall Motion		
F-18 FDG Uptake Index	**Present**	**Absent**	**Total**
Increased	**45**	**14**	**59**
Not increased	**6**	**65**	**71**
Total	**51**	**79**	**130**

Table 30. Performance of PET F-18 FDG Uptake Index When Used to Predict Improved Wall Motion in Hypoperfused, Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	88 (45/51)	(76, 96)
Specificity (%)	82 (65/79)	(72, 90)
PPV (%)	76 (45/59)	(63, 86)
NPV (%)	92 (65/71)	(82, 97)
Accuracy (%)	85 (110/130)	(78, 91)
Likelihood ratio (+)	5.0	
Likelihood ratio (-)	0.14	

Table 31. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to Rest Perfusion with N-13 ammonia

	Improved Segmental Wall Motion		
Rest Perfusion with N-13 Ammonia	Present	Absent	Total
≥50% of maximum	43	25	68
<50% of maximum	8	54	62
Total	51	79	130

Table 32. Performance of Rest Perfusion with N-13 Ammonia When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	84 (43/51)	(71, 93)
Specificity (%)	68 (54/79)	(57, 78)
PPV (%)	63 (43/68)	(50, 75)
NPV (%)	87 (54/62)	(76, 94)
Accuracy (%)	75 (97/130)	(67, 82)
Likelihood ratio (+)	2.7	
Likelihood ratio (-)	0.23	

Table 33. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to Stress Perfusion with N-13 Ammonia

	Improved Segmental Wall Motion		
Stress Perfusion with N-13 Ammonia	Present	Absent	Total
> 10% Lower than Resting Perfusion	47	51	98
<10% Lower than Resting Perfusion	4	28	32
Total	51	79	130

Table 34. Performance of Stress Perfusion with N-13 Ammonia When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	Value (no. of segments)	95% CI
Sensitivity (%)	**92 (47/51)**	**(81, 98)**
Specificity (%)	**35 (28/79)**	**(25, 47)**
PPV (%)	**48 (47/98)**	**(38, 58)**
NPV (%)	**87.5 (28/32)**	**(71, 96)**
Accuracy (%)	**58 (75/130)**	**(49, 66)**
Likelihood ratio (+)	**1.4**	
Likelihood ratio (-)	**0.22**	

Safety: The safety of F-18 FDG and N-13 ammonia PET imaging were not addressed in this manuscript.

Conclusions in manuscript: F-18 FDG PET provided the best predictive value for improvement in wall motion after revascularization. On the other hand, N-13 ammonia PET is useful for predicting nonreversible myocardial scarring when it shows severe hypoperfusion at rest or hypoperfusion without stress-induced ischemia.

Reviewer's comments: One of the strengths of this study was that analyses were performed on 42 patients, the second largest sample size among the principal studies. Wall-motion assessments were performed blindly by multiple readers. The study compared different diagnostic tests, and the predictive performance of F-18 FDG PET, rest perfusion with N-13 ammonia, and stress perfusion with N-13 ammonia were each evaluated with respect to the functional outcome ("truth"). Such direct comparisons of diagnostic test performance provide useful data to the practicing health care providers, who often lack sufficient comparative performance data upon which to base a choice. In this study, the success of coronary revascularization was assessed with coronary arteriography. Thus, the diagnostic performance data are not confounded by non-drug factors, such as the success of coronary revascularization. However, additional analyses that included all patients, including those with unsuccessful revascularization, would have provided useful data on the diagnostic performance as might be expected in actual use and would have provided more information on the ultimate clinical usefulness of the diagnostic test.

A limitation of the study is that the manuscript did not specify the nature of the information to which the readers were blinded when they performed the wall-motion analyses. The manuscript did not specify the number of readers for the PET image analyses, nor did it indicate whether

these analyses were blinded. However, these analyses were quantitative, limiting potential bias that might be introduced by unblinded evaluations. "By-patient" analyses were not performed. Global ventricular function and clinical outcomes were not assessed.

10. Tillisch J, Brunken R, Marshall R, et al. Reversibility of Cardiac Wall-Motion Abnormalities Predicted by Positron Tomography. N Engl J Med 1986;314:884-888.

Description of Study

Objective: The objective of this study was to determine whether preserved myocardial uptake of F-18 FDG in a region with abnormal wall motion at rest is an indication of myocardial metabolic viability, and whether reversibility of the wall-motion disturbance (as assessed by radionuclide or contrast ventriculography) by adequate surgical revascularization can be predicted with these criteria.

Design and sequence of events: The study enrolled consecutive patients with resting regional wall-motion abnormalities who were to undergo CABG. Prior to revascularization, left ventricular wall motion was assessed with either radionuclide or contrast ventriculography. PET studies with F-18 FDG and N-13 ammonia were performed to assess myocardial metabolism and perfusion. After CABG, adequate revascularization of an abnormally contracting region was assessed by review of the operative report and the preoperative coronary angiogram. Left ventricular wall motion was reassessed with radionuclide or contrast ventriculography.

The wall motion assessment was performed by three experienced contrast radiologists who were blinded to clinical or (sic) tomographic data. The analysis of the PET studies with F-18 FDG and N-13 ammonia were quantitative. The manuscript did not specify the number of readers of these PET images, or whether these readers were blinded.

N-13 ammonia and F-18 FDG positron emission tomographic studies: Imaging was performed when patients were post-prandial. Patients were administered 50 grams of glucose by mouth, 60-90 minutes before F-18 FDG administration. N-13 ammonia (15-20 mCi) was injected intravenously, and three minutes later, six sequential cross-sectional PET images 1.0-1.5 cm apart were obtained. Subsequently, F-18 FDG (10 mCi) was injected, and 45 minutes later cross-sectional imaging was performed again.

Image analysis: For PET images, the left ventricle was divided into twelve 30^{o} sectors. N-13 ammonia and F-18 FDG counts were normalized to maximum counts in all planes, and the counts were compared sector by sector. Normalized N-13 ammonia and F-18 FDG counts for each sector that had already been established were applied in this study. Infarction was represented as a concordant reduction in normalized N-13 ammonia and F-18 FDG counts two standard deviations below normal for each of three or more continuous sectors. Ischemia was

indicated by a difference between normalized F-18 FDG and N-13 ammonia counts that was greater than two standard deviations above the normal value for the difference in a given sector.

Resting regional wall-motion abnormalities were predicted preoperatively to be reversible if F-18 FDG uptake was normal or increased in the region, and if N-13 ammonia uptake was either normal or decreased. An abnormality was predicted to be irreversible if both N-13 ammonia and F-18 FDG uptake were depressed.

For wall-motion analysis, images from radionuclide or contrast ventriculography were divided into seven regions. Regional wall-motion was graded on a scale of 0 to 4 (normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic) by three blinded readers. Improved wall motion, from before revascularization to afterwards, was defined as an improvement of at least one grade.

Each PET image was anatomically correlated with a ventriculographic image by reconstructing the PET image in 3 dimensions and assigning anatomical regions on the PET scan to comparable regions on the ventriculogram (isotopic or contrast). Regional concordance was then maintained for each isotopic or contrast study.

Statistics: Interobserver variation was determined by analysis of variance. All other statistics were determined with a two-tailed Student's t-test.

Results:

Patient disposition and characteristics: Seventeen consecutive patients were included in the study, all of whom were included in the analysis. The 17 patients included 16 men and 1 woman. Eleven patients had a left ventricular ejection fraction of less than 40%. Sixteen patients had a previous myocardial infarction: two patients were studied within two weeks of myocardial infarction; the other 15 had infarction an average of 8 weeks (range, 6 to 14 weeks) before the study.

Segment disposition and functional outcome: Follow-up of wall motion occurred 12-18 weeks after CABG in 13 patients, in 6-10 weeks in 2 patients, and in 3 weeks in 2 patients. For wall-motion analysis, the left ventricle of each of the 17 patients was divided into seven segments, yielding 119 segments for possible evaluation. Of the 119 possible segments, 73 had abnormal resting wall motion, of which 67 were considered to have been adequately revascularized. Thus, 67 of 119 (56%) segments were used to evaluate functional recovery. Postoperatively, 37 of these 67 segments (51%) improved, whereas the remaining 30 did not. Improvement of at least one full grade occurred in 9/21=43% mildly hypokinetic regions, 21/37 (57%) severely hypokinetic regions, 6/14 = 43 % akinetic regions, and in the single dyskinetic region.

The mean preoperative wall-motion score of the regions predicted to improve was 2.0±0.8 (equivalent to severe hypokinesis), which improved significantly to 0.6±0.6 postoperatively

($p<0.05$). The mean preoperative wall-motion score of those regions predicted not to improve was 2.4±0.5, and the postoperative score 2.6±0.4 (difference not significant).

PET imaging results: Among the 67 asynergic segments that had been adequately revascularized, 41 were predicted to have reversible wall motion abnormalities. Specifically, of these 41 regions, 25 of these had normal preoperative N-13 ammonia and F-18 FDG uptake (22 improved postoperative wall motion, 3 not improved). The remaining 16 regions had decreased N-13 ammonia uptake, but either normal or increased F-18 FDG uptake (13 improved postoperative wall motion, 3 not improved). Thus, 35 of the 41 predictions of reversible wall motion were correct, yielding a positive predictive value of 85%. Conversely, of the 26 regions that were predicted to have irreversible abnormalities, 24 failed to improve, yielding a negative predictive value of 92%. These results are summarized in the tables below.

Table 35. Number of Asynergic Myocardial Segments with Improved Segmental Wall Motion after Revascularization: Relation to Pattern of F-18 FDG and N-13 Ammonia Uptake

	Improved Segmental Wall Motion		
Pattern of F-18 FDG and N-13 Ammonia Uptake	**Present**	**Absent**	**Total**
Mismatch	**35**	**6**	**41**
Match	**2**	**24**	**26**
Total	**37**	**30**	**67**

Table 36. Performance of PET F-18 FDG and N-13 Ammonia Uptake Patterns When Used to Predict Improved Wall Motion in Asynergic Myocardial Segments

Performance Measure	**Value (no. of segments)**	**95% CI**
Sensitivity (%)	**95 (35/37)**	**(82, 99)**
Specificity (%)	**80 (24/30)**	**(61, 92)**
PPV (%)	**85 (35/41)**	**(70, 94)**
NPV (%)	**92 (24/26)**	**(75, 99)**
Accuracy (%)	**88 (59/67)**	**(78, 95)**
Likelihood ratio (+)	**4.7**	
Likelihood ratio (-)	**0.07**	

Other Findings: The mean left ventricular ejection fraction in the study population was 32±14% before CABG, and 41±15% afterward ($P<0.05$). In the subset of 11 patients in whom resting

wall motion in two or more regions improved postoperatively, the mean ejection fraction increased from 30±11% to 45±14% ($P<0.05$).

The predictive value of electrocardiograms was evaluated. Twenty-eight of the 73 abnormally contracting regions were in areas believed to have "transmural" infarcts as evidenced by Q waves with a duration of at least 0.04 seconds. After revascularization, wall motion did not improve in 12 of these 28 regions, yielding a negative predictive value of only 43%. Note, however, that unlike the evaluation of the predictive value of PET imaging, the evaluation of the predictive value of electrocardiography utilized all 73 asynergic segments, regardless of whether adequately revascularized or not.

Safety: The safety profiles of F-18 FDG PET and N-13 ammonia PET imaging were not addressed in this manuscript.

Conclusions in manuscript: PET imaging with N-13 ammonia to assess blood flow and F-18 FDG to assess the metabolic viability of the myocardium is an accurate method of predicting potential reversibility of wall-motion abnormalities after surgical revascularization.

Reviewer's comments: Published in 1986, this study is one of the seminal articles for the use of F-18 FDG PET in the evaluation of the reversibility of left ventricular dysfunction in patients with coronary artery disease. Although the study was relatively small (n=17), many desirable features were incorporated into the design. The wall motion assessments were performed by blinded readers, decreasing potential bias that might arise from unblinded assessments. Wall motion assessments were made by several readers, allowing interreader variability to be assessed and increasing the generalizability of the results. Consecutive patients were enrolled, decreasing potential selection bias, and data on all were included in the analysis. The success of revascularization was assessed. The manuscript describes how regional concordance of myocardial segments was maintained when several imaging procedures were performed.

One limitation of the study is its small sample size. In addition, the manuscript did not specify the number of readers for the PET images, or whether these readers were blinded. However, the quantitative nature of the PET analysis decreases the amount of potential bias that might be introduced by an unblinded image analysis. Few patient characteristics were described, increasing the difficulty of being able to describe the population to which the results apply most directly. As in several of the other principal studies, only adequately revascularized segments were included in the analysis, making more difficult the assessment of the ultimate clinical benefit of performing the PET evaluation. The study did not include "by patient" analyses, preventing direct assessments of clinical benefit. Although changes in global left ventricular function were evaluated, the results were not correlated with the PET findings. Thus, it is unclear whether PET imaging allows prediction of global functional improvement (in addition to segmental functional improvement). Clinical outcomes were not assessed.

D. Secondary Published Literature

The review of the ten primary published articles focused on whether PET imaging with F-18 FDG, when used in combination with assessments of myocardial perfusion, is able to predict the recovery of regional or segmental systolic function in the left ventricle after myocardial revascularization. Of greater clinical significance, is whether such improvements in segmental ventricular function are also indicative of improvements in global ventricular function. Moreover, the most important concerns for the care of patients with coronary artery disease are a) whether such predictions of regional recovery of ventricular function appropriately influence clinical decision making, and b) whether such improvements in regional or global ventricular function lead to clinical benefits to patients such as amelioration of symptoms, increases in exercise tolerance, or enhancement of survival. The abstracts of several published literature articles submitted by the Institute for Clinical PET that address these issues are reproduced below. These articles provide support that cardiac PET imaging with F-18 FDG in this context provides information that is clinically useful. However, because of the design of the studies (e.g., retrospective, nonrandomized, small size), the articles fall short of providing sufficient evidence to support a patient-management indication. Such a patient management indication would specify explicitly that cardiac imaging with PET F-18 FDG in this context directly results in appropriate diagnostic or therapeutic management of patients. The articles fall short of providing sufficient evidence to support an indication that cardiac imaging with PET F-18 FDG is able to predict improvements in global ventricular function, symptoms, clinical functioning, or survival.

1. Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994;73:527-533.

Objective: The objective of this study was to evaluate the prognostic value of PET mismatch, and its interrelation with the choice of medical therapy or revascularization for predicting survival and improvement in symptoms of heart failure in patients with coronary artery disease and left ventricular dysfunction.

Description of study: The study evaluated 93 consecutive patients with angiographic coronary artery disease and a mean left ventricular ejection fraction of 25%. The patients underwent cardiac PET studies for assessment of hypoperfused yet viable myocardium ("mismatch pattern") using N-13 ammonia and F-18 FDG and were followed for an average of 13.6 months. Fifty patients underwent medical treatment and 43 underwent revascularization.

Results: A stepwise Cox model analysis showed that the extent of mismatch had a negative effect on survival (p=0.02), whereas revascularization had a positive effect on survival (p=0.04). The annual probability of survival of patients with mismatch receiving medical therapy was lower than of those without mismatch (50 vs. 92%, p=0.007). Patients who underwent revascularization had a higher survival rate than those treated medically (88 vs 50%, p=0.03).

The presence of mismatch also predicted improvement in heart failure symptoms after revascularization ($p<0.001$).

Conclusions in manuscript: These results suggest that the presence of mismatch in patients with coronary artery disease and severe left ventricular dysfunction is associated with poor annual survival with medical therapy. Revascularization in patients with PET mismatch appears to be associated with improved survival and symptoms of heart failure.

Reviewer's comments: This was a retrospective, nonrandomized study, which limits the conclusions that can be drawn.

2. Di Carli M, Asgarzdie, BA, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. Circulation 1995;92:3436-3444.

Objective: The purpose of this study was to test the hypothesis that improvement in heart failure symptoms after CABG in patients with ischemic cardiomyopathy would be related to the extent, magnitude, and location of viable myocardium, as determined by quantitative analysis of preoperative PET images.

Description of study: The study evaluated 36 patients with ischemic cardiomyopathy and a mean left ventricular ejection fraction of 28% who were undergoing CABG. Preoperative extent and severity of perfusion abnormalities and myocardial viability (flow-metabolism mismatch) were assessed by use of quantitative analysis of PET images with N-13 ammonia and F-18 FDG. Each patient's functional status was determined before and after CABG by use of a Specific Activity Scale.

Results: The total extent of PET mismatch correlated linearly with percent improvement in functional status after CABG ($r=0.87$, $p<0.0001$). A blood flow-metabolism mismatch of ≥18% was associated with a sensitivity of 76% and a specificity of 78% for predicting a change in functional status after revascularization. Patients with mismatches ≥18% achieved a significantly higher functional status compared with those with mismatch <5% (5.7±0.8 versus 4.9±0.7 metabolic equivalents, $p=0.009$). This resulted in an improvement of 107% in patients with mismatches ≥18% compared with only 34% in patients with mismatch <5%

Conclusions in manuscript: These results suggest that in patients with ischemic cardiomyopathy, the magnitude of improvement in heart failure symptoms after CABG is related to the preoperative extent and magnitude of myocardial viability as assessed by use of PET imaging. Patients with larger perfusion-metabolism mismatches exhibit the greatest clinical benefit after CABG.

Reviewer's comments: This was an observational study.

3. Depré C, Vanoverschelde JJ, Gerber B, et al. Correlation of functional recovery with myocardial blood flow, glucose uptake, and morphologic features in patients with chronic left ventricular ischemic dysfunction undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 1997;113:371-8

Objectives: The objective of this study was to investigate the influence of preoperative myocardial ultrastructure and metabolism on recovery of systolic function after coronary artery bypass grafting in patients with coronary artery disease and left ventricular dysfunction.

Description of Study: Dynamic positron emission tomography with N-13 ammonia and F-18 FDG was used to assess myocardial perfusion and glucose uptake in 53 patients scheduled for coronary revascularization because of coronary artery disease and left ventricular dysfunction. The degree of tissue fibrosis and the presence of potentially reversible alterations of cardiomyocytes (loss of myofilaments and accumulation of glycogen) were quantified from transmural biopsy specimens. These were harvested from the center of the dysfunctional area during the operation and analyzed with a light microscope. The recovery of systolic performance was assessed from the changes in left ventricular function at contrast ventriculography or echocardiography before and six months after the operation.

Results: According to postoperative changes in regional wall motion, left ventricular function was considered to have improved in 34 patients, whereas dysfunction persisted in 19 patients. In patients with improved wall motion, ejection fraction rose by 12% and end-systolic volume decreased by 28%. By contrast, in patients with persistent dysfunction, ejection fraction decreased by 6% and end-systolic volume increased by 25%. Before revascularization, myocardium with reversible dysfunction displayed higher levels of absolute myocardial blood flow, higher myocardial glucose uptake, less tissue fibrosis, and more altered cardiomyocytes than myocardium with persistent dysfunction. Significant correlations were found between regional blood flow and the surface of the biopsy specimen covered by fibrosis, as well as between glucose uptake and the density of altered cardiomyocytes.

Conclusions in manuscript: In patients with left ventricular ischemic dysfunction, the recovery of regional and global left ventricular function after surgical revascularization is associated with higher preoperative blood flow and glucose uptake, with less tissue fibrosis and a higher amount of viable cardiomyocytes in the dysfunctional area.

Reviewer's comments: This study provided morphologic associations of PET with F-18 FDG and N-13 ammonia.

4. Marwick TH, Nemec JJ, Lafont A, et al. Prediction by postexercise fluoro-18-deoxyglucose positron emission tomography of improvement in exercise capacity after revascularization. Am J Cardiol 1992;69:854-859

Objectives: This study was designed to determine whether the combined extent of hibernating and transiently ischemic myocardium detected by F-18 FDG imaging could be used to predict the occurrence of functional benefits from revascularization. The study examined the influence of the amount of F-18 FDG-avid myocardium on changes in left ventricular function and exercise parameters after revascularization.

Description of Study: Echocardiography and exercise testing were performed before and after intervention in 23 patients who had undergone positron emission tomography for the evaluation of myocardial perfusion (using Rb-82), and postexercise F-18 FDG imaging in the fasting state. Follow-up echocardiography (22±14 weeks after revascularization) was compared with preoperative FDG activity in 7 myocardial regions per patient.

Results: Systolic function improved after intervention in 19 of 26 malperfused dysfunctional F-18 FDG-avid regions (73%), and did not improve in 35 of 47 dysfunctional regions without increased F-18 FDG uptake (74%). The influence of the amount of F-18 FDG-avid tissue on changes in functional state was examined by comparing nine patients with multiple (≥2) F-18 FDG-avid regions with the remainder. Those with multiple F-18 FDG-avid regions demonstrated improvement in peak rate-pressure product 20±4 to 26±4 x 10^3, $p<0.02$), and percentage of maximal heart rate achieved at peak 84±10% to 93±6%, $p=0.04$), neither of which changed significantly in the remaining patients. Exercise capacity increased from 5.6±2.7 to 7.5±1.7 METS in the group with multiple F-18 FDG-avid regions; this increase of 55±18% exceeded the increase of 13±10% in the remainder ($p=0.04$).

Conclusions in manuscript: Imaging of postexercise F-18 FDG uptake in patients with previous myocardial infarction may predict improvement of regional systolic function and exercise parameters after revascularization.

5. Eitzman D, Al-Aouar Z, Kanter HL, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. J Am Coll Cardiol 1992;20:559-65.

Objectives: The objective of this study was to determine whether the identification of jeopardized myocardium with positron emission tomography predicts subsequent cardiac events and whether revascularization affects the clinical outcome in patients with advanced coronary artery disease and impaired left ventricular function. The study also examined the relation between scintigraphic results and subsequent change in functional status in this patient group.

Description of study: Eighty-two patients with advanced coronary artery disease and impaired left ventricular function underwent PET imaging to assess myocardial viability before coronary artery revascularization.

Results: Forty patients underwent successful revascularization. Patients who exhibited evidence of metabolically compromised myocardium by PET (decreased blood flow with preserved metabolism) who did not undergo subsequent revascularization were more likely to experience a myocardial infarction, death, cardiac arrest or late revascularization due to development of new symptoms than were the other patient groups ($p<0.01$). Concordantly decreased flow and metabolism in segments of previous infarction did not affect outcome in patients with or without subsequent revascularization. Those with a compromised myocardium who did undergo revascularization were more likely to experience an improvement in functional class than were patients with preoperative PET findings of concordant decrease in flow and metabolism.

Conclusions in manuscript: PET myocardial viability imaging appears to identify patients at increased risk of having an adverse cardiac event or death. Patients with impaired left ventricular function and PET evidence for jeopardized myocardium appear to have the most benefit from a revascularization procedure.

E. Safety Evaluation:

At the time of its approval in 1994, F-18 FDG was found to be safe and effective in PET imaging for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. As specified in the labeling, the recommended dose for this use in an adult (70 kg) is 185-375 MBq (5-10 mCi), by intravenous injection. Since its approval, no adverse event reports have been reported to FDA for this use.

None of the reviewed articles for cardiac applications of F-18 FDG included any information about its safety. Thus, it is not clear in these studies whether a) safety parameters were monitored and no adverse events were noted; b) safety parameters were monitored, and adverse events occurred but were not reported, or; c) safety parameters were not monitored. Doses that were used for cardiac imaging generally were in the range of 185-375 MBq (5-10 mCi).

Edward B. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine performed a review of the prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine.[vii] The authors evaluated adverse reactions to PET radiopharmaceuticals (including F-18 FDG) from several PET institutions, apparently using a consensus definition of "adverse reaction" developed by the Pharmacopeia Committee. No adverse reactions to F-18 FDG were identified in either the retrospective examination of records of administered radiopharmaceutical doses or the prospective examination of administered doses. These data provide additional support for the safety of F-18 FDG.

Because F-18 FDG is often administered for cardiac imaging after ingestion of a glucose load or may be administered after fasting, possible safety concerns arise in patients with impaired glucose homeostasis (e.g., patients with diabetes mellitus). However, these are not safety concerns that arise from the administration of the drug per se, but from patient preparation for F-18 FDG administration and for PET imaging.

The dosimetry of F-18 FDG in humans has been published[viii] and has been summarized in the biopharmaceutics review. The estimated absorbed radiation doses to organs were calculated using the data published by the International Commission on Radiological Protection for F-18 FDG.[ix] The bladder is the organ that receives the highest dose of radiation. For an F-18 FDG dose of 370 MBq (10 mCi) in a 70-kg adult, the estimated absorbed radiation dose is 6.29 rads for the bladder wall based on a fixed bladder content for three hours. The estimated absorbed radiation dose to the bladder wall decreases to 4.40 rads if voiding occurs two hours after F-18 FDG administration, and to 2.20 rads if voiding occurs one hour after F-18 FDG administration. The estimated absorbed radiation dose to the heart is 2.41 rads.

In summary, specific safety concerns were not identified in this review of the use of F-18 FDG in cardiac imaging, or in the types of patients who were included in these studies.

F. Overall Assessment

Trial Design:

Prospective studies: The ten principal studies were prospective and several evaluated consecutive patients. Consecutive enrollment of patients helps to decrease potential selection bias in the choice of patients for inclusion in the study. Just as in prospective randomized clinical trials of therapeutic agents in which patients are assigned to treatment group, prospective study designs for diagnostic agents decrease biases that may arise when patient outcomes and results of imaging are already known (e.g., as in retrospective data analyses). However, publication bias, in which only "positive" studies are accepted for publication, may have limited the sample of studies that were available for this review.

Adequacy of controls: As discussed in the introduction, the ten principal studies that were reviewed for efficacy were all of a similar trial design. In each study, the performance of PET imaging with F-18 FDG was measured against a functional outcome: improvement of segmental systolic function after myocardial revascularization. For the purposes of this review, this functional outcome was the endpoint of primary interest. Changes in myocardial function were assessed by evaluating segmental wall motion before revascularization and afterwards. The methods by which segmental wall motion were assessed include echocardiography, radionuclide ventriculography, and contrast ventriculography. All three of these methods are sufficiently valid and reliable for the purpose of evaluating segmental wall motion. All three methods are able to adequately assess the "true" functional status of the myocardium. Thus, each of the ten principal studies was appropriately controlled.

Blinding: Because it helps to minimize potential bias, blinding the readers during image analysis is one of the most important design features of imaging trials. For the purposes of this review, two types of blinding were deemed to be most critical: a) blinding of those who evaluated changes in segmental systolic function to the results of the PET imaging studies and, conversely, b) blinding of those who analyzed the PET images to the results of the analysis of segmental systolic function. Stated differently, readers who were analyzing truth (i.e., segmental systolic function) should have been blinded to the imaging results from the test article (i.e., PET F-18 FDG scans), and vice versa.

Blinding of image analyses for assessment of ventricular function: In the ten principal studies, the analysis of segmental systolic function was generally qualitative (e.g., an ordinal wall-motion scale where 1=normal, 2=hypokinesia, 3=akinesia, 4=dyskinesia), whereas the analysis of the PET images was generally quantitative. Qualitative wall-motion analyses are visual and involve substantial judgement on the part of the reader (as is also true for qualitative interpretation of PET images). Thus, for the purposes of this review, blinding of those who performed these qualitative analyses was felt to be particularly important. Seven of the ten principal studies specified that the analysis of segmental systolic function was performed by blinded readers (i.e., studies 1, 3, 4, 7, 8, 9, and 10). Unfortunately, in four of these studies the manuscripts specified only that these readers were blinded, without indicating to what information they were

blinded (studies 4, 7, 9, and 10). For example, readers may be blinded to the results of the PET studies, to clinical information, to the results of imaging with other modalities, etc. However, it seemed likely that in these four cases the readers were in fact blinded to the PET results, in part because that interpretation is consistent with the conventional use of the term "blinding" in imaging trials, and in part because the trials were prospective, suggesting that the PET images obtained before revascularization may have been analyzed before follow-up assessments were made of ventricular function after revascularization.

Blinding of PET image analyses: Quantitative analyses of PET images also may involve judgement by the reader, which may influence the results of the analyses (e.g., operator-interactive programs, identifying regions of interest, delineating segments, choosing the sites from which counts are sampled). Generally, however, the possibility of bias during quantitative analyses was felt to be substantially less than during qualitative analyses. Most of the principal studies employed quantitative or semi-quantitative analyses of the PET images. Overall, therefore, blinding readers of the PET images to whether the myocardial segments regained systolic function was less of a concern than vice versa. However, in one study (study #5) the PET images were analyzed qualitatively and the manuscript did not specify that the readers were blinded to the wall-motion analysis. These readers in this study were blinded to the perfusion results. Similarly, in another study (study #8), the PET images were analyzed visually for match-mismatch patterns, but the manuscript did not indicate if the readers were blinded to the wall-motion analysis.

The use of several blinded readers who interpret images independently of one another is an important design feature of imaging clinical trials. Independent blinded image evaluations by multiple readers allow interreader variability to be assessed. Such evaluations increase the generalizability of the image evaluations and decrease the likelihood that the study conclusions result from the idiosyncracies of a particular reader. Conversely, blinded image evaluations by only a single reader are suboptimal, as are consensus (non-independent) image evaluations. Several of the principal clinical trials included blinded image evaluations by multiple readers, and a few specified that the readers were independent of each other.

Overall, considering these ten studies in aggregate, blinding of the readers to critical information was sufficient, though not optimal, in this set of articles.

Study size: A total of 298 patients were evaluated in the ten principal studies. As shown in the first column of the following table, the smallest study evaluated 14 patients and the largest evaluated 48 patients. Thus, even the largest study evaluated relatively small numbers of patients. Larger sample sizes in each of these studies would have been preferable because as a rule, the greater the number of patients, the greater the generalizability of the study. Moreover, large sample sizes typically provide better estimates of the diagnostic performance of a drug and narrower confidence intervals than small sample sizes (with all other things being equal).

Table 37: Numbers of Patients and Myocardial Segments, and Prevalence of Hibernating Asynergic Myocardial Segments and of Patients with Hibernating Myocardium in the Ten Principal Trials[a]

Study	No. of Patients Included in Analysis	Total No. of Segments	No. of Asynergic Segments	No. of Asynergic Segments Included in Analysis	Prevalence (%) of Hibernating Asynergic Segments (# of segs)[f]	Prevalence (%) of Patients with Hibernating Myocardium (# of pts)
1 Baer[b]	42	1176	405	371	49 (180/371)	62 (26/42)
2 Gerber[c]	39	39	39	39	62 (24/39)	62 (24/39)
3 Gropler	34	272	141	116	40 (46/116)	--
4 Knuuti	48	384	106	90	30 (27/90)	--
5 Lucignani	14	70	54	54	74 (40/54)	--
6 Maes[c]	23	23	23	23	52 (12/23)	52 (12/23)
7 Marwick	16	208	85	85	41 (35/85)	--
8 Tamaki[d]	22	110	46	46	50 (23/46)	91 (20/22)
9 Tamaki[e]	43	215	130	130	39 (51/130)	--
10 Tillisch	17	119	73	67	55 (37/67)	--
Total	298	--	--	--	--	--

[a] Because the left ventricle was divided into a different number of segments by the different investigators, the total number of segments in a study does not have a constant relationship to the number of patients in the study.
[b] Analyses were limited to akinetic or dyskinetic segments (i.e., hypokinetic segments were not included in the analyses).
[c] Evaluations were limited to the anterior wall of the left ventricle for each patient (i.e., one segment per patient).
[d] Tamaki et al (1989)
[e] Tamaki et al (1995)
[f] Prevalence of hibernating segments = Number of hibernating segments/Number of analyzed asynergic segments

Study Endpoints:

For purposes of this review, the ten principal studies all had a similar endpoint that was of primary interest: the degree of recovery (or lack of recovery) of regional systolic function after myocardial revascularization with either CABG or angioplasty. Unfortunately, the studies generally did not evaluate changes in global ventricular function (e.g., ejection fraction), changes in patient functional status (e.g., changes in NYHA functional category, exercise tolerance), changes in symptoms (e.g., dyspnea, fatigue), or changes in survival as predicted by PET imaging with F-18 FDG. Had these been performed, these additional study evaluations might have provided a clearer picture of the potential clinical utility of PET cardiac imaging with F-18 FDG. Instead, other literature articles were identified in the literature that suggested that PET cardiac imaging with F-18 FDG has clinical usefulness.

In most studies, the assessment of the degree of recovery of regional systolic function was evaluated only at one time point after revascularization (e.g., three months after revascularization). Hence, the time course of myocardial recovery was not well described by any of the studies. Not only would such information be helpful in optimizing the efficiency and design of other clinical studies, but such information has direct clinical usefulness.

Table 38 summarizes the diagnostic performance of PET imaging with F-18 FDG in the ten principal studies. These data have not been pooled in this review because the definition of a myocardial segment differed among the studies, and because myocardial segments in a given study weren't necessarily mutually exclusive of one another.

Patient Disposition and Characteristics:

The summary of each study in this review described the study's enrollment criteria, specifically noted the disposition of enrolled patients, and specified the characteristics of the patients who ultimately were enrolled or included in the analyses. An adequate accounting of patients helped in the determination of whether only selected patients were retained for purposes of analysis, which could have undermined the usefulness of the study for this review. Overall, the description of patient disposition in the manuscripts was acceptable, but not always optimal.

The patient characteristics of those enrolled and of those analyzed help to delineate the population to whom the results of the study are generalizable. All of the studies included patients with coronary artery disease and left ventricular dysfunction. In most of the studies, ventricular dysfunction was chronic, regional, and tended to be mildly or moderately depressed. Thus, the results of the studies are most relevant to similar patients and may not be directly generalizable to others, such as patients with acute myocardial dysfunction, global ventricular dysfunction, or in patients with profound ventricular dysfunction. In particular, the diagnostic performance of F-18 FDG PET, as assessed by measures such as sensitivity and specificity, may differ in these other clinical settings.

In general, the manuscripts only included a few major demographic characteristics (e.g., sex, age) and a few baseline characteristics (e.g., ejection fraction). The manuscripts could have been strengthened by more detail in this area. No studies with pediatric patients were identified. Therefore, safety and efficacy of cardiac PET imaging with F-18 FDG have not been established.

Table 38: Sensitivity, Specificity, PPV, and NPV in the Ten Principal Trials[a]: By-Segment Analysis

Study	No. of Patients Included in Analysis	Prevalence (%) of Hibernating Asynergic Segments (# of segs)[f]	Sens (%) 95% CI	Spec (%) 95% CI	PPV (%) 95% CI	NPV (%) 95% CI
1 Baer[b]	42	49 (180/371)	93 (88, 96)	66 (59, 72)	72 (66, 78)	91 (84, 95)
2 Gerber[c]	39	62 (24/39)	75 (53, 90)	67 (38, 88)	78 (56, 92)	62.5 (35, 85)
3 Gropler	34	40 (46/116)	83 (68, 92)	50 (38, 62)	52 (40, 64)	81 (67, 92)
4 Knuuti	48	30 (27/90)	100 (87, 100)	63 (50, 75)	54 (39, 68)	100 (91, 100)
5 Lucignani	14	74 (40/54)	92.5 (80, 98)	80 (52, 96)	95 (83, 99)	80 (52, 96)
6 Maes[c]	23	52 (12/23)	83 (52, 98)	91 (58, 100)	91 (58, 100)	83 (52, 98)
7 Marwick	16	41 (35/85)	71 (54, 85)	76 (62, 87)	28 (50, 80)	79 (65, 89)
8 Tamaki[d]	22	50 (23/46)	78 (56, 92)	78 (56, 92)	78 (56, 92)	78 (56, 92)
9 Tamaki[e]	43	39 (51/130)	88 (76, 96)	82 (72, 90)	76 (63, 86)	92 (82, 97)
10 Tillisch	17	55 (37/67)	95 (82, 99)	80 (61, 92)	85 (70, 94)	92 (75, 99)
Total	298	--	--	--	--	--

[a] Because the left ventricle was divided into a different number of segments by the different investigators, the total number of segments in a study does not have a constant relationship to the number of patients in the study.
[b] Analyses were limited to akinetic or dyskinetic segments (i.e., hypokinetic segments were not included in the analyses).
[c] Evaluations were limited to the anterior wall of the left ventricle for each patient (i.e., one segment per patient).
[d] Tamaki et al (1989)
[e] Tamaki et al (1995)
[f] Prevalence of hibernating segments = Number of hibernating segments/Number of analyzed asynergic segments

Segment Disposition, Characteristics, and Functional Outcome:

This review also described in some detail the disposition of myocardial segments. As with patient disposition, an adequate accounting of segments helped in the determination of whether only selected segments were retained for purposes of analysis, which could have undermined the usefulness of the study for this review. For example, one study was excluded from this review because the analysis included one segment per patient, and that segment had "clearly PET-documented blood flow metabolism match or mismatch."[x] Diagnostic performance measures (e.g., sensitivity, specificity) based on data derived from such segments are likely to be biased. However, as mentioned above, publication bias may have further limited the sample of studies that were available for this review. Overall, the description of segment disposition in the manuscripts was acceptable, but not always optimal.

Just as noted above with patients, describing the characteristics of the segments helps to delineate the segments to which the results of the study are generalizable. For example, most of the studies included an assessment of segmental function before revascularization across the full spectrum of motion (e.g., normal, hypokinetic, akinetic, dyskinetic). In general, however, only those segments with asynergy before revascularization were included in analyses, and changes in function for these asynergic segments were recorded after revascularization. Thus, the performance of PET F-18 FDG has been best characterized in a subset of asynergic myocardial segments (but across the full spectrum of asynergy). As the potential to recover systolic function is the main parameter of clinical interest, such a limited analysis was deemed acceptable. The value of PET F-18 FDG imaging of segments with normal motion before revascularization has not been established.

In several studies, analyses were restricted not only to segments with asynergy before revascularization, but were restricted only to those segments that had been successfully revascularized. The ways in which the success of revascularization was assessed, in those studies in which it was assessed, ranged from being nearly anecdotal (e.g., reliance on a surgical report) to the rigorous (e.g., cardiac catheterization after revascularization, assessment of perfusion after revascularization). Limiting the analysis to only those segments or patients with successful revascularizations, as was done by many authors, provides estimates of diagnostic performance that reflect the "true" capabilities of F-18 FDG PET. That is, such analyses provide estimates of drug performance that are not confounded by the vagaries of coronary revascularization. However, additional analyses that included all segments or patients, including those with unsuccessful revascularization, would have provided useful data on the diagnostic performance as might be expected in actual use. Such additional analyses would have provided more information on the ultimate clinical usefulness of the PET F-18 FDG as a diagnostic test.

Because the majority of patients included in the ten principal studies had chronic myocardial dysfunction, spontaneous recovery of segmental wall motion would be expected to be uncommon. Thus, if patients and segments with unsuccessful revascularizations had been included in the analysis, they generally would not be expected to improve in function. On the

other hand, factors other than revascularization (e.g., changes in cardiac medications) could lead to improved segmental function in some cases, even in the absence of successful coronary revascularization.

Assuming that the unsuccessfully revascularized segments usually would not improve in function, then sensitivity (and positive predictive value) likely would have decreased, and specificity (and negative predictive value) likely would have increased. Performing analyses under both revascularization scenarios would have been helpful. However, the absence of the latter analyses (i.e., inclusion of all segments or patients regardless of the success of revascularization) was not considered to be essential, so long as the consequences of such omissions are understood and are explicit.

The data in this review speak primarily to the performance of PET F-18 FDG under the ideal circumstance of successful coronary revascularization. However, the clinical usefulness of being able to identify myocardium with reversible dysfunction with PET F-18 FDG appears to be limited substantially by the possibility of unsuccessful coronary revascularization. If the likelihood of successful revascularization is very slight, then the clinical usefulness of predictions with PET F-18 FDG will be limited, regardless of how good the diagnostic performance of PET F-18 FDG may be. Therefore, in clinical use, health care providers who are contemplating PET F-18 FDG studies should carefully consider the likelihood of successful revascularization before performing the test.

In addition, evaluation of functional outcomes in segments that were not successfully revascularized would also have provided an estimate of a spontaneous recovery rate or improvements due to other causes (e.g., changes in medications). However, given that the patients in the principal studies tended to have longstanding ventricular dysfunction, the likelihood of spontaneous recovery was considered to be negligible for the purposes of this review. Effects of medication changes or other changes, however, can not be excluded.

F-18 FDG Preparation and Administration:

Few of the manuscripts described the methods and controls by which F-18 FDG was prepared, and few described the specific activity and radiochemical purity of the final product. Such information, or at least a reference to such information, would be highly desirable in all articles describing clinical studies with F-18 FDG or other PET imaging agents. However, because the focus of this review is on the clinical data, and because regulatory standards for Chemistry, Manufacturing, and Controls and for Good Manufacturing Practices (GMPs) for PET products are being developed, this deficiency in the clinical study manuscripts will not be addressed further in this review.

Most studies, but not all, specified the radiation dose of F-18 FDG and its route of administration. In studies where F-18 FDG was readministered to the patient (e.g., at rest and again after exercise), the time interval between doses tended to be vague. Few studies mentioned the rate of administration, and none of the studies mentioned the mass dose of F-18

FDG. Such information, or at least a reference to such information, would be highly desirable in all articles describing clinical studies with F-18 FDG or other PET imaging agents. However, because most of the ten principal manuscripts clearly specified the radiation dose of PET F-18 FDG (e.g., typically between 5-10 mCi), the product has a history of use that spans several decades, and one F-18 FDG product has been approved for other uses, the omission of these characteristics of drug administration was felt to be tolerable.

F-18 FDG PET Image Acquisition, and Image Interpretation:

Particularly for the clinical studies published in imaging journals, the methods by which patients were prepared (e.g., fasting, glucose load) and by which PET images with F-18 FDG were obtained and analyzed tended to be reasonably well described in the manuscripts. However, the description of such methodology for some of the clinical studies was rather sparse. A description of such information, or at least a reference to such a description, would be highly desirable in all articles describing clinical studies with F-18 FDG or other PET imaging agents.

In particular, for the purpose of this review, it was essential to understand how two particular parameters were defined: a) the criteria on PET F-18 FDG (and perfusion) image analysis by which myocardial segments were predicted to have reversible myocardial dysfunction (i.e., criteria for "viability" and "nonviability"), and; b) the criteria on image analysis of wall motion that were used to determine whether a change in wall motion had occurred from before revascularization to after revascularization. In most of the ten principal studies, these criteria were specified adequately. It would be highly desirable for the manuscripts to state explicitly whether these criteria were specified prospectively (i.e., before any data had been gathered), although this was virtually never done.

It should also be noted that because the evaluations of wall motion have a subjective component and because the ordinal scale used in most studies to assess wall motion is not linear, moving from one category to the next was felt to be the minimally acceptable change in wall motion that had clinical significance (e.g., moving from akinetic to hypokinetic, or from hypokinetic to normal). Moreover, because changes in wall motion from dyskinetic to akinetic are of uncertain clinical meaning, it would have been desirable to limit the criteria further to mean moving from a dyskinetic or akinetic state before revascularization to a normal or hypokinetic state after revascularization. In some studies this was done.

An assessment of the reproducibility of the analyses of wall motion, the PET F-18 FDG scans, and the perfusion scans was a highly desirable feature that was described in some studies. For example, some studies described formal evaluations of the reproducibility of image analysis. Although several of the studies included image analysis by multiple readers, none mentioned the degree to which the readers agreed with one another. Such use of multiple readers allows for potential assessment of interreader variability. Moreover, use of multiple readers decreases the likelihood that the results reflect the idiosyncracies of any particular reader (i.e., the results are more likely to be generalizable).

Some manuscripts also included a reasonably detailed description of how segmental alignment was maintained when images were obtained with more than one modality (e.g., PET with echocardiography) or when imaging was done by the same modality but on different occasions (e.g., PET F-18 FDG imaging on one day, with PET N-13 ammonia imaging on another day). This feature of some manuscripts was highly desirable, because segmental misalignments could undermine the integrity of the data.

Analyses of Data:

All of the ten principal studies performed "by segment" analyses of the results. A "by-patient" analysis was performed in addition in only one study (study #1). However, in two studies (studies #2 and #6) the by-segment analysis was interpreted in this review as being identical to the by-segment analysis because analyses were limited to one segment per patient (the anterior left ventricular wall). Because potential clinical benefits and risks of diagnostic procedures are ultimately conferred upon patients (i.e., patients, not wall segments, are the units of ultimate interest), such by-patient analyses facilitate assessments of clinical benefit as compared to risk. In addition, as noted by the authors of study #1, such by-patient analyses decrease the potential influence of segmental misalignments that may have occurred between F-18 FDG PET studies and assessments of recovery of left ventricular systolic function. Performance of both by-segment and by-patient analyses would have been a highly desirable feature of each of these studies.

As mentioned in the beginning of this review, given the relatively small number of patients in each study, the performance measures (e.g., sensitivity, specificity, positive predictive value, negative predictive value, accuracy) from any particular study should be interpreted with caution. Because of the small sample sizes, the widths of the confidence intervals for these measures are rather broad, and these measures may not be generalizable to larger populations. Moreover, performance measures such as positive predictive value, negative predictive value, and accuracy will vary depending on prevalence and should therefore be interpreted even more carefully. Finally, the studies divided the left ventricle into different numbers of segments and divided the left ventricle in different ways. This means that a diagnostic performance measure made "by segment" in one study, including sensitivity, specificity, PPV, NPV, and accuracy, may have a somewhat different clinical meaning than the same measure in other studies.

Most manuscripts only provided perfunctory details of statistical procedures and plans. A formal statistical description of the prospective hypotheses that were to be tested, along with details of the originally statistical analytic plan would have been highly desirable. Such prospective statistical plans help limit potential biases that may arise, for example, from retrospective analyses or subset analyses. Many articles failed to correct for multiple endpoints or to address other statistical issues. Therefore, statistical levels of significance as specified in the articles should generally be interpreted with a great deal of caution. In addition, none of the principal articles provided confidence intervals for estimates of sensitivity, specificity, positive predictive value, negative predictive value, or accuracy. However, these were calculated by the FDA statistician.

Safety:

None of the ten principal articles described safety monitoring or safety results from performance of PET studies with F-18 FDG. Thus, it is unclear whether safety parameters were monitored as part of the studies or whether safety was monitored but the results were not reported. However, as described earlier, the overall safety data base for F-18 FDG is adequate, though not optimal, in support of its safe use.

G. Conclusions

The published literature contains sufficient data to conclude that F-18 fluorodeoxyglucose is effective for use in cardiac PET imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, to identify left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function. This reversal of systolic dysfunction assumes successful coronary revascularization, the likelihood of which should be considered carefully by the health care provider before the PET evaluation is performed. PET imaging with F-18 FDG for this purpose appears to be safe.

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