Relation of Regional Function, Perfusion, and Metabolism in Patients With Advanced Coronary Artery Disease Undergoing Surgical Revascularization

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Background  Imaging of myocardial glucose metabolism using $[^{18}F]$fluorodeoxyglucose (FDG) with positron emission tomography (PET) has been proposed for identification of tissue viability in patients with advanced coronary artery disease. This study was designed to evaluate the predictive value of flow and metabolic imaging for functional recovery after revascularization in myocardial segments of varying degrees of dysfunction.

Methods and Results  Thirty-seven patients (mean age, 59±11 years) with coronary artery disease and impaired left ventricular function (ejection fraction, 34±10%) were studied with PET using FDG and $[^{13}N]$ammonia before surgical coronary revascularization (3±1 grafts per patient). Tissue was scintigraphically characterized as normal, nonviable (concordant reduction of perfusion and FDG uptake), viable without discordance of perfusion and metabolism (mildly reduced perfusion and metabolism), or ischemically compromised (mismatch of reduced perfusion and maintained FDG uptake). Functional outcome was assessed by serial radionuclide ventriculography before and at 13±13 weeks (median interval of 8 weeks) after coronary revascularization. Preoperatively impaired regional wall motion improved significantly in ischemically compromised (mismatch) revascularized segments but not in nonviable myocardium or in viable myocardium without discordance of perfusion and metabolism. The negative predictive value of PET for functional recovery was 86%, whereas the positive predictive value in revascularized regions ranged from 48% to 86% depending on severity of baseline wall motion abnormalities.

Conclusions  PET identifies metabolically active tissue, which benefits from revascularization. Although the negative predictive value of PET for recovery was high, functional improvement of viable but ischemically compromised tissue was less frequent than previously reported. The predictive value of PET was highest in left ventricular segments with severe dysfunction and a mismatch or reduced perfusion but preserved metabolism. Integration of PET, angiographic, and functional data is necessary for the optimal selection of patients with advanced coronary artery disease and impaired left ventricular function for revascularization. (Circulation. 1994;90:2356-2366.)

Key Words: • revascularization • metabolism • tomography

Despite remarkable advances in therapy, coronary artery disease remains a major health care problem in our society. With improved therapeutic approaches such as thrombolysis, more patients survive myocardial infarction but may subsequently present with congestive heart failure and recurrent ischemia. In addition, patients with previous revascularization suffer from progression of underlying coronary artery disease with a higher risk/benefit ratio for repeated revascularization procedures. Therefore, an increasing number of patients with advanced and complex coronary artery disease require medical attention.

The clinical and prognostic benefits of revascularization appear to be greatest in patients with extensive coronary artery disease and impaired left ventricular function.

Functional improvement has been observed after surgical revascularization in patients with advanced coronary artery disease and low left ventricular ejection fraction. The assumed mechanism for this functional recovery after revascularization is related to reversible dysfunction of myocardium. The term “hibernating” myocardium has been introduced to characterize chronically hypoperfused but viable myocardium that recovers after restoration of perfusion. Since the evaluation of regional contractile performance does not allow for the differentiation between hibernating myocardium and scar tissue, the need for techniques to specifically identify hibernating myocardium is well appreciated.

PET imaging, in combination with metabolic tracers, is appealing because of its ability to detect metabolic changes at the cellular level that occur with ischemia and necrosis. Since glucose utilization is augmented in ischemically compromised myocardium, the glucose analogue $[^{18}F]$fluorodeoxyglucose (FDG) has been used as a metabolic marker of viability. Accordingly, myocardial segments with concordant reduction of perfusion and metabolism (“matched defect”) have been demonstrated to represent necrosis, while segments with preserved glucose metabolism appear to represent viable and salvageable tissue.
Several studies have addressed the predictive value of PET imaging for recovery of regional and global left ventricular function after coronary revascularization.\textsuperscript{5,10-15} Furthermore, the impact of PET imaging results, on clinical outcome and mortality in patients with coronary artery disease and evidence for ischemically compromised myocardium, has been reported recently.\textsuperscript{16-19} In addition to PET imaging of both perfusion and metabolism, an alternative approach using Tc\textsuperscript{99m} isonitriles and single photon emission tomography for assessment of perfusion in combination with metabolic imaging using FDG and PET has been evaluated.\textsuperscript{20-23} However, in studies with follow-up assessment of left ventricular function, global ejection fraction, if reported, was normal or only slightly impaired at baseline, with the exception of the studies by Tillisch et al.,\textsuperscript{5} Carrel et al.,\textsuperscript{13} and Lucignani et al.,\textsuperscript{16} and, therefore, represented a relatively "low-risk" subgroup of patients with coronary artery disease. Such patient selection may not fully account for the common clinical problem of selecting patients with advanced coronary artery disease and severely impaired left ventricular function for revascularization. In addition, most previous studies evaluated functional outcome based on "fixed" scintigraphic criteria, which were used to differentiate viable from nonviable myocardium in hyperperfused segments.

This study was designed to evaluate the relation between the severity of myocardial perfusion and metabolism abnormalities as assessed by preoperative PET imaging and regional and global left ventricular function before and after coronary revascularization in patients with advanced coronary multivessel disease and impaired global ventricular function.

Methods

Patient Population and Selection

Patients being referred to the University of Michigan Medical Center between August of 1988 and March of 1991 for evaluation of myocardial viability by PET were the source of this study. Overall, 179 patients (82% men; age, 56±7 years) were studied by PET using \textsuperscript{13N}ammonia and FDG, with 17 FDG studies (9%) being of nondiagnostic image quality. Seventy-eight percent had a history of myocardial infarction, 19% had previous bypass surgery, and 25% had previous coronary angioplasty. Approximately one third of the patients were referred for diagnostic studies from outside facilities and could therefore not be included in the study population. Subjects were enrolled in this study if they were assigned for coronary bypass surgery at the University of Michigan Hospital, underwent a radionuclide ventriculography preoperatively, and could be followed postoperatively.

Inclusion criteria for enrollment were (1) impaired regional wall motion by radionuclide ventriculography and (2) coronary bypass surgery within 2 months after positron emission tomography.

Exclusion criteria were (1) normal regional and/or global left ventricular function at baseline (ejection fraction, >55%); (2) PET study of nondiagnostic quality due to poor myocardial glucose uptake; (3) concomitant cardiac disease influencing ventricular function or nuclear studies (eg, left bundle branch block, nonischemic valve disease); (4) left ventricular aneurysmectomy or valve replacement during bypass surgery; and (5) cardiac events after enrollment (unstable angina, myocardial infarction, emergency revascularization procedure) indicating changes in clinical status.

Image Acquisition and Processing

Positron Emission Tomography

All patients were studied according to a standardized protocol for viability studies.\textsuperscript{14} This consisted of oral glucose loading (50 g Glucola) in all patients without evidence of diabetes mellitus. Patients with known diabetes mellitus or abnormal glucose tolerance received insulin before and during the imaging sequence according to a standardized protocol. This protocol used intermittent intravenous bolus administration of 5 IU human insulin until a serum glucose level of approximately 120 mg\% had been achieved and kept in steady state. During imaging, plasma glucose levels were 128±32 mg\% for all 37 patients and 134±35 mg\% for 7 patients with diabetes mellitus.

Images were acquired with a two-ring, multislice (15 planes with 6.25-mm width), whole body PET scanner (ECAT 351, CTI, Siemens) interlinked to a DEC Microvax II System V computer.

After positioning of the patient in the scanner gantry, a transmission scan for attenuation correction was performed using a retractable \textsuperscript{68}Ge ring source. Consistency in patient positioning was achieved by marking the chest with washable ink and aligning the marks with a low-power laser light beam from the tomograph. Patients were not moved out of the scanner between transmission and acquisition of emission data. The transmission scan was followed by an intravenous bolus injection of 20 mCi \textsuperscript{13N}ammonia. Three minutes after injection, static image acquisition for 10 minutes was performed. After the \textsuperscript{13N} decay, 10 mCi of \textsuperscript{18F}2-fluoro-2-deoxy-D-glucose was injected intravenously. After 40 minutes, static images were obtained for 10 to 20 minutes.

For both data sets, the attenuation-corrected data were reconstructed to transverse image sets with the following reconstruction parameters: matrix size, 128×128 pixels; Hann reconstruction filter, cutoff frequency 0.30 cycles per pixel and computed decay correction. With a computer workstation and dedicated software (Heartool, CTI), images were realigned perpendicular to the long axis of the left ventricle, resulting in sets of 12 planes of cross-sectional (short-axis view) and vertical and horizontal long-axis images, which were then transferred to the image display system for further visual analysis.

Radioisotope Ventriculography

Resting radionuclide ventriculography was performed in the supine position. After in vivo red blood cell labeling, 25 mCi of \textsuperscript{99m}Tc was injected intravenously, and equilibrium-gated images were obtained with a small-field-of-view gamma scintillation camera (Basicam, Siemens) interlinked to a computer workstation (MicroDelta, Siemens). Three different projections (anterior, left anterior oblique, and left lateral) with at least 3 million counts per projection were acquired.

Data Analysis

Positron Emission Tomography

The three image sets (short-axis, horizontal long-axis, vertical long-axis) for both the perfusion and metabolic studies were displayed with a color screen display system and customized software, allowing direct comparison of perfusion and metabolic images on one screen for each projection. Regional tracer uptake of \textsuperscript{13N} and \textsuperscript{18F} was evaluated visually by two experienced observers, blinded to clinical and radionuclide ventriculography data, using the following grading scale for both studies: 1, normal; 2, slight reduction; 3, severe reduction; and 4, tracer uptake comparable to background activity.

Nine left ventricular segments of the anterior, septal, lateral, and inferior walls, each divided into a basal and a midventricular segment and the left ventricular apex, were evaluated in all image sets and graded.

In a representative subset of 20 studies, analysis of the interobserver variability using this scoring approach was de-
terminated. Mean [15N]ammonia score for all regions was 1.77±0.95 (SEM, ±0.06) for observer 1 and 1.74±0.98 (±0.06) for observer 2, which was not statistically different. Direct comparison revealed a correlation coefficient of r=.86 (intercept, 0.17; slope, 0.89). Average score for FDG imaging was 1.58±0.90 (±0.06) for observer 1 and 1.50±0.86 (±0.06) for observer 2. Both readings correlated with r=.88 (intercept, 0.21; slope, 0.82). The mean value for the absolute difference between both readings was 0.24±0.46 (±0.03) for [15N]ammonia uptake and 0.29±0.44 (±0.03) for [18F]FDG uptake. Readings were identical in 78% for [15N]ammonia, with disagreement of 1 score point in 20% and of 2 score points in 2%. For FDG uptake, readings were identical in 83%, with disagreement of 1 score point in 15% and of 2 score points in 2%.

Analysis of intraobserver variability revealed no significant differences between two repetitive readings for [15N]nitrate uptake (1.78±1.37 [SEM, ±0.10] versus 1.79±1.38 [±0.10], P=NS; r=.96; intercept, 0.06; slope, 0.97), and for FDG uptake (1.68±1.37 [±0.10] versus 1.66±1.37 [±0.10], P=NS; r=.98; intercept, 0.02; slope, 0.97). Reading was identical in 85%, with differences of 1 score point in 15% for [15N]ammonia reading, and scoring was identical in 92% of FDG readings, with 8% difference of 1 score point.

### Radionuclide Ventriculography

The global ejection fraction was calculated from the time-activity curve by use of a varying region of interest approach (MicroDelta, Siemens). Regional wall motion was evaluated by replaying the ventriculogram in a closed-loop display in the above-mentioned projections. Two experienced observers analyzed the preoperative and postoperative studies independently in a randomized order and blinded to clinical and tomographic data. Nine left ventricular wall segments, anterior, septal, lateral, and inferior wall, with two segments each, were evaluated from the three projections. The anterior and anterolateral walls were graded from the anterior view, the septal and lateral walls from the left anterior oblique projection, and the inferior and posterior walls from the lateral images. If the apex was analyzable in all three projections, the score was averaged. Regional wall motion was graded visually using a five-point grading scale: 1, normal; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis.

Analysis of interobserver variability, for the evaluation of regional wall motion in a representative study sample, demonstrated agreement between the two readers (observer 1, 2.43±1.21 [0.20]; observer 2, 2.37±1.12 [0.09]; P=NS; mean absolute difference between the two readings, 0.34±0.50 [±0.04]). Regression analysis revealed an r value of .87 (intercept, 0.19; slope, 0.95). Reading was identical in 76% of the regions; in 23%, there was a difference in reading of 1 score point, and in 1%, the analyses differed by 2 score points.

Evaluation of interobserver variability by repetitive reading resulted in identical scores in 81%, a difference of 1 score point in 18%, and of 2 score points in 1%. Mean values were 2.43±1.21 (±0.20) and 2.40±1.14 (±0.12), with an absolute mean difference of 0.20±0.43 (±0.04) and a correlation with r=.91 (intercept, 0.07; slope, 0.96).

### Assignment of Myocardial Regions and Revascularization

The procedure reports of coronary angiography and bypass surgery were reviewed for coronary anatomy and location of revascularization. The anterior and anterolateral walls were considered the revascularization territory of the left anterior descending coronary artery and its side branches. The lateral wall was designated the distribution territory of the left circumflex artery and posterolateral branches. The right coronary artery was assigned to the inferior and posterior walls. Depending on the coronary distribution type, the apex was assigned to either the left anterior descending or the right coronary artery.

The septum was excluded from the analysis because of the known effect of open heart surgery, which may result in paradoxical or abnormal septal motion without evidence for perfusion abnormalities.24

### Definitions of Tissue Viability and Functional Outcome

Tissue viability by PET was assessed by the combined interpretation of perfusion and metabolism. The following criteria were chosen: (1) normal: resting perfusion score =1; (2) viable without mismatch: FDG uptake score ≤2 and perfusion minus FDG uptake <1; (3) viable with mismatch: FDG uptake score ≥2 and perfusion minus FDG uptake ≥1; and (4) nonviable: perfusion ≥2 and FDG uptake ≥2.

Regional wall motion analysis by radionuclide ventriculography was used to define functional outcome after revascularization. Improvement in contractile performance was defined as baseline minus follow-up wall motion score ≥1.

### Statistical Analysis

Values are presented as mean±SD. Comparisons between paired data sets were made with Student’s t test or Wilcoxon rank-sum test. Unpaired data were analyzed by t test or Mann-Whitney U test. The influence of tissue characterization by PET imaging on functional outcome was tested by the Kruskal-Wallis test. A probability value of P<.05 was considered to represent significant differences. Statistical analysis was performed with the analysis software package STATVIEW 4.02 (Abacus Concepts, Inc.).

### Results

#### Patient Characteristics and Baseline Results

Thirty-seven patients (34 men, 3 women) with a mean age of 59±11 years, who fulfilled the inclusion criteria and could be followed postoperatively, completed the protocol. Twenty-seven patients (73%) had a documented previous myocardial infarction. Eleven of 27 patients were studied between 2 and 6 weeks after myocardial infarction and 18 patients more than 6 weeks after the acute event. Six patients (16%) had previous coronary angioplasty, and 4 patients (11%) were studied for evaluation before a second surgical revascularization. Seven patients (19%) had diabetes mellitus. Coronary angiography revealed multivessel disease in all patients.

Baseline ventriculography was performed with a mean interval of 1±2 weeks before PET with a mean left ventricular ejection fraction of 34±10%. Revascularization was performed 2±2 weeks after PET. All patients underwent aortocoronary bypass surgery with 3±1 (1 to 5) venous or internal mammary artery bypass grafts per patient. No patient had aneurysmectomy or valve replacement.

There was no evidence for a myocardial infarction between revascularization and follow-up ventriculography by clinical and ECG criteria. Follow-up radionuclide ventriculography was performed 13±13 weeks (range, 5 to 45 weeks; median, 8 weeks) after revascularization.

#### Baseline Results and Functional Outcome in All Left Ventricular Segments

Of 333 left ventricular segments (37 patients with 9 segments each), 74 segments were assigned to the septum and were therefore excluded from further analysis. Of the remaining 259 segments, 197 (76%) were revascularized and 62 (24%) were not revascularized. In those 62 regions not being revascularized, regional wall
Table 1. Results of All Revascularized Segments Defined as Normal (n=50), Viable Without Mismatch (n=43), Mismatch (n=36), or Nonviable (n=62) by Positron Emission Tomography Before Revascularization

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=50)</th>
<th>Viable Without Mismatch (n=43)</th>
<th>Viable With Mismatch (n=36)</th>
<th>Nonviable (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion</td>
<td>1.00</td>
<td>1.66±0.30$</td>
<td>2.62±0.55</td>
<td>3.13±0.61</td>
</tr>
<tr>
<td>Metabolism</td>
<td>1.01±0.07</td>
<td>1.40±0.39‡</td>
<td>1.30±0.41</td>
<td>3.03±0.52</td>
</tr>
<tr>
<td>RWM score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RWM 1</td>
<td>1.54±0.66</td>
<td>1.97±1.04‡</td>
<td>2.24±1.09</td>
<td>2.87±1.08</td>
</tr>
<tr>
<td>RWM 2</td>
<td>1.37±0.54*</td>
<td>1.92±0.95‡</td>
<td>1.87±1.98†</td>
<td>2.82±1.06</td>
</tr>
</tbody>
</table>

PET indicates positron emission tomography; RWM 1 and RWM 2, regional wall motion at baseline and follow-up, respectively. Comparison of perfusion and metabolism score, RWM 1, and RWM 2 revealed (by group definition) significant differences (P<.01) between normal, viable with and without mismatch, and nonviable regions. The comparison of viable regions with and without a mismatch is indicated in the table.

*P<.05 vs RWM 1; †P<.01 vs RWM 1; ‡P=NS vs viable with mismatch; §P<.01 vs viable with mismatch.

motion did not change significantly, from 1.6±0.8 at baseline to 1.7±0.9 at follow-up.
Six of the 197 revascularized segments (3%) could not be analyzed for technical reasons in either one of the diagnostic procedures (eg, part of the left ventricular myocardium out of the field of view due to enlarged heart size). The following data represent the analysis of 191 revascularized left ventricular segments.

The results of regional wall motion evaluation by ventriculography and PET findings are summarized in Table 1. The average [15N]ammonia uptake score for all revascularized segments was 2.1±0.9, and mean FDG uptake score was 1.8±1.0. Mean regional wall motion score at baseline for all revascularized segments was 2.2±1.1.

Overall, 129 of 191 segments (68%) were identified as viable by PET. Fifty of 191 segments (26%) displayed a normal pattern by PET, while 36 of 191 (19%) demonstrated a perfusion/metabolism “mismatch” of ≥1 score point with reduced [15N]ammonia uptake (≥2) but maintained or augmented FDG uptake (≤2). Forty-three of 191 myocardial segments (23%) did not fulfill the criteria for being either completely normal or representing a “mismatch” pattern but had evidence for maintained viability by only slightly reduced perfusion (≤3) and/or preserved glucose metabolism (FDG uptake ≤2).

In contrast, 62 of 191 segments (32%) did not fulfill the criteria for preserved viability by PET and were categorized as nonviable.

Segmental Correlation Between PET Tissue Characterization and Functional Outcome

For all 191 revascularized segments, regional wall motion score increased from 2.20±1.10 to 2.06±1.07 (P<.01). Mean values for regional wall motion at baseline and follow-up and the statistical comparisons for normal segments, nonviable segments, and viable segments with and without a mismatch pattern are summarized in Table 1. Average values for perfusion and metabolism scores were (by definition) significantly different between normal, viable regions with and without a mismatch, and nonviable regions, with the exception of FDG uptake, which was not different between viable regions with and without a mismatch.

Wall motion scores differed significantly between normal regions, all viable regions, and nonviable regions at baseline and at follow-up. Comparison of wall motion scores of viable regions with and without a mismatch at baseline and follow-up revealed no significant differences. Kruskal-Wallis analysis to test the influence of tissue characterization by preoperative PET imaging on functional changes after revascularization (baseline regional wall motion score minus follow-up score) revealed that viable regions with mismatch had a significantly better functional outcome at follow-up compared with normal, nonviable, and viable regions without a mismatch (P<.01).

Normal Segments

In 50 segments with normal resting perfusion at baseline, wall motion improved significantly, from 1.54±0.66 preoperatively to 1.37±0.54 at follow-up (P<.05). As expected, there was no change in those regions with already nearly normal function at baseline (1.16±0.24 and 1.19±0.42 at follow-up), but regions with impaired function at baseline (≥2) improved significantly (2.43±0.42 and 1.79±0.57; P<.01).

Nonviable Segments

In contrast, in 62 segments categorized as nonviable by PET, regional wall motion did not change significantly, from 2.87±1.08 at baseline to 2.82±1.06 at follow-up. With regard to severity of baseline wall motion abnormalities, there was no subgroup demonstrating significant changes in either direction after revascularization (Fig 1A).

Viable Segments With Mismatch

Mean regional wall motion improved in 36 segments with PET mismatch (perfusion ≥2, FDG ≤2, and perfusion minus FDG uptake ≥1) from 2.24±1.09 to 1.87±0.98 (P<.01). There was a significant relation between the severity of baseline wall motion abnormality and the magnitude of functional recovery, which is illustrated in Fig 1B. In 11 segments with normal or nearly normal
baseline wall motion (score ≥1 and <2), there was, as to be expected, no further improvement at follow-up (1.06±0.21 and 1.20±0.39, respectively). In 15 segments with a score ≥2 and <3 at baseline, regional wall motion improved from 2.14±0.22 to 1.77±0.84 at follow-up (P<.05). In 10 segments with a wall motion score ≥3 at baseline, function improved from 3.85±0.45 to 2.85±0.99 (P<.01). Functional improvement in these 10 regions with a baseline score ≥3 was significantly higher (P<.05) than in those 15 regions with a baseline score ≥2. Thus, segments with severe regional wall motion abnormalities, but evidence of resting hypoperfusion in the presence of preserved metabolism before revascularization, benefited most postoperatively.

Segments Without Mismatch

Overall, 43 regions with reduced perfusion and maintained viability (FDG uptake ≤2) but no evidence for a mismatch demonstrated no significant change of regional function after surgery (wall motion score, 1.97±1.04 and 1.92±0.95, respectively; P=NS). As Fig 1C illustrates, there was no improvement in regions with impaired function at baseline (2.74±0.74 and 2.71±0.83, respectively; P=NS).

Predictive Accuracy of PET Imaging for Functional Outcome

Table 2 illustrates the results of the analysis with regard to the predictive accuracy of tissue characterization by PET imaging for functional improvement of individual regions.

Absence of myocardial viability was highly predictive for absence of improvement, averaging 86%.

As expected from the results of mean wall motion analysis, the predictive accuracy for regions with preserved viability was different within the three subgroups as categorized by PET. For normal regions, prediction of improvement was 53% in regions with mild wall motion abnormalities at baseline and increased to 75% in those with marked dysfunction at baseline.

In regions with a mismatch of flow and glucose metabolism, there was a close relation between the severity of baseline wall motion and the prediction of functional recovery. The predictive accuracy was 48% for regions with mild hypokinesia and increased to 67% with more severe wall motion abnormalities at baseline. After exclusion of the apical segments, the positive predictive accuracy for recovery was 86% for the remaining left ventricular regions with mismatch.

Regions with evidence of preserved viability by mildly reduced perfusion and FDG uptake at baseline, but without a significant discordance between flow and metabolism, showed improvement at follow-up in only 21% to 31%.

Comparison of Perfusion and Metabolism With Functional Outcome

Fig 2 summarizes the relation between preoperative FDG uptake (Fig 2A), perfusion (Fig 2B), and regional wall motion at follow-up for revascularized regions. In regions demonstrating normal glucose metabolism, function at follow-up was normal or nearly normal (<2) in 72% but severely hypokinetic or worse (≥3) in only 7%. In contrast, in regions with markedly reduced metabolic activity (>3) at baseline, only 11% displayed mild hypokinesia or better wall motion (<2) at follow-
up, whereas 61% of the segments were severely hypo-
kinetic or akinetic (≥3). Segments with mildly or moder-
ately reduced but preserved FDG uptake displayed
intermediate patterns.

Fig 2B outlines the relation between preoperative
regional perfusion as assessed by [13N]ammonia uptake
and regional wall motion at follow-up.

Functional recovery was predicted by normal perfu-
sion or metabolism in 55% and 60%, respectively. With
progressive reduction of [13N]ammonia or FDG uptake,
prediction for absence of functional recovery was 86%
for perfusion and 92% for glucose metabolism.

Changes in Global Ventricular Function and Tissue
Characterization by PET

For all patients, global ventricular function, as deter-
dined by left ventricular ejection fraction, increased
from 34±10% at baseline to 36±10% at follow-up
(P<.05).

As could be demonstrated above for regional func-
tion, the degree of global functional improvement was
related to the severity of dysfunction at baseline. Twelve
patients with an ejection fraction ≤30% benefited most
from revascularization, with an increase from 23±6% to
28±7% (P<.01), which is illustrated in Fig 3A.

In contrast, patients with a baseline ejection fraction
>30% (Fig 3B) did not improve functionally after
surgery (39±7% and 40±8%, P=NS). The difference in
functional changes between those two groups was sig-
nificant (P<.05).

Seven patients with a preoperative mismatch pattern
by PET in >50% of revascularized segments demon-
strated improved of ejection fraction of 7±7%. In
contrast, global function did not change significantly in
13 patients without mismatch regions being revascular-

TABLE 2. Predictive Value of Baseline Parameters for Functional Outcome of Regional
Wall Motion After Coronary Revascularization

<table>
<thead>
<tr>
<th>Baseline RWM</th>
<th>Tissue Viability by PET</th>
<th>n</th>
<th>Improvement ≥1</th>
<th>No Improvement</th>
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<tbody>
<tr>
<td>≥2</td>
<td>Not viable</td>
<td>51</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>15</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viable, no mismatch</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mismatch ≥1</td>
<td>25</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>Not viable</td>
<td>32</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>4</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viable, no mismatch</td>
<td>15</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mismatch ≥1</td>
<td>9</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>≥3 (apex excluded)</td>
<td>Viable, no mismatch</td>
<td>13</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mismatch ≥1</td>
<td>7</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

RWM indicates regional wall motion; PET, positron emission tomography.
ized (1±6%), which was significantly (P<.05) different from those patients with predominantly mismatch regions being revascularized. Patients with postoperative improvement of global ejection fraction >5% had a significantly higher incidence of viable segments (80±18%) compared with patients without significant change (<±5%) in left ventricular ejection fraction (60±16%, P<.01) and a significantly lower incidence of scar tissue (20±18% versus 40±16%, P<.05).

Patients Without Previous Bypass Surgery

Four patients had previous bypass surgery. To investigate the influence of previous surgery on the predictive value of PET FDG imaging, the data analysis was repeated without these four patients. The results in 33 patients without previous bypass surgery were comparable to the entire study group.

As in all patients, regional wall motion improved significantly in segments with mismatch (n=30; 2.26±1.02 at baseline, 1.80±0.91 at follow-up, P<.01) with the above-mentioned relation between severity of dysfunction at baseline and improvement after revascularization. Change at follow-up in 41 regions with evidence for preserved viability but no mismatch was not significant (2.02±1.04 and 1.97±1.05, P=NS), while regions with normal PET patterns improved slightly (1.56±0.68 and 1.37±0.55, P<.05), showing the same relation to baseline dysfunction as regions with mismatch. In contrast, regions categorized preoperatively as nonviable did not change at follow-up (2.92±1.07 and 2.84±1.04, P=NS).

The predictive value for improvement ≥1 score point at follow-up was 37% for all 30 mismatch regions and increased to 88% in those regions with baseline wall motion abnormalities ≥3. In 41 regions without evidence for a resting mismatch at baseline, prediction of recovery was 10% for all regions and increased to 33% in regions with marked dysfunction at baseline. As for all patients, prediction of lack of recovery was 88% for all regions, 85% for those with baseline wall motion ≥2 and 83% for those with baseline function ≥3.

Global ejection fraction improved slightly, from 33±10% to 36±10% (P<.05).

Discussion

The results of this study confirm previous observations indicating that functional recovery of regional myocardial dysfunction after revascularization can be predicted by combined imaging of myocardial perfusion and metabolism with PET.\(^5\)\(^-\)\(^15\) Our study addressed for the first time the relation between the predictive value of various PET findings and the severity of baseline wall motion abnormalities. The predictive accuracy of metabolic imaging for functional outcome was high either for regions with severely reduced perfusion and metabolic activity or for those with evidence for preserved tissue viability in the presence of reduced \(^13\)N]ammonia uptake ("mismatch"). In contrast, the scintigraphic pattern with mild to moderate concordant decrease of flow and metabolism displayed a poor predictive value for functional recovery after revascularization. These findings support the concept of "hibernating" myocardium, which has been defined as myocardium with chronically reduced perfusion at rest but reversible functional impairment after revascularization.\(^5\)\(^-\)\(^7\) Regional PET evaluation of perfusion and FDG uptake allows for the unique identification of this form of ischemically compromised myocardium.

Independent of these results, which define the predictive accuracy of various scintigraphic patterns for subsequent functional recovery, we and others have previously shown that patients with PET mismatch have a poor clinical prognosis without subsequent revascularization.\(^16\)\(^-\)\(^18\) Furthermore, Yoshida and Gould\(^19\) demonstrated that size of myocardial infarction or scar and myocardial viability in vascular territories at risk, assessed by PET imaging of \(^82\)Rb washout, were good prognostic indicators of 3-year mortality. All these observations suggest the clinical usefulness of PET in selecting patients with advanced coronary artery disease and impaired left ventricular function for revascularization.

There was close agreement between the data of this study and those of previous investigations, as far as the negative predictive value of metabolic imaging for functional changes is concerned. Concordantly reduced FDG uptake and perfusion were highly specific for scar tissue, as demonstrated by no improvement of wall motion after revascularization. As previously shown in animal studies, reduced FDG uptake after an ischemic injury is associated with histochemical evidence of tissue necrosis.\(^20\) This scintigraphic pattern identifies completed myocardial infarction with necrosis or scar formation, which results in markedly reduced metabolic demand com-

Fig 3. Graphs showing individual change of global left ventricular function between baseline study and follow-up after 13±13 weeks. A, Results of 12 patients with severely impaired function (≤30%) preoperatively; B, results for 25 patients with a baseline ejection fraction >30%. The difference of functional change between both groups was statistically significant (P<.05).
pared with surrounding viable myocardium. Our data, in a relative small number of segments, suggest that absence of FDG uptake is diagnostically more accurate than reduced regional [18F]fluorodeoxyglucose (FDG) uptake in segments with severe wall motion abnormalities.

The positive predictive value of PET imaging for functional recovery varied for different scintigraphic patterns as well as for various degrees of wall motion abnormalities. Functional improvement after revascularization was less frequently observed in those regions with only moderately impaired function. Although those regions demonstrated functional improvement by statistical comparison of mean wall motion scores at baseline and at follow-up, preserved FDG uptake infrequently predicted substantial improvement in individual segments. However, a significant proportion of those regions demonstrated normal wall motion or only mild hypokinesis at baseline and therefore could not be expected to improve substantially after revascularization. Assessment of regional wall motion, not only under resting but also under stress conditions, may be necessary to reveal a possible greater functional improvement after restoration of perfusion in these segments.

For all myocardial segments categorized as viable by PET, prediction of functional recovery was lower than previously published in the literature. Tillisch et al reported a positive predictive value of 85% in 17 patients with impaired regional left ventricular function for functional improvement of regions with PET mismatch. Similarly, Tamaki et al described functional recovery in 78% of regions with maintained FDG uptake but reduced perfusion. In contrast, we observed a predictive value of only 53% in all left ventricular segments with such a scintigraphic pattern. The discrepancy between our results and previous observations may depend on several factors, including methodology, physiology, and patient selection. The study by Tillisch et al used a first-generation PET instrumentation with a spatial resolution of >2 cm. With the improved imaging performance provided by current PET techniques (spatial resolution ≈1 cm), the sensitivity for detecting small areas of metabolic activity may increase considerably. Therefore, the higher predictive value of previous studies may reflect the greater specificity of PET criteria for large viable myocardial segments due to poorer spatial resolution.

Improved definition of myocardial FDG uptake by current PET instrumentation may make the interpretation of scintigraphic findings more difficult. Reduced but maintained FDG uptake may now be observed in the presence of subendocardial infarction. The presence of scarred endocardial layers and metabolically normal epicardium may result in mildly to moderately reduced overall transmural FDG uptake in segments with nontransmural infarction. Revascularization of such left ventricular segments does not appear to improve resting functional performance, as shown by our data, since this tissue was not ischemically compromised under resting conditions before revascularization. However, the benefit of improved perfusion reserve may become apparent under stress conditions. Therefore, revascularization of these segments with nontransmural infarction and residual evidence of PET viability may protect an epicardial rim of viable tissue from recurrent ischemia and be clinically important even in the absence of improvement of resting wall motion. On the other hand, reduced flow and preserved metabolism across the myocardium (mismatch), in the absence of previous infarction, reflects ischemically compromised myocardium under resting conditions, which has the potential of measurable functional recovery at rest after revascularization.

The relatively limited spatial resolution of nongated PET images used in this study limits the differentiation between subendocardial infarction and homogeneously reduced perfusion and metabolism. Little experimental information is available regarding the transmural extent of tissue viability required for normalization of contractile function after revascularization. Animal data defining the relation of blood flow and function in various layers of the myocardium during ischemia indicate that subendocardial ischemia alone can result in severe impairment of myocardial wall thickening. Further improvement of imaging technology is required to resolve transmural gradients of metabolism and perfusion with PET imaging to study the relation between functional recovery and transmural extent of tissue viability in the human heart. Such quantitative measurements may improve the characterization of tissue viability in the future and provide definition of absolute thresholds of metabolic activity necessary for functional recovery after revascularization.

Although methodological differences between studies may help to explain the lower predictive value of FDG-PET imaging observed in this study, a major limitation in the definition of the diagnostic accuracy of PET is the lack of a "true" gold standard for tissue viability. The commonly used assessment of functional recovery after revascularization as retrospective evidence for preserved tissue viability reflects the very complex effect of restoration of blood flow. Functional recovery after revascularization is influenced by many factors, such as completeness of revascularization, peri-interventional ischemia, loading conditions, and recurrence of stenosis in native vessels or grafts. Furthermore, myocardial islands of viable cells intermixed with scar tissue may lead to a PET imaging pattern of viable myocardium, which may not improve function substantially, since the relative amount of reversibly injured tissue is too small to result in improvement of transmural function detectable by radionuclide ventriculography. In this case, lack of functional recovery does not indicate a "false-positive" PET signal, but it does reflect a limitation of the reference technique.

Although myocardial infarction preceded PET imaging and radionuclide ventriculography by at least 2 weeks, effects of myocardial "stunning" on functional recovery cannot be completely excluded. These prolonged effects or repetitive "stunning," as described recently by Vanoverschelde et al using PET technology, may account for functional recovery, particularly in those regions with normal resting perfusion and metabolism but reversibly impaired function. Despite possible effects of prolonged "stunning," we intentionally recruited patients with a history of both recent and remote myocardial infarction, since both situations reflect common clinical settings in the assessment of myocardial viability. However, functional outcome and its relation to baseline PET findings and wall motion...
abnormalities did not differ in these two patient subgroups.

Despite these outlined limitations in assessing the diagnostic accuracy of PET for tissue viability, the data clearly show a significant improvement of regional function after revascularization in dysfunctioning segments with maintained FDG uptake compared with those without.

The segmental analysis was further supported by the fact that global left ventricular function improved most in patients with PET mismatch pattern and baseline ejection fraction <30%. Changes in global left ventricular function may be clinically and prognostically more important than regional changes in wall motion. Our data indicate a relation between extent of viable but compromised myocardium and changes in global function. Similar data were published by Marwick et al.27 In their study, seven patients with two or more “hibernating” regions demonstrated improvement of global ejection fraction of 7±4% after revascularization, which is similar to the results of our study, with improvement of 7±7% in seven patients, with >50% of revascularized segments demonstrating a mismatch pattern. Thus, PET appears most useful in these patients with severe impairment of left ventricular function, who are known to benefit most from aggressive revascularization but are also at increased risk for procedural complications. Because of the difficult management decisions in this group of patients, the higher cost of PET may be offset by the improved selection of patients for higher-risk procedures.

Limitations

Conclusions from our study are somewhat limited because no angiographic or scintigraphic follow-up studies were performed in these patients to identify the status of revascularization in individual vascular territories. However, the follow-up period in most patients was relatively short, which limits the incidence of graft stenosis or closure in these patients. On the other hand, the patient population studied had advanced coronary artery disease. Restoration of regional perfusion may not have been complete in all patients because of distal coronary artery disease even in the presence of open grafts. Furthermore, the functional recovery may not have been completed in some segments within the observation period, affecting the predictive accuracy of the PET studies.11

The correlation of PET findings with regional wall motion as assessed by radionuclide ventriculography may not be ideal. PET represents a tomographic image modality, and the results were compared with radionuclide ventriculography in three planar views. Correlation of tomographic findings with those of radionuclide ventriculography is challenging, especially for the comparison of areas such as the left ventricular apex. Changes of activity on radionuclide ventriculograms represent volume changes and not true wall motion and may therefore be sensitive to overlap of opposing wall segments and passive motion. This technical difficulty may explain the low predictive value of PET, especially in apical segments of the left ventricle. Ideally, PET data should be correlated with functional high-resolution studies using tomographic approaches such as cine-CT or gated magnetic resonance imaging.28 However, no such data were available in the patient population studied.

Technical Considerations

In previously published investigations, PET using FDG has been performed either after oral glucose loading to identify glucose metabolism in hypoperfused myocardium,8,29,30 under fasting conditions to detect the metabolic effects of myocardial ischemia after exercise or pharmacological stress testing10,31,32 or during continuous intravenous insulin/gluclose clamping.33 Imaging with FDG is significantly affected by the dietary state due to glucose being only one of several substrates utilized by the myocardium. In this study, patients were imaged postprandially after an oral glucose load to enhance myocardial glucose utilization.29 This approach was supplemented by intravenous insulin in patients with proven or suspected diabetes mellitus, which has been shown to improve the diagnostic quality in this patient subgroup.34

PET images and radionuclide ventriculograms were independently analyzed by visual interpretation by two experienced investigators. This reflects clinical practice in many institutions, despite the availability of quantitative or semiquantitative analysis programs for the interpretation of perfusion studies. These programs rely on the normalization of regional myocardial tracer activity to a “normal” segment, which is defined as “highest tracer uptake” in perfusion imaging. Since FDG uptake may vary considerably in normal myocardium depending on the metabolic state,35,36 standardization of tracer uptake has proved difficult. However, this limitation also accounts for visual analysis. Although approaches have been published with normalization of FDG uptake to regions with “normal” or highest perfusion,20,22,37 no widely accepted and prospectively validated semiquantitative analysis approach is currently available for the evaluation of clinical FDG-PET studies. Visual interpretation with its inherent limitations is currently used in most PET laboratories for analysis of clinical FDG-PET viability studies.

Conclusions

Combined imaging of myocardial perfusion and metabolism using PET provides sophisticated tissue characterization in patients with advanced coronary artery disease and impaired left ventricular function. Absence of metabolic activity as assessed by regional FDG uptake was highly predictive for no functional change after revascularization, confirming previous reports about the high negative predictive value of metabolic imaging. The positive predictive value for tissue recovery based on FDG uptake alone was considerably lower in this study than reported previously. Combined evaluation of regional myocardial perfusion and FDG uptake is necessary to identify segments with reduced perfusion and relatively increased FDG uptake. Such a “mismatch” pattern had a higher predictive value than FDG uptake or perfusion criteria alone. More importantly, the functional improvement and its prediction by combined PET imaging patterns was related to the severity of baseline myocardial dysfunction, indicating that the PET information should be used in context with wall motion analysis to maximize the predictive value for tissue recovery after revascularization. Thus, PET
imaging represents a complementary technique that should be carefully integrated with functional and angiographic characterization of patients with advanced coronary artery disease and impaired left ventricular function.

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