Prognosis of Patients With Left Ventricular Dysfunction, With and Without Viable Myocardium After Myocardial Infarction

Relative Efficacy of Medical Therapy and Revascularization

Kamthorn S. Lee, MD; Thomas H. Marwick, MD; Sebastian A. Cook, MD; Raymundo T. Go, MD; James S. Fix, MD; Karen B. James, MD; Shelly K. Sapp, MS; William J. MacIntyre, PhD; James D. Thomas, MD

Background The uptake of F-18 deoxyglucose into dysfunctional segments after myocardial infarction identifies metabolically active (FDG+) or inactive (FDG-) myocardium. Although patients with FDG+ segments have been found to be at risk for adverse events, the prognostic significance of viable myocardium in relation to other influences on postinfarction prognosis, including revascularization, remain ill defined. The purpose of this study was to investigate the relative prognostic significance of FDG+ tissue and to establish whether myocardial revascularization in patients with viable tissue attenuates the risk of adverse outcome.

Methods and Results One hundred thirty-seven patients with left ventricular dysfunction and resting perfusion defects after myocardial infarction underwent positron emission tomography with both dipyridamole stress Rb-82 perfusion imaging and FDG imaging. After the exclusion of 4 patients proceeding to transplantation, 2 with uninterpretable scans and 2 lost to follow-up, 129 patients were followed clinically for 17±9 months. Four groups were defined: patients with FDG+ dysfunctional myocardium who were revascularized (n=49) or treated medically (n=21) and those with FDG- segments who were revascularized (n=19) or treated medically (n=40). The groups of patients with FDG+ or FDG- findings, with and without revascularization, did not differ with respect to known determinants of postinfarction prognosis: age, left ventricular ejection fraction, or the prevalence of multivessel disease. Nonfatal ischemic events occurred in 48% of medically treated FDG+ patients compared with 8% of revascularized patients with FDG+ tissue (P<.001) and 5% of patients with FDG- myocardium (P<.001). Thirteen patients died from cardiac causes; 11 (85%) had a left ventricular ejection fraction of <30%, and these patients were evenly distributed between FDG+ and FDG- groups. Using Cox's proportional hazards model, only the presence of FDG+ myocardium (odds ratio, 12.9; P<.001) and the absence of revascularization (odds ratio, 5.8; P=.002) independently predicted ischemic events, while only age (P=.02) and ejection fraction (P<.001) but not the presence of viable myocardium were predictive of death.

Conclusions Residual viable myocardium after myocardial infarction may act as an unstable substrate for further events unless it is revascularized. Despite this association, age and left ventricular dysfunction remained the strongest predictors of cardiac death after myocardial infarction in these patients with a spectrum of left ventricular dysfunction. (Circulation. 1994;90:2687-2694.)

Key Words • tomography • myocardial infarction • myocardium • prognosis

The prognosis of patients after myocardial infarction is dependent upon the severity of left ventricular damage and the presence and extent of jeopardized myocardium (viable tissue supplied by a diseased vessel). Prognostic data obtained hitherto from myocardial perfusion scintigraphy have been based on determination of the extent of both infarcted and ischemic myocardium. However, recurrent ischemic events probably relate more specifically to jeopardized myocardium; at conventional thallium-201 perfusion scintigraphy, this is not restricted to segments with stress-induced perfusion defects but also may be present in viable tissue within perfusion defects present at redistribution imaging. Such dysfunctional and chronically malperfused segments may remain viable and may recover after revascularization. Thallium reinfusion techniques have recently been shown to be useful in prediction of functional recovery after revascularization within segments showing persistent defects, but the prognostic implications of tissue thus identified remain to be established.

Positron emission tomography (PET) is able to identify this viable tissue in segments demonstrating a perfusion-metabolism mismatch. The revascularization of segments showing a mismatch pattern has been shown to predict the recovery of regional and possibly global ventricular function. Conversely, recent studies have suggested that patients with nonrevascularized viable myocardium have a propensity to suffer later cardiac events. However, the role of myocardial viability relative to other aspects determining postinfarction prognosis, including angiographic, scintigraphic, clinical, and functional factors and the influence of revascularization, remain to be defined. The
aims of this study were to document the frequency, nature, and timing of cardiac events in patients with and without viable myocardium, with and without revascularization. We also compared the relative roles of viable tissue and known determinants of prognosis (inducible perfusion defects and resting left ventricular function) on outcome.

**Methods**

**Patient Selection**

Between July 1989 and April 1991, 137 patients who had known coronary anatomy, left ventricular dysfunction related to previous myocardial infarction, and a resting perfusion defect on PET imaging underwent dipyridamole stress Rb-82 and F-18 fluorodeoxyglucose (FDG) metabolic imaging under established institutional guidelines. These patients had been referred for investigation of chest pain, symptoms of left ventricular dysfunction, or both, with a view to potential myocardial revascularization. Patients presenting with unstable angina or with a history of bronchospasm were excluded (reflecting the use of intravenous dipyridamole stress), as were patients with blood sugar levels exceeding 120 mg/dL (because of technical difficulties this imposes on the performance of the FDG imaging). After the exclusion of 2 patients with technically inadequate studies, 4 patients due to subsequent cardiac transplantation, and 2 other patients lost to follow-up, the remaining 129 patients constituted the study group.

**Positron Emission Tomography**

All PET data were obtained using a Posicam camera and acquisition system (Positron Corp) with a 256×256 matrix in 21 slices of 5-mm thickness. After fluoroscopic localization of the inferior border of the heart, patients were positioned in the camera in the same way for both sets of scans. A transmission scan of approximately 200 million counts was performed with a Ga-68-filled Plexiglas ring; these data were used for attenuation correction for both the perfusion and FDG images. Both sets of images were processed using the same system, with reconstruction and backprojection using a Butterworth filter (order 5; cutoff, 0.4). Images were displayed in tomographic (transverse, sagittal, and coronal) views as well as a polar map display with a quantitative color scale. They were read in a segmental fashion using 13 myocardial segments (septal, anteroseptal, anterior, lateral, inferolateral, and inferior at the basal and midventricular level and one apical segment).

**Dipyridamole Stress Rb-82 PET**

The perfusion imaging protocol corresponded to that routinely used for PET studies at our center.17 Resting and stress perfusion data were obtained 75 seconds after intravenous injection of 40 to 60 mCi of Rb-82, derived from a strontium/rubidium generator (Cardiogen, Squibb). Resting and stress images were derived from 20 to 40 million counts over a 7-minute resting and a 4-minute stress acquisition. Patients underwent dipyridamole (0.56 mg/kg IV) handgrip stress using a conventional protocol.18

After image processing and display, the segments were categorized in accordance with previously defined criteria by two blinded observers. Segments were classified as normal, showing a reversible perfusion defect (>20% relative reduction of Rb-82 activity after stress), or a fixed perfusion defect (>20% relative reduction of Rb-82 activity than the maximum counts). Segments were designated as abnormal only if perfusion defects were identifiable in more than one tomographic slice and in more than one orthogonal plane.

**Fluorodeoxyglucose Imaging**

FDG (5 to 10 mCi) was administered either after ingestion of a 75-g glucose load 60 minutes before the scan (n=57) or under fasting conditions (n=70). While FDG images show relative distribution of myocardial uptake and do not reflect or parallel glycolysis,19,20 both fasting and fed protocols have been used previously to identify viable myocardium with comparable accuracy.21–23 With either approach, FDG was injected intravenously 30 minutes after the dipyridamole stress. Forty-five minutes later, FDG images were then acquired over 20 minutes, with the patients placed in identical position in the PET camera to that used for perfusion scanning.

The interpretation of FDG positivity was based on qualitative identification of a perfusion-metabolism mismatch in any of the 13 myocardial segments demonstrating a resting perfusion deficit by observers using only the resting Rb-82 and FDG images without reference to the stress Rb-82 scan. Patients were classified as FDG+ in the presence of ≥1 FDG+ segment. Using the fasting protocol, a “reference normal” site of metabolic activity was defined based on 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 the range of normal FDG uptake for each patient. The presence of FDG activity ≥2 SD above the reference normal segment were classified as abnormal provided that perfusion was reduced; segments with this pattern were classified as showing metabolism-perfusion mismatch (FDG+). In the glucose-loaded (fed) protocol, areas of viable myocardium were characterized by glucose uptake within resting perfusion defects.

**Evaluation of Coronary Anatomy and Left Ventricular Function**

All patients underwent coronary angiograms, which were reviewed by observers blinded to the clinical and PET results. A lesion of >50% in a large epicardial coronary artery was considered hemodynamically significant. Patients were considered to have multivessel disease if two or more of the epicardial arteries were stenosed.

The left ventricular ejection fraction was calculated by digitization of the ventricular outline in diastole and systole from ventriculograms performed in the right anterior oblique projection.19 In 61 patients, in whom contrast ventriculography was of inadequate quality, ejection fractions obtained from echocardiographic (n=21) or gated blood pool imaging (n=40) performed at the time of PET imaging were substituted.20,21

**Events**

A treatment strategy comprising revascularization or medical therapy was formulated for each patient based upon clinical, angiographic, and imaging data. On these grounds, not all patients with viable myocardium were planned to undergo revascularization, often because the benefits of intervention on a small area were not thought to justify the risk of operation and sometimes because of the presence of anatomically unfavorable lesions for angioplasty and refusal of the patient to consider surgery. Conversely, some patients without viable myocardium were revascularized, particularly if they suffered from anginal symptoms. Patients were then grouped into revascularization or medical therapy groups on an intention-to-treat basis.

Patients were then followed for a period of 17±9 months, with data being recorded from clinic visits and/or telephone calls to patients and their physicians. Three cardiac events were identified: unstable angina, myocardial infarction, and cardiac death. Unstable angina pectoris was defined by accelerating anginal symptoms requiring hospitalization or rapid progression of symptoms requiring revascularization. Myocardial infarction was defined by enzymatic and ECG documentation during hospital admission. Cardiac death was defined by
the hospital record documenting bradyarrhythmic death, arrhythmic death, or death attributable to congestive heart failure, myocardial infarction, or cardiac arrest. Functional class status for angina pectoris and heart failure was noted initially and at follow-up.

**Data Analysis**

Groups based on FDG results and revascularization status were compared using t tests for continuous variables and \( \chi^2 \) tests (with Yates’ correction or Fisher’s exact test in smaller sample sizes). The relations between clinical features, reversible Rb-82 defects, FDG uptake, revascularization, and events of ischemia and cardiac death were examined by univariate analysis and a multivariate (Cox proportional hazards) model. Kaplan-Meier survival curves were used to compare the event-free intervals for ischemic events and death in patients with and without FDG+ tissue and with or without revascularization. Results are expressed as mean±SD. A \( P \) value of <.05 was considered statistically significant.

**Results**

**Clinical Characteristics**

The study group comprised 102 men and 27 women, aged 62±11 years. Moderately severe or severe symptoms of angina (Canadian Cardiovascular Association class 3 or 4) or heart failure (New York Heart Association class III or IV) were present in 52 (40%) and 24 (19%) patients, respectively. All patients had left ventricular dysfunction, and the mean ejection fraction was 38±16%. Multivessel coronary disease was present at angiography in 96 patients (74%). All patients had a resting perfusion defect at Rb-82 perfusion imaging. During dipyridamole stress, chest pain occurred in 31 patients (24%), and ST segment changes consistent with ischemia occurred in 36 patients (28%). A reversible Rb-82 perfusion defect consistent with myocardial ischemia was present in 43 patients (33%).

Sixty-eight patients were referred for myocardial revascularization (50 by bypass surgery, 16 by angioplasty, and 2 by atherectomy), with the remainder being treated medically. The decision to revascularize was made on clinical grounds.

**Results of FDG Imaging**

Evidence of viable (FDG+) myocardium within resting perfusion defects was apparent in ≥1 segment in 70 patients (54%). The presence of viable myocardium was not predicted by clinical features; angina was present in 60 FDG+ patients (86%) and in 45 FDG− patients (76%, \( P=NS \)). Neither was FDG+ tissue predicted by events during dipyridamole stress: there was no relation with angina (23% versus 22% in patients with FDG− myocardium, \( P=NS \)) or ST segment changes (23% versus 36%, \( P=NS \)). The presence of impaired flow reserve within areas of myocardium with resting hypoperfusion (Rb-82 activity >20% below maximum) was observed in 14 of 70 patients with FDG+ tissue (20%) compared with 12 of 59 patients with FDG− tissue (20%, \( P=NS \)). However, stress-induced perfusion defects in any segment were less common among patients with FDG+ myocardium (24% versus 42%, \( P=.05 \)). At segmental analysis, although hypoperfused areas with viable (FDG+) myocardium demonstrated a significantly higher level of perfusion relative to the area of maximum perfusion within each patient than did areas of nonviable myocardium (58±9% versus 53±10%, \( P<.0006 \)), there was no clear threshold between the relative flows in FDG+ and FDG− tissue.

Based on the results of metabolic PET imaging and revascularization status, the population was divided into four groups comprising patients with positive or negative FDG results with and without revascularization. The presence of characteristics known to influence postinfarction prognosis in each group are listed in Table 1. Groups were comparable with respect to age, left ventricular function, and the prevalence of multivessel disease. Myocardial ischemia (as evidenced by a stress-induced Rb-82 defect) was more prevalent in the group undergoing revascularization in the absence of positive FDG findings and constituted the reason for intervention in this group.

**Table 1. Comparison of Clinical Characteristics in Patients With and Without FDG+ Myocardium, With and Without Revascularization**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>FDG+ RVS</th>
<th>FDG+ MED</th>
<th>FDG− RVS</th>
<th>FDG− MED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>49</td>
<td>21</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>60±11</td>
<td>62±12</td>
<td>64±9</td>
<td>62±12</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>37±17</td>
<td>39±18</td>
<td>34±12</td>
<td>38±17</td>
</tr>
<tr>
<td>Stress Rb defects, patients</td>
<td>15 (31%)</td>
<td>3 (14%)</td>
<td>13 (74%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Ischemic events</td>
<td>4 (8%)</td>
<td>10 (48%)</td>
<td>1 (5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4 (8%)</td>
<td>3 (14%)</td>
<td>1 (5%)</td>
<td>5 (12.5%)</td>
</tr>
</tbody>
</table>

FDG indicates F-18 fluorodeoxyglucose; FDG+, metabolically active myocardium; FDG−, metabolically inactive myocardium; RVS, revascularized; MED, medical treatment; CAD, coronary artery disease; LV, left ventricular.

**Total Cardiac Events**

Of the 129 patients studied, 101 pursued an uneventful cardiac course during follow-up and 28 (22%) suffered a cardiac event. These comprised 17 nonfatal ischemic events in 16 patients (12% of the study group) and cardiac death in 13 (10%), with 1 patient having suffered an episode of unstable angina 3 months before death. There was no difference in the frequency of cardiac events among patients studied using oral glucose loading (12 of 57, 21%) or in the fasting state (16 of 72, 22%, \( P=.96 \)). The relation of these events to the presence or absence of segments showing FDG+ tissue or reversible perfusion defects is shown in Table 2.

**Nonfatal Cardiac Events**

Of the 16 patients suffering nonfatal events, all presented with unstable angina and 1 suffered a myocardial
TABLE 2. Relation of Cardiac Events to the Presence or Absence of Regional FDG Uptake (FDG+) and Reversible Perfusion Defects in Patients Treated Medically or With Revascularization

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Ischemic Events</th>
<th>No Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG+ only (n=52 patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td>3</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>RVS</td>
<td>4</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>RbRev only (n=25 patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>RVS</td>
<td>1</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Both (n=18 patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>RVS</td>
<td>0</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Neither (n=34 patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td>5</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>RVS</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

RbREV indicates reversible perfusion defects. See Table 1 for other abbreviations.

infarction. The clinical characteristics of these patients are listed in Table 3. Those suffering ischemic events did not differ from the group without ischemic events with respect to age, clinical status, or ejection fraction. These ischemic events were not predicted by the presence of stress-induced Rb-82 perfusion defects or by the presence of multivessel disease. Viable myocardium was present in 14 patients with ischemic events (88%) compared with 56 of the 113 patients without ischemic events (50%, P=.003).

The frequency of ischemic events in the four viability and treatment groups is portrayed in Fig 1. In medically treated patients with positive FDG results, 10 of 21 patients (48%) suffered an ischemic event. This frequency significantly exceeded the rate of ischemic events in revascularized patients with a positive FDG scan (8%, P<.001) and in all patients without FDG+ tissue (5%, P<.001). The timing of these ischemic events from the treatment decision is expressed in a Kaplan-Meier curve (Fig 2), which shows the actuarial freedom (survival) from ischemic events in medically treated FDG+ patients differed rapidly from that of the other three groups, which remained relatively event free during the follow-up period. Medically treated FDG+ patients suffered ischemic events after a significantly shorter interval than the other three groups (P=.008). Patients with FDG+ tissue who were revascularized had equivalent freedom from ischemic events as those without FDG+ tissue treated medically (P=.25) or with revascularization (P=.62). In a Cox proportional hazards model, FDG+ segments (odds ratio, 12.9; P<.001) and the absence of revascularization (odds ratio, 5.8; P=.002) were found to be independent predictors of ischemic events.

The occurrence of ischemic events did not correlate with the presence of reversible perfusion defects at stress Rb-82 perfusion imaging (Table 3). However, to avoid any association between stress-induced perfusion defects and ischemic events, the groups were reanalyzed after exclusion of all patients with evidence of myocardial ischemia at Rb-82 imaging. In this subgroup, the rate of ischemic events in medically treated FDG+ patients (44%) continued to exceed that in revascularized FDG+ patients (9%) and FDG− patients, who had no ischemic events (Fig 3).

Table 3. Comparison of Clinical Characteristics of Patients With and Without Ischemic Events

<table>
<thead>
<tr>
<th></th>
<th>No Ischemic Events</th>
<th>Ischemic Events</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>113</td>
<td>16</td>
<td>.99</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>61±10</td>
<td>.98</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>83 (74%)</td>
<td>13 (81%)</td>
<td>.42</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>37±17</td>
<td>39±14</td>
<td>.82</td>
</tr>
<tr>
<td>Stress Rb defects</td>
<td>36 (32%)</td>
<td>5 (31%)</td>
<td>.06</td>
</tr>
<tr>
<td>Viable (FDG+)</td>
<td>56 (50%)</td>
<td>14 (88%)</td>
<td>.003</td>
</tr>
<tr>
<td>Revascularized</td>
<td>63 (56%)</td>
<td>5 (31%)</td>
<td>.36</td>
</tr>
<tr>
<td>Class III,IV angina</td>
<td>47 (42%)</td>
<td>4 (25%)</td>
<td>.79</td>
</tr>
<tr>
<td>Class III,IV heart failure</td>
<td>22 (20%)</td>
<td>2 (13%)</td>
<td>.79</td>
</tr>
</tbody>
</table>

See Tables 1 and 2 for abbreviations.

Fig 1. Bar graph shows frequency of ischemic events in four groups of patients with metabolically active (FDG+) and inactive (FDG−) myocardium undergoing revascularization (RVS) or medical therapy (MED). The incidence of events in medically treated FDG+ patients exceeds that in revascularized FDG+ patients (P<.001), revascularized FDG− patients (P=.008), and medically treated FDG− patients (P<.001). FDG indicates F-18 fluorodeoxyglucose.

Determinants of Cardiac Death

Thirteen patients died from cardiac causes (myocardial infarction, congestive heart failure, or arrhythmia)
over the period of follow-up. The clinical characteristics of those with and without fatal cardiac events are compared in Table 4. The mean ejection fraction in those who died (22 ± 13%) was less than in those with nonfatal events (39 ± 14%) and without events (39 ± 16%). The age of patients suffering fatal events was greater than that of patients who remained event free (69 ± 7 versus 61 ± 11 years, P < .01). Neither multi-vessel disease nor the presence of positive PET findings—either stress Rb-82 defects or FDG+ segments—were associated with cardiac death. The absence of revascularization, severity of angina pectoris symptoms, or of heart failure symptoms were also not significantly associated the occurrence of cardiac death. The frequency of cardiac deaths in the four groups classified on the basis of revascularization and viability status was not significantly different (Fig 4). Of 48 patients with an ejection fraction <30%, 11 died (23%) compared with only 2 cardiac deaths among the 81 patients with an ejection fraction >30% (2%, P < .001). In patients with an ejection fraction of <30%, the Kaplan-Meier survival curves (Fig 5) of fatal outcome in those with and without FDG+ tissue were not significantly different (P = .32). Twenty-five of the 48 patients with left ventricular ejection fraction <30% had FDG+ tissue; of these, 7 patients died and 6 suffered ischemic events. Revascularization of FDG+ patients with low ejection fraction had an impact on ischemic but not fatal events. Thus, 4 of the 7 medically treated patients, compared with 2 of 16 revascularized patients, had a subsequent ischemic event (P = .03), while cardiac death occurred in 4 of 14 patients who were revascularized and 3 of 7 patients treated medically (P = NS).

### Discussion

Hitherto, studies addressing the contribution of FDG imaging to the detection and treatment of hibernating myocardium have concentrated on the functional responses of this tissue to myocardial revascularization.10-13 Whatever the benefits on cardiac function, however, the revascularization of such segments would be more readily accepted if there were evidence of prognostic benefit. In this study, while there was a frequency of nonfatal cardiac events of approximately 12% per year in the group as a whole, patients with viable segments who do not undergo revascularization had an annualized incidence of 34%. Such events did not occur in patients with revascularized viable tissue or nonviable tissue. In particular, this risk was associated with metabolically active myocardium within resting defects rather than the presence of coexisting myocardial ischemia. In contrast, the presence of viable myocardium did not appear to influence the frequency of cardiac death, which predominantly correlated with the conventional risk factors of age and left ventricular dysfunction.

### Determinants of Prognosis After Myocardial Infarction

After hospital discharge in patients treated without thrombolytic drugs,23,24 annual mortality and reinfar-
tion rates in published series (respectively 5% to 10% and 5% per year) parallel those witnessed in this study. In these series, involving exercise testing, ventriculography, or angiography, mortality has been correlated with the age and functional state of the patient, the severity of left ventricular dysfunction, and the presence of multivessel disease.\textsuperscript{1,2}

Recurrent ischemic events have proven more difficult to predict.\textsuperscript{35} Myocardium involved in this process must be viable as well as being supplied by a stenosed coronary artery involving another or the same territory. Although exercise testing should identify residual ischemic tissue, \textit{ST} segment depression does not predict subsequent nonfatal cardiac events.\textsuperscript{26,27} Moreover, the highest-risk patients are also those who are either unable to exercise or can perform only limited exercise.\textsuperscript{28} Dipyridamole stress perfusion scintigraphy does not require patients to exercise and has been found to predict both cardiac death and infarction,\textsuperscript{29} reflecting its strength in identifying coronary stenoses supplying non-infarcted territories.

Despite the efficacy of stress perfusion imaging for risk stratification, this study suggests that problems pertain to the use of this test for identification of residual viable myocardium within the territory of the infarct-related vessel. First, the presence of a significant stress-induced alteration of perfusion within a resting perfusion defect was not predictive of segmental FDG activity, nor did the presence of such reversible defects predict events. Second, while resting \textit{Rb}-82 activity was higher in viable than in nonviable myocardium—consistent with previous data obtained at thallium imaging\textsuperscript{13}—the difference between these segments was so small (approximately 5%) that a reliable cutoff based on relative perfusion was difficult to define. As relative hyperemia due to compensatory hyperkinesis of the noninfarcted myocardium causes underestimation of flow by measurements of relative perfusion,\textsuperscript{30} prediction of myocardial viability from perfusion data may be performed optimally using absolute rather than relative flow. Identifying myocardial viability directly, by FDG imaging, is superior to reversible perfusion defects for identifying underperfused viable myocardium needing revascularization. Although FDG was used as a marker of viability in this study, others have demonstrated that \textit{Rb}-82 imaged by a resting washout protocol provides images comparable to FDG,\textsuperscript{18} which also have clinical prognostic value.\textsuperscript{17} Failure to recognize viable myocardium may preclude these patients from undergoing coronary revascularization, thereby missing an opportunity to enhance the function of involved segments and improve prognosis.\textsuperscript{31,32} The use of metabolic imaging has permitted the detection of viable myocardium within about 50% of fixed thallium defects,\textsuperscript{33} and the revascularization of these segments has been shown to correlate with enhancement of regional function.\textsuperscript{10-13}

\begin{table}
\centering
\begin{tabular}{|l|c|c|}
\hline
 & \textbf{Total Patients} & \textbf{Patients With RVS Decision} \tabularnewline & & \textbf{Incompatible With PET} \tabularnewline \hline
Di Carli et al\textsuperscript{15} & 93 & 34 (37\%) \tabularnewline Eitzman et al\textsuperscript{16} & 82 & 32 (39\%) \tabularnewline Yoshida and Gould\textsuperscript{17} & 35 & 13 (37\%) \tabularnewline Current study & 129 & 40 (31\%) \tabularnewline \hline
Average & 339 & 119 (35\%) \tabularnewline \hline
\end{tabular}
\caption{Concordance Between Revascularization Decision and PET Findings of Viability}
\end{table}

The presence of viable myocardium within infarcted segments is suggestive of incomplete infarction. This entity has previously been recognized on the basis of low peak serum creatine kinase levels and correlated with a greater incidence of postinfarction angina and mortality.\textsuperscript{34} However, whether FDG+ tissue represents the same entity with similar prognostic significance remains to be established.

Recent investigations have begun to address the prognostic significance of a perfusion-metabolism mismatch pattern in patients with and without revascularization (Table 5). Eitzman et al\textsuperscript{16} studied the role of viable myocardium in the occurrence of cardiac events in 82 patients, 40 of whom underwent myocardial revascularization. Patients with perfusion-metabolism mismatch who were revascularized showed an improvement in functional class, but of 18 patients failing to undergo intervention, 6 died and 3 suffered a myocardial infarction. Similarly, a 1-year follow-up of 79 patients with severe left ventricular dysfunction (ejection fraction <30%) presented by DiCarli et al\textsuperscript{15} suggested that unrevascularized patients with hibernating myocardium showed an excessive prevalence of cardiac death. In comparison to our experience, both studies were smaller (involving, respectively, 16 and 6 events), and neither involved the use of stress-perfusion imaging. The comparison with stress-perfusion imaging in this study suggests that resting ischemia is more predictive of events than stress-induced ischemia.

The relative importance of perfusion defects and FDG+ myocardium with respect to the genesis of late events has been addressed in a recent study by Tamaki et al.\textsuperscript{14} This study differed from ours on several methodological grounds: thallium rather than rubidium was used as the perfusion marker, perfusion was evaluated qualitatively, a fasting FDG protocol was used, and most patients were treated medically. Over a 2-year follow-up in 84 patients, a 39% event rate was reported, mainly comprising unstable angina and revascularization procedures in patients with viable myocardium—results that are concordant with ours. However, there was some discordance between the studies with respect to the importance of reversible perfusion defects, which were not associated with events in our experience but were shown by univariate (but not multivariate) analysis to correlate with events in the study of Tamaki et al. This discrepancy may reflect differences in patient selection; in the latter study, 51 (61\%) had reversible perfusion defects, few of whom underwent revascularization, in contrast to 43 patients (40\%) in our study having reversible defects, 25 of whom were revascularized. Moreover, Table 2 demonstrates that four events occurred in 11 medically treated ischemic patients (36\%) compared with four events in 25 revascularized

\textbf{Prognostic Significance of a Metabolism-Perfusion Mismatch}

The presence of viable myocardium within infarcted segments is suggestive of incomplete infarction. This entity has previously been recognized on the basis of low peak serum creatine kinase levels and correlated with a greater incidence of postinfarction angina and mortality.\textsuperscript{34} However, whether FDG+ tissue represents
patients (12%). Thus, the risk of events in patients with ischemia may have been attenuated by revascularization in our series.

Our findings confirm in a large cohort the reports of Eitzman et al16 and DiCarli et al15 that, in patients with viable, underperfused myocardium, revascularization is associated with lower event rates than medical antianginal treatment. Although most revascularization was carried out at the beginning of the follow-up period in these studies, the data of Yoshida and Gould17 suggest that revascularization done later during a 3-year follow-up period was associated with relatively favorable mortality of 10% (2 of 20) compared with 8% (4 of 49) in our study, in which revascularization was more frequently done early in the follow-up period. Our results also confirm in a large cohort that low ejection fraction predicts high cardiac mortality, as reported by Yoshida and Gould17 and explained in their study by large infarct size without remaining viable myocardium. Their higher mortality than our series for patients with large infarct size, low ejection, and absence of viable myocardium may be due to their longer follow-up period in which death due to poor left ventricular function could occur (Also see Table 6).

Clinical Implications

The experience reported here reflects a selected subgroup of patients after myocardial infarction with impaired left ventricular function and a predominantly fixed perfusion defects. Inferences regarding the place of FDG imaging in the evaluation of postinfarction patients therefore must be limited. In this group, however, the association of nonfatal events (unstable angina necessitating hospital admission or revascularization and myocardial infarction) with failure to revascularize viable myocardium and their avoidance in patients undergoing revascularization suggest that intervention may be justified on prognostic grounds. The prospect of avoiding the cost of recurrent cardiac events by immediate revascularization of patients with FDG+ myocardium may balance the expense of PET imaging.

Table 6. Relation of Event Rates to the Concordance Between Revascularization and Positron Emission Tomography Findings of Viability

<table>
<thead>
<tr>
<th></th>
<th>F+R+</th>
<th>F+R-</th>
<th>F-R+</th>
<th>F-R-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eitzman et al16</td>
<td>26</td>
<td>18</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Patients</td>
<td>3</td>
<td>9</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Events</td>
<td>20</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Patients</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Yoshida and Gould17</td>
<td>26</td>
<td>17</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Patients</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Events</td>
<td>49</td>
<td>21</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Patients</td>
<td>8</td>
<td>13</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>61</td>
<td>56</td>
<td>101</td>
</tr>
<tr>
<td>Events (% events)</td>
<td>61 (13%)</td>
<td>29 (48%)</td>
<td>7 (13%)</td>
<td>15 (15%)</td>
</tr>
</tbody>
</table>

F+ indicates FDG (F-18 fluorodeoxyglucose) uptake indicating viability or mismatch; F-, no FDG uptake indicating no viability or no mismatch; R+, revascularization by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); R-, no revascularization; Events, patients with myocardial infarction, acute unstable coronary syndromes, or mortality; and % Events, percent of patients with events.

patients (12%). Thus, the risk of events in patients with ischemia may have been attenuated by revascularization in our series.

Our findings confirm in a large cohort the reports of Eitzman et al16 and DiCarli et al15 that, in patients with viable, underperfused myocardium, revascularization is associated with lower event rates than medical antianginal treatment. Although most revascularization was carried out at the beginning of the follow-up period in these studies, the data of Yoshida and Gould17 suggest that revascularization done later during a 3-year follow-up period was associated with relatively favorable mortality of 10% (2 of 20) compared with 8% (4 of 49) in our study, in which revascularization was more frequently done early in the follow-up period. Our results also confirm in a large cohort that low ejection fraction predicts high cardiac mortality, as reported by Yoshida and Gould17 and explained in their study by large infarct size without remaining viable myocardium. Their higher mortality than our series for patients with large infarct size, low ejection, and absence of viable myocardium may be due to their longer follow-up period in which death due to poor left ventricular function could occur (Also see Table 6).

Clinical Implications

The experience reported here reflects a selected subgroup of patients after myocardial infarction with impaired left ventricular function and a predominantly fixed perfusion defects. Inferences regarding the place of FDG imaging in the evaluation of postinfarction patients therefore must be limited. In this group, however, the association of nonfatal events (unstable angina necessitating hospital admission or revascularization and myocardial infarction) with failure to revascularize viable myocardium and their avoidance in patients undergoing revascularization suggest that intervention may be justified on prognostic grounds. The prospect of avoiding the cost of recurrent cardiac events by immediate revascularization of patients with FDG+ myocardium may balance the expense of PET imaging.

Limitations of the Study

This study has certain methodologic and design limitations. First, FDG metabolic imaging involved the use of two protocols. In part, the use of both fasting and glucose-loaded scans reflects some controversy regarding the optimal imaging approach, both having been validated for the prediction of viable myocardium. In view of the tendency for ischemic as well as hibernating myocardium to contribute to areas of increased FDG activity, we used the presence of reversible perfusion defects to identify ischemic segments and analyzed the data with and without the exclusion of patients showing evidence of ischemia. Statistical analysis for ischemic and fatal cardiac events revealed no difference in event rates for patients undergoing either protocol, supporting the use of either method as a valid choice for evaluation of ischemia and viable tissue. Second, the use of a qualitative mismatch between Rb-82 and FDG (rather than more complete analyses of metabolism or coronary flow, for example, with O-15 labeled water) reflects the performance of the study in a busy clinical laboratory, in the absence of an on-site cyclotron. However, it does reflect the reality of practice in most "clinical PET" centers, and the use of a more quantitative approach is likely to strengthen the value of PET rather than diminish it. Third, the use of various techniques to define ejection fraction is a reflection of the technical shortcomings of each of these methods in individual patients.

This study is a retrospective analysis examining the outcomes of treatment decisions made on clinical grounds in patients with and without viable myocardium. Due to this methodological design, the lack of randomization to treatment groups generated some uncertainty as to whether the observed differences corresponded to undefined factors determining selection for medical or revascularization therapy. However, there was no statistical significance in the four groups analyzed with respect to presence of viable myocardium and impact of revascularization. The homogeneity of these patient groups reflected the lack of significant selection bias in the patients studied. Moreover, even when the role of major postinfarction prognostic factors were taken into account, the association of FDG+ tissue in recurrent ischemic events was confirmed by multivariate analysis.

Conclusions

The results of this study suggest that metabolically active, dysfunctional myocardium is an unstable substrate after myocardial infarction and is likely to lead to lead to ischemic events if left unrevascularized. However, patients with FDG+ tissue, when revascularized, have the same occurrence of ischemic events as those without FDG+ tissue. This study supports the use of revascu-
larization as an effective treatment in the presence of metabolically active tissue after myocardial infarction.

Acknowledgments

This study was supported in part by a Grant-in-Aid from the American Heart Association, NE Ohio Affiliate.

References


17. Yoshida K, Gould LK. Quantitative relation of myocardial infarction size and myocardial viability by positron emission tomography to left ventricular ejection fraction and 3-year mor-
Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization.

K S Lee, T H Marwick, S A Cook, R T Go, J S Fix, K B James, S K Sapp, W J MacIntyre and J D Thomas

_Circulation_. 1994;90:2687-2694
doi: 10.1161/01.CIR.90.6.2687

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/6/2687

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/