Regional Oxidative Metabolism in Patients After Recovery From Reperfused Anterior Myocardial Infarction
Relation to Regional Blood Flow and Glucose Uptake

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Background. Enhanced uptake of the glucose analogue 18F-fluorodeoxyglucose (FDG) in relation to flow has been proposed as an accurate method of identifying viable myocardium. The evaluation of myocardial oxidative metabolism could be an alternate way to identify reversible injury. The aim of the present study was to investigate in patients with reperfused anterior infarction whether differences in regional oxidative metabolism exist among regions with and without flow-metabolism mismatch.

Methods and Results. Fifteen patients with reperfused anterior myocardial infarction were studied between 2 weeks and 3 months after the acute event. Regional myocardial blood flow (13N-ammonia; three-compartment model), oxidative metabolism (14C-acetate; monoexponential clearance), and glucose uptake (FDG, linear graphic analysis) were evaluated with dynamic positron emission tomography. Flow-metabolism patterns were used to differentiate reversibly (FDG/flow > 1.2) from irreversibly injured myocardium (FDG/flow < 1.2) using circumferential profile technique. Relative 13N-ammonia uptake was reduced in 71 of 90 anterior and/or septal segments, including 24 with (seven patients) and 38 without (eight patients) flow-metabolism mismatch. Acetate clearance (k), reflecting oxidative metabolism, was reduced by 51% in the center of the infarct area versus remote segments (27±12 versus 55±13 min⁻¹.10⁻³, p<0.001). Compared with infarct segments without flow-metabolism mismatch, segments exhibiting increased glucose uptake relative to flow had faster acetate clearance (35±14 versus 23±9 min⁻¹.10⁻³, p<0.01). Similarly, myocardial blood flow was better preserved in segments with flow-metabolism mismatch (54±13 versus 45±8 ml/min/100 g, p<0.01) compared with segments without mismatch. However, at similar levels of hypoperfusion, there was no significant difference in acetate clearance among segments with and those without flow-metabolism mismatch: 37±14 versus 41±15 min⁻¹.10⁻³, respectively. A positive correlation (r=0.89, p<0.001) was found between absolute myocardial blood flow and acetate clearance, regardless of the flow-metabolism pattern.

Conclusions. In patients with reperfused myocardial infarction studied between 2 weeks and 3 months after the acute event, regional oxidative metabolism is reduced in proportion to residual myocardial blood flow and does not differ significantly among similarly hypoperfused segments with and without flow-metabolism mismatch. (Circulation 1992;85:9–21)
distribution and wall motion, both of which may be reduced without being necessarily indicative of irreversible injury. It is widely recognized that regional wall motion can remain impaired for a prolonged period of time after an ischemic insult, even in reversibly injured tissue.\textsuperscript{1-3} On the other hand, identifying myocardial scar using stress redistribution \textsuperscript{201}TI imaging may lead to significant overestimation of irreversible injury.\textsuperscript{4-7} More recently, metabolic imaging with \textsuperscript{18}F-fluorodeoxyglucose (FDG) and positron emission tomography (PET) has proved more specific for differentiating reversibly from irreversibly injured tissue. Reversibly injured myocardium exhibits increased FDG uptake relative to blood flow (so-called “flow-metabolism mismatch”), whereas necrotic segments show a concordant depression of flow and FDG uptake (flow-metabolism match).\textsuperscript{7-9} However, the biochemical significance of these metabolic patterns is not fully understood,\textsuperscript{10} even though the functional outcome after revascularization is usually favorable.\textsuperscript{7-9,11}

Theoretically, an appealing alternate way to identify reversible injury might arise from the evaluation of myocardial oxidative metabolism, since the energy required for contraction can be provided only by aerobic metabolism.\textsuperscript{12,13} Experimental studies have demonstrated that restoration of contractile function after an acute ischemic event was predicted by recovery of myocardial oxidative metabolism.\textsuperscript{14,15} Noninvasive determination of myocardial oxygen consumption might thus prove useful in assessing the potential for recovery of the posts ischemic dysfunction.

Accordingly, the present study was undertaken to evaluate whether differences in regional oxidative metabolism exist within reperfused anterior myocardial infarction and to determine whether assessment of regional oxidative metabolism provides additional independent information on myocardial viability compared with the flow-metabolism mismatch concept. Regional blood flow and glucose metabolism were assessed with PET. The clearance kinetics of \textsuperscript{11}C-acetate, which is readily oxidized to carbon dioxide, were used to assess the regional oxidative metabolism.\textsuperscript{16-20}

Methods

Study Population

The study population consisted of 15 patients (13 men and two women; mean age, 56±10 years; range, 38–67 years) admitted to the coronary care unit for treatment of a first acute anterior myocardial infarction. Upon admission 13 patients received intravenous thrombolytic therapy, and two patients were treated with intravenous heparin. Nine patients received streptokinase (500,000 IU), and four patients received recombinant human tissue-type plasminogen activator (100 mg). The interval from onset of chest pain to beginning of thrombolytic therapy was 207±183 minutes. Peak serum levels of creatine kinase averaged 2,393±1,249 IU/l (normal values, 40–160 IU/l). All patients subsequently developed anterior Q waves on 12-lead surface ECGs.

Angiography and Ventriculography

Selective coronary angiography and contrast left ventriculography in the 30° right anterior oblique projection were performed in every patient an average of 20±18 days after the acute myocardial infarction and visually interpreted by two observers. In each patient, the infarct-related coronary artery (i.e., the left anterior descending coronary artery) was found to be patent, with a residual luminal diameter stenosis of 80±11% (range, 50–95%). Eight patients had one-vessel and seven had multivessel coronary disease, including six with two-vessel and one with three-vessel disease. None of the patients underwent angioplasty or bypass surgery before the study. The regional ventricular wall motion was reviewed by two experienced observers and defined in each of five segments (anterobasal, anterolateral, apical, inferior, and posterobasal) as normal, 0; hypokinetic, 1; akinetic, 2; or dyskinetic, 3 to provide a regional wall motion score. Severe anterior wall dysfunction was observed in 14 patients: seven patients had akinesis, and seven had dyskinesis. The remaining patient only showed mild hypokinesis of the anterior wall. Mean global left ventricular ejection fraction was 52±11% (range, 29–70%), and mean wall motion score was 5.0±1.3.

Stress \textsuperscript{201}TI Myocardial Imaging

Symptom-limited exercise testing was performed on a bicycle ergometer in 12 of 15 patients an average of 20 days after the acute myocardial infarction (range, 8–51 days). No intercurrent event occurred between the exercise tests and the PET studies. Three patients did not undergo exercise testing because of residual angina pectoris. Digitized ECG samples were averaged and analyzed by computer as previously described.\textsuperscript{21} The amount of ST segment depression during maximal exercise was measured 60 msec after the end of QRS complex with the PR interval as reference level. An abnormal ECG response during exercise was defined as horizontal ST depression ≥0.1 mV. Abnormal ECG findings were found in one of 12 patients, whereas another patient had chest pain during exercise. During the last minute of the same bicycle exercise, 1.5–2.0 mCi \textsuperscript{201}TI was injected intravenously. Planar myocardial images were obtained in the anterior and left anterior oblique 45° and 65° projections within 10 minutes on the completion of exercise and again 4 hours after initial tracer injection (redistribution scintigraphy). \textsuperscript{201}TI studies were visually interpreted by two independent observers blinded to the clinical and angiographic data. Each view was separated into five segments, yielding a total of 15 segments. \textsuperscript{201}TI uptake in each of the 15 segments was classified as normal, 0; possibly reduced, 1; reduced, 2; or absent, 3. A score change of at least 2 between exercise and redistribution was considered a tran-
sient defect. \(^{201}\)TI anterior defects were observed after exercise in all patients. \(^{201}\)TI defect score during exercise was not different in patients with (22±4) and those without (19±7) flow-metabolism mismatch. Transient defects between exercise and redistribution were observed in only three patients.

**PET**

Acquisitions were performed an average of 42±25 days (range, 13–90 days) after the acute event with an ECAT III (CTI, Knoxville, Tenn.) one-ring tomograph, the characteristics of which have been described previously.\(^{22}\) Measurements were performed with a stationary ring, and images were reconstructed with a Hann filter, giving an in-plane resolution of 8-mm full width at half maximum (FWHM). The collimator aperture was set at 30 mm, resulting in a slice thickness of 15 mm FWHM. Regular calibration of the tomograph versus a well counter was performed by measuring a uniform cylindrical phantom (diameter, 20 cm) filled with a solution of \(^{60}\)Ge. All patients were studied after overnight fasting. In an attempt to standardize the dietary state and maximize the exogenous glucose uptake by the normal myocardium, a venous line was inserted in the antecubital vein and continuously perfused using a 10% dextrose in water solution (15 \(\mu\)M/kg/min). The stability of the plasma glucose levels during the 4-hour PET study and glucose infusion was checked in a separate group of 10 patients. No patient had more than 15% variability of plasma glucose levels during the infusion. Patients were carefully positioned in the tomograph. Serial transmission scans at different levels were obtained to allow subsequent correction for photon attenuation. All transmission scans were viewed before collection of emission data to verify proper positioning of the patient. The selected imaging plane corresponded to a midventricular plane. Correct positioning was maintained throughout the study with the use of a light beam and indelible felt-pen marks on the patient torso. Every time the patient moved during the study, new transmission scans were performed for proper repositioning.

Myocardial perfusion was assessed with \(^{13}\)N-ammonia, myocardial oxidative metabolism with \(^{11}\)C-acetate, and exogenous glucose uptake with \(^{18}\)F-FDG. All tracers were injected intravenously with an infusion pump (model 351, Sage Instruments). After collection of attenuation data, 10–15 mCi \(^{13}\)N-ammonia was injected over a 20-second period. Beginning with tracer injection, 28 serial cross-sectional images were acquired in a decay-compensated mode for 10 minutes. After a 50-minute interval for decay of \(^{13}\)N radioactivity to baseline levels, 10–15 mCi \(^{11}\)C-acetate was injected over a 20-second period. Beginning with tracer injection, 25 serial cross-sectional images were acquired for 25 minutes. After an additional 60-minute interval (three times the \(^{11}\)C period) for decay of \(^{11}\)C radioactivity, 15 mCi \(^{18}\)F-FDG was infused over 60 seconds, followed by acquisition of 34 serial cross-sectional images for 45 minutes.

Venous blood samples for determination of hematocrit and plasma glucose, lactate, fatty acids, and insulin were obtained at the end of the FDG study.

**Analysis of Tomographic Images**

One transaxial tomographic slice per patient was analyzed for dynamic studies. Each reconstructed tomographic image was corrected for physical decay. Nine circular regions of interest of approximately 1 cm\(^3\) were assigned to each image of the left ventricular myocardium, and another region was assigned to the center of the left ventricular blood pool. Three of these regions of interest were located in the interventricular septum, three other regions were in the anterior wall, and the remaining three regions were in the lateral free wall of the left ventricle. The maximal count rate in each myocardial region was between 5,000 and 8,000 counts per second. Counts of each region of interest were corrected for partial volume and spillover effects as well as for dead time losses using a specially developed Monte Carlo simulation. Both phantom measurements and comparisons of in vivo with in vitro data have shown the validity of these correction schemes for dead time losses and for the finite resolution effects in cardiac studies (Reference 23 and “Appendix”). These circular regions of interest were used to estimate absolute perfusion, oxidative metabolism, and exogenous glucose uptake.

**Circumferential profiles.** \(^{13}\)N-ammonia and FDG cross-sectional images were analyzed with an operator-interactive computer program using circumferential profiles. The program normalized \(^{18}\)F and \(^{13}\)N counts within a given myocardial cross section to maximal activity in the same ventricular slice. Each cross section of the left ventricle was then divided into serial adjacent 30° segments. The previously described regions of interest are encompassed within these segments. Activity within each segment was expressed as a percent of the maximal activity and subsequently normalized to peak \(^{13}\)N-ammonia segmental activity at the same level. Flow-metabolism mismatch was defined as a relative segmental FDG–to–ammonia activity ratio exceeding 1.2 according to data obtained in normal volunteers with a ratio of FDG to flow ranging from 1.02 to 1.12.\(^{24}\) Regions of interest in tomograms obtained after administration of \(^{13}\)N-ammonia were subdivided to encompass regions of interest in remote, adjacent, and infarcted tissue. Remote (normal) regions were identified as those with normal perfusion (>80% of maximal activity in the same slice). Infarct-related regions were identified as anterior or septal regions of hypoperfusion with <80% of maximal ammonia activity in the same slice. The regions of interest located in the center of this zone of hypoperfusion were defined as central infarct. Adjacent regions were delineated as the regions of interest located at the borders of the infarct zone (on both sides).

**Regional myocardial perfusion.** The kinetic behavior of \(^{13}\)N-ammonia in myocardial tissue was approached
using a three-compartment model developed by Hutchins et al.\textsuperscript{25} and validated in dogs.\textsuperscript{26} This model describes the transport and partition of \textsuperscript{13}N-ammonia between the vascular compartment and the extracellular space as well as its intracellular incorporation in the form of \textsuperscript{13}N-glutamine by way of the glutamine synthetase activity. In this model, \( k_1 \) represents the combined processes of the delivery of the tracer to the tissue by blood flow as well as its extraction by the myocardium. \( k_2 \) and \( k_3 \) reflect the probability for a single radionuclide to be lost by the system \((k_2)\) or to be incorporated into another compartment \((k_3)\). In addition, this model incorporates the spillover fraction of the ventricular blood pool activity, which spills over to the myocardium as well as the blood volume contained in myocardial tissue, both factors being lumped into a single constant term referred to as “total fractional blood volume.” Estimates of the parameters of the ammonia compartment model were obtained by nonlinear least-squares curve-fitting algorithm using the MINUIT program.\textsuperscript{27}

\textbf{Regional oxidative metabolism.} After injection of \textsuperscript{11}C-acetate, the \textsuperscript{11}C radioactivity typically clears exponentially from the myocardium. With multieponential least-squares routines, regional time–activity curves were fitted for calculation of clearance slopes and half-times of the curve components. The first component was shown to reflect immediate oxidation of acetate via the tricarboxylic acid cycle, whereas the second component, when present, probably reflects \textsuperscript{11}C activity in equilibrium with the amino acid pools via the transamination of tricarboxylic acid cycle intermediates.\textsuperscript{16,17}

\textbf{Exogenous glucose uptake.} A three-compartment FDG tracer kinetic model and the linear graphic analysis were used to estimate regional myocardial glucose uptake. This method is used for models in which the tracer is irreversibly trapped into a system and can be applied to dynamic FDG studies if one assumes that the dephosphorylation rate constant \((k_4)\) of FDG is equal to zero. The following equation was used:\textsuperscript{28}

\[
\frac{A_m(t)}{C_p(t)} = \frac{(k_1 \times k_3) / (k_2 + k_3)}{C_p(t)} \int_0^t C_p(s) ds + W
\]

where \( A_m(t) \) is the myocardial tissue \textsuperscript{18}F activity at time \( t \), \( C_p(t) \) is the plasma activity at time \( t \), and \( W \) is a function of the steady-state volume of the reversible compartments and the effective plasma volume. The plot of \( \frac{A_m(t)}{C_p(t)} \) versus \( \int C_p(s) ds / C_p(t) \) has been shown to be linear at late times with a slope equal to \( K = (k_1 \times k_3) / (k_2 + k_3) \) and a \( Y \) intercept equal to \( W \), that is, \( (k_1 \times k_2) / (k_2 + k_3)^2 \). The \( Y \) intercept represents a kinetic volume and has no particular physical meaning. The graphic approach allows estimation of glucose uptake by simply giving an estimate of \( K \) from the slope of the linear regression of the plot. Regional myocardial glucose uptake was calculated as \((C_p/LC) \times K\), where \( C_p \) is the plasma concentration of glucose, \( K \) is the slope of the graphic analysis, and \( LC \) is the lumped constant that accounts for differences in the transport and phosphorylation of FDG and glucose. For the present study, the lumped constant was assumed to be 0.665.\textsuperscript{29}

\textbf{Statistical Analysis}

Values are expressed as mean±1 SD. For statistical analysis, least-squares regression routines, the Student’s \( t \) test for unpaired data, and the Mann-Whitney test were used. When comparing flow and metabolic data (Tables 2 and 3), a one-way analysis of variance with the Bonferroni test was applied; \( p<0.05 \) was considered statistically significant.

\textbf{Results}

\textbf{Relative Regional Myocardial Blood Flow and Glucose Metabolism}

PET revealed diminished perfusion in 71 anterior and/or septal segments, corresponding to the tomographic area of infarction in all 15 patients. Relative \textsuperscript{13}N-ammonia uptake in these segments averaged 61±13\% of maximal activity. Segments with decreased blood flow showed three different patterns of FDG uptake: parallel decreases of ammonia and FDG uptake (flow-metabolism match), increased uptake of FDG relative to flow throughout the infarcted zone (central flow-metabolism mismatch), and a combination of concordant decreases of flow and FDG uptake in the center of the infarcted zone with increased FDG uptake relative to flow at the periphery of the infarcted zone ( peripheral flow-metabolism mismatch). As indicated in Table 1, eight patients showed concordant decreases of flow and metabolism in the infarcted area (FDG/flow, 0.9–1.06), two patients had peripheral flow-metabolism mismatch (FDG/flow, 1.25 and 1.35), and five patients had central flow-metabolism mismatch (FDG/flow, 1.21–1.99). The average values of the FDG/flow ratios were 1.57±0.3 in patients with mismatch and 0.97±0.05 in patients with a match pattern. Relative \textsuperscript{13}N-ammonia uptake averaged 60±10\% in infarcted segments with flow-metabolism mismatch and 61±14\% in infarcted segments without flow-metabolism mismatch (\( p=NS \)). In the same segments, relative FDG uptakes were 108±26\% and 60±15\%, respectively.

No difference in regional wall motion score was observed between patients with and those without increased FDG uptake (5.1±1.5 versus 4.9±1.4, \( p=NS \)). Similarly, left ventricular ejection fraction was not different in the eight patients with concordant decreases of flow and metabolism versus the seven patients with flow-metabolism mismatch (53±10\% versus 51±13\%, \( p=NS \)). Only two of seven patients with flow-metabolism mismatch had reversible \textsuperscript{203}TI defects after exercise testing.
Acetate Kinetics in Reperfused Anterior Infarcted Segments

Figure 1 illustrates the myocardial uptake and clearance of $^{13}$C-acetate in a patient with anterior myocardial infarction and central flow-metabolism mismatch. Multieponential least-squares fitting routines were used to analyze the myocardial $^{13}$C clearance kinetics. From the time–activity curves analyzed, $^{13}$C clearance was always monoeponential, in both infarcted and remote segments. The clearance of $^{13}$C-acetate was reduced in the center of the infarcted region compared with remote segments ($27\pm12$ versus $55\pm13$ min$^{-1}$10$^{-3}$, $p<0.001$). Adjacent segments also showed reduced uptake and clearance of the tracer, although to a lesser extent than in the center of the infarcted area ($41\pm12$ min$^{-1}$10$^{-3}$, $p<0.001$ versus central, $p<0.001$ versus remote).

When segments with and without flow-metabolism mismatch showing identical levels of hypoperfusion were compared (Table 2), no differences in acetate clearance were found ($41\pm15$ min$^{-1}$10$^{-3}$ in mismatch segments versus $37\pm14$ min$^{-1}$10$^{-3}$ in match segments). In segments with hypoperfusion (<80% of maximal activity) ranked according to different values of acetate clearance (Table 3), the corresponding myocardial blood flow values were significantly different, whereas absolute glucose uptake and relative FDG-to-ammonia ratios were not different.

Absolute Myocardial Blood Flow and Glucose Metabolism

Estimation of regional myocardial blood flow was not possible in two of 15 patients because of inadequate left ventricular input function. In the remaining 13 patients, absolute transmural myocardial blood flow averaged $80\pm16$ ml/min/100 g in remote segments, $67\pm15$ ml/min/100 g in adjacent segments, and $49\pm11$ ml/min/100 g in segments located in the center of the infarcted area. Compared with infarcted segments without flow-metabolism mismatch, segments exhibiting increased glucose uptake relative to flow had significantly higher residual myocardial blood flow: $54\pm13$ versus $45\pm8$ ml/min/100 g, $p<0.01$. Similarly, residual oxidative metabolism was better preserved in segments with flow-metabolism mismatch ($35\pm14$ min$^{-1}$10$^{-3}$) than in segments with concordant decreases of flow and metabolism ($23\pm9$ min$^{-1}$10$^{-3}$, $p<0.01$).

Individual metabolic rates for glucose utilization in remote, adjacent, and central infarct regions are shown in Table 4. Both flow-metabolism patterns were associated with a wide range of absolute regional myocardial glucose uptake. Rates of glucose utilization in remote myocardium were lower in patients with mismatch ($25\pm15$ µM/min/100 g) than in patients without mismatch ($55\pm20$ µM/min/100 g). The patients with mismatch also had higher plasma fatty acids levels. However, the presence of a mis-

### Table 1. Individual Values of FDG-to-Ammonia Ratios in Hypoperfused Segments and Corresponding Ratios of Hypoperfused-to-Remote Absolute Flow and Glucose Utilization

<table>
<thead>
<tr>
<th>Patients with flow-metabolism match</th>
<th>FDG-to-ammonia ratio in hypoperfused regions</th>
<th>No. of hypoperfused regions (n=38)</th>
<th>Hypoperfused-to-remote ratio of MBF</th>
<th>Hypoperfused-to-remote ratio of rMGU</th>
</tr>
</thead>
<tbody>
<tr>
<td>P542</td>
<td>1.06</td>
<td>5</td>
<td>0.50</td>
<td>0.51</td>
</tr>
<tr>
<td>P568</td>
<td>1.01</td>
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<td>P582</td>
<td>0.99</td>
<td>5</td>
<td>0.62</td>
<td>0.69</td>
</tr>
<tr>
<td>P601</td>
<td>0.95</td>
<td>4</td>
<td>*</td>
<td>0.84</td>
</tr>
<tr>
<td>P658</td>
<td>0.99</td>
<td>6</td>
<td>0.66</td>
<td>0.55</td>
</tr>
<tr>
<td>P668</td>
<td>0.90</td>
<td>5</td>
<td>0.51</td>
<td>0.25</td>
</tr>
<tr>
<td>P683</td>
<td>0.91</td>
<td>4</td>
<td>0.58</td>
<td>0.47</td>
</tr>
<tr>
<td>P699</td>
<td>0.99</td>
<td>5</td>
<td>0.56</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.97±0.05</td>
<td>4.8±0.7</td>
<td>0.60±0.09</td>
<td>0.59±0.19</td>
</tr>
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<table>
<thead>
<tr>
<th>Patients with flow-metabolism mismatch</th>
<th>FDG-to-ammonia ratio in mismatch regions</th>
<th>No. of mismatch regions (n=24)</th>
<th>Mismatch-to-remote ratio of MBF</th>
<th>Mismatch-to-remote ratio of rMGU</th>
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<tbody>
<tr>
<td>P537</td>
<td>1.35</td>
<td>1</td>
<td>0.73</td>
<td>0.95</td>
</tr>
<tr>
<td>P602</td>
<td>1.25</td>
<td>3</td>
<td>0.80</td>
<td>1.06</td>
</tr>
<tr>
<td>P611</td>
<td>1.21</td>
<td>2</td>
<td>*</td>
<td>0.79</td>
</tr>
<tr>
<td>P622</td>
<td>1.79</td>
<td>3</td>
<td>0.52</td>
<td>1.22</td>
</tr>
<tr>
<td>P652</td>
<td>1.99</td>
<td>5</td>
<td>0.68</td>
<td>1.76</td>
</tr>
<tr>
<td>P669</td>
<td>1.64</td>
<td>5</td>
<td>0.63</td>
<td>1.13</td>
</tr>
<tr>
<td>P701</td>
<td>1.76</td>
<td>5</td>
<td>0.66</td>
<td>1.68</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.57±0.3</td>
<td>4.4±1.6</td>
<td>0.67±0.09</td>
<td>1.23±0.36</td>
</tr>
</tbody>
</table>

FDG, $^{18}$F fluorodeoxyglucose; MBF, myocardial blood flow; rMGU, regional myocardial glucose uptake; *, not available.
Figure 1. Upper panels: Schematic representation of patient P669's anatomic cross section (left) and corresponding images obtained after administration of $^{13}$N-ammonia (middle) and $^{18}$F-fluorodeoxyglucose (FDG) (right) 20 days after reperfused acute anterior myocardial infarction. Uptake of $^{13}$N-ammonia is decreased in anterior wall (area of infarction), whereas $^{18}$F-FDG uptake is increased, relative to flow (flow-metabolism mismatch) in same territory. Lower panels: Serial cross-sectional images obtained after administration of $^{13}$C-acetate. Times below images represent min/s images acquired by myocardium, which is proportional to flow. Note reduced uptake in hypoperfused anterior segments. Later images (middle and right) allow an appreciation of the clearance of the tracer. Note delayed $^{13}$C clearance from the anterior segments.
match pattern was not a function of substrate utilization in remote myocardium or of fatty acid levels. As indicated in Table 1, the ratios of glucose utilization in infarcted to that in remote myocardium were equal or greater than 1 in all except one patient with mismatch (1.23±0.36). Conversely, these ratios were less than 1 in all patients with a match pattern (0.59±0.19). There was no relation between absolute glucose utilization in infarcted myocardium and fatty acid levels in either mismatch or match regions. Also, there was no relation between glucose utilization measurements and plasma insulin levels.

As shown in Figure 2, a positive correlation (r=0.89, p<0.001) was found between absolute transmural myocardial blood flow and acetate clearance slope, irrespective of the flow-metabolism pattern. No relation was found in the hypoperfused regions with a match pattern between regional myocardial glucose uptake and myocardial blood flow or acetate clearance slope. However, in the 24 regions with flow-metabolism mismatch, there was a relation between regional myocardial glucose uptake and myocardial blood flow (r=0.66, p<0.001) and acetate clearance slope (r=0.74, p<0.001).

**Plasma Substrate Concentrations**

Venous plasma glucose, fatty acids, lactate, and insulin concentrations obtained at the time of the tomographic study at the end of the FDG study are listed in Table 5. A significant difference (p<0.05) in fatty acid plasma levels was observed between patients with and those without flow-metabolism mismatch.

**Discussion**

The results of the present study indicate that 40 days after an acute myocardial infarction, regional oxidative metabolism, as assessed by PET and the myocardial clearance kinetics of 11C-labeled acetate, is reduced in the area of infarction. The slope of the acetate clearance, reflecting the turnover of the tricarboxylic acid cycle and the overall oxidative metabolism, is reduced by an average of 51% in the infarct zone compared with the remote normal myocardium. Peri-infarction (adjacent) segments also manifest reduced oxidative capacity, albeit to a lesser extent than central infarct segments.

Our findings confirm and extend recently reported data showing that early after myocardial infarction, oxygen consumption is reduced in both infarcted and peri-infarcted segments. In addition, Walsh et al. made the important observation that in the absence of interventions aimed at restoring adequate coronary blood flow, oxidative metabolism did not improve over time in either infarcted or adjacent segments.

The present data also demonstrate that regional oxidative metabolism in reperfused segments remains tightly coupled to regional myocardial blood flow, irrespective of the presence of a flow-metabolism mismatch. A high degree of covariance between coronary blood flow and myocardial oxygen consumption has been documented in normal myocardium over a wide range of flow and metabolic conditions. However, reports on the relation between

<table>
<thead>
<tr>
<th>TABLE 2. Relative Perfusion, Glucose Uptake, and Acetate Clearance in Normally Perfused and Hypoperfused Segments With and Without “Flow-Metabolism” Mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow-metabolism pattern</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Normal flow/FDG</td>
</tr>
<tr>
<td>↓ Flow ↑ FDG</td>
</tr>
<tr>
<td>↓ Flow ↓ FDG</td>
</tr>
<tr>
<td>↓ ↓ Flow ↓ ↓ FDG</td>
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FDG, 18F-fluorodeoxyglucose, %, percent of maximal activity within the same slice, normalized to peak 13N-ammonia segmental activity at the same level.

*p<0.01 vs. normal flow/FDG.

†p<0.01 vs. ↓ flow ↑ FDG and vs. ↓ flow ↓ FDG.

<table>
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<tbody>
<tr>
<td><strong>k (min⁻¹·10⁻³)</strong></td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>&lt;20</td>
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<tr>
<td>20–30</td>
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<tr>
<td>30–40</td>
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<tr>
<td>40–50</td>
</tr>
<tr>
<td>&gt;50</td>
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<tr>
<td>p</td>
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</table>

*p values are from one-way analysis of variance.

FDG, 18F-fluorodeoxyglucose; k, acetate clearance slope; MBF, myocardial blood flow; rMGU, regional myocardial glucose uptake.
TABLE 4. Individual Regional Myocardial Blood Flow, Glucose Utilization, and Acetate Clearance Among Remote (Normal Relative Perfusion), Adjacent, and Infarcted Segments (<80% of Relative Perfusion) in Patients With and Without Flow-Metabolism Mismatch

<table>
<thead>
<tr>
<th>Patient</th>
<th>MBF</th>
<th>rMGU (min⁻¹·10⁻³)</th>
<th>k</th>
<th>MBF</th>
<th>rMGU (min⁻¹·10⁻³)</th>
<th>k</th>
<th>MBF</th>
<th>rMGU (min⁻¹·10⁻³)</th>
<th>k</th>
<th>RPP</th>
<th>Glucose</th>
<th>FA</th>
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<tbody>
<tr>
<td>Flow-metabolism match</td>
<td></td>
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<tr>
<td>P542</td>
<td>80±12</td>
<td>71±10</td>
<td>57±15</td>
<td>65±14</td>
<td>66±23</td>
<td>49±15</td>
<td>40±5</td>
<td>36±13</td>
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<td>7,920</td>
<td>115</td>
<td>339</td>
</tr>
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<td>74±6</td>
<td>44±6</td>
<td>67±2</td>
<td>63±5</td>
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<td>54±2</td>
<td>62</td>
<td>30±4</td>
<td>6,930</td>
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<td>390</td>
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<td>64±8</td>
<td>68±6</td>
<td>30±4</td>
<td>47</td>
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<td>27±8</td>
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<td>47±10</td>
<td>60±2</td>
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<tr>
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<td>61±5</td>
<td>86±16</td>
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<td>55±20</td>
<td>55±11</td>
<td>71±11</td>
<td>44±21</td>
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<tr>
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<td>*</td>
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<td>*</td>
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<td>82±4</td>
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<td>31±6</td>
<td>61±10</td>
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<td>56±9</td>
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<tr>
<td>Mean±SD</td>
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<td>74±13</td>
<td>26±12</td>
<td>52±12</td>
<td>53±14</td>
<td>24±11</td>
<td>36±16</td>
<td>8,340±902</td>
<td>103±28</td>
<td>864±828</td>
</tr>
</tbody>
</table>

FA, fatty acids; k (min⁻¹·10⁻³) acetate clearance slope; MBF (ml/min/100 g), myocardial blood flow; rMGU (µM/min/100 g), regional myocardial glucose uptake; RPP (beats per minute×mm Hg), rate-pressure product; *, not available.

Oxygen consumption and myocardial blood flow in the postischemic myocardium remain controversial. Studies in open-chest dogs showed that regionally stunned myocardium exhibited higher mean oxygen extraction and consumption relative to flow. However, in patients with reperfused infarction, Hennes et al showed that myocardial perfusion, as assessed by O water positron imaging, returned rapidly (18±6 hours) to normal values after reperfusion, whereas oxidative metabolism recovered more progressively and remained in fine (9±7 days) significantly depressed (68±17% of normal). These discrepancies could be related to the type of ischemic model. The animal study investigators were looking at "stunned myocardium," which means that injury is entirely reversible and coronary blood flow is fully restored. Studies in humans, including ours, focused on infarcted myocardium, which is made up of a mixture of necrotic, reversibly injured but viable, and perhaps normal cell populations, all coexisting within the same risk area. Such heterogeneity may account for the difference in oxidative metabolism observed between myocardial infarction and "stunning." Other factors include the persistence of a significant residual stenosis on the infarct-related epicardial artery in a large number of our patients or the possibility of reperfusion-induced microvascular failure (the so-called "no-reflow" phenomenon). Each of these conditions may limit the oxygen supply to the postischemic myocardium, possibly blunting any uncoupling.

FIGURE 2. Scatterplots of correlation between acetate clearance slope and myocardial blood flow, in absolute terms in all the regions. ○, Normally perfused and hyperperfused (match pattern) myocardium; ×, hypoperfused myocardial regions showing mismatch pattern. There was no statistically significant difference between correlation of normal and match regions (n=70, y=0.81×-10, r=0.89, SEE=8.1, p<0.001) and regression equation for mismatch regions (n=45, y=0.81×-11, r=0.91, SEE=6.6, p<0.001).
between flow and oxidative metabolism. Last, it should be emphasized that the present group of patients was studied between 2 weeks and 3 months after the acute event. At earlier times after reperfusion, preliminary data obtained in patients suggest that acetate clearance could predict functional recovery better than a simple measurement of flow.\textsuperscript{35,36}

The finding of a similarly depressed oxidative metabolism in similarly hypoperfused segments despite opposite patterns of exogenous glucose uptake is also of interest. Increased glucose uptake relative to flow has been considered potentially useful for detection of the presence of viable myocardium in mechanically dysfunctional zones. This approach has been shown to accurately distinguish irreversibly injured from potentially viable myocardium.\textsuperscript{8,9,11} On the other hand, it has been anticipated in dogs that the maintenance of a residual oxidative activity was a prerequisite for the return of function after complete reperfusion.\textsuperscript{14,15} Combining both approaches in patients with reperfused infarction, we were unable to find any difference in oxidative metabolism between similarly hypoperfused myocardial segments with and without flow-metabolism mismatch. In the present study, most of the patients were left with a significant residual epicardial coronary artery stenosis, which may have limited blood and oxygen supply to the infarcted segments. Higher myocardial blood flow and oxidative metabolism were observed in patients with flow-metabolism mismatch than in patients without it. Whether these observations support the contention that reperfusion after thrombolysis should be completed by angioplasty and/or bypass surgery remains speculative. Obviously, follow-up data on regional function and metabolic patterns in larger patient groups would be needed.

**Methodological Considerations and Potential Limitations**

PET allows the noninvasive assessment and quantitation of regional myocardial metabolism in vivo. Although widely used to assess regional myocardial blood flow and metabolism, the quantitation capability of this technique is limited by its inability to accurately measure true tissue tracer concentrations when the thickness of the imaged object is less than twice the spatial resolution of the imaging device.\textsuperscript{37} This underestimation of tracer concentration increases nonlinearly as wall thickness decreases. Therefore, the degree of underestimation is expected to be greatest in thin-walled objects, such as dysfunctional infarcted myocardial segments. To circumvent these limitations, we recently developed a geometric approach that allows regional recovery coefficients to be computed.\textsuperscript{23} This method uses automatically detected isocontours of the imaged object and processes the recovery coefficients and spillover factors using a Monte Carlo simulation. Four correction factors (F_{bb}, the recovery coefficient of radioactivity in the left ventricular chamber; F_{mn}, the fraction of radioactivity spilling over from the cavity to the myocardium; F_{mb}, the recovery coefficient of radioactivity in myocardium; and F_{mb}, the fraction of radioactivity spilling over from myocardium into blood) are calculated and used to estimate true tracer concentrations. This approach was validated in dogs by comparing FDG imaging with direct tissue counting. Regional myocardial corrected counts from the tomograph were found to compare favorably with those measured by in vitro counting of postmortem samples (see “Appendix”). Myocardial blood flow, in absolute terms, was estimated from dynamic \textsuperscript{13}N-ammonia acquisitions using a three-compartment tracer kinetic model.\textsuperscript{25} \textsuperscript{13}N-ammonia is highly extracted by the normal myocardium and retained in proportion to regional myocardial blood flow. The metabolic dependence of the myocardial uptake and retention of \textsuperscript{13}N-ammonia has been frequently advocated as a significant limitation to its use as a reliable flow tracer.\textsuperscript{38,39} It has been demonstrated that both of these processes were affected by ischemia and reperfusion, resulting in erroneous flow estimates. In addition, it has been anticipated that at high-flow states, metabolic trapping would become the rate-limiting step of tracer incorporation, again leading to underestimation of flow. The tracer kinetic model used in this study separates extraction from retention. In this model, k1 represents the product of blood flow and extraction fraction, whereas k3 describes the metabolic incorporation of the tracer. Using this approach, Hutchins et al\textsuperscript{25} recently reported quantitative assessment of myocardial blood flow and computation of the coronary flow reserve that agreed in magnitude with data obtained by other means. Preliminary data from our laboratory indicate that myocardial blood flow estimates obtained with this tracer kinetic model correlate closely with estimates of myocardial blood flow calculated with the microsphere technique in conscious dogs.\textsuperscript{26} at both low and high flows. Additional limitation to the use of \textsuperscript{13}N-ammonia for calculation of myocardial blood flow in absolute terms may arise from the rapid accumulation of \textsuperscript{13}N-labeled metabolic intermediates in the blood after intravenous administration of the

**Table 5. Plasma Substrates Levels**

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mg/100 ml)</th>
<th>Insulin (mIU/ml)</th>
<th>Fatty acids (mM/l)</th>
<th>Lactate (mM/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>110±25</td>
<td>19±9</td>
<td>555±548</td>
<td>1.02±0.28</td>
</tr>
<tr>
<td>Flow-metabolism match</td>
<td>118±26</td>
<td>16±7</td>
<td>347±103</td>
<td>0.91±0.21</td>
</tr>
<tr>
<td>Flow-metabolism mismatch</td>
<td>102±24</td>
<td>22±11</td>
<td>778±724\textsuperscript{a}</td>
<td>1.16±0.31</td>
</tr>
</tbody>
</table>

\textsuperscript{a}p<0.05.
labeled compound.\textsuperscript{40} Metabolite production will probably contaminate the arterial input function and, consequently, alter flow estimation. However, contamination of the arterial input function by \textsuperscript{13}N metabolites remains nonsignificant during the first 2 minutes after tracer injection, at least in humans.

Regional myocardial oxidative metabolism was assessed from the regional myocardial clearance of \textsuperscript{13}C radioactivity after intravenous administration of \textsuperscript{13}C-labeled acetate. Acetate is metabolized exclusively via mitochondrial oxidation and incorporation into the tricarboxylic acid cycle.\textsuperscript{41,42} Because tricarboxylic acid cycle turnover is tightly coupled to oxidative phosphorylation, measurements of tricarboxylic acid cycle flux should provide a reliable index of oxidative metabolism. Previous studies have shown that the turnover rate of radiolabeled acetate in isolated, perfused rat or rabbit hearts closely paralleled myocardial oxygen consumption over a wide range of physiopathological conditions, including ischemia and reperfusion.\textsuperscript{16–20} Similarly, in intact animals, close correlations were reported between the rate constant for the first exponential of myocardial clearance of \textsuperscript{13}C-labeled acetate (detected externally with PET) and direct measurements of global myocardial oxygen consumption. These correlations were not altered by the pattern of substrate utilization or by changes in myocardial work.\textsuperscript{19,43} There is, however, no direct validation of this method in humans. Nevertheless, good correlations between acetate clearance slope and the rate–pressure product have been reported in healthy volunteers, supporting the use of \textsuperscript{13}C-labeled acetate as a marker of myocardial oxidative metabolism in humans as well.\textsuperscript{43–46}

Previous experimental studies have validated \textsuperscript{18}F-FDG as a tracer of exogenous glucose utilization in both normal and ischemic myocardium.\textsuperscript{47,48} Based on the experimental evidence that increased glucose uptake may persist for a prolonged period of time in reversibly injured posts ischemic tissue,\textsuperscript{49,50} PET imaging with FDG and \textsuperscript{13}N-ammonia has been proposed to identify myocardial ischemia and define tissue viability in patients with ischemic heart disease. Most of the studies on FDG as a tracer of tissue viability have relied so far on qualitative evaluation of regional FDG uptake and its relation to flow and did not attempt to quantitate metabolic rates for glucose utilization.\textsuperscript{7–9,11} In the present study, we combined both approaches in patients with reperfused myocardial infarction. FDG and ammonia circumferential profiles were used to determine flow-metabolism patterns, whereas a three-compartment kinetic model was applied to dynamic FDG studies to derive metabolic rates of glucose utilization.\textsuperscript{28} Our data indicate that the different flow-metabolism patterns were associated with a wide range of absolute regional myocardial glucose uptake. Different rates of glucose utilization in remote myocardium were observed between the group of patients with a mismatch pattern and the group with a match pattern. This was due to different plasma fatty acid levels.\textsuperscript{51} It is unlikely, however, that the presence or absence of a mismatch occurred simply as a function of glucose utilization in normal myocardium; the normalized glucose utilization in infarcted regions was higher in patients with a relative flow-metabolism mismatch than in patients without a flow-metabolism mismatch. Because glucose utilization rates were shown to increase less in reperfused than in normal canine myocardium after hyperglycemia,\textsuperscript{52} the use of hyperinsulinemic-euglycemic clamping (rather than oral or intravenous glucose loading) might minimize the variability in glucose uptake between regions.\textsuperscript{53}

**Clinical Implications**

The results of the present study indicate that noninvasive assessment of regional oxidative metabolism is made possible in patients with myocardial infarction using PET and the myocardial clearance kinetics of \textsuperscript{13}C-labeled acetate. PET might therefore prove useful in the course of infarction to assess the results of acute interventions aimed at restoring adequate coronary blood flow to the jeopardized tissues. At an average of 42 days after this acute event, oxidative metabolism remained significantly reduced in the area of infarction, in both necrotic and presumably viable tissue. We found that regional oxidative metabolism was intimately coupled to myocardial blood flow. It therefore appears unlikely that assessment of myocardial oxidative activity will provide additional independent information in terms of myocardial viability over the combined evaluation of residual myocardial blood flow and glucose metabolism. However, only serial measurements of mechanical function allow the determination of the reversibility or irreversibility of injury. Further studies may thus be warranted, particularly earlier after infarction, to address the impact of oxidative metabolism assessment on the prediction of functional recovery in patients showing the flow-metabolism mismatch pattern.

**Acknowledgment**

The authors greatly appreciate the expert secretarial assistance of M. Delgadillo-Redaway.

**Appendix: Monte Carlo Calculation of Finite Resolution Effect Corrections**

The limited resolution of PET tomographs affects the quantitative measurement of both blood pool and myocardial tracer concentrations in two ways. First, the cross contamination of activity between adjacent structures (spillover) leads to a distortion of the recorded time–activity curves. Second, the myocardial wall thickness is of the same order of magnitude as the resolution, so the observed concentrations are underestimated due to the partial volume effect. If regional spillover factors and recovery coefficients are known, true concentrations in blood pool (C\textsubscript{b}) and myocardium (C\textsubscript{m}) can be obtained from their imaged concentrations (C\textsubscript{b} and C\textsubscript{m}) by the following equations:


\[
\begin{align*}
C_b &= k \cdot (F_{bb} \cdot C_{im} - F_{mb} \cdot C_{ib}) \\
C_m &= k \cdot (F_{mm} \cdot C_{ib} - F_{mb} \cdot C_{im})
\end{align*}
\]

where

\[k = 1/(F_{bb} \cdot F_{mm} - F_{mb} \cdot F_{bm})\]

and \(F_{bb}\) and \(F_{mm}\) are the recovery coefficients for blood pool and myocardium, respectively, and \(F_{mb}\) and \(F_{mb}\) are the spillover fractions from blood pool to myocardium and from myocardium to blood pool, respectively.

The magnitudes of the four correction factors \((F_{bb}, F_{mm}, F_{mb}, F_{mb})\) depend mainly on the geometric dimensions of the objects and of the resolution function of the tomograph.

To determine these factors, we developed a Monte Carlo simulation that assumes a bigaussian spatial resolution in the tomographic plane. The accuracy of the method has been tested by comparing the simulation results, both with phantoms and with in vitro measurements performed during dynamic FDG studies in eight dogs.

**Step 1**

The shapes and sizes of blood pool and myocardium are first determined by isocontours on a selected image from the dynamic study where all the activity is concentrated in the myocardium. To test the validity of this step, the geometric dimensions determined by isocontours have been compared with the known sizes of different heart phantoms showing a good agreement (within 3%). Furthermore, we compared the mean radii of the contours obtained on the latest dynamic FDG image (approximately 70 minutes after injection) with the ones measured on the corresponding heart slice in four dogs after death. The results show a good correlation between in vivo and ex vivo measurements \((y = 0.062 + 0.921x; r = 0.98)\).

Nevertheless, one must be aware that this geometric dimension determination method necessitates images with high statistics and is not valid for objects for which the recovery coefficient becomes too small (i.e., whose size is less than 6 mm). For small objects, the geometric dimension should be determined by other imaging modalities with better spatial resolution (e.g., magnetic resonance imaging).

**Step 2**

From the cavity and myocardium contours, four images are randomly generated: “true” uniform activity distributions in both cavity and myocardium and the corresponding “imaged” distributions distorted by the resolution effect.

The measured in-plane spatial resolution of our tomograph (CTI 911/01) follows a gaussian distribution with a FWHM of 8 mm when reconstructed with a Hann filter at a cutoff frequency of 0.5. With this resolution function in the Monte Carlo simulation, the recovery coefficients computed as a function of object size showed excellent agreement with those measured with a hot spot phantom. However, when applying this resolution function (8 mm, FWHM) to compute the correction factors for the dynamic FDG studies, the agreement with in vitro measurements was unsatisfactory. Because of heart motion, the geometric dimensions determined from the latest image of the FDG dynamic study are averaged over the entire heart cycle. The resulting errors on the correction factors have been estimated by adding to the Monte Carlo simulation a simplified model of wall motion derived from gated studies. In this model, the outer shape of the myocardium is kept constant during the heart cycle, while the cavity radius is allowed to vary between two values empirically determined from contours drawn on the different phases of the gated study. The comparison of results shows that by neglecting wall motion, one overestimates the recovery coefficients and underestimates the spillover factors. Because gated dynamic studies are tedious to perform, we decided to use the averaged dimensions from nongated studies and to compensate for the discrepancies in the correction factors by increasing the FWHM of the resolution function from 8 to 10 mm, as determined from the comparison with in vitro measurements.

**Step 3**

The regions of interest defined on the dynamic PET study are projected on the Monte Carlo images. The ratios of their integrals with and without the resolution effect allow the determination of both recovery coefficients for each region of interest and spillover factors between the different regions.

**Comparison With In Vitro Measurements**

For the eight dogs, the blood pool curve derived from corrected PET data compares successfully with the input function obtained by rapid arterial sampling. The mean of all angular coefficients obtained
by linear regression of tomographic data versus blood samples improves from 0.82 to 0.95 when corrections are applied.

In four studies the dogs were killed at the end of the PET acquisition, and tissue samples from the imaged slice were counted in a cross-calibrated well counter. These in vitro measurements showed a good agreement with the in vivo results after correction for the finite resolution effect, as shown in a representative case (Figure 3).

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Regional oxidative metabolism in patients after recovery from reperfused anterior myocardial infarction. Relation to regional blood flow and glucose uptake.
J L Vanoverschelde, J A Melin, A Bol, R Vanbutsele, M Cogneau, D Labar, A Robert, C Michel and W Wijns

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