Identification and Differentiation of Resting Myocardial Ischemia and Infarction in Man with Positron Computed Tomography, $^{18}$F-labeled Fluorodeoxyglucose and N-13 Ammonia

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SUMMARY Studies have shown that the extraction of glucose per unit flow is increased in moderately ischemic myocardium primarily due to anaerobic glucose metabolism manifested as lactate production, whereas myocardial infarction is characterized by the loss of metabolically active myocardium. To determine the feasibility of demonstrating these metabolic abnormalities reflecting both ischemia and infarction, we used positron computed tomography (PCT) to evaluate relative regional myocardial exogenous glucose utilization and perfusion in 15 patients with recent myocardial infarction. The positron-emitting tracers of glucose metabolism and perfusion, $^{18}$F-2-fluoro-2-deoxyglucose (FDG) and N-13 ammonia, respectively, were used. Fourteen of 19 documented infarctions were demonstrated by PCT to have concordantly decreased glucose utilization and perfusion. However, in an additional 11 regions, glucose utilization was disproportionately increased relative to perfusion, consistent with ischemic glucose consumption. These findings correlated with the presence of postinfarction angina, the site of ischemic electrocardiographic changes during chest pain, and the presence of regional left ventricular dysfunction and severe coronary artery disease. Because three ECG infarct zones not detected by PCT demonstrated ischemic glucose utilization, only two of 19 electrocardiographically defined infarctions had no detectable metabolic abnormality.

We conclude that the changes in regional FDG and N-13 ammonia concentrations detected with PCT in patients who had had a recent myocardial infarction are consistent with regional exogenous glucose utilization and perfusion in moderately ischemic and irreversibly infarcted myocardium. This approach has the potential to identify and differentiate resting myocardial ischemia from infarction and to assess tissue viability after an ischemic event.

POSITRON computed tomography (PCT)$^1$ has made possible noninvasive evaluation of in vivo regional biochemical processes. The information obtained by PCT is analogous to that obtained by in vitro autoradiography.$^2$ Use of the positron-emitting radionuclides $^{15}$N, $^{17}$O, $^{13}$C and $^{18}$F allows labeling of a variety of biologically important compounds whose physiologic fate is either identical to that of their naturally occurring analogs or altered in a predictable fashion. PCT can be used to measure exogenous glucose utilization quantitatively in brain and myocardium using $^{18}$F-2-fluoro-2-deoxyglucose (FDG) and relative regional perfusion can be evaluated accurately with N-13 ammonia.$^3-12$ Clinically and experimentally, the glycolytic flux that is maintained or accelerated and manifested as lactate production in moderately ischemic myocardium is absent in infarcted myocardium.$^{13-16}$ This observation suggests that the increased extraction of glucose per unit flow in ischemic myocardium with modest flow reductions will result in increased myocardial FDG accumulation relative to N-13 ammonia,$^{17}$ whereas the reduced glucose metabolism and perfusion in infarcted myocardium will be associated with equivalent reductions in both tracers.

The present investigation was undertaken to determine the feasibility of demonstrating relative regional myocardial metabolic alterations indicative of both myocardial ischemia and infarction with PCT, FDG and N-13 ammonia. Patients with a recent myocardial infarction were studied to see if myocardial regions could be identified by a discordant increase in FDG tissue concentration relative to N-13 ammonia consistent with the presence of maintained ischemic glucose consumption. In addition, myocardial regions were examined for the presence of concordant reductions in both FDG and N-13 ammonia activities consistent with the reduced glucose utilization and perfusion characteristic of infarcted myocardium.

Methods

Study Population

PCT images of relative myocardial exogenous glucose utilization (assessed with FDG) and perfusion (assessed with N-13 ammonia) were obtained in 15 patients with coronary artery disease who had had a myocardial infarction within 3 months of imaging and in 10 normal volunteers. Myocardial infarction was documented in all 15 patients by the presence of at
least two of the following criteria: an appropriate history, characteristic evolutionary electrocardiographic changes, and characteristic shifts in serum enzymes. Patients with clinical evidence of continued ischemia manifested as postinfarction angina at rest more than 48 hours after the onset of symptoms were studied in preference to patients with uncomplicated infarctions.

Patients with both Q-wave and non-Q-wave infarcts were evaluated. Localization of infarction electrocardiographically was based on the development of significant Q waves (> 0.04 second) or T-wave inversions in leads V1–V6 (anterior), I and aVl (lateral), and II, III and aVr (inferior). Electrocadiographic evidence of postinfarction ischemia was considered present if there was transient ST-segment depression greater than 1 mm or if T waves during chest pain were hyperacute or inverted. Hemodynamic evidence of continued postinfarction ischemia was based on pain-related transient elevations in pulmonary capillary wedge pressure of at least 10 mm Hg.

Twelve of the patients were male and three were female, average age 53 years (range 41–76 years). Fourteen patients had no historical or chemical evidence of diabetes. One patient had a history of chemical diabetes, and had a fasting serum glucose immediately after infarction of less than 200 mg% on no therapy.

Nine patients had postinfarction resting angina similar to that during infarction. Five of these patients had transient ST-T-wave changes during chest pain and two had chest pain–related hemodynamic deterioration. Six patients were severely hemodynamically compromised and had an initial pulmonary capillary wedge pressure exceeding 25 mm Hg and cardiac index less than 2.2 l/min.m⁻². Nine patients demonstrated no or mild clinical evidence of congestive heart failure (Killip class I or II) during the acute phase of their illness, which had cleared by the time of imaging.

No patient was studied during the hyperacute stage of infarction. The average time from the onset of symptoms to PCT imaging was 2.9 weeks (range 2 days to 13 weeks), and was not significantly different in patients with and without postinfarction angina (2.2 ± 3.0 vs 3.7 ± 3.9 weeks, respectively; NS). Three patients required i.v. unloading therapy (nitroglycerin or nitroprusside) for maintenance of a physiologic filling pressure and cardiac output or prevention of chest pain. Seven patients were receiving oral unloading agents. No patient required i.v. inotropic support during the imaging procedure and no patient was taking β-blocking drugs. No patient experienced chest pain during the study period. In the nine patients with postinfarction angina, the average time from the last episode of chest pain to imaging was 20.2 hours (range 2–56 hours).

Additional clinical information is listed in table 1.

Control studies were performed in normal volunteers to characterize the normal distribution of perfusion and glucose utilization as determined with PCT, N-13 ammonia and FDG. The volunteers were 24–32 years old, had a normal medical history and physical examination and were without risk factors for the development of early coronary artery disease. Six were females and four were males. Body surface area in the volunteers was 1.45–2.2 m², a range that included all CAD patients evaluated.

Informed consent was obtained from all subjects before imaging.

Data Acquisition and Analysis

Sequential resting tomographic N-13 ammonia and FDG transaxial cross-sectional images were obtained in the 15 coronary artery disease patients and 10 normal volunteers during a single study period using the UCLA positron tomograph, ECAT19 (Ortec Inc.). One coronary artery disease patient underwent tomographic imaging twice; the second study was obtained after spontaneous reversal of an infarct-related regional wall motion disturbance.

After recording transmission images for correction of photon attenuation, 20–25 mCi of N-13 ammonia (half-life 9.9 minutes) were injected into a peripheral vein. Imaging commenced 3 minutes after introduction of the isotope and five or six contiguous cross-sectional images 1.0–1.5 cm apart were acquired starting at the base of the heart. Then, 10 mCi of FDG (half-life 109.8 minutes) were administered intravenously and a 45-minute waiting period was allowed for N-13 ammonia decay, clearance of FDG from the blood pool, and transport and phosphorylation of FDG in the myocardium. Subsequently, five or six contiguous cross-sectional images were acquired at levels through the heart that were identical to those for N-13 ammonia. Identical patient positioning for both image sets was accomplished by carefully checking patient alignment using a low-power neon laser beam on the tomograph and ink dots on the patient’s chest.

Production of FDG and N-13 ammonia and characteristics and performance of the ECAT have been described. Imaging was performed at a resolution of 18 mm at full-width half-maximum of a line source. N-13 ammonia cross-sectional images were collected in the decay-compensated mode such that the time per image increased as N decayed in order to collect comparable counts per image. Each FDG image was recorded for 10–12 minutes and corrected for decay. Total acquisition times for the N-13 ammonia and FDG images were 30 and 60 minutes, respectively. Total counts in each FDG and N-13 ammonia cross-sectional image averaged 1,850,000 ± 440,000 (± srs) and 900,000 ± 340,000, respectively.

Tomographic imaging was initiated 1–2 hours after a carbohydrate-containing breakfast. Additional oral glucose (40–50 g) was given 60–90 minutes before introduction of FDG to allow better evaluation of nonischemic myocardium by increasing the ratio of normal myocardial glucose to free fatty acid utilization. Similar dietary conditions for volunteers and coronary artery disease patients were documented by obtaining blood samples for analysis of serum substrates at the time of introduction of FDG. Serum free fatty acids and lactate concentrations were not signifi-
### Clinical Characteristics of Coronary Artery Disease Patients

<table>
<thead>
<tr>
<th>ECG site of infarction</th>
<th>Anginal status</th>
<th>Stenotic coronary arteries</th>
<th>Regional &amp; global ventricular performance</th>
<th>Results of PCT imaging</th>
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</thead>
<tbody>
<tr>
<td>Pts without tracer discordance</td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
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<td>LVEF 0.52 (CA)</td>
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<td>Rest angina</td>
<td>RCA</td>
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<td>7</td>
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<td>Rest angina, anterior ECG changes</td>
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<td>LVEF 0.47 (RA)</td>
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</table>

Clinical and tomographic findings are listed for all 15 CAD patients. Only coronary arteries with significant stenoses are listed.

Abbreviations: Ant = anterior; Lat = lateral; Inf = inferior; Sep = septal; R = remote; LAD = left anterior descending coronary artery; Circ = circumflex coronary artery; RCA = right coronary artery; Hypo = hypokinetic; Ak = akinetic; RV = right ventricular; LVEF = left ventricular ejection fraction; CA = contrast left ventricular cineangiography; RA = radionuclide angiography; Isch = ischemia; LBBB = left bundle branch block; MI = myocardial infarction; PCT = positron computed tomography; RWM = regional wall motion.

Significantly different in normal volunteers and postinfarction patients. Infarct patients had significantly higher serum glucose levels than the volunteers (116 ± 20 vs 96 ± 15 mg%, p < 0.05). The magnitude of this difference is of doubtful physiologic significance and would not serve to enhance regional differences in normal and ischemic glucose utilization.23

Visual interpretation of the tomographic images can be accomplished with excellent interobserver agreement.24 However, at the resolution available with the existing tomograph, recovery of tissue tracer concentrations in PCT images depends on object size (partial volume effect).25 Detected wall thickness in the left ventricle varies because of the different angles with which specific myocardial segments traverse the tomographic image plane; therefore, the partial volume effect in conjunction with patient motion can produce changes in regional tracer activity in normal myocardium that can be misinterpreted as reflecting either infarction or ischemia. To prevent this, we used the PCT
images from the 10 normal volunteers to develop criteria for excluding regional changes in FDG and N-13 ammonia tissue concentrations produced by the partial volume effect and subject motion in normal myocardium. Regional tracer concentrations were generated by placing multiple contiguous 0.43-cm² regions of interest circumferentially along the left ventricular wall by interactive computer techniques. After operator identification of the center of the left ventricular cavity, each FDG and N-13 ammonia cross-sectional image was divided into 12–30° sectors containing up to 10 regions of interest (figs. 1 and 2). The mean values and population standard deviations for FDG, N-13 ammonia and FDG minus N-13 ammonia tissue concentrations were computed for each sector by pooling the corresponding regional data determined by matching plane and sector number for all 10 normal volunteers. Although random sectors were observed with tracer concentrations or differences exceeding 2 standard deviations from their respective means, no normal subject had regional reductions in both FDG and N-13 ammonia concentrations or positive difference in FDG minus N-13 ammonia concentration that deviated by more than 2 standard deviations from the corresponding mean sector value in two contiguous sectors (a total of 60°, or one-sixth of a complete transaxial cross section). Therefore, based on the hypothesized metabolic differences in moderately ischemic and infarcted myocardium, a myocardial segment in the coronary artery disease patients was identified as infarcted on PCT images if there was a regional reduction in both FDG and N-13 ammonia concentrations by more than 2 standard deviations below the corresponding mean sector value as determined in the normal subjects in at least two contiguous 30° sectors. Similarly, myocardial regions were classified as ischemic on PCT images if the positive difference in FDG minus N-13 ammonia concentration exceeded the corresponding mean FDG minus N-13 ammonia sector value in normal subjects by at least 2 standard deviations in two or more contiguous 30° sectors. The results obtained in the coronary artery disease patients using these criteria developed in normal subjects were then compared to clinical data as described below.

Statistical differences between groups were determined with the t test for unpaired data.

Cardiac Catheterization

Coronary arteriography and left ventricular cineventriculography were performed within an average of 14 days (range 1–60 days) of PCT imaging in 12 of the 15 coronary artery disease patients. The angiographic data were interpreted by the responsible angiographer, who was unaware of the results of PCT imaging. Coronary artery narrowings causing greater than a 70% reduction in luminal diameter were considered critical. Regional wall motion was analyzed from a right anterior oblique ventriculogram as normal, hypokinetic or akinetic. In the three patients who did not undergo cardiac catheterization, regional wall motion was analyzed in similar fashion from left anterior oblique and anterior equilibrium gated cardiac blood pool images. In the seven patients who did not undergo catheterization within 10 days of PCT imaging, potential changes in regional ventricular performance were excluded by evaluating radionuclide ventriculograms obtained within 10 days of tomographic evaluation and comparing the results with those of contrast ventriculography.

Results

Normal Myocardium Assessed with PCT, FDG and N-13 Ammonia

Figure 2 shows corresponding N-13 ammonia and FDG cross-sectional images and the corresponding superimposed normalized regional distribution of tissue FDG and N-13 ammonia tissue tracer concentrations obtained in a normal volunteer. Visual inspection of the cross-sectional images reveals a reasonably uniform distribution of FDG and N-13 ammonia tissue concentrations throughout the left ventricular wall. Although activity is also present in the right ventricle, the disproportionately lower perfusion, metabolism and mass of the right ventricular myocardium account for its poor visualization in these images of a normal heart. Analysis of the normalized regional tissue tracer concentrations confirms the homogeneous tracer distribution in two of three cross-sectional image pairs (panels 2c and 3c). Variations in both FDG and N-13 ammonia activities are also present in the normalized regional activities from the first cross-sectional image pair (panel 1c) because of the partial volume effect. However, because the partial volume effect affects the detection of each tracer in corresponding myocardial segments equivalently, the fluctuations in regional FDG and N-13 ammonia activities occur in parallel.

Figure 3 shows the application of regional criteria
for infarct and ischemia identification developed from the pooled data of all 10 volunteers to the first pair of cross-sectional images in figure 2. Consistent with the absence of infarction in the young volunteer, the regional tissue concentrations for both FDG and N-13 ammonia fall well above the corresponding criteria for infarct identification. Similarly, the positive difference between regional FDG and N-13 ammonia concentrations is considerably less than the corresponding criteria for identification of ischemic glucose utilization.

In eight of the 10 volunteers, patterns of regional FDG and N-13 ammonia tissue distributions were similar to those in figure 2. However, in two normal subjects, visual assessment of the images revealed a discordant increase in FDG tissue concentration relative to N-13 ammonia in the inferolateral wall of the left ventricle. The partial volume effect in conjunction with patient motion and the difficulty of evaluating the inferior wall with transaxial tomography probably account for these findings. The results from these two normal subjects were included in the pooled data used to develop regional criteria. Therefore, greater tracer discordance was required to identify ischemia in inferolateral segments than in other myocardial segments (fig. 3b).

**Myocardial Infarction Assessed by PCT and N-13 Ammonia**

Fourteen of the 19 documented infarctions (17 re-
cent, two remote) in the 15 coronary artery disease patients were identified by visual assessment of the tomographic images and analysis of normalized regional tracer concentrations as areas with concordant reductions in FDG and N-13 ammonia activities consistent with myocardial infarction (figs. 4 and 5, table 1). The location of infarction identified tomographically corresponded to the electrocardiographic infarct site in the 13 infarcts in which electrocardiographic localization was possible. In two patients with recent inferior infarctions and three patients with non-Q-wave infarcts, corresponding regions with concordantly decreased tissue tracer concentrations could not be identified by visual or tracer concentration analysis. However, the latter three patients had evidence of ischemic changes by PCT, as described below.

Myocardial Ischemia Assessed by PCT, FDG and N-13 Ammonia

In 10 patients, additional regions in the left and right ventricles showed a discordant increase in FDG uptake
relative to N-13 ammonia, reflecting the presence of ischemic glucose utilization (figs. 6 and 7, table 1). In eight patients, tracer discordance was apparent by both visual assessment of the cross-sectional images and analysis of normalized regional tracer concentrations. In two patients, significant tracer discordance was detected only by analysis of the normalized regional tracer concentrations. In the patients with right ventricular tracer discordance, criteria developed for the anterior wall of the left ventricle were applied because of the similar orientation of these two myocardial regions to the tomographic image plane.

Eleven regions with ischemic glucose utilization were detected in the 10 patients (table 1). In the nine patients in whom the infarct could be localized electrocardiographically, ischemic glucose utilization was detected in the distribution of the coronary artery supplying the infarct zone in five and in a remote coronary artery in three (ischemia at a distance29). One patient had ischemic glucose utilization in both infarct and remote zones. The three patients with non-Q-wave infarctions without PCT evidence of infarction had ischemic glucose utilization in the infarct zone (fig. 8).

**Clinical Correlation of the PCT Images**

Table 1 details the clinical variables evaluated in the 15 coronary artery disease patients and the results of PCT imaging. Eight of the 10 patients with ischemic glucose utilization had postinfarction angina at rest. In contrast, only one patient without ischemic glucose utilization had postinfarction angina at rest. In the five patients with transient ECG changes during pain, the area of significant tracer discordance on the PCT images reflecting ischemic glucose utilization correlated with the ischemic zone determined from the ECG. All eight patients with ischemic glucose utilization in whom regional wall motion analysis could be performed in the affected zone had corresponding regional
left ventricular dysfunction (figs. 8–10, table 1). In the nine patients with ischemic glucose utilization who underwent cardiac catheterization, seven had three-vessel and one two-vessel coronary artery disease. All regions with ischemic glucose utilization were supplied by severely stenotic coronary arteries. Of the four patients without ischemic glucose utilization who underwent cardiac catheterization, two had one-vessel and two had two-vessel coronary artery disease. Thus, ischemic glucose utilization was positively associated with more extensive coronary artery disease (2.9 ± 0.4 vs 1.5 ± 0.6 coronary artery obstructions in patients with and without ischemic glucose consumption, respectively, \( p < 0.02 \)).

Two patients died 4 weeks and 10 days, respectively, after PCT imaging. The PCT images in the patient who died 10 days after imaging (fig. 6) were consistent with the presence of inferior and septal left ventricular infarction, ischemic but viable anterior wall and a normal lateral wall. Pathologic examination confirmed a recent, extensive nontransmural septal infarction, a remote transmural inferior infarction and a hypertrophied, noninfarcted anterolateral wall. The results of PCT imaging and pathologic evaluation correlated similarly in the other patient.

**Discussion**

Three patterns of myocardial FDG and N-13 ammonia tissue distributions were detected with PCT in this study. Within the limits imposed by the partial volume effect, FDG and N-13 ammonia were uniformly distributed throughout the left ventricle in young volunteers. In patients with recent myocardial infarction, FDG and N-13 ammonia activities were reduced in infarcted myocardium, reflecting the infarct-related loss of functioning, metabolically active myocardium. In 10 of 15 coronary artery disease patients, additional zones of myocardium showed discordant increases in FDG activity relative to N-13 ammonia, which is consistent with the previously documented increased extraction of glucose in ischemic myocardium. Alterations of perfusion and metabolism detected with PCT consistent with the presence of ischemic and infarcted myocardium correlated well with clinical evaluation of the coronary artery disease patients after recent myocardial infarction.

In the patient who underwent tomographic evaluation twice, a large zone of potentially reversible myocardium showed ischemic glucose utilization and abnormal regional function in studies obtained early after infarction (figs. 8–10). Six weeks after infarction, this zone had spontaneously reverted to normal glucose utilization and contraction. These observations suggest that PCT evaluation of regional glucose utilization and perfusion might be used to assess tissue viability after an ischemic event.

The magnitude of the changes in regional tracer concentrations reflecting both infarction and ischemia exceeded comparable deviation in corresponding regional tissue tracer concentrations in the 10 volunteers, providing evidence that the changes were due to abnormalities of metabolism, rather than to the partial volume effect and patient motion. Young, normal volunteers were chosen to evaluate the significance of the partial volume effect and subject motion in normal hearts because of the difficulty in excluding latent coronary artery disease with routine clinical evaluation in age-matched controls and the existence of electrocardiographic, perfusion and contraction abnormalities in patients with normal coronary arteries undergoing coronary arteriography. The use of young volunteers is justifiable because the partial volume effect and patient motion are limitations inherent in current PCT, are independent of age and apply equally to normal controls and coronary artery disease patients. Furthermore, because the partial volume effect affects detection of both FDG and N-13 ammonia equivalently in corresponding myocardial regions, alterations in ventricular geometry due to regional infarction in the coronary artery disease patients cannot account for the discordant uptake of FDG relative to N-13 ammonia. Although the effect of ventricular dilatation and regional dyssynergy on regional tracer detection and infarct identification cannot be addressed from the present data, the correct identification of 14 of 19 recent and remote infarctions suggest that this is not a major
problem. Quantification of regional exogenous glucose utilization using higher-resolution tomographs will reduce problems due to the partial volume effect.12

The interpretation of regionally discordant increases in FDG accumulation relative to N-13 ammonia as indicative of ischemic glucose consumption is based on the continued or accelerated utilization of glucose under conditions of inadequate perfusion documented in both patients with coronary artery disease and in experimental myocardial ischemia.13, 32-36 However, under experimental conditions, documentation of maintained or accelerated metabolism of glucose despite inadequate perfusion has been obtained only during ischemia produced by modest flow reductions and, more recently, during ischemia produced by excessive oxygen demand.34, 35 During experimental myocardial ischemia produced by severe restrictions in perfusion, glucose metabolism is not maintained, presumably because of the inability to wash out inhibitory metabolic end products.36 Although it is unclear whether extreme reduction of myocardial perfusion is consistent with reversible myocardial ischemia, this experimental observation suggests that failure to observe a discordant increase in FDG relative to N-13 ammonia with PCT

**Figure 8.** Positron computed tomographic (PCT) evaluation of relative regional perfusion and exogenous glucose utilization 2 days (1a, 1b, 2a, 2b, 2c) and 6 weeks (3a, 3b, 3c, 4a, 4b, 4c) after anterior subendocardial infarction in a patient who had a spontaneous return of normal regional function in the infarct zone. All four cross-sectional images are through the body of the left ventricle. In the early postinfarction image, FDG and N-13 ammonia cross-sectional images, a discordant increase in FDG tissue concentration relative to N-13 ammonia suggestive of ischemic glucose metabolism is apparent in the anterior wall of the left ventricle (arrows). In contrast, in the PCT images obtained 6 weeks after infarction, the discordant increase in FDG accumulation relative to N-13 ammonia has disappeared. Despite the documented infarction, no region can be identified in either the early or late postinfarction images with concordant reductions of both FDG and N-13 ammonia uptake suggestive of myocardial infarction.
does not exclude the presence of ischemia due to severely reduced coronary blood flow.

We evaluated exogeneous glucose utilization using FDG, a glucose analog that is transported into the cell and phosphorylated competitively with glucose. However, the end product, FDG-6-PO₄, is not a substrate for other glycolytic enzymes or glycogen synthesis and remains trapped in the cell. Therefore, the net accumulation of myocardial FDG-6-PO₄ over a specific time period (e.g., 45 minutes) reflects the steady-state extraction and phosphorylation rate of exogeneous glucose. Phelps, Huang and co-workers developed an extension of the tracer kinetic model originated by Sokoloff et al. for ¹⁴C-2-deoxyglucose and validated its use for the measurement of cerebral glucose utilization using FDG and PCT. Recently, these observations have been extended to the heart under a wide range of nonischemic and ischemic conditions. Although the use of PCT and FDG to quantitatively measure regional myocardial exogenous glucose utilization requires further validation under more varied conditions of substrate supply and metabolic rate, available evidence supports the use of the current approach under the conditions encountered in this study.

N-13 ammonia accurately measures relative regional perfusion under a variety of physiologic and ischemic conditions. Its ability to measure regional blood flow is based on its high, relatively constant extraction and subsequent metabolic trapping in the myocardium. However, N-13 ammonia slightly underestimates perfusion during myocardial ischemia because of a small decrease in extraction fraction. Therefore, an alternative explanation for the observed discordance between FDG and N-13 ammonia uptake in the present study is that regional perfusion was underestimated by N-13 ammonia in ischemic myocardium. Although this possibility cannot be totally excluded, evidence against this interpretation is that the small decrease in extraction fraction during myocardial ischemia (< 5%) cannot account for the magnitude of the discordance between FDG and N-13 ammonia uptake observed in this study. In addition, tracer discordance was not observed routinely in electrocardiographically identified infarcted myocardium with equal or greater flow reductions.

In 10 of 15 patients with severe coronary artery disease who had a recent myocardial infarction, abnormalities of perfusion and metabolism consistent with ischemia were identified.
with myocardial ischemia were detected with FDG, N-13 ammonia and PCT an average of 20.2 hours after chest pain. Numerous reports using both diffusible and ion-atomic indicators of perfusion have documented decreased global and regional perfusion in patients with severe coronary artery disease without evidence of infarction or acute ischemia. More recently, regional lactate production has been observed in patients with coronary artery disease without evidence of acute ischemia that correlated with the severity of coronary artery obstruction. The results of these previous, independent investigations support the use of FDG, N-13 ammonia and PCT to evaluate the presence of ischemic glucose utilization in patients with severe coronary artery obstruction in between episodes of acute chest pain.46, 47

A dual tracer approach combined with PCT imaging has been employed in this investigation to provide information about two separate physiologic processes, myocardial perfusion and glucose utilization. In contrast, thallium-201 perfusion imaging and technetium-99m radionuclide ventriculography each evaluate a single physiologic process: perfusion and function, respectively. Although myocardial perfusion imaging and radionuclide ventriculography have been used to differentiate regional wall motion disturbances due to ischemia from those due to infarction, both techniques are frequently used in conjunction with exercise and do not reliably distinguish resting myocardial ischemia from infarction. Application of single-photon tomographic techniques and quantitative analysis of tracer kinetics to radionuclide evaluation of ventricular performance and perfusion might improve diagnostic and functional assessment of patients with coronary artery disease. However, in contrast to single-photon techniques, differentiation of resting myocardial ischemia and infarction through the near-simultaneous evaluation of regional myocardial perfusion and glucose utilization requires the use of appropriate tracers labeled with short-lived, positron-emitting isotopes and PCT.

Because the dual-tracer, tomographic approach is noninvasive and unique in its ability to differentiate resting myocardial ischemia and infarction, there are important and extensive clinical applications of this technique in patients with coronary artery disease. In patients with acute myocardial infarction, considerable financial and human resources are being invested in attempts to salvage ischemic myocardium. However, maneuvers designed to salvage jeopardized myocardium by increasing oxygen supply or decreasing oxygen demand assume that reversibly ischemic tissue is still present at the time the intervention is made. This assumption is undocumented in humans. Identification of zones with ischemic glucose utilization and evaluation of the natural history of these regions with PCT in acute infarct patients might serve as a basis for performing and evaluating the effectiveness of specific therapeutic interventions. In patients undergoing coronary artery bypass surgery, the decision to bypass stenotic coronary arteries supplying dysynergic myocardial segments assumes that the loss of myocardial contractility is due to reversible ischemia. Preoperative resting evaluation of such regions with FDG, N-13 ammonia and PCT to identify the presence of ischemia-related glucose utilization or infarct-related absence of glucose utilization in the basal state might provide unique pathophysiologic information about the significance of resting regional ventricular dysfunction not available with rest-exercise myocardial perfusion imaging or radionuclide ventriculography.

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References
41. Mymin D, Sharma GP: Total and effective coronary blood flow in...
Effects of Ischemic-like Insult on Myocardial Thallium-201 Accumulation

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SUMMARY Despite extensive clinical use of thallium-201 (201Tl) for myocardial imaging, the effect of ischemia on myocardial accumulation and release of 201Tl independent of flow has not been fully defined. Therefore, myocardial accumulation of 201Tl in response to ischemic-like myocardial injury was assessed in vitro using the cultured fetal mouse heart preparation. Cultured fetal mouse hearts (n = 311) were subjected to injury simulating ischemia by deprivation of oxygen and oxidizable substrates for periods ranging from 15 minutes to 10 hours. The extent of irreversible injury was determined by the percentage of lactate dehydrogenase (LDH) lost from the hearts to the culture medium during recovery from injury. Injury was essentially reversible at 1 hour of insult. The fraction of 201Tl content in injured compared with control hearts was not significantly lower after 1 hour of insult. By 3 hours of insult, irreversible injury as assessed by loss of LDH was detectable and the extent of injury increased progressively through 10 hours. During the 3-10-hour period of irreversible injury, 201Tl accumulation within injured hearts compared with controls was related in a monotonically decreasing fashion to the loss of LDH as described by a mathematical kinetic model that fit the observations closely (R² > 0.99). These results indicate that in this organ culture preparation, in which there is effectively an unlimited reservoir of 201Tl and no confounding effects of perfusion, the time-dependent 201Tl accumulation is determined by the extent of irreversible injury.

THALLIUM-201 (201Tl) is widely used as a myocardial perfusion imaging agent for the detection of coronary artery disease and myocardial infarction. Nevertheless, because of the confounding effect of perfusion on myocardial 201Tl availability, the direct impact of ischemic damage on myocardial accumulation of 201Tl has not been fully defined. Studies of myocardial 201Tl accumulation in dogs and man do not allow differentiation between the effects of reductions in coronary blood flow and the intrinsic ability of the myocardium to extract the tracer.

We used the cultured fetal mouse heart preparation to study the direct impact of ischemic-like injury on accumulation of 201Tl by diffusion. This organ culture preparation does not depend upon blood flow to provide metabolic substrate. Instead, each heart is placed on a stainless-steel grid at a gas-medium interface and is supplied with nutrients by diffusion from the culture medium. Thallium-201 availability is essentially unlimited because the hearts are bathed in a relatively large volume of thallium-containing culture medium. Therefore, myocardial 201Tl accumulation

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Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, 18F-labeled fluorodeoxyglucose and N-13 ammonia.
R C Marshall, J H Tillisch, M E Phelps, S C Huang, R Carson, E Henze and H R Schelbert

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