Regional Assessment of Myocardial Metabolic Integrity in Vivo by Positron-emission Tomography with \(^{11}\text{C}\)-labeled Palmitate

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SUMMARY To determine whether positron emission tomography (PET) after the combined administration of \(^{11}\text{C}\)-palmitate intravenously to image myocardium and \(^{14}\text{CO}\) by inhalation to image the cardiac blood pool with \(^{14}\text{CO}\)-hemoglobin provides quantitative delineation of the locus and extent of myocardial infarction, 28 patients with suspected myocardial infarction were studied. Twenty-one patients had electrocardiographically documented transmural infarction and in seven, the diagnosis of infarction was ultimately excluded based on enzymatic and electrocardiographic criteria. To assess reproducibility, four patients were studied on two occasions 1 month apart. Inferior and apical infarcts were readily localized with sagittal and coronal as opposed to transaxial reconstructions. Complete electrocardiographic and tomographic concordance was observed for the locus of all transmural infarcts. Reproducibility of tomographic estimates was within 10%. Tomographic estimation of the extent of infarction with \(^{11}\text{C}\)-palmitate in a subset of patients in whom right ventricular contributions to overall enzyme release could be excluded was facilitated by delineation of the endocardial border with the \(^{14}\text{CO}\)-hemoglobin cardiac blood pool image in the same plane. The correlation between enzymatic (serial plasma MB-CK method) and tomographic estimates of infarct size was close \((r=0.92)\). Thus, as has been shown in experimental animals, PET with \(^{11}\text{C}\)-palmitate permits quantification and localization of myocardial infarcts in patients.

THE EXTENT of myocardium undergoing irreversible injury is an important determinant of prognosis after acute myocardial infarction.\(^{1-8}\) Because it may be possible to limit the extent of infarction during its early evolution,\(^{8-10}\) accurate, reliable and serially applicable objective indexes are needed to define both the extent of tissue jeopardized by ischemia and the magnitude of irreversible injury evolving ultimately.

During the past several years we have been exploring the possibility of assessing the metabolic integrity of myocardium quantitatively and noninvasively by positron tomography with radioactively labeled metabolic substrates of myocardium, based on the premise that prolonged depression of regional myocardial metabolism will quantitatively reflect underlying pathology.\(^{11-13}\) The application of this approach requires that the fate of the labeled substrate and of the radioactive label itself reflect changes in endogenous metabolites indicative of the altered metabolic state — a condition best fulfilled by radionuclides with chemical identities akin to physiologic substrates such as \(^{13}\text{C}, \(^{15}\text{O}\) and \(^{15}\text{N}\), in contrast to the case when substrates such as fatty acids are labeled with an atom such as \(^{15}\text{F}\).\(^{14,15}\) The brief physical half-lives of these radionuclides \((\text{\(^{13}\text{C}\)-20 minutes, \(^{15}\text{N}\)-10 minutes, \(^{15}\text{O}\)-2 minutes})\) permit repeated measurements within a brief interval and delivery of only a modest dose of radiation to the patient. Unfortunately, because of their fleeting existence, these isotopes must be prepared in the immediate vicinity of their application, generally requir-
ing a cyclotron on site.14 On the other hand, quantification of the spatial and temporal distribution of such radionuclides is facilitated considerably by positron emission tomography (PET).16 17

Delineation of regional metabolic integrity of the heart provides information fundamentally different from that obtained with techniques such as transmission computer-assisted tomography (x-ray CT scanning). Transmission CT permits better resolution and more definitive delineation of anatomic detail and is therefore particularly useful for defining structural relationships or, with contrast-medium enhancement, for characterizing vascular structures and their patency.18 However, metabolic changes induced by ischemia and the early evolution of infarction are not accompanied by marked changes in x-ray attenuation of tissue. Delineation of metabolic changes such as those contributing to cardiomyopathy may permit early recognition of cellular dysfunction and facilitate diagnosis, assessment of the efficacy of therapy and characterization of pathogenesis.

The preferred substrate of myocardium is fatty acid.19 The extensive information already available regarding uptake, transport, accumulation, oxidation and overall metabolism of fatty acid extracted from the blood by the myocardium indicates that net accumulation of fatty acid is closely coupled to fatty acid oxidation.20 Under conditions of constant coronary perfusion, externally detectable diminished uptake of \(^{11}\text{C}\)-palmitate is a concomitant of ischemia sufficiently prolonged to impair myocardial metabolism, but not of the reduced perfusion per se.20, 21 This diminished uptake reflects the metabolic consequences of decreased perfusion.21 Diminished accumulation of \(^{11}\text{C}\)-palmitate in regions of myocardial ischemia in vivo in canine hearts is readily detectable with PET.19 after intravenous injection of the tracer, and quantitatively reflects morphometrically and enzymatically determined infarct size 48 hours after coronary occlusion (\(r = 0.97\)).10 11 However, results in experimental animals with infarction cannot be translated directly to the clinical setting for several reasons, including: differences between humans and dogs in the anatomy of the coronary vasculature, the fact that infarction in patients is frequently not associated with complete occlusion of a coronary artery, and the well-recognized different rates of evolution of tissue injury in the two species.

The net amount and distribution of \(^{11}\text{C}\)-palmitate extracted into cardiac lipids are altered within ischemic zones. A larger fraction of the palmitate initially extracted is deposited in triglyceride, but the net amount of palmitate accumulated by ischemic myocardium early after its intravenous administration is markedly reduced.22 Nevertheless, preliminary results with PET in patients with prototype instrumentation23 identified several problems requiring solution before accurate quantification could be expected, including the need for: 1) delineation of the blood pool in contrast to mural myocardium, 2) simultaneous acquisition of data from enough regions of the heart to permit reconstruction of a large series of sections within a reasonably brief imaging interval, 3) reconstruction in sagittal and coronal as well as transaxial planes for patients with inferior or posterior infarctions, and 4) development and verification of an algorithm for quantifying infarction in each section, with results verified by comparison with an independently acquired index of the extent of tissue injury.

In view of these considerations, instruments were designed and developed to permit delineation and quantification of both the intracardiac blood pool and viable mural myocardium in coronal, sagittal and transaxial planes for use in the present study. The primary goal of this study was to determine whether PET could accurately delineate and quantify myocardial infarction by visualization and reconstruction of the entire heart, and compare the tomographic estimate of the extent of infarction with that assessed independently by analysis of plasma MB-CK time-activity curves. For this purpose, only patients whose infarction had evolved for at least 24 hours were studied, because it is likely that diminished \(^{11}\text{C}\)-palmitate uptake in jeopardized myocardium very early during the evolution of infarction would reflect a larger zone of myocardium at risk than the zone of irreversible injury ultimately sustained. The natural history of this relationship requires elucidation in future studies, for it may be useful in defining the efficacy of therapeutic interventions implemented early to protect jeopardized tissue. Because of numerous potential difficulties, especially ambiguity in identification of the time of onset of an ischemic insult responsible for a given infarction, we have elected first to examine the efficacy of PET with \(^{11}\text{C}\)-palmitate for detection of relatively completed infarctions. The problem of confusing reversible injury with irreversibly injured is probably more apparent than real, even early in the course of ischemic injury. Prolonged (greater than several hours) diminution of metabolic function reflected by persistently decreased \(^{11}\text{C}\)-palmitate uptake and readily detectable with serial studies is probably not compatible with myocardial viability based on results from several studies.11

**Methods**

**Patients**

Twenty-eight patients (23 males and five females) admitted consecutively to the Barnes Hospital Cardiac Care Unit who survived suspected acute myocardial infarction for at least 24 hours and who were willing to provide informed consent were evaluated by PET. Twenty-one subjects (mean age 57 years [range 26–84 years]) had transmural myocardial infarction characterized by evolution of new Q waves or loss of R-wave amplitude on the ECG and characteristic serial changes in plasma MB-CK activity in samples collected at 2-hour intervals for 12 hours and at 4-hour intervals for an additional 60 hours. Data obtained from a subset of the 13 patients who had initial anterior, anterolateral, lateral or apical infarction, based on history and electrocardiographic criteria at
the time of admission, were used to evaluate the quantitative accuracy of tomographic compared with enzymatic estimations of infarct size. This group was selected so that potential contributions to the tomographically detectable lesions could be excluded from previous remote myocardial infarctions that were not assessed enzymatically. To assess the reproducibility of tomographic estimates of infarct size, four patients were studied initially an average of 5 days after the onset of infarction (range 2–10 days) and again 1 month later. To determine whether systematic differences occurred between tomographic and enzymatic estimates as a function of time after the onset of acute myocardial infarction, two groups of patients were studied at two general intervals. Seven were imaged an average of 5 days after infarction (range 2–10 days) and six were imaged substantially later, an average of 2.5 months after infarction (range 1–6 months).

An additional group of seven subjects without clinical, electrocardiographic or enzymatic evidence of infarction and without objective evidence of remote or recent myocardial injury were studied to permit comparison of tomograms from patients with and without infarction and to identify potential false-positive results with the algorithm used for defining zones of metabolically compromised tissue. A third group of six patients with electrocardiographically demonstrable transmural infarction was included to determine whether PET provided adequate delineation of such zones in sagittal and coronal reconstructions. This group was not used for comparison of enzymatic and tomographic estimates of infarction because enzymatic estimates in such patients are influenced by contributions to enzyme release from concomitant right ventricular wall damage.24 Thus, the patients with inferoposterior infarction, as well as two patients with nontransmural (defined electrocardiographically) or with repeat infarction, were included primarily to explore the potential of PET in detecting and localizing the insult.

Tomographic Imaging Procedure

Labeling with Carbon-11

\(^{13}\)C-palmitate was prepared from cyclotron-produced \(^{13}\)CO\(_2\) as described previously.25 In order to label the blood pool, \(^{13}\)CO-labeled carboxyhemoglobin (\(^{13}\)CO-hemoglobin) was formed in vivo by permitting the patient to inhale 5–10 mCi of \(^{13}\)C-labeled carbon monoxide prepared as previously described.26

The Detection System

After intravenous administration of approximately 20 mCi of \(^{13}\)C-palmitate bound to 250 mg of human serum albumin in a total volume of 10 ml over an interval of approximately 30 seconds, detection of the distribution of tracer within the heart is accomplished with a positron emission transaxial tomograph (PETT IV),27 which provides data during each single imaging interval and permits reconstruction of seven sections of the heart.

During all tomographic studies, careful monitoring of the ECG and vital signs is maintained and the patient is constantly attended by a physician. Alignment and positioning of the patient within the hexagonal detector array of the PETT IV system is accomplished and maintained constant by means of two fixed laser beams spanning a 10-cm line from 1 cm inferior to the apex of the heart to the second intercostal space.27

The PETT IV system has 48 NaI(Tl) scintillation detectors in a hexagonal array with groups of eight detectors that constitute banks mounted on a gantry permitting programmed rotational and rectilinear motion controlled by an interdata computer. Coincidence events are detected between each detector and the eight detectors on the opposing bank, producing 64 coincidence lines per pair of opposing sides, or a total of 192 (64 x 3) coincidence lines for each position of the system. Data are obtained for each of 240 positions of the detectors during an imaging interval of approximately 6–15 minutes. PETT IV yields seven transverse images simultaneously.

Tomographic measurements are initiated 3 minutes after completion of the injection of the tracer to permit sufficient time for clearance of \(^{13}\)C-palmitate from the blood pool. In these studies, PETT IV is operated with a resolution of 13.5 mm FWHM (full width at half maximum) in the plane of the section, for a section thickness of 16 mm. After sufficient data have been obtained to permit reconstruction of the first set of seven sections, the patient is moved (indexed) by 9.5 mm in a cephalad direction on a mobile table. Imaging is then continued to provide reconstruction of seven additional, interlaced tomographic sections. The total reconstruction of 14 sections provides tomographic definition of a region with a total height of 12.35 cm, of which the heart typically occupies 6–7 cm. The time course of a typical tomographic study and the total number of counts obtained in the sections reconstructed are shown in table 1.27 Radiation exposure associated with administration of \(^{13}\)C-palmitate to a patient is shown in table 2, which also

| Table 1. Scanning Time and Number of Counts Per Section Obtained During a Typical \(^{13}\)C-palmitate Cardiac Study with PETT IV |
|-----------------|-----------------|-----------------|
| Section | Scan 1 | Scan 2 |
| 1 | \(503 \times 10^3\) | \(606 \times 10^3\) |
| 2 | \(725 \times 10^3\) | \(955 \times 10^3\) |
| 3 | \(851 \times 10^3\) | \(1174 \times 10^3\) |
| 4 | \(1252 \times 10^3\) | \(1637 \times 10^3\) |
| 5 | \(1188 \times 10^3\) | \(1495 \times 10^3\) |
| 6 | \(1218 \times 10^3\) | \(1355 \times 10^3\) |
| 7 | \(833 \times 10^3\) | \(823 \times 10^3\) |
| Total | \(6570 \times 10^3\) | \(8945 \times 10^3\) |

Patient 65, studied 3 weeks after infarction; activity administered: 23 mCi \(^{13}\)C-palmitate; scanning time: scan 1–6 minutes; scan 2–12 minutes.
left ventricular wall thickness, the extent of infarction in each transverse section was quantified by outlining on the grid the total area of infarction in both the endocardial and epicardial borders of the left ventricular wall; an extrapolated epicardial border was used for regions in which 11C-palmitate uptake was less than 50% of maximum (i.e., regions of presumed epicardial infarction) (fig. 1). A region of infarction was defined as one with 11C-palmitate uptake less than 50% of maximum uptake anywhere in the left ventricular wall after all values had been corrected for background radioactivity (see below). This approach is based on morphometric correlations obtained in studies with dogs. Values for radioactivity in regions of defects were used to calculate the overall volume of the region of the infarction (infarct size in PET gram-equivalents [PET g-Eq]) according to the following formula:

$$V_i = \frac{100 - a_i}{100} \times \left[ \frac{g}{cm^3} \right]$$

where $n$ is the number of transverse sections with a defect, $V$ is the volume of infarction in a section (i) calculated from the thickness of each section multiplied by the total area of the defect (defined as the region exhibiting activity less than 50% of maximal left ventricular activity), and $n$ is the average activity within the entire region of the defect in a section (i) expressed as a percentage of maximum activity in left ventricular myocardium, with both corrected for background. The volume of the defect was converted to grams of myocardium, assuming a specific density of tissue to be 1 g/cm$^3$. The use of this formula introduces a modification into the overall estimate of the region of infarction based on the magnitude of depression of radioactivity throughout the entire region compared with activity in normal myocardium. Thus, total infarct volume was calculated by summing the mass of infarction in each section after adjustment of the total area involved in outlined portions exhibiting less than 50% of maximal ventricular myocardial radioactivity by a factor taking into account the extent of depression of 11C-palmitate uptake throughout the region (fig. 1).

Background radioactivity was estimated from 11C-palmitate activity in an area in each section selected from the center of the left ventricular chamber (sic) to correct for 11C-palmitate activity remaining in the blood pool.

Infarct size estimated in this fashion provides a value expressed as the mass of tissue exhibiting diminution of radioactivity equivalent to a mass exhibiting complete and homogeneous lack of uptake of tracer expressed as a percentage of maximal uptake in normal myocardium. Accordingly, the results are expressed in units referred to as PET-gram-equivalents (PET-g-eq). Such estimates were compared with estimates obtained from analyses of plasma MB-CK time-activity curves in which infarction is expressed in terms of CK-gram-equivalents.
Enzymatic Estimation of Infarct Size

Infarct size was estimated by analysis of serial changes in the activity of the MB isoenzyme of creatine kinase (CK) in plasma samples obtained every 4 hours as previously described.\textsuperscript{28, 29} Despite unavoidable limitations of this approach, enzymatic estimates of infarct size have correlated closely with CK depletion after coronary occlusion measured directly in the hearts of experimental animals,\textsuperscript{30} microscopic and ultrastructural criteria of infarction,\textsuperscript{31} regional ischemia detected with microspheres\textsuperscript{32} and other biochemical and morphologic criteria of the severity of ischemic injury. In patients, enzymatically estimated infarct size has been found to correlate with the severity of impaired ventricular function,\textsuperscript{3} cardiac electrical instability,\textsuperscript{2} and morbidity and mortality,\textsuperscript{3} as well as morphologic criteria of the extent of infarction among those dying under conditions in which complete plasma enzyme time-activity curves were available and a protracted agonal interval was not present before either death or postmortem evaluation of the heart.\textsuperscript{33}

Results

Tomography in Normal Subjects

The time course of concentration of carbon-11 activity per gram of myocardium, liver, and blood after injection of $^{11}$C-palmitate is shown in figure 2. Activity in myocardium and liver was assessed with the PETT IV system and activity in blood samples obtained from an antecubital vein assayed with a well-type scintillation counter. Activities in blood, myocardium and liver were compared by means of
Figure 2. Time-activity curves reflecting the concentration of carbon-11 activity per gram of myocardium, liver and blood beginning 3 minutes after intravenous administration of $^{11}$C-palmitate to a human subject (#P-27) without known cardiovascular disease. The term "washout" in the figure refers to the decline in activity due to combined processes, including physical washout via the circulation and loss of radioactivity from the fields of view due to conversion of the $^{11}$C-palmitate to $^{11}$CO$_2$ and its diffusion. Activity at each interval is corrected for physical decay of the tracer.

Calibrations obtained by well-counter determinations of activity in an aliquot of the material used in the PETT IV phantom. These data show the rapid disappearance of carbon-11 activity from the blood and the relatively slow rate of washout of activity from the myocardium in a normal subject. It is necessary, of course, to complete the tomographic reconstruction of the distribution of $^{11}$C-palmitate in myocardium before a late rise of carbon-11 activity in blood (due to release of short-chain catabolites of hepatic fatty acids) can occur.

Figure 3 shows two images from the PET reconstruction of the heart from a normal subject. For comparisons, two sections of the chest of a cadaver at nearly comparable levels are also displayed. The PET images clearly resolve the outlines of the left ventricle, but the right ventricular wall is not depicted clearly, probably because of both its thinness and lower metabolic rate (secondary to more modest pressure generation and oxygen requirements) compared with the left ventricle. The membranous ventricular and atrial septa are not visualized, as anticipated, because of their very low overall metabolic rate. In transverse sections at the level of the atroventricular valves, $^{11}$C-palmitate is not taken up posteriorly because the thin valve apparatus and atrial wall, with their low metabolic rates, constitute the cardiac border at this level.

Figure 4 shows eight of 14 PET images from a normal subject. The large organ to the right of the heart is the liver, which accumulates a substantial amount of $^{11}$C-palmitate. All of the images encompassing the heart are included within a vertical distance of only 6.65 cm. The section adjacent to the most inferior one through the cardiac apex resolves the cardiac cavity only poorly, because the overall thickness of this section (16 mm) encompasses both confluent myocardium and the tip of the left ventricular chamber. Although a zone of infarction may be apparent on a
PET image obtained after intravenous injection of $^{11}$C-palmitate, the extent of the lesion may be difficult to assess if the outlines of the ventricular chambers are not well delineated. To overcome this potential difficulty, we visualized the left and right ventricular cavities by PET imaging of blood labeled with $^{11}$C-carboxyhemoglobin. The comparison of images obtained in this fashion with those related directly to myocardium that accumulates $^{11}$C-palmitate permits improved delineation of the endocardial border. When the $^{12}$CO-hemoglobin and $^{11}$C-palmitate images are superimposed by computer and exhibited in two colors (fig. 5), the homogeneous nature of $^{11}$C-palmitate in mural left ventricular myocardium in a normal subject is evident, as is the typical endocardial border depicted by the interface between them. The $^{11}$CO-blood-pool image shows a clear separation between right and left ventricular cavities. Blood in the right atrium located immediately posterior to the right ventricle contributes to the larger cross-sectional area of the right side of the heart compared with that of the left. This appearance is accentuated in the more cephalad transverse views because the right atrium is a major constituent of the cardiac cross section at these levels. The membranous portion of the interventricular septum is not visualized and the interventricular and interatrial septa have the continuity expected from their anatomic relations. The same geometric relationships are evident in cross sections of a cadaver at corresponding levels. Blood in the descending aorta is visualized adjacent to the vertebral column. Because the spleen traps red cells labeled with $^{11}$C-carboxyhemoglobin, it is well visualized in the caudad blood-pool tomograms.

A gray-scale representation corresponding to an image from a normal subject is shown in figure 1. The
TOMOGRAPHY WITH $^{11}$C-PALMITATE/Ter-Pogossian et al.

The left ventricular wall has a typical, relatively uniform thickness. The dark portion of the gray scale is used to depict the blood pool.

These features in $^{11}$C-palmitate and $^{11}$CO-hemoglobin images were evident in tomograms from all subjects without infarction. None of these seven subjects had recognizable abnormalities in images of either type.

Tomography in Patients with Myocardial Infarction

Figure 4 shows seven of 14 PET sections of the heart from a patient with transmural anterior myocardial infarction. Regions of infarction corresponding to the electrocardiographically defined locus are reflected by diminished uptake of $^{11}$C-palmitate and appear as zones of diminished activity in each section. Infarcts at different locations are shown in figure 6 in comparison with corresponding PET images obtained from one normal subject and one patient with a clinically unsuspected but electrocardiographically confirmed area of old injury anteriorly. As shown in figure 5, comparison of images obtained by $^{11}$CO-blood-pool labeling and $^{11}$C-palmitate administration permits improved delineation of zones of infarction. The endocardial border of the zone of diminished uptake is recognizable on the basis of the perimeter of the blood-pool image in the same cross section. In ad-

Figure 5. Two-color superimpositions of PETT IV images obtained in a normal subject (panel A) and in patients with anteroseptal myocardial infarction (panel B) and lateral myocardial infarction (panel C) after administration of $^{11}$C-labeled palmitate (displayed in green) and, subsequently, inhalation of $^{11}$C-labeled CO (displayed in red) in each case.
dition, the dilatation of the left ventricle reflecting functional (or aneurysmal) impairment related to the infarction and the outward bulging of the wall of the heart in the region involved with infarction are evident from the blood-pool image.

Regions of inferior or apical infarction are not readily detectable by evaluation of transaxial tomographic images. However, inspection of coronal or sagittal longitudinal sections derived from data obtained during transaxial imaging, and therefore not requiring additional data acquisition, readily demonstrates zones of inferior infarction with diminished uptake of $^{11}$C-palmitate. Examples of transverse, coronal and sagittal tomographic reconstructions are shown in figure 7. Midventricular transaxial images from the patient with an apical myocardial infarction appeared completely normal. However, both the coronal and sagittal sections had decreased uptake of $^{11}$C-palmitate compared with the images from normal subjects, reflecting the electrocardiographically documented inferior region of infarction. The white lines in the transverse images identify the loci at which the coronal and sagittal reconstructions were obtained.

All patients with enzymatically detectable infarction had clearly identifiable regions of diminished accumulation of $^{11}$C-palmitate on transaxial, coronal or sagittal positron-emission tomograms.

Quantitative Considerations

When data obtained by PET are displayed with the combined use of 1) gray-scale image (displayed with a line printer) of the distribution of palmitate and carbon monoxide (fig. 1) and 2) a numerical printout of the relative distribution of $^{11}$C-palmitate in the entire left ventricular mural myocardium in the section being examined, the fraction of myocardium with diminished uptake, defined as less than 50% of the maximum uptake of activity anywhere in the left ventricle, is readily delineated (fig. 1). The gray-scale image permits delineation of the region of the image properly ascribed to mural myocardium as opposed to blood pool, and the numerical printout permits quantitative
evaluation of activity throughout the area representing mural myocardium.

Representative $^{11}$C-palmitate and $^{11}$CO-blood-pool images from a patient with a transmural myocardial infarction are shown in figure 5. Disruption of the normal ventricular contour and diminution of $^{11}$C-palmitate accumulation anteriorly is evident, and aneurysmal bulging of the left ventricular cavity in the same region is evident from the blood-pool image. Figure 5 also shows a tomogram from a patient with a lateral wall infarction. An example of a numerical printout characterizing the relative distribution of radioactivity throughout a transverse section is shown in figure 1. The relative distribution of radioactivity summed over the total scan time is indicated on a scale of 0–256 arbitrary units (PET numbers). The solid line excludes regions in which radioactivity was less than 50% of maximum activity in any region in the left ventricular wall and identifies regions of infarction. Because of the relatively uniform thickness of the normal left ventricular wall, an idealized outline can be constructed (fig. 1), and regions with diminished uptake can be described in terms of the fraction they constitute of the total left ventricular cross-sectional area within the section. The mean radioactivity in the zone in which infarction is detected is expressed as a percentage of maximum activity in a corresponding zone of normal myocardium once both have been corrected for background radioactivity, based on values obtained from the center of the $^{11}$C-palmitate image of the left ventricular chamber to permit correction for blood pool $^{11}$C-palmitate counts. This factor, i.e., the average percentage of activity within infarction zones, is used to calculate the total mass of the infarct in order to take into account the heterogeneity of tissue within the zone, because such zones are a mixture of viable and nonviable cells, both of which contribute to average radioactivity detected within a resolution element.

When tomographic estimates of the extent of infarction based on analysis of tomographic reconstructions encompassing the entire heart of each patient with transmural anterior or lateral myocardial infarction were compared with enzymatic estimates of infarct size in the same patients, all of whom had initial infarctions based on clinical and electrocardiographic criteria, the correlation between the two estimates was close ($r = 0.92$) (table 3). A comparably close correlation would not necessarily be anticipated between measurements made with these two indexes in patients with inferior or posterior wall infarctions with the tomographic assessment confined to the left ventricle, because the enzymatic estimate of the extent of infarction is influenced by the release of enzyme from the frequently concomitantly injured right ventricular myocardium.

The average value for enzymatically estimated infarct size among these patients was 58 CK-g-Eq

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**Figure 7.** Examples of transverse, coronal and sagittal tomographic reconstructions in a normal subject (left) and in a patient with an apical infarct (right) obtained with PETT IV after intravenous administration of $^{11}$C-palmitate.
TABLE 3. Tomographic Compared with Enzymatic Estimates of the Extent of Myocardial Infarction

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<th>Estimates based on plasma MB-CK time-activity curves (CK-g-Eq)</th>
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Data are arranged in descending rank order based on the values for enzymatic estimates of infarct size. The correlation for the linear regression (p < 0.001) for the two sets of data is close (r = 0.92).

(range 9–155 CK-g-Eq). The two patients with very extensive infarction had severe hemodynamic and clinical sequelae (Killip class III). In this study, neither tomographic nor enzymatic estimates of infarct size were expressed as indexes (i.e., corrected for body surface area or weight), although the correlation between values of the two indexes was as close as the correlation between the uncorrected values themselves. Correlations between enzymatic and tomographic estimates of infarct size are shown in table 3. Among the seven patients imaged early after infarction (average 5 days; range 2–10 days), the mean enzymatically estimated infarct size was 52 CK-g-Eq (range 9–153 CK-g-Eq) compared with a mean of 49 PET-g-Eq (range 13–97 PET-g-Eq) estimated by PET. In this small group, the correlation between the two estimates was close (r = 0.94). Among the six patients imaged relatively late after infarction (average 2.5 months), the corresponding values were 66 CK-g-Eq (range 17–155 CK-g-Eq), compared with 65 PET-g-Eq (range 14–109 PET-g-Eq; r = 0.91). Despite the disparate intervals at which patients were studied tomographically after occurrence of infarction and after enzymatic estimates had been obtained, the correlation between enzymatic and tomographic estimates based on results from all patients was close (r = 0.92) (PET-g-Eq = 0.6 (CK-e-Eq) + 18). The intercept of this linear regression is positive and the slope differs from unity for at least two reasons. First, potential contributions of previously ischemic tissue adjacent to zones of infarction may increase PET estimates of small infarcts relative to CK estimates. Second, large infarcts may be overestimated by the CK method (tending to decrease slope and hence increase the intercept) due to augmented washout of myocardial enzyme and decreased local degradation.

In four patients, PET was performed twice after infarction, 1 month apart, in order to evaluate the reproducibility of tomographic estimates. The average of the two tomographic estimates for each patient was 43 PET-g-Eq (range 15–57 PET-g-Eq). In this small sample, the two values that constitute the pairs of tomographic estimates from each patient differed by an average of only 1 ± 2.8 PET-g-Eq (SEM).

Discussion

Evaluation of Metabolism with 14C-Palmitate

Oxidation of long-chain fatty acids provides most of the energy required by the heart during physiologic aerobic conditions.19 Extraction of fatty acids by myocardium is 15–40% under physiologic conditions in vivo20 and varies as a function of several factors, including chain length of the fatty acid,24 the molar ratio of fatty acid to albumin,25 oxygen requirements,26 cellular metabolic integrity, regional perfusion,19 concentration of the fatty acid in blood16 and the size of lipid pools in myocardium.23 A small, freely exchangeable pool of fatty acid permits some back diffusion of intracellular fatty acid into the interstitial fluid and blood.27 However, fatty acid is generally trapped within the cytosol by thioesterification before intermediary metabolism involving several pathways. A portion is incorporated into phospholipids, major constituents of cell membranes. A substantial portion is incorporated into triglycerides, before subsequent lipolysis and oxidation.28 Hydrolysis of triglycerides to liberate fatty acid from temporary intracellular storage is accelerated during conditions of increased energy requirements.28 Some of the extracted and thioesterified fatty acid is transported into mitochondria via a system of chain-length-specific carnitine transferases, where it undergoes beta-oxidation with production of acetyl-CoA, ultimately oxidized to CO2.24

Because of the complex interrelationships of factors influencing the uptake, accumulation and egress of 14C-counts from the heart exposed to 14C-labeled fatty acid in vivo, we recently evaluated isolated perfused hearts under conditions of constant flow and imposed alterations in oxidation requirements induced by inflation of an intraventricular balloon and monitored by indexes such as tension-time index and peak dP/dt. Prolonged diminution of perfusion sufficient to induce metabolic consequences of ischemia results in markedly diminished accumulation of 14C-palmitate and an altered proportion of deposition of tracer, with an increased fraction stored in neutral fat and a diminished fraction of radioactivity in the tissue associated with oxidation products of fatty acid.29 Under conditions of constant flow, the disappearance of radioactivity associated with 14C-palmitate initially incorporated in the heart was directly related to the tension-time index and peak dP/dt, regardless of the absolute magnitude of perfusion.30 Analogous results
have been obtained in open-chest, anesthetized rabbits
given intra-atrial bolus injection of 100–200 μCi of
11C-palmitate, with cardiac time-activity curves
recorded by coincidence detection with two NaI (TI)
crystals placed on either side of the chest to encom-
pass the heart in the field of view. In both
preparations, markedly diminished uptake of tracer
was found to reflect the metabolic consequences of
ischemia rather than transiently reduced flow with
diminished delivery of tracer to the myocardium per
se.

These observations, coupled with results that in-
dicate a close correlation between morphometric dis-
tribution of infarction and diminished uptake of 11C-
palmitate antemortem in corresponding regions of
canine hearts in vivo,11 support the interpretation that
decreased accumulation of 11C-palmitate detected in
the present study delineates zones of persistently
depressed myocardial metabolism. Because it is well
known that myocardium preferentially oxidizes fatty
acid (whenever it is available in the perfusate),19 and
that sustained diminution of aerobic myocardial
metabolism persisting for an hour or more is
associated with irreversible injury,11 it is not surprising
that the zones of diminished uptake of 11C-palmitate
detected in the present study correspond to the locus
of infarction detected electrocardiographically and to
the extent of infarction quantified enzymatically.

Potential Limitations of PET
for Quantification of Myocardial Injury

PET is capable of assessing, with a high degree of
accuracy and precision, the distribution of a
radionuclide in vivo.11 However, quantification is
limited by several physical constraints that must be
considered.

The linear relationship between the values yielded
by PET and the distribution of the radionuclide in the
subject under study requires either a negligible
amount of both scattered radiation and random
coincidences in the image or some correction for these
two sources of noise. In the present study, the con-
tribution of random coincidences was minimized by
performing studies at reasonably low counting rates
(table 1) and by incorporating a circuit that monitors
and subtracts random coincidences. Scattered radia-
tion is a more difficult problem. Its contribution was
minimized by pulse-height discrimination and by
calibrating the PETT IV system with a multicom-
partmental phantom designed to mimic the size and
scattering properties of the object under study and
containing activities which bracket the activity in the
organ under study.

Additional potential sources of error in these
studies result from three factors: 1) limited resolution
of PET systems; 2) relatively small dimensions of the
section of myocardium visualized; and 3) cardiac mo-
tion.

A truly quantitative relationship between the
number supplied by a PET system and the quantity
of activity in the sampled volume of tissue is maintained
only if the sampling volume of the system (the voxel)
contains only the tissue to be sampled.19 If the physical
dimensions of the resolution element of the PET
system exceed those of the volume of tissue to be
sampled, then the “partial volume principle” averages
out the activity in the tissue sampled with the other
structures contained in the voxel. In fact, in order to
assess quantitatively the amount of activity in an
anatomic structure by PET imaging, the sampled
volume should exceed the physical dimensions of the
resolution element of the PET by a factor of at least
two. In the case of PETT IV, the present minimal
resolution practically achievable is approximately
13.5 × 13.5 × 16 mm. Therefore, an accurate
relationship between the PETT value and the distribu-
tion of activity in myocardium can be achieved only if
a block of myocardium with linear dimensions larger
than these dimensions is sampled, a condition not
necessarily always achieved. Furthermore, motion of
the heart often mixes myocardium with a cardiac
chamber blood-pool component in a PETT voxel.

In the cardiac imaging reported here, the number
of counts collected is adequate to provide the desired
statistical precision, and the contribution of random
coincidences is subtracted from the image, yielding a
precision of measurement within a few percent.
Indeed, the pixels represented in the image for a voxel
of 1.35 × 1.35 × 1.6 cm contain on the average over
2000 counts. The linearity of PETT IV over a broad
range of energies has been verified.27 However, the
voxels obtained by means of PETT IV do not achieve
uniform sampling throughout the section of myocar-
dium because the thickness of the myocardium is not
large with respect to the voxel size. Furthermore, with
our present instruments, neither respiratory motion
nor motion associated with the cardiac cycle has been
excluded with gating techniques. In the case of
patients with infarction, the situation is further com-
plicated by dyskinesia and akinesis. Despite these
difficulties, however, images of the heart can be ob-
tained in dogs and in humans with delineated zones of
infarction that correspond closely to morphometric
estimates of infarction (based on previous results with
dogs)11 and enzymatic estimates (judging from results
in the present study). The concordance results to a
considerable extent from the fact that diastole con-
stitutes a large percentage of the cardiac cycle, and
cardiac motion during diastole is modest, producing
only a generalized blurring effect and minimal distor-
tion of the image. Nevertheless, it is clearly desirable
to minimize such causes of distortion by 1) gating data
acquisition with respect to the cardiac cycle, and 2)
accelerating data acquisition during PET imaging
such that the interval required is short with respect to
the interval required for breath holding (ap-
proximately 12 seconds in patients who are ill). We
are in the process of implementing a cardiac gating
system for PETT IV, and have developed a prototype
instrument (PETT V)41 for use in experimental
animals capable of producing PET images of the heart
within a few seconds.
Similarities and Differences Between PET and Other Approaches to External Delineation of Zones of Infarction

Although conventional gamma-emitting radioisotopes have been valuable for detecting zones of ischemia or infarction, their use entails appreciable quantitative limitations because of several factors, including superimposition of normal and abnormal zones of myocardium in the two-dimensional display of an image that may obscure the altered distribution of radioactivity attributable to zones of ischemia or infarction; redistribution of tracer between ischemic and nonischemic zones blunting the differentiation attributable to altered perfusion and its metabolic consequences; dependence of extraction of tracer on flow as well as metabolism, with a decrease in delivery of tracer in ischemic zones potentially overshadowed by effects of increased residence time, during which cell surfaces are in contact with the tracer in interstitial and vascular fluids resulting in an augmented extraction; variable attenuation of radioactivity in tissue as a function of distance of the tracer from the detector; heterogeneous distribution of the tracer dependent on its avidity for aqueous as opposed to lipid media, and the nonphysiologic nature of some tracers that clouds the interpretation of their altered distribution.

To overcome some of these difficulties, efforts have been made to obtain tomograms based on computer reconstruction techniques such as single-photon emission tomography. Although images obtained with such methods provide distinct border definition and good correlation with infarct size in dogs, their accuracy, particularly in larger subjects such as humans, is impaired because the assessment of distribution within the tissue is compromised by the difficulty of adequately correcting for the variable attenuation characteristic of gamma emitters in tissue as a function of distance of tracer from the detector. Furthermore, even if such reconstructions could accurately depict the distribution of tracer within a plane of the heart, limitations related to the nonbiologic character of tracers might distort quantitative relationships between regional metabolism and the images.

Ammonia labeled with nitrogen-13 has been proposed as an agent for imaging the heart. Although we as well as others, have evaluated the use of PET and 13NH3 for visualization of zones of myocardial infarction, the distribution of nitrogen-13 after the intravenous administration of 13NH3 reflects not only flow per se but also metabolic factors. Although decreased sequestration of 13NH3 qualitatively demarcates zones of compromised, ischemic myocardium, the dependence of myocardial uptake and retention of nitrogen-13 on perfusion, myocardial metabolism and pH is complex. Thus, quantitative interpretations are limited by difficulty in identifying the role of the variables involved. In the present study, 11C-palmitate was selected for the assessment of myocardial metabolism because it participates in a well-characterized fashion in intermediary metabolism, and because its deposition and use reflect alterations in regional metabolism independent of the effects of flow per se. With the use of this tracer, PET provides insight into regional metabolic integrity of the heart.

The ultimate relative clinical usefulness of transmission compared with emission tomography in the diagnosis and assessment of the natural history of coronary artery disease and its response to therapy remains to be clarified. However, it is clear that the two approaches provide insight based on entirely different image-forming variables and hence define entirely different characteristics of normal and diseased myocardium. Both appear to be of considerable potential clinical importance because both permit noninvasive, quantitative characterization of specific features of the heart.

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