Myocardial Uptake of Carbon-11-Acetate as an Indirect Estimate of Regional Myocardial Blood Flow

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The rate of clearance of myocardial carbon-11 (^{11}C) activity (after the administration of ^{11}C-acetate) has been shown to correlate closely with myocardial oxygen consumption. In the present study, we hypothesized that regional net myocardial uptake of ^{11}C-acetate, which reflects primarily delivery and extraction of tracer, would be markedly flow-dependent and potentially useful as an indirect index of regional myocardial blood flow. In 22 patients with stable coronary artery disease, the regional distribution of early net uptake of ^{11}C-acetate was correlated with estimates of regional myocardial blood flow assessed with oxygen-15-water. The myocardial images of ^{11}C-acetate uptake were of high quality. The correlation between the two approaches was close (r = 0.88) and not affected by the metabolic state of the tissue. Thus, in patients with stable coronary artery disease, under resting conditions, direct estimates of myocardial oxygen consumption in relation to the level of delivery of tracer to the tissue can now be obtained by PET with use of a single radiopharmaceutical, ^{11}C-acetate. This approach may prove particularly useful in streamlining clinical protocols designed to assess myocardial oxygen consumption.

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Positron emission tomography (PET) with physiologic substrates permits evaluation of myocardial metabolism and tissue viability in patients with coronary artery disease (CAD) (*1,2*). With these PET approaches, determining whether regional alterations in substrate metabolism are related to a specific pathophysiologic process also requires that regional myocardial blood flow must be measured to determine the level of tracer delivery to the tissue. Bergmann et al. have previously demonstrated that regional myocardial perfusion can be accurately assessed with oxygen-15-(^{15}O)-water, in both relative and absolute terms (*3–5*). Quantitative

estimates of myocardial blood flow are needed for many research applications. On the other hand, when evaluation of regional myocardial metabolic activity is the primary objective, as is true in many clinical applications, qualitative assessment of regional flow in relative terms may be sufficient. Both nitrogen-13-ammonia and ^{15}O-water have been used for this purpose (*1,6*). Regardless of the flow tracer employed, the requirement for administration of another radiopharmaceutical (separate from the metabolic tracer) increases the duration and complexity of the study, as well as the radiation burden to the subject.

It has been shown by investigators from this institution and by others that clearance of carbon-11 (^{11}C) activity from the myocardium, after i.v. administration of ^{11}C-acetate, correlated closely with myocardial oxygen consumption (*7–9*). In addition, in anesthetized dogs under resting conditions, significant myocardial clearance of ^{11}C activity does not occur until approximately 4.5 min after initial delivery of the tracer to the tissue (*8*). In human myocardium under resting conditions, the first-pass extraction fraction for acetate is relatively high and the clearance of ^{11}C activity is considerably slower than in canine myocardium (*8*). Accordingly, we hypothesized that, under resting conditions, regional activity within this early interval (defined as net myocardial uptake for purposes of this study) should reflect primarily delivery of the tracer. Thus, early uptake of tracer should be useful as an indirect index of regional myocardial perfusion. We chose to test this hypothesis by comparing the regional distribution of early net uptake of ^{11}C-acetate with regional perfusion measured with ^{15}O-water in patients with stable coronary artery disease.

METHODS

Subjects

We studied 22 patients (14 men and 8 women) with a mean age of 62 yr (range 30–78 yr). All of the patients had angiographically documented CAD and secondary left ventricular wall motion abnormalities at rest. These patients were selected because of their high likelihood of having perfusion abnor-

malities at rest. Fourteen patients had previously suffered at least one myocardial infarction (range 3 days–2 yr prior to the study). The experimental protocol was approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine. Informed written consent was obtained from each patient.

Radiopharmaceuticals

Oxygen-15-water, ^{15}O-carbon monoxide, and ^{11}C-acetate were prepared as previously described (7,10,11). Radiochemical purity for ^{11}C-acetate was typically greater than 99%.

Protocol

The PET studies were performed with either Super PETT I or Super PETT IIB. Super PETT I is a whole-body positron tomograph that permits the simultaneous acquisition of time-of-flight-corrected data sufficient for reconstruction of seven contiguous transaxial slices; the performance specifications of this tomograph have been reported previously (12). Data were acquired in the high-resolution mode with an effective reconstructed slice separation of 11.4 mm and an in-plane reconstructed resolution of 13.5 mm (full width of half maximum). Super PETT IIB is a whole-body time-of-flight tomograph composed of four rings, each containing 320 barium fluoride crystals, permitting the acquisition of list-mode data sufficient to generate seven transaxial slices with a slice thickness of 9.0 mm and a center-to-center separation of 14 mm. The tomograph has a transverse field of view of 48 cm and an axial field of view of 11.2 cm; the intrinsic resolution in the transverse plane is better than 5.0 mm (full width at half maximum). With time-of-flight gain applied, the tomograph has a sensitivity of 158,000 cps/μCi/cm^3 (13). Data were reconstructed with a tomographic slice thickness of 11.0 mm and an in-plane reconstructed resolution of 12.2 mm (full width at half maximum). Activity detected with both tomographs was displayed in "PET" counts, which are linearly proportional to the true count rate.

At the beginning of the PET study, a transmission scan was obtained with a germanium-68/gallium-68 source external to the patient. This transmission scan was used to correct for attenuation of the emitted photons and to insure proper positioning of the patient. Stable positioning was assessed with the use of a low-energy laser and the placement of indelible marks on the patient's torso. A polyurethane mold of the torso and neck was constructed for each patient to minimize motion between data acquisitions.

After completion of the transmission scan, the subject first underwent assessment of regional myocardial blood flow with ^{15}O-water. This required the acquisition of list-mode data for 150 sec commencing with the bolus i.v. injection of ^{15}O-water (0.25–0.30 mCi/kg body weight). Then, a 40-mCi dose of ^{15}O-carbon monoxide was administered by inhalation to label the blood pool (see below), with the subsequent collection of list-mode data for 300 sec. Next, to assess the early regional myocardial accumulation of ^{11}C-acetate, data were obtained in an 1800-sec list-mode collection that started immediately with the bolus i.v. injection of ^{11}C-acetate (0.25–0.30 mCi/kg). Appropriate time delays to allow for decay of tracers were interspersed between each of these data collections. The time for completion of the entire PET study was approximately 60–70 min, during which time the patient remained in the tomograph. These patients were studied as part of another
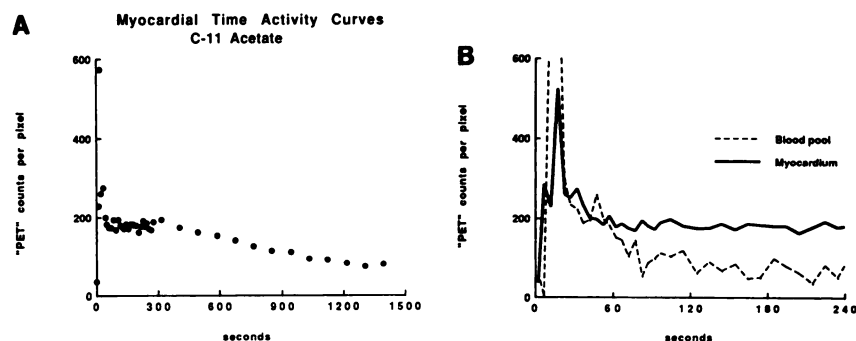
ongoing research project designed to identify metabolic determinants of viable but dysfunctional myocardium. This latter protocol included the administration of the radiopharmaceuticals listed above, as well as a second dose of ^{15}O-water and a 10-mCi dose of fluorine-18 fluorodeoxyglucose. The estimated radiation exposure (expressed as the effective dose equivalent) for the complete PET protocol for this study was approximately 0.75 rem (and approximately 1.75 rem with the additional radiopharmaceutical administrations).

Analysis of PET Images

To assess regional myocardial blood flow in relative terms, PET images were reconstructed with 120 sec of ^{15}O-water data beginning with the arrival of the bolus in the left atrium. To correct for the contribution of [15]O activity emanating from the intravascular compartment, images were reconstructed from the 300-sec ^{15}O-carbon monoxide data collection. This tracer binds avidly to the hemoglobin in red blood cells. In each pixel, ^{15}O-water activity within the intravascular compartment was calculated from the product of ^{15}O-carbon monoxide counts in that pixel and the ratio of ^{15}O-water to ^{15}O-carbon monoxide counts in the left ventricular blood pool. The calculated value was subtracted from the total ^{15}O-water activity within the 120-sec reconstruction. The resultant subtraction image represents ^{15}O-water tissue activity, and hence, reflects regional perfusion (3). We have previously shown that myocardial perfusion is spatially homogeneous in normal subjects when assessed in the fashion (14).

To assess the regional net myocardial uptake of ^{11}C-acetate, PET images were reconstructed with 120-sec of ^{11}C-acetate data beginning 60 sec after the administration of tracer. This time interval was chosen based on our observations in normal subjects of: (1) minimal myocardial clearance of retained ^{11}C activity within the first 4 min following the administration of ^{11}C-acetate; and (2) an adequate differential ratio of myocardial activity-to-blood-pool activity by 60 sec after the administration of tracer (Fig. 1A-B). To determine the influence of spillover of ^{11}C activity from the intravascular compartment to myocardial tissue, myocardial images representing net ^{11}C-acetate uptake from five randomly selected patients were corrected for spillover with use of a "subtraction" process analogous to that described above for ^{15}O-water. That is, ^{11}C-acetate activity within the intravascular compartment in each pixel was calculated from the product of ^{15}O-carbon monoxide counts in that pixel and the ratio of ^{11}C-acetate to ^{15}O-carbon monoxide counts in the left ventricular blood pool. The calculated value was subtracted from the total ^{11}C-acetate activity within the 120-sec reconstruction.

To assess the effect of altered myocardial metabolism on the correlation between net myocardial uptake of ^{11}C-acetate and regional myocardial blood flow, we determined regional myocardial oxidative metabolism by analyzing time-activity curves of myocardial ^{11}C activity, generated from sequential 90-sec framing of the entire 30-min data collection. The time-activity curves were analyzed with the use of a least-squares multi-exponential curve-fitting algorithm, described previously (15). Data from the "plateau" during the first 120–180 sec were excluded from the analysis, since they were influenced by continued uptake of tracer. All curves conformed best to a mono-exponential fit. Previous studies have demonstrated that the myocardial turnover rate constant, k_1, which describes

A

Myocardial Time Activity Curves
C-11 Acetate

"PET" counts per pixel

seconds

B

"PET" counts per pixel

- - - - - Blood pool
———— Myocardium

seconds

FIGURE 1

(A) Representative myocardial time-activity curve for ^{11}C-acetate derived from a normal healthy volunteer. The curve is typified by (1) an early peak, which represents delivery of tracer to the tissue; (2) a rapid decline representing primarily clearance of unextracted tracer from the blood pool; and then (3) a short interval during which the curve is essentially flat, representing extracted but not yet oxidized ^{11}C-acetate. The variance in the early portion of the curve is secondary to rapid sampling. Subsequently, myocardial clearance of ^{11}C activity is rapid. (B) The interval from 0–240 sec of the myocardial time-activity curve depicted in panel A is displayed with an expanded time scale. The curve is indicated by the continuous tracing. The arterial input function, derived from analysis of a ROI within the left atrial cavity, is superimposed. This curve is indicated by the dashed-line tracing (with its off-scale peak interrupted). These curves demonstrate rapid clearance of ^{11}C activity from the blood pool in the face of retained myocardial ^{11}C activity, with significant divergence of the two curves occurring after 60 sec.

the clearance of ^{11}C activity from the myocardium after the injection of ^{11}C-acetate, correlates closely with myocardial oxygen consumption and is spatially homogeneous in normal subjects (7–9,13). This rate constant was determined for each region of interest (see below). Myocardial oxidative metabolism was considered to be normal when the regional value for k_1 fell within 2 standard deviations of the average k_1 value for myocardium of normal healthy volunteers (normal mean, standard deviation, and range are 0.049, 0.006, and 0.037–0.061 min^{-1}, respectively) (13). Values for $k_1 < 0.037$ min^{-1} were considered indicative of myocardium with decreased oxidative metabolism.

Images of the distribution of myocardial ^{15}O-water and ^{11}C-acetate activity were analyzed by interactively defining transmural regions of interest. Two regions of interest (ROIs) (anterior and lateral) were defined for midventricular reconstructions and three ROIs (anterior, lateral, and posterior) were defined for the more apical reconstructions (Fig. 2). Due to increased spillover of ^{15}O-water activity from both the left and right ventricular blood pools into the interventricular septum, "over-subtraction" within this region (leading to an artificially low value for regional perfusion) is a common problem. Accordingly, septal regions were not included in the regional data analysis. All ROIs were initially defined on the ^{15}O-water reconstructions and corresponding regions of inter-

est then used on the ^{11}C-acetate reconstructions. Placement of irregular ROIs is quite reproducible with low interobserver and intraobserver variability (6,15,16).

The values within each region for myocardial blood flow determined with ^{15}O-water and for net myocardial uptake of ^{11}C-acetate were normalized to the peak value on the corresponding tomographic reconstruction.

Statistics

The normalized values for early myocardial uptake of ^{11}C-acetate were compared with normalized estimates of regional myocardial blood flow assessed with ^{15}O-water by linear regression.

RESULTS

Reconstructions of ^{11}C-acetate data acquired from 60 to 180 sec after administration of tracer gave myocardial images of good quality, such that myocardial activity was readily discerned from blood-pool activity and from that of noncardiac structures. The images of early myocardial uptake of ^{11}C-acetate were routinely of equivalent or higher quality than the images of regional myocardial perfusion obtained with ^{15}O-water (Fig. 3). Total counts per reconstructed tomographic slice of
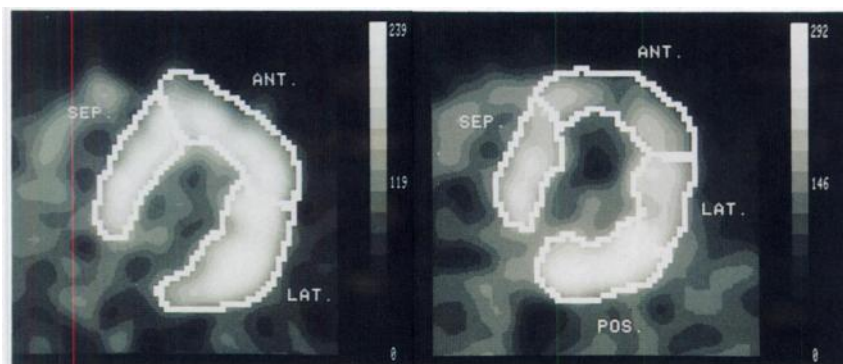
FIGURE 2

Two transverse tomographic reconstructions of left ventricular myocardium demonstrating the placement of irregular ROIs. The image on the left is at the mid-ventricular level while the image on the right is at a more apical level. The top of each image represents anterior and the left of each image represents the patient's right side.
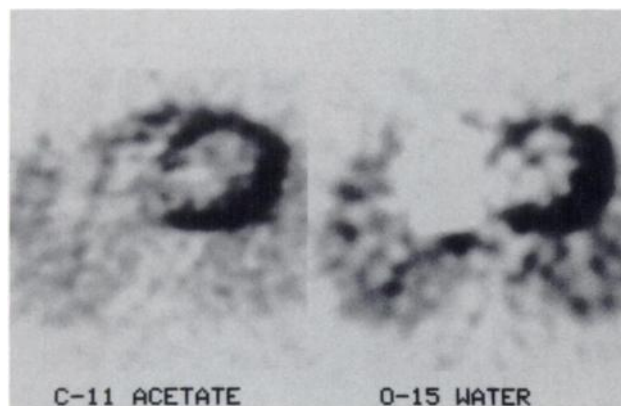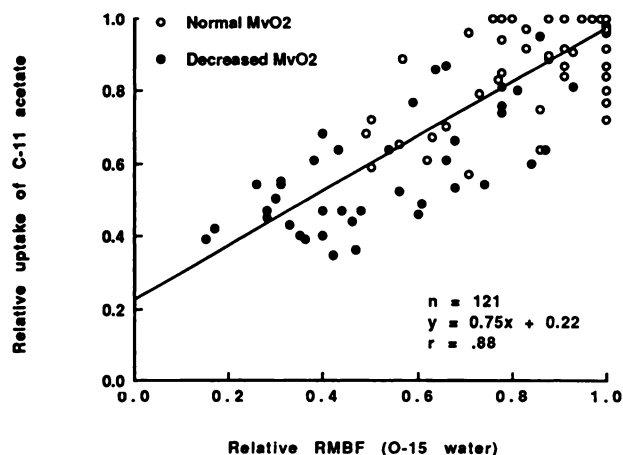
FIGURE 3

Representative images of relative perfusion obtained with ^{15}O-water (right) and relative myocardial uptake of ^{11}C acetate (left) from a patient with a high-grade stenosis of the left anterior descending coronary artery. The top of each image represents anterior and the left of each image represents the patient's right side. The myocardial image with ^{11}C-acetate is of high quality and demonstrates a moderately high myocardial-to-background ratio. Both images show a decrease in blood flow in the anterior wall.

FIGURE 4

Correlation between net myocardial uptake of ^{11}C-acetate, as an index of relative perfusion, and regional myocardial blood flow assessed with ^{15}O-water in the total study group of 22 patients. Myocardial zones with normal oxidative metabolism (i.e., k_1 of acetate clearance > 0.037 min^{-1}) are indicated by the open circles while zones with decreased myocardial oxygen consumption ($k_1 < 0.037$ min^{-1}) are indicated by closed circles.

^{11}C-acetate data ranged from 0.3–0.6×10^6 counts and from 0.5–1.0×10^6 counts for straight and cross slices, respectively ("straight slices" employ data from a single ring of detectors; "cross slices" employ data from coincidence events occurring between detectors in adjacent rings). Total counts per reconstructed tomographic slice of ^{15}O-water data (prior to blood-pool subtraction) ranged from 0.4–1.5×10^6 counts and from 0.7–2.2×10^6 counts for straight and cross slices, respectively.

A total of 121 ROIs were defined in the images of 22 patients. Figure 4 demonstrates the relationship between the regional normalized values for net myocardial uptake of ^{11}C-acetate and the regional normalized measurements of myocardial blood flow obtained with ^{15}O-water. Although there is some degree of scatter, the early myocardial uptake of ^{11}C-acetate correlated closely with regional perfusion [with a regression line slope of 0.75 and a correlation coefficient of .88, (Fig. 4)]. Estimates of blood flow for myocardium with normal or decreased oxidative metabolism were clustered around the right and left portions of the regression line, respectively, demonstrating the expected close coupling of myocardial perfusion and oxygen consumption. However, the scatter about the regression line was similar for regions with normal myocardial oxygen consumption and regions demonstrating decreased oxidative metabolism suggesting that the correlation between net myocardial uptake of ^{11}C-acetate and regional myocardial blood flow is relatively insensitive to altered myocardial metabolism.

The coupling of blood flow and metabolism was further evident by the direct correlation between indirect estimates of blood flow and direct estimates of

myocardial oxidative metabolism with ^{11}C-acetate ($r = 0.66$). To determine whether the presence of myocardial infarction would affect the correlation between the two approaches for estimating regional blood flow, the data from the eight patients without previous infarction were analyzed separately (Fig. 5). In these patients, the correlation between the two approaches remained close ($r = 0.78$). Accordingly, the close correlation between the two approaches in the total group of 22 patients was not chiefly attributable to the inclusion of patients with previous infarction.

Correction for spillover of ^{11}C activity from the intravascular compartment to the myocardium did not significantly alter the correlation between direct estimates of regional blood flow with ^{15}O-water and indirect estimates of regional blood flow with ^{11}C-acetate ($r = 0.90$), but did reduce the Y-intercept of the regression
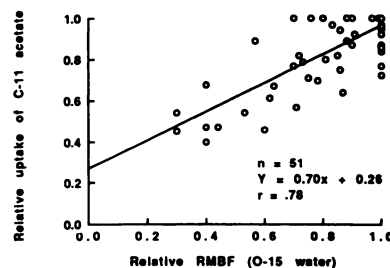
FIGURE 5

Correlation between net myocardial uptake of ^{11}C-acetate, as an index of relative perfusion and regional myocardial blood flow assessed with ^{15}O-water in the subset of eight patients without prior myocardial infarction.

line by 29% (compared with the regression line representing uncorrected ¹¹C-acetate data).

DISCUSSION

In the present study, we have described an approach that provides an indirect estimate of regional myocardial perfusion based on an evaluation of the regional distribution of early myocardial uptake of ¹¹C-acetate. This information is derivable from a PET study with ¹¹C-acetate in addition to the estimates of regional myocardial oxygen consumption determined by measuring the myocardial clearance rates of ¹¹C activity. Consequently, from the administration of a single radiopharmaceutical, ¹¹C-acetate, indirect estimates of regional myocardial blood flow (indicating levels of tracer delivery to the tissue) and direct estimates of regional myocardial oxygen consumption can be obtained.

Previous investigators using ¹¹C-acetate have focused on the relationship between the myocardial clearance of ¹¹C activity and myocardial oxygen consumption. It has been demonstrated that the turnover rate constant describing this clearance rate correlates closely with myocardial oxygen consumption over a wide range of myocardial work loads and under a variety of pathologic conditions (6–9,14). In contrast, in the present study we focused on the early portion of the myocardial time activity curve for ¹¹C-acetate (the time interval from 60 to 180 sec after the administration of tracer). We chose this interval for multiple reasons. First, it is well established that for various metabolic tracers, initial myocardial uptake is at least partially dependent on blood flow. Second, it has been shown previously in canine myocardium that significant production of ¹¹CO₂ (the primary metabolic end-produce of ¹¹C-acetate metabolism within the heart) does not occur for at least 4–4.5 min after the delivery of tracer to the heart (8). Third, human myocardium has a slower rate of oxygen consumption than canine myocardium (8). Consequently, we postulated that the net myocardial accumulation of ¹¹C-acetate through 3 min after injection of tracer should be markedly dependent on myocardial blood flow. Thus, the regional distribution of myocardial ¹¹C-acetate activity on images reconstructed from data within this time interval should indirectly reflect regional myocardial perfusion. Although there was some degree of scatter, the close correlation between the regional distribution of early myocardial uptake of ¹¹C-acetate and regional myocardial blood flow assessed with ¹⁵O-water supports this hypothesis. Fourth, based on our preliminary data in normal subjects, we chose to omit the first 60 sec of data to allow for adequate clearance of ¹¹C-acetate activity from the blood pool. The high quality of the ¹¹C-acetate myocardial images we obtained supports waiting 60 sec prior to initiating data reconstruction.

The measurements of regional myocardial uptake of ¹¹C-acetate were compared with those of regional perfusion obtained with ¹⁵O-water. Oxygen-15-water is a virtually freely diffusible tracer, and its entry into tissue is independent of the metabolic state of the tissue. By using ¹⁵O-water to assess blood flow, it is possible to account for transient intermittent episodes of hypoperfusion (i.e., intermittent "stunning") that could induce prolonged changes in the metabolic state of the tissue and thus alter the net uptake of ¹¹C-acetate. If such intermittent "stunning" occurs, there will be discordance between the myocardial uptake of ¹¹C-acetate and blood flow measured with ¹⁵O-water. Our data suggest that the severity of metabolic derangements in patients with stable CAD is not great enough to cause a significant alteration in the relationship between net uptake of ¹¹C-acetate and regional myocardial blood flow. It has been demonstrated previously that regional myocardial blood flow in both relative and absolute terms can be accurately assessed with ¹⁵O-water (3–5). However, because of the decreased sensitivity of the quantitative approach in zones of myocardium with severe hypoperfusion (as a consequence of poor counting statistics), we chose to assess regional myocardial blood flow in relative terms. With this approach, relative myocardial flow rates as low as 20% of normal can be determined accurately (3,4).

Limitations

Net myocardial uptake of ¹¹C-acetate during the interval from 1 to 3 min after the administration of tracer is a reflection of both regional myocardial blood flow (tracer delivery) and the first-pass extraction fraction of this tracer by tissue. Consequently, if the first-pass extraction fraction varies significantly with differing flow rates, particularly in a nonlinear fashion, or if the extraction fraction is affected by the metabolic state of the tissue, the direct relationship between net myocardial uptake of ¹¹C-acetate and flow could be altered. Previous studies suggest that the first-pass extraction fraction for acetate in humans is approximately 30% (17). In addition, previous studies in isolated rabbit hearts suggest that the first-pass extraction fraction of ¹¹C-acetate is inversely related to the flow rate (7), as is true for other partially extracted tracers used to assess flow. Although we did not measure the first-pass extraction fraction, the close correlation between net myocardial uptake of ¹¹C-acetate and regional myocardial blood flow suggests that, under resting normal and low flow conditions, the extraction fraction does not vary greatly enough to preclude use of this approach for indirectly assessing myocardial flow. The utility of this approach in high flow states is unclear. Certainly, other partially extracted flow tracers such as rubidium-82 or nitrogen-13-ammonia have been shown to be useful in assessing regional blood flow in relative terms following

the administration of i.v. dipyridamole (*18*). Potentially, the approach we have described employing ^{11}C-acetate could provide similar information, but further studies are needed to validate this application.

However, given the relative short duration of the hyperemic response to either exercise or i.v. dipyridamole, the close coupling of myocardial blood flow and oxygen consumption, and the sensitivity of ^{11}C-acetate tissue kinetics to changes in myocardial oxidative metabolism, it is unlikely that simultaneous estimates of perfusion and oxidative metabolism can be achieved in high flow states using routine noninvasive hyperemic stimuli (*19*). In addition, this approach may be limited where severe metabolic derangements may exist, such as in the early reperfusion period where uncoupling of flow and net uptake may occur, and where quantitative estimates of regional myocardial blood flow are desired.

Partial volume effects, particularly in zones of wall thinning secondary to ischemia or scar, constitute a limitation of any method that assesses relative regional activity. Such effects could partially account for the correlation between net uptake of ^{11}C-acetate and regional blood flow. However, estimates of relative myocardial blood flow with ^{15}O-water were originally validated against measurements of regional blood flow with radiolabeled microspheres (*3,4*). Consequently, partial volume effects, although certainly present, are unlikely to account solely for the close correlation between the two techniques.

The explanation for the positive Y-intercept of the regression line remains uncertain. We estimated the contribution of spillover of ^{11}C activity from the intravascular compartment into myocardial tissue to account for approximately 29% of the total Y-intercept value. However, applying the spillover correction did not significantly alter the correlation between indirect estimates of regional blood flow obtained with ^{11}C-acetate and direct estimates of myocardial blood flow obtained with ^{15}O-water. Consequently, the basis for the positive Y-intercept appears to be multifactorial. These factors include the spillover effect and such other reasons as increased residence time of the tracer in zones of ischemia and disparate rates of early clearance of ^{11}C activity for normal versus ischemic myocardium. Irrespective of the reasons for the positive Y-intercept, the correlation between the indirect estimates of regional blood flow obtained with ^{11}C-acetate (uncorrected for spillover) and direct estimates of myocardial blood flow obtained with ^{15}O-water suggest that the spillover correction need not be performed when estimates of relative perfusion are desired.

Clinical Implications

Approaches employing PET are now being developed to assess alterations in myocardial metabolism associated with numerous pathologic conditions (*1,2*). For example, in patients with ischemic cardiomyopathy, the matching or mismatching of regional glucose metabolism relative to flow is assessed in order to differentiate scar from viable but dysfunctional myocardium (*1*). Regardless of the metabolic process being assessed, regional myocardial blood flow must be measured to determine the level of tracer delivery to the tissue. Clearly, in those situations where accurate estimates of regional myocardial blood flow are needed, the quantitative approach is desired. However, when the primary reason for assessing regional perfusion is to determine the level of tracer delivery to the tissue, the approach we describe now makes it possible during a metabolic study with ^{11}C-acetate to obtain the requisite information regarding tracer delivery to the heart without the separate administration of a flow tracer. Consequently, in patients with stable CAD studied under resting conditions, direct estimates of myocardial oxygen consumption in relation to the level of delivery of tracer to the tissue can be obtained from the administration of a single radiopharmaceutical, ^{11}C-acetate. This approach may prove particularly useful in streamlining clinical protocols designed to assess regional myocardial oxidative metabolism using ^{11}C-acetate for the purposes of clinical decision making.

ACKNOWLEDGMENTS

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