Noninvasive Estimation of Regional Myocardial Oxygen Consumption by Positron Emission Tomography with Carbon-11 Acetate in Patients with Myocardial Infarction

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We previously demonstrated in experimental studies that myocardial oxygen consumption (MVO_2) can be estimated noninvasively with positron emission tomography (PET) from analysis of the myocardial turnover rate constant (k) after administration of carbon-11 (^{11}C) acetate. To determine regional k in healthy human subjects and to estimate alterations in MVO_2 accompanying myocardial ischemia, we administered [^{11}C]acetate to five healthy human volunteers and to six patients with myocardial infarction. Extraction of [^{11}C]acetate by the myocardium was avid and clearance from the blood-pool rapid yielding myocardial images of excellent quality. Regional k was homogeneous in myocardium of healthy volunteers (coefficient variation = 11%). In patients, k in regions remote from the area of infarction was not different from values in myocardium of healthy human volunteers (0.061 ± 0.025 compared with 0.057 ± 0.008 min^{-1}). In contrast, MVO_2 in the center of the infarct region was only 6% of that in remote regions ($p < 0.01$). In four patients studied within 48 hr of infarction and again more than seven days after the acute event, regional k and MVO_2 did not change. The approach developed should facilitate evaluation of the efficacy of interventions designed to enhance recovery of jeopardized myocardium and permit estimation of regional MVO_2 and metabolic reserve underlying cardiac disease of diverse etiologies.

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Noninvasive quantification of regional myocardial oxygen consumption has been an elusive and long-standing objective of cardiovascular research. Its utility is analogous to that of delineation of ventricular function, now readily accomplished by ventriculography or echocardiography among other methods; or of assessment of myocardial blood flow. Its potential value is underscored by clinical issues such as optimization of treatment of patients with ischemic heart disease requiring titration of myocardial oxygen requirements and ventricular performance, and by the importance of delineating viable myocardium after interventions such as coronary thrombolysis, essential for identification of patients who may benefit from subsequent additional measures such as angioplasty or coronary artery bypass grafting. In addition, elucidation of the pathophysiology of syndromes such as angina with angiographically normal coronary arteries (syndrome X) or of cardiomyopathies of diverse etiologies requires quantification of regional myocardial oxygen consumption and estimation of oxidative metabolic reserve.

Despite the quantitative power of positron emission tomography and its sensitivity for detection of labeled, physiologic substrates, quantification of carbohydrate or fatty acid metabolism alone does not provide a direct measure of regional myocardial oxygen consumption (*1,2*). We have shown that admixture of diverse substrates obscures changes in myocardial oxygen consumption estimated on the basis of metabolism of individual substrates such as glucose or fatty acid (*2*). In addition, the myocardial handling of either labeled palmitate or glucose (or the glucose analogue, fluorodeoxyglucose) is critically dependent upon the level of

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arterial substrate content as well as on the hormonal milieu (*3–6*).

We recently hypothesized that measurement of oxidation of acetate would provide an indirect measure of myocardial oxygen consumption (*7–9*). In contradistinction to the case with glucose or fatty acid, metabolism of acetate is confined virtually exclusively to mitochondrial oxidation. We have demonstrated in isolated perfused hearts (*7*) and canine hearts in vivo (*8*) that the extraction of carbon-11- (^{11}C) labeled acetate by myocardium is avid and that the clearance from the tissue is very closely correlated with both oxidation of labeled acetate to $^{11}CO_2$ and with myocardial oxygen consumption over a wide range of cardiac workloads. Furthermore, we have demonstrated that the quantitative relationship between myocardial oxygen consumption and turnover of [^{11}C]acetate is persistent despite marked changes in the proportion of substrate presented to the heart in vivo (*9*).

The present study was undertaken to characterize the turnover rate constant of [^{11}C]acetate by positron emission tomography in normal human subjects and in patients with acute myocardial infarction and to use the ^{11}C myocardial turnover rate constant to estimate regional myocardial oxygen consumption.

METHODS

Subjects

The protocol used was approved by the Washington University Institutional Review Board (Human Studies Committee). After the nature of the study had been explained to each subject, written informed consent was obtained.

Five male volunteers with mean age of 28 yr (range 25 to 36 yr) comprised the control group. All had normal electrocardiograms, no history of cardiac disease, and no known cardiac risk factors. Six patients (five male and one female) with transmural myocardial infarction (documented by analysis of plasma creatine kinase activity and by Q waves on the electrocardiogram) were studied as well. None had been subjected to acute interventions such as coronary thrombolysis or balloon angioplasty. Their mean age was 48 yr (range = 38 to 61 yr). One patient had sustained inferior infarction, and five had sustained anterior infarctions. Four (one with inferior and three with anterior infarction) studied initially within 48 hr of infarction were studied again at least 7 days after infarction to define sequential changes in [^{11}C]acetate metabolism in normal and infarct zones.

Protocol

Each subject was positioned in Super PETT I, a whole-body positron emission tomograph that provides simultaneous acquisition of data sufficient for reconstruction of seven transaxial slices with a center-to-center slice separation of 1.5 cm, and a slice thickness of 1.14 cm (*10*). A transmission scan of the chest was obtained with a ring of germanium-68/gallium-68 to correct for photon attenuation of the emitted radiation. The transmission scan was viewed prior to the collection of emission data to verify proper positioning of the patient so that four to six of the seven cross-sectional transaxial imaging planes transected the heart. Correct positioning was maintained throughout the study with the use of a light beam and indelible marks on the subject's torso. Polyurethane molds were made individually for each subject prior to each study and used to stabilize the head, neck, and upper torso to minimize movement and maintain identical positions for multiple tomograms. Emission data were collected in the high resolution mode with a reconstructed resolution (full width at half maximum) of 13.5 mm.

To characterize myocardial perfusion, we used the diffusible tracer oxygen-15- (^{15}O, $t_{½}$ = 2.1 min) labeled water and a method previously developed in our laboratory and validated in animals and patients (*11–14*). After collection of attenuation data, 0.4 mCi/kg of $H_2{}^{15}O$ were injected as a bolus via a large bore catheter inserted into an antecubital vein. Data were collected beginning at the time of administration of tracer and continued for 150 sec in list mode with time-of-flight correction. After a 5-min interval for decay of activity of tracer to baseline levels, 40 to 50 mCi of oxygen-15-labeled carbon monoxide ($C^{15}O$) were administered by inhalation to label the blood pool. After a subsequent interval of 30 to 60 sec for clearance of $C^{15}O$ from the lungs, data were collected for 5 min. After an additional 5-min interval for decay of radioactivity to baseline levels, 0.4 mCi/kg of [^{11}C]acetate ($t_{½}$ = 20.3 min) were injected as a bolus. In general, ^{11}C data were collected for 30 min. In some controls, collections were continued for as long as 60 min after administration of tracer.

Analysis of Tomographic Data

Perfusion. To display the distribution of nutritional perfusion after administration of ^{15}O water, radioactivity emanating from the blood pool was corrected with the use of $C^{15}O$ and a method validated previously in our laboratory (*11–14*). In each pixel of the tomographic reconstruction obtained after administration of $H_2{}^{15}O$, radioactivity emanating from the blood pool was subtracted to provide an image of blood flow in the myocardium. Data reconstructed into cumulative 120-sec images were used to identify regions of diminished perfusion in hearts of patients with myocardial infarction.

Metabolism. To characterize qualitatively the distribution of radiolabeled acetate in the heart and obtain a myocardial image, data were reconstructed into a single static 5-min composite scan. The reconstruction encompassed data collected from 3 to 8 min after administration of tracer, an interval when blood-pool radioactivity had declined substantially. Images were used subsequently for placement of regions of interest but not for quantitative analysis.

For quantitative analysis, a single midventricular tomographic slice was selected from the reconstructed tomograms in normal control subjects. In patients, the reconstruction containing the infarct region, as delineated from the $H_2{}^{15}O$ perfusion scan, was used for analysis. In the case of anterior infarction, midventricular tomograms were used. In the case of inferior infarction a more apical tomographic plane was used.

Regions of interest with a volume of ~1 cm^3 were placed circumferentially on each tomographic reconstruction. For midventricular tomograms, nine regions of interest were employed. For more apical tomograms, three posterior regions were identified as well. An additional region of interest was

assigned to the center of the left atrium or the left ventricular cavity for determination of activity of tracer in the blood pool.

Regions of interest in tomograms obtained after administration of [^{11}C]acetate to patients were subdivided to encompass regions of interest in normal, infarcted, and peri-infarct tissue. Normal regions were identified as those fully contained within regions of myocardium with normal perfusion (> 50% of maximum flow) judging from the $H_2{}^{15}O$ tomograms. "Infarct" zones were identified as regions of hypoperfusion with < 50% of maximum perfusion. In addition, the 1 cm^3 region of interest in the center of this zone of hypoperfusion was identified as being the most ischemic zone and designated "central infarct". Peri-infarct regions on either side of the infarct zone were delineated as the regions of interest immediately adjacent to the infarct but within a zone of perfusion with counts exceeding 50% of maximum activity of $H_2{}^{15}O$.

The [^{11}C]acetate myocardial turnover rate constant (k), was obtained from the equation:

$$q = e^{-kt}$$

where,

q = counts/voxel/minute corrected for physical decay,
k = myocardial turnover rate constant, and
t = time

It was calculated from sequential 90–120-sec frames. A multiexponential, least squares, curve fitting procedure was used to fit myocardial time-activity curves beginning at the time of occurrence of maximal myocardial ^{11}C activity. Data were expressed also as the myocardial clearance half-time ($t_{½}$ = ln2/k).

Myocardial oxygen consumption (MVO_2) was estimated for each defined region of interest based on the relationship between the myocardial turnover rate constant, k, and directly measured MVO_2 in 33 individual studies in intact dogs (Fig. 1) (*8,9*). Although this relationship has not been established directly in humans, because of ethical considerations, we did not feel that coronary sinus catheterization was justifiable in normal subjects. Coronary sinus catheterization in patients and determination of arterial-venous differences could provide estimates of myocardial oxygen consumption, but would provide global, rather than regional, values.

Because clearance of radioactivity from the arterial blood was so rapid (see Results) spillover from blood to myocardium did not require correction. We have previously demonstrated in experimental animals that spillover correction of data obtained after administration of [^{11}C]acetate is unnecessary because of the rapid clearance from arterial blood (*8*).

Preparation of Tracers

Oxygen-15 water, C^{15}O and [^{11}C]acetate were prepared as previously described in detail (*7,15,16*). Purity of [^{11}C]acetate was typically greater than 99.5%. Preparations of 200–300 mCi, with a specific activity of greater than 1 Ci/mmol, were achieved routinely.

Statistics

Data are reported as means ± standard deviations. Significance of differences between groups were assessed with analysis of variance and post-hoc unpaired analysis. Within groups differences were compared with the use of paired tests. Differences with a $p < 0.05$ were considered to be significant.

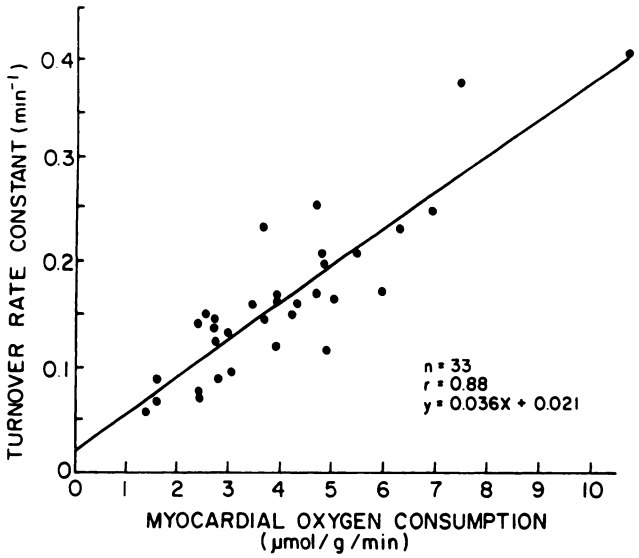

FIGURE 1
Correlation between the myocardial turnover rate constant measured noninvasively with PET after i.v. administration of [^{11}C]acetate and MVO_2 measured by direct arterial-coronary venous sampling obtained from 33 individual measurements in 18 anesthetized, intact dogs studied at rest or after myocardial work had been altered with sympathetic stimulation or blockade, or after the pattern of myocardial substrate use had been changed by altering arterial substrate content after infusion of either glucose or lipid. The data presented here is a summary of the results from previously published studies from our laboratory (*8,9*). This relationship was used to estimate regional MVO_2 in humans from the myocardial turnover rate constant.

RESULTS

Hemodynamics

No adverse effects of administration of any tracer were observed. All subjects tolerated the tomographic procedures well. The rate-pressure product (heart rate × systolic blood pressure), an index of global myocardial work, was calculated for all subjects. The rate pressure product was lower in control subjects undergoing tomography than it was in patients with infarction (7051 ± 1131 bpm × mmHg compared with 9517 ± 3023, $p < 0.05$), presumably because of differences in autonomic nervous system activity. The rate-pressure product was also lower at the time of follow-up 1 wk after infarction in the four patients studied than it was in studies within 48 hr of onset of infarction (7082 ± 2654 at follow-up compared with 9879 ± 3332 acutely, $p < 0.05$).

Assessment of Myocardial Perfusion

Nutritional perfusion, assessed with $H_2{}^{15}O$, was homogeneous in all subjects in the control group (Fig. 2). In contrast, all patients with myocardial infarction displayed diminished perfusion in a tomographic region that corresponded to the locus of the region of infarction

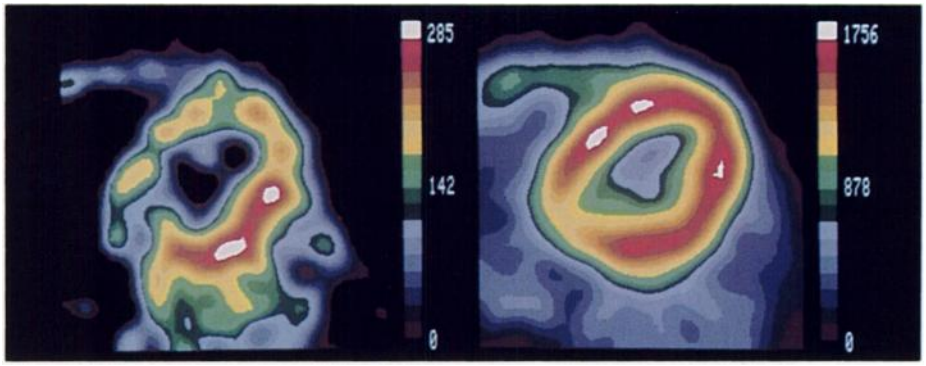

FIGURE 2
Mid-ventricular, transaxial, tomographic reconstructions from a representative control subject (P360). On the left is the reconstruction obtained after administration of ^{15}O water, corrected for vascular radioactivity. On the right is the corresponding tomogram obtained after administration of [^{11}C]acetate. In these mid-ventricular, transaxial reconstructions, the septum is on the left, the lateral free wall on the right, the anterior myocardium toward the top, and the mitral valve plane, devoid of significant tracer uptake, toward the bottom. Concordance of distribution of tracer in the perfusion and metabolic images is evident. The slight discontinuity of tracer uptake seen in the septum in the $H_2{}^{15}O$ image is related to statistical noise induced by correcting the image for radioactivity emanating from the blood pool. Uptake of [^{11}C]acetate was avid and resulted in myocardial images of high quality in all subjects.

delineated electrocardiographically (Fig. 3). The region of diminished perfusion defined with $H_2{}^{15}O$ was used to distinguish infarct, normal, and peri-infarction regions.

Analysis of Data after Administration of [^{11}C]Acetate

An example of a midventricular tomographic reconstruction obtained after intravenous administration of [^{11}C]acetate on a normal subject is shown in Figure 2. The homogeneity of myocardial ^{11}C activity observed and the quality of the image are representative of results in each control.

A reconstruction from a patient with anterior myocardial infarction is displayed in Figure 3. Both the $H_2{}^{15}O$ and the [^{11}C]acetate tomograms show markedly decreased tracer in the anterior myocardium and relatively normal distribution of perfusion and metabolism in the septal and lateral walls.

Quantitative Analysis

As shown directly in studies in experimental animals (*8,9*), and confirmed in the human subjects studied here, [^{11}C]acetate radioactivity in the blood pool diminished by 90% to 95% from peak radioactivity, usually within 2 min (Fig. 4).

For each of the 9–12 regions of interest placed on tomographic reconstructions, a multi-exponential curve fit was used to characterize decay-corrected myocardial time-activity curves from the time of occurrence of maximal myocardial ^{11}C radioactivity. In contrast to the biexponential clearance of ^{11}C radioactivity observed in isolated rabbit hearts (*7*) and in hearts of dogs in vivo (*8,9*), clearance of ^{11}C was monoexponential in both controls and patients (Fig. 5). This observation is consistent with the lower workload seen at rest in nonanesthetized, noninstrumented human subjects compared with that in anesthetized dogs and with preliminary observations in humans reported by Pike et al (*17*) and by Henes et al. (*18*). No second exponential component could be identified even in two subjects studied for as long as 1 hr after administration of tracer.

Clearance of ^{11}C radioactivity from the myocardium was homogeneous in control subjects (Table 1, Fig. 5). The variation of the turnover rate constant within each tomogram, reflected by the coefficient of variation, was

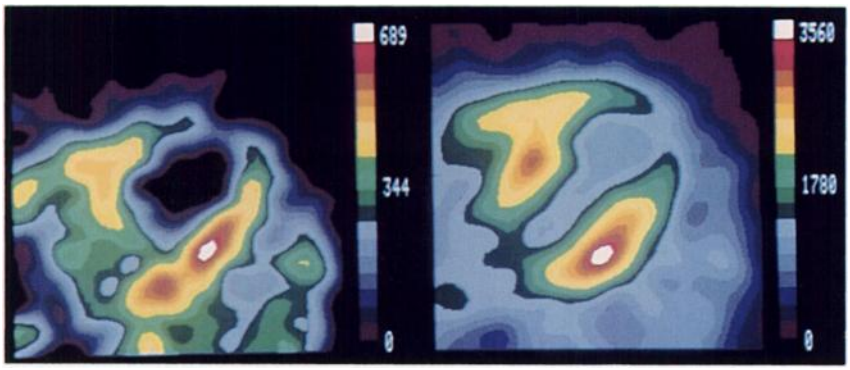

FIGURE 3
Mid-ventricular tomographic reconstructions of perfusion (left) and oxidative metabolism (right) in a patient with acute, anterior, myocardial infarction (P354). A large anterior flow deficit is evident in the perfusion tomogram and a concordant decrease in myocardial oxygen consumption reflected by decreased [^{11}C]acetate uptake is evident in the tomogram obtained after administration of [^{11}C] acetate.

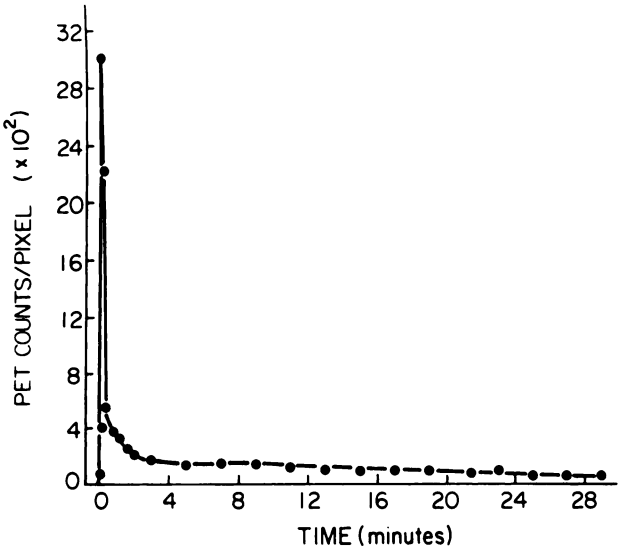

FIGURE 4
Clearance of ^{11}C radioactivity from the blood was rapid. Radioactivity cleared to < 10% of maximum within 2 min after administration of tracer.

11 ± 3% in control subjects. Mean values of k, clearance half-time and estimates of MVO_2 averaged from all regions, were similar to values obtained from a region of interest drawn to encompass the entire left ventricle (Table 1). On the basis of extrapolation from analyses in experimental animals in which the myocardial turnover rate constant was compared with MVO_2 measured directly to yield a regression equation to estimate MVO_2 from k (Fig. 1), in normal human subjects, calculated MVO_2 averaged 0.97 ± 0.23 μmol/g/min (Table 1).

In contrast to the homogeneous clearance observed in hearts of control subjects, clearance of radioactivity from the myocardium of patients with infarction was heterogeneous (Table 2, Fig. 5). Uptake of tracer in the zones of infarction was decreased and the turnover rate constant within the infarct zone was markedly diminished, indicative of a profound diminution of regional MVO_2 (Fig. 6). Regions immediately adjacent to the infarct zone also had diminished MVO_2 in comparison to those regions more remote from the infarct (Fig. 6).

To define changes in oxidative metabolism over time in infarct and peri-infarct zones, four patients studied initially within 48 hr of the onset of symptoms were studied again at least 7 days after the infarction. In each of these patients, uptake of [^{11}C]acetate remained markedly diminished in the infarct zone. The turnover rate constant, clearance half-time, and estimated myocardial oxygen consumption did not change with time (Table 3, Fig. 7).

DISCUSSION

Myocardial Imaging with [^{11}C]Acetate

In this study, uptake of [^{11}C]acetate was found to be avid in normal myocardium permitting acquisition of myocardial tomographic images of high quality. The rapid clearance of tracer from the blood pool results in good contrast between blood and myocardium and

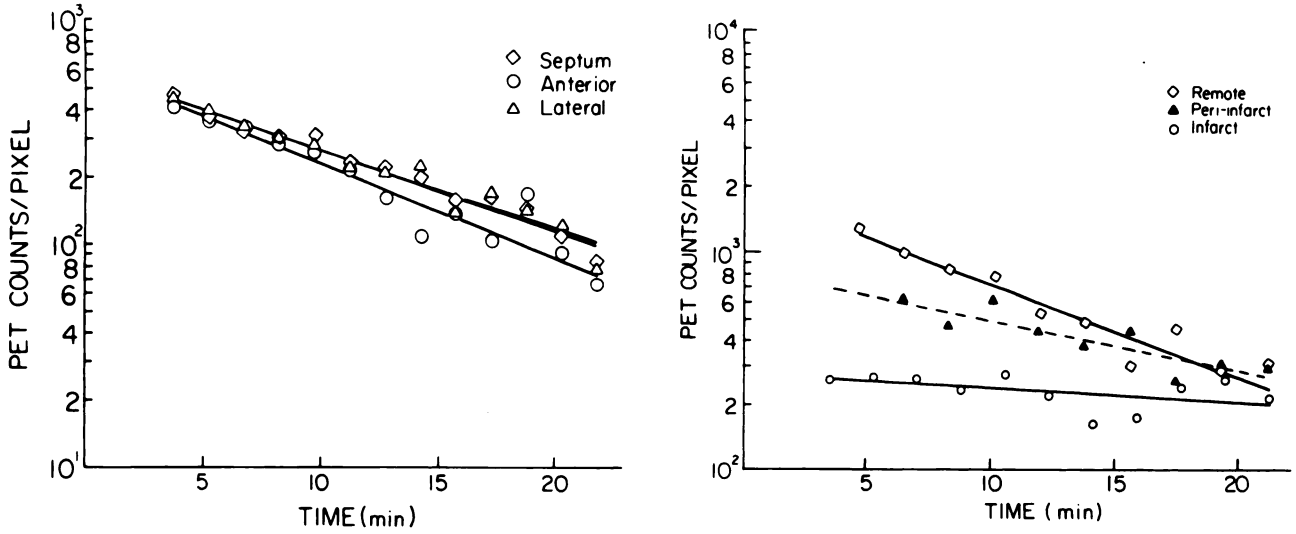

FIGURE 5
Representative myocardial time-activity curves obtained from one control subject (P336, A) and one patient with anterior myocardial infarction (P362, B). Three of the 9–12 regions of interest comprising 1 cm^3 each are displayed. In hearts of individuals without cardiac disease, clearance of tracer is uniform, monoexponential, and homogeneous. In contrast, in patients with myocardial infarction, initial uptake of [^{11}C]acetate in the infarct zone is diminished, and clearance is prolonged, consistent with a decrease in myocardial oxygen consumption. These examples from a control subject and from a patient with acute myocardial infarction are typical of those seen in all subjects studied.

TABLE 1
Myocardial Turnover Rate Constant (k), Clearance Half-time ($t_{½}$), and Calculated Myocardial Oxygen Consumption (MVO_2) Obtained from Normal Subjects*

	Septal			Anterior			Lateral			Posterior						
SUBJECT	1	2	3	1	2	3	1	2	3	1	2	3	Mean ± s.d.	COV (%)	Global	RPP
A. Myocardial turnover rate constant, k (min^{-1})																
336	0.060	0.062	0.063	0.063	0.060	0.072	0.064	0.076	0.072	—	—	—	0.066 ± 0.006	9.0	0.064	
360	0.045	0.050	0.053	0.047	0.050	0.050	0.045	0.047	0.051	0.044	0.038	0.044	0.047 ± 0.004	8.5	0.049	
375	0.049	0.051	0.055	0.050	0.053	0.048	0.052	0.050	0.040	—	—	—	0.050 ± 0.004	8.0	0.047	
378	0.048	0.065	0.054	0.060	0.067	0.053	0.066	0.065	0.050	—	—	—	0.059 ± 0.007	11.9	0.064	
386	0.072	0.067	0.069	0.068	0.056	0.067	0.067	0.071	0.056	0.052	0.048	0.045	0.062 ± 0.010	16.1	0.063	
mean ± s.d.													0.057 ± 0.008	10.7 ± 3.4	0.057 ± 0.009	
B. Clearance half-time, $t_{½}$ (min)																
336	11.6	11.2	8.4	11.0	11.6	9.6	10.8	9.1	9.6	—	—	—	10.3 ± 1.2	11.3	10.8	
360	15.6	13.9	13.1	14.8	13.9	13.9	15.4	14.8	13.6	15.8	18.2	15.8	14.8 ± 1.6	10.5	14.2	
375	14.2	13.6	12.6	13.9	13.1	14.4	13.3	13.9	17.3	—	—	—	14.1 ± 1.3	9.2	14.8	
378	14.4	10.7	12.8	11.6	10.4	13.1	10.5	10.7	13.9	—	—	—	12.0 ± 1.6	13.2	10.8	
386	9.4	10.4	10.1	10.2	12.4	10.4	10.4	9.8	12.4	13.3	14.4	15.4	11.6 ± 2.0	17.1	11.4	
mean ± s.d.													12.6 ± 1.9	12.3 ± 3.1	12.4 ± 1.9	
C. Calculated myocardial oxygen consumption (μmol/g/min)																
336	1.08	1.14	1.72	1.17	1.08	1.42	1.19	1.53	1.42	—	—	—	1.31 ± 0.23	17.2	1.19	8450
360	0.67	0.81	0.89	0.72	0.81	0.81	0.67	0.72	0.83	0.64	0.47	0.64	0.72 ± 0.11	15.3	0.78	5301
375	0.78	0.83	0.94	0.81	0.89	0.75	0.86	0.81	0.53	—	—	—	0.80 ± 0.12	15.0	0.72	7360
378	0.75	1.22	0.92	1.08	1.28	0.89	1.25	1.22	0.81	—	—	—	1.05 ± 0.21	20.0	1.19	7044
386	1.42	1.28	1.33	1.31	0.97	1.28	0.67	0.72	0.83	0.64	0.47	0.64	0.96 ± 0.34	35.4	0.97	7098
mean ± s.d.													0.97 ± 0.23	20.6 ± 8.5	0.97 ± 0.22	7051 ± 1131

* — indicates that a region was not able to be evaluated. The mean and standard deviation of the 9–12 regions was calculated, as was the coefficient of variation (COV). The results indicate homogenous clearance from all regions of the myocardium. The rate pressure product (RPP) during the scan is also presented.

TABLE 2

Myocardial Turnover Rate Constant (k), Clearance Half-time ($t_{½}$), and Myocardial Oxygen Consumption (MVO_2) in Each of Six Patients with Transmural Myocardial Infarction.*

	Remote regions			Peri-infarct regions			Infarct regions			Central infarct			
Patient	k	$t_{½}$	MVO_2	k	$t_{½}$	MVO_2	k	$t_{½}$	MVO_2	k	$t_{½}$	MVO_2	RPP
P354	0.090 ± 0.012	7.8 ± 1.1	1.93 ± 0.32	0.065 ± 0.012	10.9 ± 2.0	1.21 ± 0.33	0.055 ± 0.032	15.7 ± 2.2	0.95 ± 0.89	0.028	24.8	0.19	11 119
P362	0.083 ± 0.015	8.5 ± 1.6	1.72	0.048	14.6	0.75	0.044 ± 0.020	20.7 ± 15.2	0.68 ± 0.50	0.016	43.3	0.00	14 142
P368	0.039 ± 0.007	18.4 ± 3.2	1.73 ± 0.41	0.019 ± 0.009	42.8 ± 21.2	0.38 ± 0.57	0.000	**	0.00	0.000	**	0.00	6 466
P385	0.076 ± 0.016	9.3 ± 1.9	0.49 ± 0.19	0.053	13.1	0.89	0.021 ± 0.025	91.4 ± 96.2	0.76 ± 1.21	0.003	231.1	0.00	10 875
P428	0.033 ± 0.004	21.5 ± 2.6	0.32 ± 0.11	0.024	28.9	0.08	0.019 ± 0.015	51.6 ± 36.2	0.17 ± 0.24	0.000	**	0.00	7 645
P435	0.043 ± 0.003	16.3 ± 1.4	0.61 ± 0.10	0.040 ± 0.004	17.6 ± 1.6	0.51 ± 0.10	0.035 ± 0.009	20.5 ± 4.5	0.25 ± 0.00	0.030	23.1	0.25	6 845
Mean ± s.d.	0.061 ± 0.025	13.6 ± 5.9	1.08 ± 0.69	0.042 ± 0.018[a]	21.3 ± 12.3[a]	0.64 ± 0.40[a]	0.029 ± 0.020[ab]	40.0 ± 32.0	0.47 ± 0.38[ab]	0.013 ± 0.014[abc]	80.6 ± 100.8	0.07 ± 0.12[abc]	9517 ± 3023

*Myocardial oxygen consumption is severely depressed in Infarcted Tissues.

** Indicates an infinite clearance half-time, not included in calculation of mean values. RPP = rate pressure product. a = $p < 0.05$ compared with remote regions; b = $p < 0.05$ compared with peri-infarct regions; c = $p < 0.05$ compared with infarcted regions.

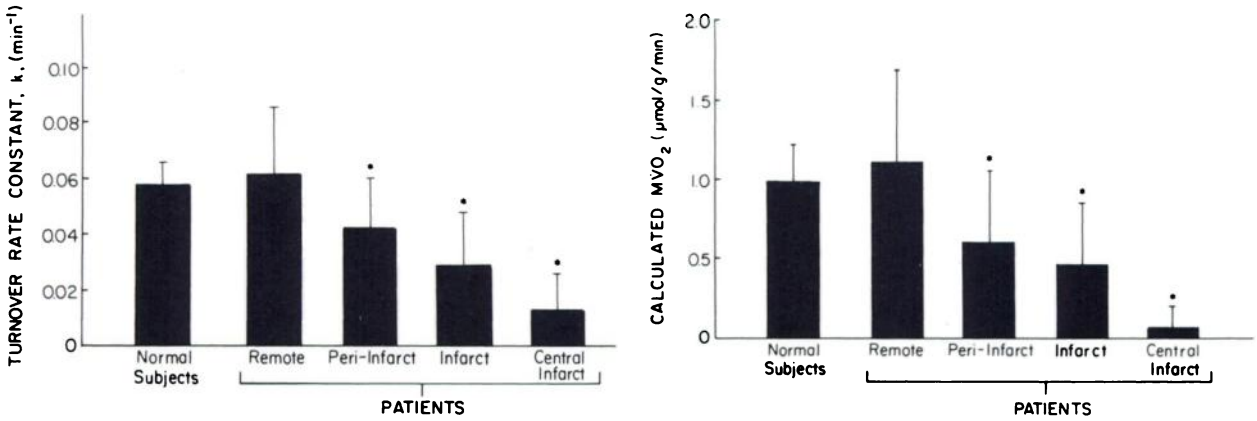

FIGURE 6

(A) Histogram depicting the regional myocardial turnover rate constant from all regions in normal subjects and in infarct, central infarct, peri-infarct, and remote regions in patients with myocardial infarction. (B) Estimates of regional myocardial oxygen consumption in all regions from normal volunteers and from infarct, central infarct, peri-infarct, and remote regions in patients with myocardial infarction. There was no statistically significant difference between regions remote from infarction in patients and regions from normal human volunteers. Regional myocardial oxygen consumption diminished in peri-infarct regions in patients, and was severely depressed in the zone of infarction ($p < 0.05$ compared with remote regions).

facilitates quantitative analysis of myocardial turnover rate without the necessity for correcting for myocardial spillover from blood into myocardium (*8,18*).

In normal subjects, uptake and clearance of ^{11}C was homogeneous and monoexponential. Use of the relationship between k and MVO_2 established previously in canine hearts in vivo and the data obtained in the present study in human subjects yielded a calculated human myocardial oxygen consumption value of 0.97 μmol/g/min, somewhat lower but close to that previously obtained by direct analysis with invasive procedures (*19–21*).

In patients with infarction, uptake of [^{11}C]acetate in the center of the infarct zone, delineated by perfusion imaging with $H_2{}^{15}O$, was markedly depressed and clearance was prolonged. Both are a result of diminished perfusion to the region. The diminished clearance directly reflects the reduction of myocardial oxidative metabolism. Overall oxygen consumption within zones of hypoperfusion delineated by $H_2{}^{15}O$ in humans was ~30% of that in normal zones, a finding consistent with the recognized magnitude of myocardial collateral perfusion in zones of infarction (*22*). Estimated oxygen consumption in the center of the hypoperfused zone was ~6% of normal. Regions remote from the center of the infarction exhibited normal myocardial uptake and turnover of tracer indicative of normal myocardial oxidative metabolism. Peri-infarction zones manifested prolongation of clearance indicative of diminished oxidative metabolism. These regions may be metabolically "stunned". Thus, the diminution of blood flow to myocardium within these regions, although not sufficient to induce infarction, is sufficient to diminish regional work and regional MVO_2. Alternatively, peri-infarction zones may contain a mixture of viable and infarcted cells constituting a heterogeneous population manifesting phenomena integrated in the tomograms within selected regions of interest because of the limited spatial resolution of PET. This latter interpretation is supported by the finding that MVO_2 in peri-infarct regions in patients with infarction studied acutely and again at least 7 days after the acute event, at a time by which function and metabolism in myocardium not destined to undergo infarction have recovered, did not change.

Studies in experimental animals have demonstrated that with reperfusion, oxidative metabolism assessed with [^{11}C]acetate recovers within 1 wk in zones destined to recover and is predictive of recovery of ventricular function (*23*). Studies by others have shown that restoration of ventricular function is predicated on recovery of myocardial oxidative metabolism (*24,25*). Although enhanced glycolytic flux is seen in reperfused myocardium (*2*) and can be demonstrated with fluorine-18 (^{18}F) fluorodeoxyglucose (*25*), the prolonged imaging intervals required with deoxyglucose as well as the dependency of myocardial uptake of this tracer on plasma substrate and hormonal concentrations precludes its use to quantify regional myocardial oxidative metabolism.

Technical Considerations

Results of this study indicate that the turnover rate constant after i.v. administration of [^{11}C]acetate can be quantified by PET. We developed [^{11}C]acetate as a tracer suitable for assessment of regional myocardial oxygen consumption because it is metabolized virtually exclusively via mitochondrial oxidation (*7–9*). Oxidation of acetate to CO_2 in mitochondria is coupled tightly to oxidative phosphorylation. We have shown previously that the turnover rate in isolated perfused hearts

TABLE 3

Myocardial turnover rate constant (k), clearance half-time ($t_{½}$), and myocardial oxygen consumption (MVO_2) for each of the four patients studied within 48 hr of myocardial infarction and at follow-up.*

	Acute					Follow-up				
Patient	Remote	Peri-infarct	Infarct	Central infarct		Remote	Peri-infarct	Infarct	Central infarct	
Myocardial turnover rate constant (k)										
P362	0.083 ± 0.015	0.048	0.044 ± 0.020	0.016		0.073 ± 0.007	0.050 ± 0.008	0.046 ± 0.011	0.000	
P385	0.076 ± 0.016	0.053	0.021 ± 0.025	0.003		0.042 ± 0.012	0.034 ± 0.012	0.000	0.007	
P428	0.033 ± 0.004	0.024	0.022 ± 0.014	0.000		0.028 ± 0.008	0.016 ± 0.001	0.011 ± 0.003	0.026	
P435	0.043 ± 0.003	0.040 ± 0.004	0.035 ± 0.009	0.030		0.060 ± 0.003	0.048 ± 0.008	0.043 ± 0.005	0.040	
Mean ± s.d.	0.059 ± 0.024	0.041 ± 0.013	0.031 ± 0.011	0.012 ± 0.014		0.051 ± 0.020	0.037 ± 0.016	0.025 ± 0.023	0.018 ± 0.018	
Clearance half-time ($t_{½}$)										
P362	8.5 ± 1.6	14.6	20.7 ± 15.2	43.3		9.6 ± 0.8	14.2 ± 2.2	15.9 ± 4.6	**	
P385	9.3 ± 1.9	13.1	91.4 ± 96.2	231.1		18.2 ± 6.8	22.1 ± 7.8	**	101.31	
P428	21.5 ± 2.6	28.9	50.6 ± 41.2	**		25.9 ± 6.2	44.3 ± 2.4	69.7 ± 21.9	26.7	
P435	16.3 ± 1.4	17.6 ± 1.6	20.5 ± 4.5	23.1		11.7 ± 0.7	14.8 ± 2.6	16.2 ± 1.7	17.3	
Mean ± s.d.	13.9 ± 6.2	18.6 ± 7.1	45.8 ± 33.5	99.2 ± 114.7		16.4 ± 7.4	23.9 ± 14.1	33.9 ± 31.0	48.4 ± 46.1	
Myocardial oxygen consumption (MVO_2)					RPP					RPP
P362	1.73 ± 0.14	0.75	0.68 ± 0.50	0.00	14 142	1.43 ± 0.18	0.79 ± 0.21	0.70 ± 0.31	0.00	11 626
P385	1.41 ± 0.36	0.89	0.76 ± 1.21	0.00	10 875	0.57 ± 0.34	0.35 ± 0.33	0.00	0.00	7 456
P428	0.32 ± 0.11	0.08	0.17 ± 0.24	0.00	7 645	0.20 ± 0.21	0.00	0.00	0.14	5 658
P435	0.61 ± 0.10	0.51 ± 0.10	0.25 ± 0.00	0.25	6 854	1.07 ± 0.09	0.74 ± 0.22	0.62 ± 0.14	0.53	6 466
Mean ± s.d.	1.02 ± 0.66	0.56 ± 0.35	0.47 ± 0.30	0.06 ± 0.13	9879 ± 3332	0.82 ± 0.54	0.47 ± 0.37	0.33 ± 0.38	0.17 ± 0.25	7802 ± 2654

* Myocardial oxygen consumption does not change in infarcted or peri-infarcted tissue, but decreases somewhat in normal regions. This decrease is consistent with diminished myocardial work as reflected by the diminished rate pressure product (RPP).

** Indicates infinite clearance half-time consistent with unmeasurably low oxygen consumption.

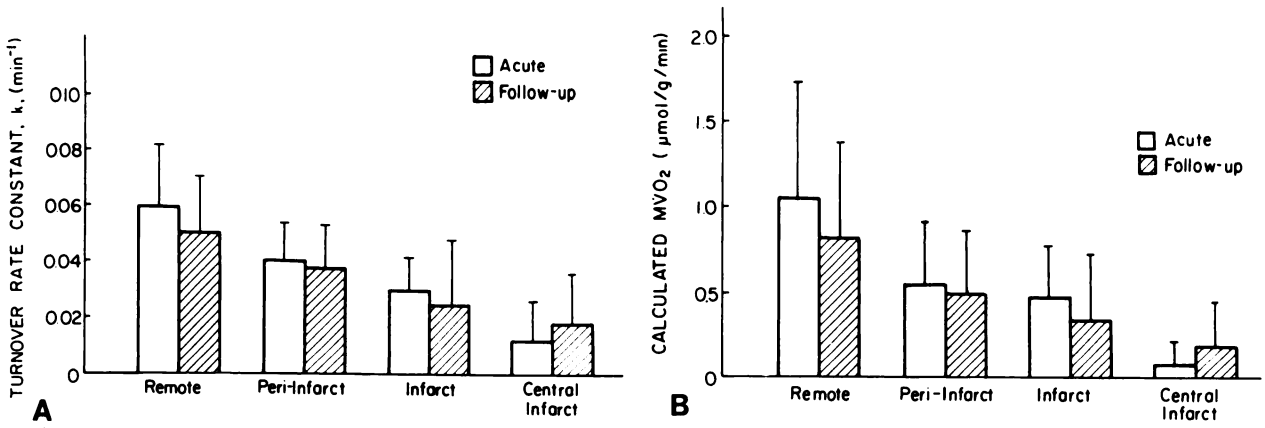

FIGURE 7

Histogram displaying the myocardial turnover rate constant, k (A), and estimated myocardial oxygen consumption (B) from four patients studied acutely and again at least 7 days after the acute event. There was no change in regional k or MVO_2 with time in any region.

parallels regional myocardial oxygen consumption over a wide range of physiologic and pathophysiologic conditions including ischemia and reperfusion (*7*). Comparisons of the myocardial turnover after intravenous administration of [^{11}C]acetate with direct measurements of myocardial oxygen consumption have demonstrated the relationship between the myocardial turnover rate constant (k) detected externally with PET, and MVO_2 over a wide range (Fig. 1) (*8,9*). This relationship is not altered by changes in myocardial work or by the pattern of substrate utilization (*9*). Despite the fact that acetate is avidly extracted by the myocardium with an extraction fraction of 30–50%, its oxidation does not account for a large fraction of myocardial energy supply because it circulates in such low concentrations in normal human subjects (80–100 μmol) (*26*). Nonetheless, the relationship between the myocardial turnover rate constant and MVO_2 has not been established directly in human beings. Values of MVO_2 in humans estimated by extrapolation of the relationship obtained directly in dogs yield values that are somewhat lower than those that have been measured in human subjects (*19–21*). We recently reported that the relationship between k and the rate-pressure product (an index of myocardial work and therefore of myocardial oxygen consumption) obtained in healthy human volunteers was indistinguishable from the relationship obtained in experimental animals (*18*). Nonetheless, the discrepancy in values of MVO_2 obtained noninvasively in the present study with values obtained by other investigators using invasive techniques may reflect a true interspecies difference in the relationship between k and MVO_2. Although the rate-pressure product can be used to estimate MVO_2 in normal subjects, it reflects global, rather than regional, MVO_2. In contrast, the PET approach developed permits sequential assessments of regional MVO_2.

In the present study, areas of normal and hypoperfusion were estimated using $H_2{}^{15}O$ and a technique developed previously in our laboratory to correct data for intravascular radioactivity. Regional perfusion using this approach correlates very closely with regional blood flow estimated with radiolabeled microspheres (*11–13*). In addition, we have demonstrated the utility of this technique in patients with coronary artery disease (*14*). Although tomography with $H_2{}^{15}O$ permitted independent delineation of normal from ischemic myocardium, correction of myocardial $H_2{}^{15}O$ for vascular radioactivity (which requires an independent measure of the blood pool with $C^{15}O$) results in images of relatively low signal-to-noise ratios. Although we recently validated a mathematical approach to quantitate myocardial perfusion in absolute terms (i.e., ml/g/min) using $H_2{}^{15}O$ and PET which does not require an independent measurement of the blood pool, we chose not to use the quantitative approach in the current study because it is less sensitive to estimates of flow in infarcted myocardium (*27*).

Clinical Implications

The results of the present study indicate that positron emission tomography with [^{11}C]acetate, a tracer of myocardial oxidative metabolism, provides myocardial images of high quality and permits estimation of regional myocardial oxygen consumption with results consistent with those obtained previously by invasive measurements. Oxidative metabolism in the center of zones of infarction is markedly depressed and, in the absence of acute interventions, does not change with time. Acute interventions are likely to restore oxidative metabolism in jeopardized myocardium and can therefore be evaluated with the approach developed here. Accordingly, quantification of myocardial oxygen consumption with [^{11}C]acetate and positron tomography offers promise for objective, noninvasive characterization of the relative benefits of diverse interventions designed to salvage

jeopardized, ischemic myocardium. In addition, the approach developed should be useful for evaluating regional MVO_2 and metabolic oxidative reserve in the hearts of patients with cardiac disease of diverse etiologies and their response to therapy.

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