Regional Myocardial Oxygen Consumption Determined Noninvasively in Humans With [1-\textsuperscript{11}C]Acetate and Dynamic Positron Tomography

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Experimental studies of animals have previously demonstrated the validity of [1-\textsuperscript{11}C]acetate as a tracer of oxidative metabolism for use with positron emission tomography. The present study was undertaken to define in normal human volunteers the relation between myocardial clearance kinetics of [1-\textsuperscript{11}C]acetate, and the rate-pressure product as an index of myocardial oxygen consumption. Twenty-two studies were performed of 12 volunteers. The rate-pressure product was increased with continuous supine bicycle exercise in six studies. Of the 16 resting studies, seven were performed in the fasted state and nine following an oral glucose load, to define possible effects of substrate availability on the tracer-tissue kinetics. Myocardial tissue time-activity curves were biexponential. Clearance of activity was homogeneous throughout the myocardium. The rate constants $k_0$, obtained from biexponential fitting, and $k_{mono}$ obtained by monoexponential fitting of the initial linear portion of the time-activity curves, correlated well with the rate-pressure product. Although the correlation coefficient was higher for $k_0$ than for $k_{mono}$ (0.95 vs. 0.91), analysis on a sectorial basis showed less regional variability in $k_{mono}$. This suggests that $k_{mono}$, which is more practical than $k_0$, because it requires shorter acquisition times, may be more clinically and experimentally useful for detection of myocardial segments with abnormal oxygen consumption. Overall, changes in myocardial substrate supply were without significant effect on the relation between the rate constants ($k_0$ and $k_{mono}$) and the rate-pressure product, although a small decrease in $k_{mono}$/rate-pressure product was observed following oral glucose by paired analysis in four subjects. It is concluded that [1-\textsuperscript{11}C]acetate can be used for the noninvasive measurement of myocardial oxygen consumption in humans with positron emission tomography, and, thus, has clinical and experimental potential as a tool for the understanding and diagnosis of myocardial disease. (Circulation 1989;80:863–872)

Mitochondrial oxidation of intermediary substrates is impaired in myocardial ischemia.\textsuperscript{1,2} Clinical efforts to characterize this impairment in oxidative function noninvasively have incorporated analyses of radiolabeled fatty acid kinetics in myocardium.\textsuperscript{3–12} Although characteristic changes in uptake and clearance of labeled fatty acids have been observed in myocardial ischemia, these changes reflect the net effect of diminished oxygen supply on each of the steps in fatty acid utilization and are not specific for impairment of $\beta$-oxidation.\textsuperscript{2} Uptake and clearance of labeled fatty acids are markedly affected by substrate availability,\textsuperscript{13–15} in addition to myocardial workload.\textsuperscript{16} To characterize more precisely the metabolic state of the myocardium, a selective tracer of mitochondrial oxidative function is required.

In the early 1980s, [1-\textsuperscript{11}C]acetate was examined both in animal studies\textsuperscript{17} and in patients with coro-
nary heart disease.18 In these largely qualitative studies, a dependency of myocardial washout of [1-14C]acetate on myocardial oxygen consumption was found. Studies of isolated rabbit hearts using [1-14C]acetate19 and of isolated rat hearts using [1-14C]acetate20 established a linear correlation between myocardial acetate clearance and myocardial oxygen consumption under a variety of different flow and metabolic conditions. Furthermore, it was shown that, by far the largest fraction of tracer leaving the myocardium after application of [1-14C]acetate and [1-14C]acetate was in the form of labeled CO2.19,20

Recent studies with positron emission tomography have indicated that [1-14C]acetate traces tricarboxylic acid (TCA) cycle activity in canine myocardium, as well.21-25 This tracer might, therefore, prove clinically useful as an indicator of myocardial oxidative capacity. In experimental canine preparations, the clearance of [1-14C]acetate from myocardium is biexponential.22,26 The decay constant of the initial component of the clearance curve was found to be linearly related to myocardial oxygen consumption. Thus, analysis of [1-14C]acetate kinetics should accurately reflect myocardial oxygen consumption and, therefore, mitochondrial oxidative flux in human subjects. To validate the clinical utility of this tracer, we used it with dynamic positron emission tomography in healthy volunteers under varying metabolic and work-load conditions to establish high temporal resolution [1-14C]acetate time-activity curves. We correlated the parameters of time-activity curve fitting with [1-14C]acetate to estimates of myocardial oxygen consumption derived from rate-pressure product (RPP) measurements.27-36

The goals of the study were, thus, to determine the relation between acetate clearance kinetics and the RPP over a range of cardiac work and to investigate the effects of changes in plasma substrate concentration on this relation.

Methods

Study Population

Twelve healthy male volunteers, 18-31 years old (mean, 24.1±4.7 years), were enrolled in the study protocol. Each volunteer underwent a structured interview to elicit a complete medical history. None had diabetes or thyroid disease, used prescription or illicit drugs, had a history of chest pain, had abnormalities noted on prior physical examination or electrocardiogram, or had known cardiac risk factors. Physical examinations and resting electrocardiograms were normal for each individual. Average height of the population was 179.9±3.0 cm (range, 173-183 cm), and average weight was 76.4±8.4 kg (range, 62.7±90.0 kg). Mean body surface area was 1.95±0.10 m2.

Positron Emission Tomography

Positron emission tomography was performed using the UCLA ECAT III whole body tomograph, which has been previously described.27 The tomograph has 1,024 detectors arranged in two circular rings around a 65-cm diameter opening, allowing the simultaneous acquisition of three image planes (two directly and an interpolated center plane). Following the intravenous administration of 5-15 mCi [1-14C]acetate as a bolus spread over 30 seconds, six sets of positron tomographic images were obtained for 30 seconds each, followed by eight image sets for 60 seconds each, five image sets for 120 seconds each, and seven image sets for 240 seconds each (total imaging time, 49 minutes). Heart rate and cuff blood pressure measurements were recorded every 5-10 minutes throughout the imaging period. Systolic arterial blood pressure averaged from 8 to 12 measurements was multiplied by the mean heart rate to determine the RPP. Venous blood samples for glucose, free fatty acid, lactate, oxygen saturation, and hemoglobin levels were obtained at 2 and 45 minutes following tracer administration.

Study Protocol

ECG was monitored throughout each study. The 12 subjects were fasted overnight. Seven of the subjects were studied initially in the fasted state, and five subjects were given a 50-g oral glucose load 30 minutes prior to injection of [1-14C]acetate. In 10 of the volunteers, a second injection of [1-14C]acetate was performed 60 minutes after the first injection and image acquisition repeated. Due to the short physical half-life (20.4 minutes) and rapid biologic clearance of 14C activity from myocardium, residual activity from the first [1-14C]acetate injection was less than 3% at the time of the second injection. Thus, residual activity at that time was negligible. Six subjects, four previously given oral glucose and two previously fasted, were imaged again during continuous supine exercise. Exercise was performed with a bicycle ergometer clamped to the sides of the tomograph bed. Two adjustable handles were attached to the sides of the bed, enabling the volunteer to anchor himself in one position. In this way, patient movement was minimized during exercise imaging. Exercise was begun with no resistance, and the work load increased over the next several minutes to a level that the subject believed he could maintain for 49 minutes. Once a steady state had been achieved, dynamic positron tomographic imaging was performed in a fashion identical to that of the baseline study. Work loads ranged from 25 to 130 W, with a mean of 62±43 W. There were no arrhythmias or repolarization changes during rest and exercise.

For four of the volunteers, studied initially following an overnight fast, a second [1-14C]acetate study was performed in the resting state 30 minutes following a 50-g oral glucose load, using the same image acquisition protocol. Thus, a total of 22 studies were performed of the 12 volunteers, consisting of seven fasting studies, nine postoral glucose studies, and six studies during exercise. The
six exercise studies were combined into a single group because there were no significant differences in plasma substrate levels during the exercise study between the four individuals previously glucose loaded and the two fasted. These three study groups were, thus, defined as rest at the fasted state, rest after oral glucose administration, and exercise conditions. For both the exercise and metabolic interventions, heart rate and cuff blood pressure measurements were obtained every 3 minutes at the beginning and every 7 minutes at the end of each experiment in a fashion identical to the baseline study. Blood samples were withdrawn twice, at 2 minutes and at 45 minutes after tracer injection. The study protocol was approved by the Human Subject Protection Committee of the University of California, Los Angeles, and each volunteer signed an informed consent form approved by that committee.

Image Analysis

A maximum of three contiguous cross-sectional images were analyzed per study. The midventricular level was analyzed in each study, the other levels only if they contained a considerable amount of myocardium. The images were analyzed using a semiautomated edge-detection routine. Following manual assignment of ellipses on an image showing optimal distinction between myocardium and blood pool to approximate the inner and outer myocardial boundaries, the routine automatically defined the endocardial and epicardial borders, using a Gaussian fitting routine, and divided the left ventricular myocardium into eight equal sectors. An alignment along the long axis was assigned to this circumferential profile by the investigator, and sectorial subdivision started at the left lower line of this long axis in a clockwise fashion. An additional small region of interest was assigned to the center of the left ventricular blood pool by the investigator in the position of lowest activity on a late image to reduce spillover from the myocardium to the region of interest in the blood pool.\(^{39}\) Tissue \(^{11}\)C time-activity curves were then generated for each myocardial sector and for arterial blood. Correction for loss of counts due to the partial volume effect\(^{40}\) was performed using the regional wall thickness determined by the edge-detection routine and a recovery coefficient derived from phantom calibration experiments.\(^{40}\) It should be noted that correction for partial volume introduces a constant that does not affect the determination of rate constants for tracer clearance. The time-activity curves were also corrected for physical decay of \(^{11}\)C activity. Using iterative least-square routines, regional myocardial time-activity curves and mean time-activity curves for each slice were then fitted biexponentially for calculating clearance rate constants (defined as \(k_1\) and \(k_2\)) and clearance half-times for the first and second exponentials (Figure 1). The linear portion of the first exponential was also fitted monoexponentially to give \(k_{\text{mono}}\) (Figure 1). The linear portion of the curve was determined visually from semilogarithmic plots of the data for the whole plane. Rate constants were also determined after subtraction of spillover activity from the blood pool into the myocardial regions of interest. The spillover fraction or the fraction of activity contained in the blood pool that is falsely projected into the myocardial region of interest depends on both blood in myocardial vessels and the limited spatial resolution of the imaging device. A spillover fraction of 42% of blood-pool activity was used. This factor was determined with C\(^{15}\)O labeling of red blood cells and PET imaging in 11 dogs in which spillover of activity from blood pool to myocardium was 42.0±8.6% (C. Niehaber, unpublished observations). Monoexponential and biexponential fitting of the summed time-activity curves for the eight sectors was used to give mean rate constants for the overall myocardial plane.

Data Analysis

Values are given as mean±SD. For statistical analysis, comparison of groups was by analysis of variance (ANOVA), followed by Bonferroni’s modified \(t\) test when significant intergroup differences were indicated by ANOVA.\(^{41}\) Paired samples were compared using Student’s \(t\) test for paired data. Regression analysis was by least-squares fitting. Statistical significance was indicated by \(p\) values equal to or less than 0.05.

Results

Hemodynamic and Metabolic Parameters

Hemodynamic and metabolic results for the 22 studies are summarized in Table 1. Exercise (group 3) significantly increased heart rate by 93%, systolic pressure by 37%, and RPP by 164%, compared with resting studies. In the resting state (groups 1 and 2), there were no significant hemodynamic differences between studies in the fasted state (group 1) and those postoral glucose (group 2). However, in the four volunteers who were studied sequentially in the fasted state and then postglucose, small but statistically significant increases in heart rate (from 52±8 beats/min to 58±8 beats/min; \(p<0.001\)) and RPP (from 5,511±1,102 mm Hg×beats/min to 6,539±1,427 mm Hg×beats/min; \(p<0.01\)) were observed with glucose by paired analysis. This increase is likely to reflect higher cardiac demand in response to elevated intestinal blood flow in the absorptive state.\(^{42}\)

Administration of oral glucose increased plasma glucose levels by 54% and decreased plasma free fatty acid levels by 55% in venous blood (Table 1). No other significant hemodynamic or metabolic differences were observed. Hemodynamic parameters remained stable throughout all experiments with a mean SD of ±2.4% for blood pressure and ±5.5% for heart rate.
Positron Emission Tomography

Tomographic images obtained at a midventricular level following intravenous administration of [1-13C]acetate at rest and during continuous supine bicycle exercise in the same subject are shown in Figure 2. In both studies, activity is initially observed in the right and left ventricular blood pools but clears rapidly from blood, moving into the left ventricular myocardium. Visually, subsequent clearance of tracer from tissue appears largely homogeneous in both studies. Also noteworthy is the more rapid disappearance of activity from myocardium in the exercise study.

Average time-activity curves generated for the entire myocardial cross-sectional plane from the volunteer shown in Figure 2 at rest and during exercise are depicted in Figure 3. The exercise study gave very similar blood-pool activity results compared with the study at rest. Peak blood-pool activity was achieved quickly, occurring in the second image 30–60 seconds after the beginning of isotope injection. Overall, there were no significant differences in arterial input function between resting and exercise studies. Myocardial tissue activity reached a maximum later, at 120 seconds in the rest study, before declining biexponentially. In exercise, tissue activity peaked earlier, at 105 seconds, and declined faster.

The time-activity curves obtained from the serial images were fitted both biexponentially, beginning with the point at which phase 1 became linear, and monoexponentially, using only the linear portion of phase 1 (Figure 1). Biexponential fitting of the time-activity curves gave rate constants of 0.100/min (k1) and 0.004/min (k2) (SEE, 0.007) at rest, giving clearance half-times of 7.0 and 196 minutes, respectively, for phases 1 and 2. During exercise, the rate constants increased to 0.222/min and 0.010/min for k1 and k2, respectively (SEE, 0.015), giving clearance half-times of 3.1 minutes and 69 minutes for the two clearance phases. Monoexponential fitting to the initial linear portion of the first exponential gave rate constant kmono of 0.068/min at rest (SEE, 0.006) and 0.144/min during exercise (SEE, 0.008); clearance half-times were 10.2 minutes and 4.8 minutes, respectively.

Blood-pool activity was best fitted with three exponentials; rate constants at rest were 3.54/min, 0.101/min, and 0.014/min, clearance half-times being 12 seconds, 6.9 minutes, and 50 minutes. During exercise, blood-pool rate constants were 3.26/min, 0.15/min, and 0.018/min, giving clearance half-times of 13 seconds, 4.6 minutes, and 39 minutes.

In Table 2, acetate kinetic parameters for the three experimental groups are summarized. Both k1, the rate constant for the first exponential obtained by biexponential fitting, and kmono, the rate constant obtained by monoexponential fitting of phase 1, were increased significantly by exercise. Peak myocardial tissue-tracer levels also occurred significantly earlier in exercise than at rest; a significant inverse relationship was found between RPP and the time to peak tissue activity (y=222–0.0053x, r=0.635, p<0.0015). No significant intergroup differences were found for the blood-pool activity-clearance constants (results not shown).

Tissue-activity data were also fitted after correction for spillover of activity from the blood pool to the myocardium, to determine whether failure to correct for blood-pool contamination of tissue activity would significantly affect the measured kinetics. In mono- and biexponential fitting, rate constants obtained without spillover correction correlated closely with those obtained from spillover-corrected data (r=0.99, y=0.005+1.17x; and r=0.97, y=0.005+1.13x, respectively), with values obtained being approximately 15% lower. However, spillover-corrected time-activity curves were noisier, and biexponential fitting was more difficult, particularly at low work loads when the second exponential is not well resolved. For this reason, nonspillowercorrected data were used for subsequent analysis.

One major goal of the study was a comparison between RPP, as an index of myocardial oxygen consumption, and myocardial [1-13C]acetate washout. The relations between the rate constants for the first exponential, k1 and kmono, and the RPP for the 22 studies are shown in Figure 4. Both rate constants showed a close linear relation with cardiac work, as measured by the RPP. Correlation coefficients were 0.91 and 0.95, respectively, for monoexponentially and biexponentially derived rate constants (p<0.001). The y intercept for the k1 versus RPP plot was negative, whereas for kmono versus RPP, the y intercept was positive.

Another objective of this study was to examine whether [1-13C]acetate clearance-rate constants for a given RPP (MVo2) were independent of substrate availability and, thus, of myocardial substrate consumption. The ratios of kmono/RPP and k1/RPP were, therefore, determined. These ratios should be constant because the relations between the rate constants and RPP are linear. The ratios were plotted against RPP to examine if this relation between k and RPP remained unchanged over the whole range of cardiac work load achieved.
Table 1. Hemodynamics and Substrate Serum Levels

| Conditions          | n  | Heart rate (beats/min) | Systolic pressure (mm Hg) | RPP (beats×mm Hg/min) | Glucose (mmol/l) | Lactate (mmol/l) | Free fatty acid (
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<td>Rest</td>
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<tr>
<td>Fasted (group 1)</td>
<td>7</td>
<td>60±13</td>
<td>108±5</td>
<td>6,516±1,553</td>
<td>4.8±0.7</td>
<td>0.68±0.11</td>
<td>0.38±0.10</td>
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<td>Glucose-loading (group 2)</td>
<td>9</td>
<td>58±8</td>
<td>112±6</td>
<td>6,496±1,154</td>
<td>7.4±1.4*</td>
<td>0.86±0.13</td>
<td>0.17±0.12†</td>
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<tr>
<td>Exercise (group 3)</td>
<td>6</td>
<td>113±16‡</td>
<td>150±17‡</td>
<td>17,198±4,121‡</td>
<td>4.6±0.6</td>
<td>1.09±0.68</td>
<td>0.24±0.14</td>
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Hemodynamic data represent the mean of 8–12 measurements per study. Plasma substrate measurements are the mean of two measurements per study.

n, number of studies.

*p<0.001, vs. fasted and exercise.

†p<0.01, vs. fasted and exercise.

‡p<0.001, vs. fasted and postglucose.

$k_{\text{mono}}$/RPP decreased with increasing RPP (p<0.05), probably because of the positive y intercept of this relation. $k_1$/RPP tended to increase with RPP; however, the relation did not reach significance (p=0.15).

Furthermore, $k_1/k_{\text{mono}}$ was plotted against the RPP to investigate whether both rate constants reflected RPP in the same way over the entire range. As would be expected from the aforementioned relations, $k_1/k_{\text{mono}}$ increased significantly (p<0.001) with increasing RPP (Figure 5). Thus, $k_1$ and $k_{\text{mono}}$ did not represent a given RPP (MV0₂), in all areas the same way, probably due to difficulties in fitting the curves exactly for $k_1$ in the low RPP range and for $k_{\text{mono}}$ in the high RPP range. Thus, this relation appeared to depend on limitations in fitting the time-activity curves.

$k_1$/RPP did not reveal any significant intergroup differences, although the value obtained for the exercise group (group 3) tended to be somewhat higher than for the fasted and postglucose groups (groups 1 and 2) (p=0.07). The k/RPP ratio was used in each metabolic group to rule out that k might represent RPP differently under various metabolic conditions. The changes in substrate blood levels were only moderate, as mentioned before. In addition, paired comparison of the six experiments in which subjects were studied first at rest and then during exercise demonstrated a significant increase in $k_1$/RPP, from 9.4±2.2 to 11.5±2.3/mm Hg/beats/10⁶ (p≤0.025). In contrast, $k_{\text{mono}}$/RPP was similar for all groups, and not significantly different between rest and exercise in the six paired studies (rest, 7.8±1.4/mm Hg/beat/10⁶; exercise, 7.3±1.8/mm Hg/beat/10⁶; NS). Comparison of $k_1$/RPP and $k_{\text{mono}}$/RPP between the fasted and postglucose groups, overall, did not demonstrate any significant differences. However, paired analysis of the four subjects studied at rest and, again, after glucose demonstrated a significant decrease in $k_{\text{mono}}$/RPP following glucose, from 8.6±1.3 to 7.7±1.2/mm Hg/beat/10⁶ (p<0.025), $k_1$/RPP was not different for the two metabolic conditions (9.4±1.0 vs. 9.3±0.7/mm Hg/beat/10⁶).

Regional time-activity curves were also generated for eight myocardial sectors to determine the degree of heterogeneity of acetate clearance kinetics throughout left ventricular myocardium. Regional time-activity curves were fitted both biexponentially and monexponentially, as described for the whole myocardial plane. Regional values of $k_1$ and $k_{\text{mono}}$ were then expressed as a percentage of the respective values obtained for the whole myocardial plane. Figure 6 shows unrolled cross-sectional plots of regional $k_1$ (A) and $k_{\text{mono}}$ (B), normalized to the whole plane values. In both cases acetate kinetics were homogeneous throughout the left ventricular myocardium, with no sectors showing significant deviation from the mean values for $k_1$ or $k_{\text{mono}}$ obtained for the whole plane. However, the sector-to-sector variability was much less for regional $k_{\text{mono}}$, with a SD of 9.0±1.3%, than for $k_1$ (standard deviation, 15.8±3%), reflecting the relative difficulty in fitting biexponentially on a regional basis due to lower counting statistics. In Figure 6, the regional 2 SD range, as depicted with a hatched area in each figure, represents the 95%-confidence interval of intersector variability within each volunteer.

Discussion

Previous studies of animal models, in vitro and in vivo, have demonstrated the potential value of [1-13C]acetate and dynamic PET for the noninvasive measurement of regional oxygen consumption in vivo.21-23 The results obtained in the present study of human volunteers confirm the potential clinical value of [1-13C]acetate and PET. Clearance of 13C activity following bolus injection of [1-13C]acetate was biexponential, in agreement with results obtained in animal studies.19-23 The first exponential has been demonstrated to reflect direct oxidation of [1-13C]acetate via the TCA cycle, whereas the second exponential is thought to represent activity in equilibrium with amino acid pools via transamination of TCA cycle intermediates.43,44 The rate constant for the first exponential of 13C activity clearance has been shown in animal studies to correlate
FIGURE 2. Sequential midventricular cross-sectional tomographic images of myocardial $^{11}$C activity obtained following bolus intravenous administration of $[1-^{11}$C]acetate. Times above the images represent midacquisition times. First two rows: Resting study. Rows 3 and 4: Study during continuous supine bicycle exercise, 25 W. Images 1 and 2 in row 1 and 3 depict tracer accumulation in the right and left ventricular activity, the following images show tracer uptake by the left ventricular myocardium. The septum is seen on the left side, the anterior wall at the top, the lateral wall on the right side. Note that acetate washout from the myocardium takes place much faster with exercise than with rest. At 15 minutes, the myocardium is still visible on the resting study, whereas tracer has practically disappeared from the heart with exercise.

Linearly with myocardial oxygen consumption. In volunteers, a close linear correlation between the rate constant for the first exponential and the RPP was found. Several studies have demonstrated the RPP to be an accurate noninvasive index of myocardial oxygen consumption, with correlation coefficients for $\text{MVO}_2$ ranging from 0.81 to 0.90 in dogs and 0.86 to 0.90 in humans. The range of RPP obtained in the present study corresponds to an $\text{MVO}_2$ range of 5.0 to 25.0 ml/100 g/min. Thus, in agreement with animal studies in which myocardial oxygen consumption was measured directly by the Fick principle and microsphere flow measurement, the rate constant for the first exponential of $^{11}$C clearance following intravenous $[1-^{11}$C]acetate administration correlates well with myocardial oxygen consumption, assessed in this case indirectly by the RPP.

Both $k_{\text{mono}}$, the rate constant obtained by monoeponential fitting of the short linear portion of the first exponential, and $k_1$, the rate constant for the first exponential obtained by biexponential fitting of the time-activity curves, correlated well with the

FIGURE 3. Myocardial time-activity curves derived from the serial images in Figure 2. Myocardial activity was determined from the mean activity of the eight sectors. Note that the $^{11}$C acetate clearance curve is markedly steeper with exercise than at rest, as indicated by a higher $k_1$ value. $k_2$ values were 0.004/min for the resting and 0.008/min for the exercise studies.
TABLE 2. [1-13C]Acetate Clearance Parameters

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<th>$n$</th>
<th>$t_{max}$ (s)</th>
<th>$k_1$ (1/min)</th>
<th>$k_{mono}$ (1/min)</th>
<th>$k_1$/RPP (1/mm Hg/beat/10^6)</th>
<th>$k_{mono}$/RPP (1/mm Hg/beat/10^6)</th>
<th>$k_1$/k_{mono} (1/mm Hg/beat/10^6)</th>
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<tr>
<td>Rest</td>
<td>7</td>
<td>189±34</td>
<td>0.059±0.016</td>
<td>0.048±0.004</td>
<td>9.1±1.9</td>
<td>7.7±1.6</td>
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<td>Fasted (group 1)</td>
<td>9</td>
<td>195±35</td>
<td>0.064±0.017</td>
<td>0.052±0.009</td>
<td>9.8±1.3</td>
<td>8.1±0.9</td>
<td>1.21±0.14</td>
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<tr>
<td>Postglucose (group 2)</td>
<td>6</td>
<td>120±16*</td>
<td>0.195±0.043†</td>
<td>0.121±0.025*</td>
<td>11.5±2.3</td>
<td>7.3±1.8</td>
<td>1.62±0.19</td>
</tr>
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*p<0.0025, vs. fasted and postglucose.
†p<0.001, vs. fasted and postglucose.
$ t_{max}$, time from injection to maximal myocardial activity.

RPP, although the correlation coefficient was better for $k_1$. At low myocardial work loads, biexponential fitting tends to be inaccurate, because fitting of the second exponential is difficult due to the longer duration of the long first clearance phase. This should lead to an underestimation of $k_1$, possibly contributing to the tendency of $k_1$/RPP to increase with RPP, as the accuracy of fitting the second exponential improves. Conversely, monoeponential fitting is less accurate at high work loads, when the first exponential is short and steep and tends to underestimate the slope of the first exponential. The negative slope of $k_{mono}$/RPP may, again, reflect this at least in part. Comparisons of MVO2 and RPP in the literature have reported both negative28,29,32,33 and positive34,36 $y$ intercepts. It is, therefore, impossible to judge the effect of the true intercept on the expected relation between acetate kinetics and RPP.

Comparison of rate constants obtained in fasting and glucose loading did not reveal any striking effects on the relation between the rate constants and the RPP. Whereas paired analysis in the four subjects studied first fasted and, then, after oral glucose showed a significant decrease in $k_{mono}$/RPP in response to glucose, the RPP also increased in response to glucose in these subjects. Because increasing RPP was shown to correlate with decreasing $k_{mono}$/RPP, the small change in response to glucose probably reflects the hemodynamic alterations, with consequent change in the accuracy of the monoeponential fitting. This is supported by the absence of a significant alteration in $k_1$/RPP in these subjects in response to glucose.

Regional kinetic analysis of time-activity curves confirmed the impression obtained visually that clearance of activity following bolus injection of [1-13C]acetate was homogeneous. Comparison of the regional variability of rate constants for the first exponential of acetate clearance obtained by monoeponential and biexponential fitting demonstrated that monoeponential fitting of the linear portion of the exponential gave much less region-to-region variability than biexponential fitting of the whole curve. Theoretically, the use of the rate constant $k_1$ appears more appropriate than measuring the artificial rate constant $k_{mono}$ because $k_1$ represents one of the two clearance phases. Calculation of $k_1$, however, is often inadequate because of difficulties in fitting accurately the second exponential curve component using regional time-activity

**Figure 4.** Relation between myocardial rate pressure product (RPP) and rate constants for the first exponential of 13C activity clearance following [1-13C]acetate administration. Panel A: $k_1$, determined by biexponential fitting of the time activity curve. Panel B: $k_{mono}$ determined by fitting the short linear portion of the first exponential.

**Figure 5.** Effect of myocardial rate pressure product on the relation between $k_1$ and $k_{mono}$.
The short segment of the time-activity curve available for fitting in this study. The turnover rate for this second component thus appeared to be relatively constant. For the six exercise studies, the relative size of the first exponential, determined by extrapolation of the two exponentials back to the time of peak tissue activity, was $84.6 \pm 6.6\%$, very similar to the results obtained in closed-chest dogs ($82.0 \pm 5.1\%$, $n=18$) over a range of metabolic conditions. The rate constant for the second exponential ($k_2$) was $0.016 \pm 0.005$/min for the six exercise studies, giving a clearance half-time of $43.6 \pm 13.7$ minutes. At low work loads, estimates of $k_2$ were unreliable, due to the slow first exponential still making a significant contribution late in the study, again favoring use of $k_{mono}$, as already evidenced by regional variability.

For $[1^{-1}C]acetate$ to be useful as a tracer of overall oxidative metabolism, acetate kinetics must be relatively insensitive to changes in myocardial substrate supply and use. Studies of dogs have demonstrated $k_2/MV_O$ to be modestly but significantly higher in dogs using predominantly carbohydrate than in fatty acid–using dogs, but the difference was small ($<15\%$). No marked effects of nutritional status on the relation between acetate kinetics and RPP were found in the present study. Administration of oral glucose to fasted volunteers led to a small decrease in $k_{mono}/RPP$ by paired analysis, but this was accompanied by an increase in RPP, that also tends to decrease $k_{mono}/RPP$. Thus, although myocardial substrate consumptions were not measured in this study, changes in nutritional state, which are expected to shift myocardial metabolism from fatty acid to carbohydrate metabolism, had little effect on the relation between acetate kinetics and RPP. These differences compared with earlier dog studies employing exact assessment of $MV_O$ might be because RPP is only an estimate rather than a measure of $MV_O$. The relative independency of $k_1$ or $k_{mono}$ for $[1^{-1}C]acetate$ is in marked contrast to results obtained with $[1^{-1}C]palmitate$, in which changes in substrate use have pronounced effects on palmitate kinetics, precluding the use of $[1^{-1}C]palmitate$ for quantitative assessment of oxygen consumption. $[1^{-1}C]acetate$ has an additional advantage in that back-diffusion of nonmetabolized acetate is minimal in ischemia and reperfusion. In contrast, when using $[1^{-1}C]palmitate$ as tracer, back-diffusion of nonmetabolized tracer is a significant problem, causing severe contamination of the tracer-kinetic curves, making interpretation of the metabolic information problematic.

Measurement of the rate constant for the first exponential of $^{13}C$ clearance following intravenous $[1^{-1}C]acetate$ administration permits accurate measurement of regional myocardial oxygen consumption in normal volunteers over a wide range of hemodynamic and metabolic conditions. Monoexponential fitting of the short linear portion of the

**FIGURE 6. Regional myocardial clearance rates of $[1^{-1}C]acetate$, $k_1$, and $k_{mono}$, are unrolled in a midleft ventricular cross-section. Sectorial time-activity curves were fitted biexponentially ($k_1$) or monoexponentially for the short linear portion of the first exponential ($k_{mono}$). The rate constants were then expressed as a percentage of the respective rate constant determined for the whole plane. Sector numbering started at the long axis and proceeded clockwise. SEPT, septum; ANT, anterior wall; LAT, lateral wall.**

Curves, rather than whole plane data with the consequent lower count rates. Clinical studies with $[1^{-1}C]acetate$ and PET are likely to involve normalization of regional acetate-rate constants to values obtained for the whole plane, followed by comparison with a data set obtained in normal volunteers to determine whether regional variability is significant. Thus, monoexponential fitting of the first exponential is likely to be clinically more useful and practical, because the 2 SD range of the normal volunteers is smaller than $k_1$, allowing detection of smaller regional abnormalities of myocardial oxidative metabolism. Additionally, monoexponential fitting can be performed without calculation of a rate constant for the second clearance phase and, thus, permits shorter acquisition times.

It is noteworthy that studies of dogs with $[1^{-1}C]acetate$ demonstrated that the relative size of the second exponential varied little over a wide range of metabolic conditions. Because the contribution of the second exponential does not vary much, $k_{mono}$ is expected to give an accurate reflection of the first exponential. Accurate assessment of the relative size of the second exponential in the current studies was precluded at low myocardial work load by the inability to fit the second exponential accurately. There was no obvious trend between $k_2$ and any hemodynamic parameters, given.
first exponential is more useful for practical purposes, gives less regional variability than biexponential fitting, and is likely to be more accurate, particularly in patients with regional ischemia. In such cases, regional oxygen consumption is low, and the second exponential, thus, is poorly resolved in the time course of the scan, making biexponential fitting inaccurate. The capability of measuring regional myocardial oxygen consumption in vivo will add a new dimension to the study of metabolic disturbances in pathophysiological disease states.

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KEY WORDS • rate-pressure product • cardiac output • metabolism
Regional myocardial oxygen consumption determined noninvasively in humans with \([1-11C]acetate and dynamic positron tomography.

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