Evaluation of Fatty Acid $\Delta^\circ$-Oxidation in Patients With Prior Myocardial Infarction in Relation to Myocardial Blood Flow, Total Oxidative Metabolism, and Left Ventricular Wall Motion

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Background Fatty acid metabolism in patients with myocardial infarction (MI) who undergo coronary reperfusion has not been fully elucidated and was investigated in the present study using positron emission tomography.

Methods and Results The clearance rate constant of $^{11}\text{C}$-acetate (acetate-$K_{\text{mono}}$) and that of $^{11}\text{C}$-palmitate (palmitate-$K_{\text{mono}}$) from the myocardium were calculated using a monoexponential equation in 14 patients with MI. A total of 155 regions of interest were classified based on coefficient of determination ($R^2$) values of monoexponential curves for $^{11}\text{C}$-palmitate clearance: well fitted regions ($R^2 \geq 0.5$) and poorly fitted regions ($R^2 < 0.5$). Regional relative myocardial blood flow calculated from the initial distribution of $^{11}\text{C}$-acetate and left ventricular (LV) wall motion were also evaluated. Peak $^{11}\text{C}$-palmitate uptake (14,434±3,052 vs 12,016±3,088 counts/s, p<0.001) and percent clearance during acquisition (38.2±10.1 vs 23.6±11.4%, p<0.001) were significantly greater in the well fitted regions (n=111) than in the poorly fitted regions (n=44). Acetate-$K_{\text{mono}}$ was significantly higher in the former than in the latter (0.0641±0.0099 vs 0.0476±0.0103 min$^{-1}$, p<0.001). LV wall motion and regional relative blood flow were also significantly greater in the former regions. Palmitate-$K_{\text{mono}}$ in the well fitted regions was significantly higher in normal LV wall motion areas than in hypokinesis areas (0.0363±0.0062 vs 0.0274±0.0057 min$^{-1}$, p<0.001)

Conclusions Maintenance of myocardial fatty acid $\Delta^\circ$-oxidation with better myocardial blood flow is substantial in the preservation of total myocardial oxidative metabolism and LV wall motion in patients with MI. The finding that the early-phase clearance of $^{11}\text{C}$-palmitate is fitted with a monoexponential curve may provide important information in the evaluation of myocardial fatty acid $\Delta^\circ$-oxidation. (Circ J 2005; 69: 1459–1465)

Key Words: Acetate; Metabolism; Myocardial infarction; Palmitate; PET

In normal, well-oxygenated myocardium, fatty acid $\Delta^\circ$-oxidation is the primary pathway for the production of energy for myocardial action. In the ischemic or infarcted myocardium with reperfusion, fatty acid $\Delta^\circ$-oxidation is easily suppressed and glucose metabolism plays the major role in supplying myocardial energy. Thus, $^{11}\text{C}$-palmitate clearance may sensitively detect myocardial ischemia and damage from the viewpoint of fatty acid $\Delta^\circ$-oxidation. However, under the conditions of rich plasma glucose and insulin levels with maintained myocardial oxygen tension, for example, after a meal, the myocardial energy supply shifts from the free fatty acid $\Delta^\circ$-oxidation to oxidative glycolysis. Therefore, a comprehensive understanding of myocardial fatty acid $\Delta^\circ$-oxidation in diseased conditions is needed and in this study, we investigated it in relation to myocardial blood flow, total myocardial oxidative metabolism, and left ventricular (LV) wall motion.

Methods

Subjects The study group comprised 14 patients (11 men, 3 women, age 49-83 years) with prior myocardial infarction (MI) (10 anteroseptal; 4 inferoposterior) who underwent coronary reperfusion therapy by percutaneous coronary angioplasty in the acute phase. In the chronic stage, they underwent selective coronary angiography and biplane left ventriculography (LVG) for reevaluation of the coronary arteries and LV wall motion and then, within 2 months (mean: 24 days, range: 12–56 days) $^{11}\text{C}$-palmitate positron emission tomography (PET) and $^{11}\text{C}$-acetate PET, which were carried out on the same day. Coronary angiography indicated that the culprit lesions of the prior MI were open in all patients and none had significant stenosis (ie, luminal narrowing <50%). The patients’ clinical characteristics are shown in Table 1.

The $^{11}\text{C}$-palmitate PET study was performed after overnight fasting and the patients had a light meal after the study.

All procedures were performed according to the regulations proposed by the Ethical Guidelines Committees of the Nagoya City University Graduate School of Medical Sci-
corrections for dead time and physical decay. These ROIs were generated from serial PET values after the entire LV wall. Time–activity curves of 11C-palmitate in the myocardium, 11C-palmitate is rapidly metabolized by β-oxidation. The PET study was performed using a whole body, multislice positron tomograph (PCT 3600W, Hitachi Medical Co, Tokyo, Japan). This camera has 8 rings that simultaneously provide 15 slices of the tomographic images at 7-mm intervals and an in-plane resolution of 10 mm as full width at half maximum. After obtaining a 20-min transmission scan to correct for attenuation, 370 MBq of 11C-palmitate were administered intravenously for 2 min. A dynamic PET scan was begun 1 min after the start of administration, with acquisition of 20 image frames over 20 min. The images were reconstructed 60 s each. On each patient’s midventricular transaxial image, 11 or 12 regions of interest (ROI) were equidistantly placed to cover the entire LV wall. Time–activity curves of 11C-palmitate in these ROIs were generated from serial PET values after corrections for dead time and physical decay.

11C-Acetate PET

Four hours after the 11C-palmitate PET studies, 370 MBq of 11C-acetate were again administered intravenously for 2 min and 1 min after the beginning of administration, dynamic PET scanning was started and 20 image frames were acquired over 23 min as reported previously. The 11C-acetate PET images were obtained as follows: each of the first 6 frames was acquired over a 30-s period during the first 3 min; each of the next 7 frames was acquired over a 60-s period (3–10 min); finally, each of the last 7 frames was acquired over a 120-s period (10–24 min). On each patient’s midventricular transaxial image, ROIs that corresponded to those used in the 11C-palmitate PET study were placed on the LV wall. Time–activity curves of 11C-acetate were also obtained as before.

Biplane LVG

Biplane (30-degree right anterior oblique and 60-degree left anterior oblique) LVG was performed. Two experienced observers reviewed the wall motion observed in the regions corresponding to the ROIs of the PET studies. Wall motion was scored as follows: normal = 3, hypokinesis = 2, and akinesis = 1.

Data Analysis

11C-Palmitate PET Study

We obtained 11C-palmitate peak counts as an index of initial myocardial 11C-palmitate uptake and calculated a percent clearance of 11C-palmitate during the acquisition in each ROI with the following formula:

\[
\text{Percent clearance (\%)} = \frac{\text{peak counts} - \text{counts at the end of acquisition}}{\text{peak counts}} \times 100
\]

In this relation, 11C-palmitate clearance is explained less than 50% by the time, suggesting 11C-palmitate clearance does not mainly depend on the time course.

It is known that if fatty acid β-oxidation works well in the myocardium, 11C-palmitate is rapidly metabolized by β-oxidation and washed out from the myocardium as 11CO₂ after its injection, and thus prompt 11C-palmitate clearance should be described by a monoexponential function during 20 min after injection. In such regions, the R² value of the exponential relations are expected to be more than 0.5, because β-oxidation produces a rapid decrease of 11C-palmitate counts in a strongly time dependent manner. In

<table>
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<th>Sex</th>
<th>Area</th>
<th>Medication</th>
<th>Blood pressure (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Heart rate-pressure product (mmHg·min⁻¹)</th>
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Inf, inferoposterior; A, aspirin; C, calcium-channel blocker; Ant, anteroseptal; S, statin; ACE, angiotensin-converting enzyme inhibitor; LN, long-acting nitrate; B, ß-blocker; ARB, angiotensin II receptor blocker.
contrast, the finding that $^{11}$C-palmitate clearance is poorly fitted to a monoexponential curve suggests that fatty acid $\beta$-oxidation in the myocardium does not work well. In the regions with impaired fatty acid $\beta$-oxidation, significant back diffusion of $^{11}$C-palmitate from the myocardium to the capillaries and a metabolic shift of $^{11}$C-palmitate from rapid oxidation to incorporation into triglycerides should exist. The continuous back diffusion and extraction in the myocardium may produce scattered $^{11}$C-palmitate activity against the time axis. The metabolic shift is most evidently observed more than 15 min after injection of $^{11}$C-palmitate, which is close to the end of acquisition in our protocol. These factors should slow the $^{11}$C-palmitate clearance with dispersion of its activity from the expected monoexponential regression line by $\beta$-oxidation and should reduce the $R^2$ value until it reaches <0.5. Accordingly, we hypothesized that in regions with an $R^2$ value $\geq 0.5$, fatty acid $\beta$-oxidation works well, whereas in those with an $R^2$ value <0.5, it does not.

$^{11}$C-Acetate PET Study  
Similar to the $^{11}$C-palmitate study, a clearance rate constant for $^{11}$C-acetate (acetate-$K_{mono}$) and a coefficient of determination were calculated from the time–activity curve for each ROI as an index of regional total myocardial oxidative metabolism. A monoexponential curve was also applied to the phase of decreasing $^{11}$C-acetate activity after it had reached its peak count. In the $^{11}$C-acetate PET study, a monoexponential curve fitted the time–activity curve well in all regions. From the counts of $^{11}$C-acetate from 60 to 180 s after its injection, the sum of myocardial uptake of $^{11}$C-acetate in this phase was calculated for each ROI. Then, profiles of percent uptake of $^{11}$C-acetate were generated. We regarded the percent uptake of $^{11}$C-acetate as an index of relative regional myocardial blood flow.

Statistical Analysis  
Data are expressed as mean±standard deviation. Relationships between 2 parameters were evaluated using univariate linear regression analysis. Differences between 2 groups were assessed using unpaired Student’s t-test. Differences among 3 groups were evaluated using one-way ANOVA with a Bonferroni adjustment. Differences with $p$ values less than 0.05 were considered significant.

Results  
In all 155 regions, significant ($p<0.001$) differences were observed in acetate-$K_{mono}$ values among the areas with
normal LV wall motion (0.0694±0.0081 min⁻¹, n=71), the areas with hypokinesis (0.0544±0.0057 min⁻¹, n=63), and those with akinesis (0.0411±0.0091 min⁻¹, n=21) (Fig 1). Relative myocardial blood flow correlated significantly with acetate-Kmono in all regions (r=0.54, p<0.001) (Fig 2).

The heart rate–systolic blood pressure product did not differ between the palmitate and acetate PET studies (9,038±1,797 vs 8,869±2,005 mm Hg·min⁻¹, NS).

Representative ¹¹C-palmitate time–activity curves are shown in Fig 3. There were 2 types: ¹¹C-palmitate clearance from the myocardium that was well fitted to a monoexponential curve (Fig 3A) and poorly fitted (Fig 3B). Peak ¹¹C-palmitate uptake (14,434±3,052 vs 12,016±3,088 counts/s, p<0.001) and percent clearance during acquisition (38.2±10.1 vs 23.6±11.4%, p<0.001) were significantly greater in the regions with well-fitted ¹¹C-palmitate time–activity curves (n=111) than in those with poorly fitted curves (n=44) (Fig 4). Relative myocardial blood flow (86.0±9.2 vs 67.2±17.8%, p<0.001) and acetate-Kmono value (0.0641±0.0099 vs 0.0476±0.0103 min⁻¹, p<0.001) were significantly higher in the former than in the latter. The LV wall motion score was also significantly higher in the former regions (2.64±0.48 vs 1.52±0.51, p<0.001) (Fig 5).

In the 111 regions with well-fitted ¹¹C-palmitate time–activity curves, 71 had normal LV wall motion and 40 had hypokinesis. No region showed akinesis. In contrast, in the 44 regions with poorly fitted ¹¹C-palmitate time–activity curves, 23 had hypokinesis and 21 had akinesis; none showed normal wall motion. In the regions with well-fitted ¹¹C-palmitate time–activity curves, the palmitate-Kmono value was significantly higher in the areas with normal wall motion than in those with hypokinesis (0.0363±0.0062 vs 0.0274±0.0057 min⁻¹, p<0.001) (Fig 6). Acetate-Kmono was also significantly higher (0.0694±0.0081 vs 0.0548±
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0.0047 min⁻¹, p<0.001) and myocardial blood flow was relatively greater in the former regions than in the latter (87.1±7.8 vs 83.9±11.1%, p=0.074). A significant positive correlation between palmitate-Kmono and acetate-Kmono was observed in the 111 regions (r=0.48, p<0.001). In the graph (Fig 7), if attention is paid to the regions with palmitate-Kmono <0.035, one notices that the patients with normal wall motion had higher acetate-Kmono values than those with hypokinetic wall motion. Statistically, acetate-Kmono in the former was significantly higher than in the latter (0.0683±0.0050 vs 0.0548±0.0047 min⁻¹, p<0.001). The relation between the acetate-Kmono and LV wall motion in 44 regions with poorly fitted ¹¹C-palmitate clearance curves is superimposed to the left of the graph. In these regions, we did not calculate palmitate-Kmono values because the statistical meaning of palmitate-Kmono with the R² value of <0.5 was considered to be vague. Interestingly, some of these poorly fitted regions had relatively better acetate-Kmono; however, local LV wall motion in such regions was not normal but hypokinetic.

Significant differences were observed in the R² values of monoexponential fitting for ¹¹C-palmitate clearance among the regions with normal LV wall motion, those with hypokinesis, and those with akinesis (0.78±0.01 vs 0.57±0.22 vs 0.41±0.18, p<0.001). The lower 95% confidence interval (CI) of the mean R² value in the regions with hypokinetic LV wall motion was 0.51. On the other hand, the upper 95% CI of the mean R² value in the regions with akinesis was 0.49. A significant positive correlation was found between the R² values of monoexponential fitting for ¹¹C-palmitate clearance and palmitate-Kmono values (Fig 8).

Discussion

In patients with prior MI who undergo coronary reperfusion therapy, initial myocardial ¹¹C-palmitate uptake is high, with better ¹¹C-palmitate percent clearance in the regions having ¹¹C-palmitate clearance well fitted to a monoexponential curve. In these regions, myocardial blood flow, total myocardial oxidative metabolism, and LV wall motion are preserved. In contrast, these parameters are deteriorated in the regions having poorly fitted ¹¹C-palmitate clearance curves. We also demonstrate that the R² value of 0.5 is a clinically important index for distinguishing those regions with better ¹¹C-palmitate oxidation.

Monoexponential Fitting in the Evaluation of Fatty Acid Oxidation and Total Oxidative Metabolism

In the normal myocardium, oxidation of long-chain fatty acids plays a major role in energy generation, whereas in ischemic or damaged myocardium, oxidation of fatty acid metabolism is easily and greatly suppressed and glucose metabolism becomes the major energy source. Thus, overall myocardial oxidative capacity cannot be assessed by analyzing the metabolism of any one substrate.
It is known that acetate metabolism reflects the activity of the tricarboxylic acid cycle in the mitochondria. Thus, many investigators have reported that the clearance rates of \(^{11}\text{C}\)-acetate evaluated by PET correlate closely with overall myocardial oxygen consumption in normal, ischemic, and infarcted myocardium.\(^{12-17,20-22}\) The clearance rate constant \(K_{\text{mono}}\), calculated by applying a monoexponential equation to the clearance curve of \(^{11}\text{C}\)-acetate, has been used as an index of regional myocardial oxidative capacity.\(^{1-5,12-17}\) On the other hand, fatty acid metabolism can be estimated noninvasively using \(^{11}\text{C}\)-palmitate PET. Several investigators have reported that the clearance curve of \(^{11}\text{C}\)-palmitate is bi-exponential: the early rapid phase reflects \(\beta\)-oxidation of fatty acid and the late slow phase represents turnover of the esterified lipid pool.\(^{8,10,23-25}\) Schöhn et al reported that in canine hearts, the relative extent of the early rapid clearance of \(^{11}\text{C}\)-palmitate to the total clearance and the half-time of the early rapid clearance curve correlate closely with regional myocardial oxygen consumption and also to the rate of \(^{14}\text{CO}_2\) production in normal and ischemic myocardium.\(^{23,24}\) In human studies, because clearance of \(^{11}\text{C}\)-palmitate is slower than in animal hearts, monoexponential curve fitting has often been used for quantitative assessment of the early rapid phase of \(^{11}\text{C}\)-palmitate clearance.\(^{1-6,8}\) Thus, we used the \(K_{\text{mono}}\) of \(^{11}\text{C}\)-palmitate clearance as an index of fatty acid \(\beta\)-oxidation. However, in contrast to \(^{11}\text{C}\)-acetate clearance curve, there were some regions where \(^{11}\text{C}\)-palmitate clearance could not be fitted to a monoexponential curve \((R^2 < 0.5)\). In such regions, we substituted peak \(^{11}\text{C}\)-palmitate uptake and percent clearance of \(^{11}\text{C}\)-palmitate for the \(K_{\text{mono}}\) as indices of palmitate metabolism. The myocardial regions having good fatty acid \(\beta\)-oxidation should have a relatively higher initial \(^{11}\text{C}\)-palmitate uptake and greater percent clearance.\(^{23,24}\)

**Initial Myocardial \(^{11}\text{C}\)-Acetate Uptake and Myocardial Blood Flow**

Because the first-pass extraction fraction of \(^{11}\text{C}\)-acetate is high, the initial uptake of \(^{11}\text{C}\)-acetate correlates with regional myocardial blood flow.\(^{16,18,19,23}\) In the clinical setting, the relative net myocardial uptake of \(^{11}\text{C}\)-acetate 60–180 s after its administration can be used as an index of regional relative myocardial blood flow.\(^{16,18,19}\)

**Relationships Among Myocardial Blood Flow, Fatty Acid \(\beta\)-Oxidation, Total Oxidative Metabolism, and LV Wall Motion**

As we have shown in this study, a significant correlation exists between the regional blood flow and regional total myocardial oxidative metabolism. The regions with good acetate-\(K_{\text{mono}}\) had good LV wall motion. In contrast, the interpretation of the relationships between palmitate \(\beta\)-oxidation, total myocardial oxidative metabolism, and LV regional wall motion may be a little complicated. In the present study, we have demonstrated that relative blood flow and acetate-\(K_{\text{mono}}\) were significantly greater in the regions having well-fitted monoexponential curves for \(^{11}\text{C}\)-palmitate clearance than in those having poorly fitted curves. As shown in Fig 5, in the regions having poorly fitted \(^{11}\text{C}\)-palmitate clearance curves, the initial uptake of \(^{11}\text{C}\)-palmitate was less and the percent clearance of \(^{11}\text{C}\)-palmitate from the myocardium was also less than the values for the segments having well-fitted \(^{11}\text{C}\)-palmitate clearance curves. These findings indicate that fatty acid \(\beta\)-oxidation was depressed in the regions with poorly fitted \(^{11}\text{C}\)-palmitate clearance curves. Thus, we consider that our hypothesis that in regions with an \(R^2\) value \(\geq 0.5\), fatty acid \(\beta\)-oxidation works well, whereas it does not in those with an \(R^2\) value <0.5, is acceptable. As shown in Fig 8, in regions with an \(R^2\) value \(\geq 0.5\), palmitate-\(K_{\text{mono}}\) values were relatively high, whereas in those with an \(R^2\) value <0.5, palmitate-\(K_{\text{mono}}\) values were relatively low. Although one should not clinically use the palmitate-\(K_{\text{mono}}\) in the poorly fitted regions as an index of \(\beta\)-oxidation, this finding may support our hypothesis that in the regions with an \(R^2\) value <0.5, \(^{11}\text{C}\)-palmitate clearance is relatively slow with impaired fatty acid \(\beta\)-oxidation. The \(R^2\) value itself has an aspect as an indicator of the activity of \(^{11}\text{C}\)-palmitate \(\beta\)-oxidation in the myocardium. In the regions with well-fitted monoexponential curves for \(^{11}\text{C}\)-palmitate clearance, palmitate-\(K_{\text{mono}}\) correlated significantly with acetate-\(K_{\text{mono}}\). Palmitate-\(K_{\text{mono}}\) was significantly higher in the LV walls with normal wall motion than in those with hypokinesis. In the akinetic areas, a monoexponential curve could not be fitted for \(^{11}\text{C}\)-palmitate clearance. The threshold \(R^2\) value of 0.5 for monoexponential fitting also should be appropriate from the viewpoint of LV wall motion, because the lower 95% CI of the mean \(R^2\) value in the hypokinetic regions was 0.51 and the upper 95% CI of the mean \(R^2\) value in the akinetic regions was 0.49.

**Energy Source Change in Oxidative Metabolism**

As shown in Fig 7, in the regions with relatively low palmitate-\(K_{\text{mono}}\) (<0.035), the segments with normal wall motion had a higher acetate-\(K_{\text{mono}}\). In addition, several segments that belonged to the poorly fitted regions had hypokinetic wall motion with a relatively higher acetate-\(K_{\text{mono}}\). A change in the metabolic source of oxidation from fatty acids to glucose may have contributed to these findings.\(^3-5\) Further investigation of the quantitative glucose uptake in such regions using \(^{18}\text{F}\)-fluorodeoxyglucose PET is needed.

**Comparison With \(^{123}\text{I}\)15-(p-Iodophenyl)-3-(R.S) Methylpentadecanoic Acid (BMIPP) Single Photon Emission Computed Tomography (SPECT) Imaging**

Resting \(^{123}\text{I}\)-BMIPP myocardial SPECT imaging is able to detect not only coronary stenosis but also coronary spasm without the need for a stress examination.\(^{26}\) Furthermore, the combined use of \(^{123}\text{I}\)-BMIPP and \(^{99m}\text{Tc}\)-tetrofosmin myocardial SPECT can predict the functional recovery of infarcted myocardium after coronary reperfusion therapy.\(^{27}\) The usefulness of \(^{123}\text{I}\)-BMIPP myocardial imaging in patients with coronary artery disease was recently emphasized in the evaluation of myocardial pathophysiology.\(^{26-28}\) The quantitative information regarding myocardial energy metabolism that we showed in this study may assist in the interpretation of \(^{123}\text{I}\)-BMIPP myocardial SPECT images in patients having coronary artery disease, although \(^{123}\text{I}\)-BMIPP imaging does not directly reflect myocardial \(\beta\)-oxidation, but rather fatty acid uptake and the turnover rate of triglycerides.\(^{29}\) Methyl branching of the fatty acid chain retains the compounds in the myocardium while protecting against metabolism by \(\beta\)-oxidation.\(^{29}\) Accordingly, the trapped \(^{123}\text{I}\)-BMIPP is incorporated into triglycerides and stays in the myocardium without rapid clearance, providing excellent myocardial images.\(^{29}\) As the incorporation of triglyceride is an energy-dependent process, insufficient
energy supply with deteriorated fatty acid ω-oxidation may provoke reduced or no 123I-BMIPP uptake by the myocardium. However, it should be realized that myocardial energy production can be evaluated by the total oxidative metabolism using the acetate-K_mono. In this study we demonstrated a comprehensive understanding of the relationship between fatty acid ω-oxidation and total oxidative metabolism.

Conclusion

In patients with prior MI and reperfusion therapy, the finding that the early-phase clearance of 11C-palmitate is fitted to a monoexponential curve may provide substantial information for the evaluation of myocardial fatty acid ω-oxidation. Acetate-K_mono and LV wall motion are better in the regions where the early-phase clearance of 11C-palmitate fits a monoexponential curve well. Maintained myocardial fatty acid ω-oxidation is important in preserving total myocardial oxidative metabolism and LV wall motion.

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