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Metabolic reserve in normal myocardium assessed by positron emission tomography with C-11 palmitate

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Positron emission tomography (PET) with C-11 palmitate has been used in estimating the myocardial utilization of free fatty acid. To assess the metabolic reserve in normal subjects, a PET study was performed at control and during dobutamine infusion at 2 hour intervals in 5 normal subjects. Following monoexponential curve fitting of the time activity curve of the myocardium, the clearance half time (min) and residual fraction (%) were calculated as indices of β-oxydation of free fatty acid. A significant increase in the heart rate and systolic blood pressure were observed during dobutamine infusion (65 ± 5 vs 100 ± 29 bpm, $p<0.05$ and 119 ± 12 vs 144 ± 16 mmHg, $p<0.01$, respectively). The clearance half time and the residual fraction were significantly decreased (23.4 ± 2.6 vs 15.8 ± 2.3 min and 67.0 ± 2.5 vs 58.6 ± 4.0%, $p<0.05$, each). When the left ventricular myocardium was divided into 4 segments, these indices were similar at control and uniformly decreased without regional differences during dobutamine infusion. These data suggest that β-oxydation of free fatty acid may be uniformly increased in the left ventricular myocardium in relation to the increase in cardiac work in normal subjects. PET with C-11 palmitate at control and during dobutamine infusion is considered to be promising in assessing metabolic reserve in the myocardium.

Key words: emission computed tomography, C-11 palmitate, fatty acid metabolism, dobutamine

INTRODUCTION

FREE FATTY ACID is a major energy substrate in the well-oxygenated myocardium. Positron emission tomography with C-11 palmitate has been used in assessing fatty acid metabolism in normal subjects and in various cardiac disorders *in vivo*.[1–8] The experimental and clinical studies showed two exponential clearance curves from the myocardium after administration of the tracer. The first component is considered to be related to the release of C-11 carbon dioxide and thus to reflect β-oxydation of free acid, while the second component may reflect incorporation of the tracer into the endogenous lipid pool.[6–8] Under various conditions, PET with C-11 palmitate showed a difference in clearance indicating changes in free fatty acid utilization.[9,10] The PET study under cardiac pacing appears to be a useful means for identifying changes in metabolic reserve in patients with coronary artery disease.[10] To extend this idea, we performed a PET study with C-11 palmitate under dobutamine infusion which is less invasive and feasible to be applied to most patients. The purpose of this study is to introduce our method and to determine the normal response during dobutamine infusion.

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METHODS

Subjects studied

We studied 3 male volunteers and 2 patients with a mean age of 45.4 (range 37 to 73) years with normal

coronary arteries on coronary angiogram. Each subject gave written informed consent approved by the Kyoto University Human Study Committee.

Study protocol

Each subject fasted for at least 5 hours to enhance myocardial utilization of fatty acid. The PET study was performed with a whole body PET camera (Positologica III, Hitachi Medico. Co., Tokyo, Japan).[11] It has 4 rings providing 7 tomographic slices at 16 mm intervals. The intrinsic spatial resolution in the tomographic plane was 7.6 mm FWHM at the center and the axial resolution was 12 mm FWHM. Each subject was positioned on the PET camera by the ultrasound technique. Transmission scan was performed for accurate correction of photon attenuation. Two sets of emission scans were obtained at control and during dobutamine infusion. Before each study, the heart rate and the blood pressure were measured to estimate cardiac work load. Venous blood was drawn to measure glucose, insulin and non-esterified fatty acid (NEFA) levels.[12] Immediately after the first injection of 370 MBq of C-11 palmitate, serial dynamic scan was taken for 40 minutes. Two hours after completion of the control study, intravenous infusion of dobutamine began at 5 μg/kg/min and was increased by 5 μg/kg/min every 5 minutes while monitoring the heart rate, blood pressure and 12 leads of the ECG.[13,14] When the heart rate reached 120 bpm or systolic blood pressure reached 160 mmHg, the second injection of C-11 palmitate was performed and another serial dynamic PET scan was acquired for 30–40 minutes. The dobutamine was constantly infused during the PET study, while monitoring the heart rate, blood pressure and ECG.

Data analysis

Four square regions of interest (2.2 by 2.2 cm) were assigned in the septal, anterior, lateral and posterior regions of the left ventricular myocardium.

Regional myocardial time activity curves were generated from the serial PET images. From these time activity curves, three variables were determined, including the peak activity, the half time of the early rapid clearance phase, and the fraction of the activity remaining in the myocardium at the end of the early rapid phase as a percentage of the maximal activity (residual fraction). Monoexponential curve fitting was performed to calculate the clearance half time of the early rapid phase and the residual fraction by a least square fitting technique (Fig. 1). These curve analyses were based on the serial PET images at control and during dobutamine infusion.

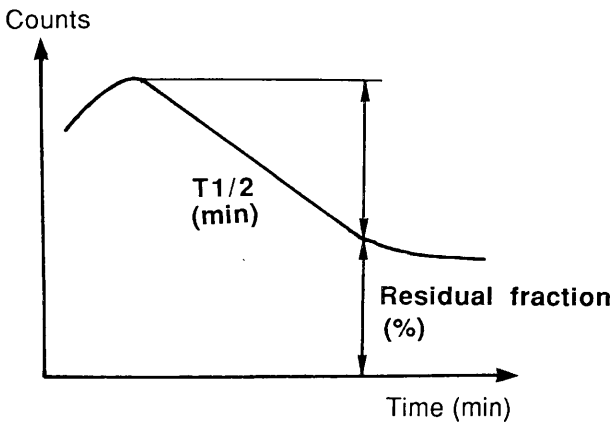

Fig. 1 Schematic curve of C-11 palmitate clearance from the myocardium and two indices calculated from the curve: Clearance half time (T1/2) and Residual fraction of the early clearance component.

Table 1 Hemodynamic and PET results at control and during dobutamine infusion

	Control	Dobutamine
Heart rate (bpm)	65±5	100±29*
SBP (mmHg)	119±12	144±16#
Pressure rate product	7,670±360	14,160±3,570#
Glucose (mg/d*l*)	102±14	94±4
NEFA (μEq/L)	508±322	744±265
Insulin (μU/m*l*)	7.9±3.0	7.0±2.0
Clearance half time (min)	23.4±2.6	15.8±2.3*
Residual fraction (%)	67.0±2.5	58.6±4.0*

SBP=systolic blood pressure; NEFA=nonesterified fatty acid. (*$p<0.05$; #$p<0.01$)

Statistical analysis

Mean values were given with standard deviations. A paired Student t-test was used to compare observation within the same patient. Significant difference was considered to be present when the p value was less than 0.05.

RESULTS

No complaints were observed during dobutamine infusion, except slight palpitation in two subjects. The hemodynamic data and PET indices at control and during dobutamine infusion were shown in Table 1.

The heart rate and systolic blood pressure were significantly increased during dobutamine infusion (65±5 vs 100±29 bpm, $p<0.05$ and 119±12 vs 144±16 mmHg, $p<0.01$). Thus, the pressure rate product was also increased (7,670±360 vs 14,160± 3,570) ($p<0.01$). data suggest that dobutamine infusion significantly increased cardiac work, as compared to the control state.

Venous glucose levels at control (102±14 mg/dl) and during dobutamine infusion (94±4 mg/dl) did not differ. Similarly, venous NEFA and insulin levels were similar in both studies (Table 1).

The serial PET images clearly showed left ventricular myocardium within 5 minutes after tracer injection and gradually cleared from the myocardium both at control and during dobutamine infusion (Fig. 2). The representative time activity curves of the myocardium at control and during dobutamine infusion are shown in Fig. 3. The clearance was accelerated during dobutamine infusion, as compared to the control study. The clearance half time of C-11 palmitate was 23.4±2.6 min at control, which was significantly shortened during dobutamine infusion (15.8±2.3 min, $p<0.05$) (Fig. 4). The residual fraction was 67.0±2.5% at control and was decreased to 58.6±4.0% during dobutamine infusion ($p<0.05$) (Fig. 4).

The segmental analysis was also performed after dividing the left ventricular myocardium into 4 segments (Table 2). The clearance half time in each segment significantly decreased during dobutamine infusion ($p<0.05$, each). The residual fraction also decreased during dobutamine infusion ($p<0.05$ in septal, anterior and posterior segments and $p=0.07$ in lateral segment). In addition, the clearance half

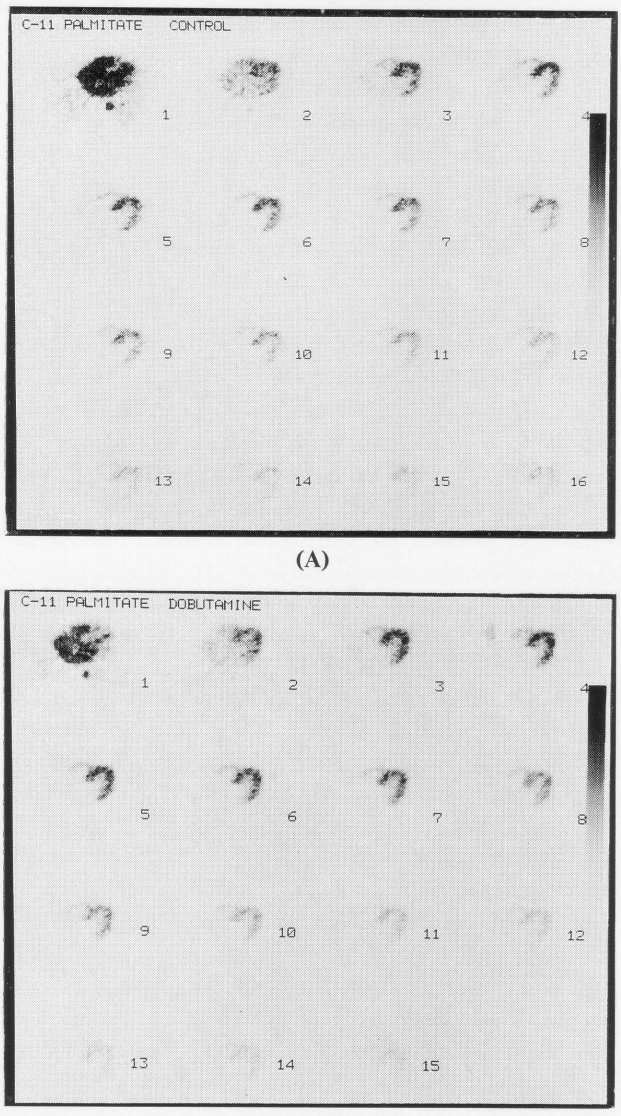

Fig. 2 Serial dynamic PET images (2 min/frame) of a normal subject after C-11 palmitate injection at control (A) and during dobutamine infusion (B). The left ventricular myocardium is clearly visualized within 5 minutes and the tracer is uniformly washed out of the myocardium in both studies.

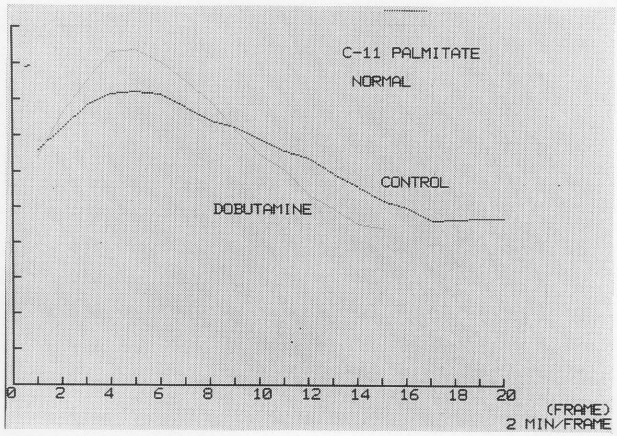

Fig. 3 The clearance time activity curve for the left ventricular myocardium at control and during dobutamine infusion in the same study as shown in Fig. 2. Note the more rapid clearance from the myocardium during dobutamine infusion.

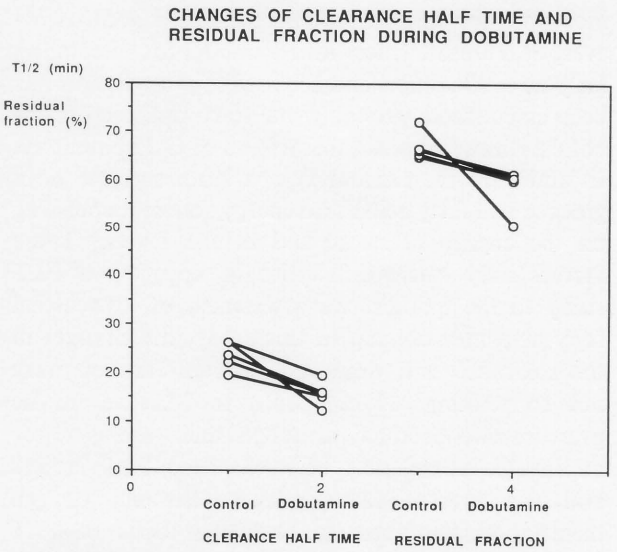

Fig. 4 The clearance half time and residual fraction at control and during dobutamine infusion in 5 normal subjects.

Table 2 Regional values for clearance half time and residual fraction of C-11 palmitate at control and during dobutamine infusion

Regions	Clearance half time		Residual fraction	
	Control	Dobutamine	Control	Dobutamine
Septal	26.1±4.7	15.7±2.5*	67.2±3.5	58.2±4.2*
Anterior	25.7±4.5	14.5±2.6*	66.2±1.9	57.8±5.3*
Lateral	25.7±4.5	15.2±2.5*	66.0±3.2	57.8±5.7§
Posterior	26.4±4.0	16.0±2.5*	70.2±3.9	60.4±3.0*

(*$p<0.05$; §$p=0.07$)

time was homogeneous both at control and during dobutamine infusion among the 4 segments. Similarly, the residual fraction was homogeneous in both PET studies. Thus, there seems to be no regional difference in free fatty acid utilization either at rest or during dobutamine infusion in normal subjects.

DISCUSSION

The present study indicates that the slope and fraction of the early clearance component of C-11 palmitate from the left ventricular myocardium, appears to be related to cardiac work. In addition, the regional analysis of C-11 palmitate kinetics demonstrated the uniform clearance of C-11 palmmitate from the myocardium both at rest and during dobutamine infusion, indicating homogeneous utilization of free fatty acid in the normal myocardium in both conditions.

Previous animal experiments with PET showed biexponential clearance of C-11 palmitate from the myocardium.[6–8] The early component is considered to be related to β-oxydation of fatty acid, while the late component is considered to be related to the incorporation into the endogenous lipid pool. However, no accurate tracer kinetic model for calculating fatty acid utilization and the rate of β-oxydation has been established, probably due to complicated metabolic pathway after administration of C-11 palmitate. In addition, the normal myocardium can use both glucose and fatty acid as an energy source, depending on the energy substrate and insulin levels.[9] These factors may cause difficulties in applying a PET study to the quantitative assessment of myocardial fatty acid metabolism. In this study, the changes in the clearance half time and residual fraction were not so striking, as compared to increase in the pressure-rate product, although there seems to be an inverse correlation between these PET indices and the pressure-rate product. Instead, oxygen metabolism has recently been the focus of PET studies with C-11 acetate in many institutions, due to the ease of preparation of the tracer, simple kinetic models, and more direct measurement of myocardial metabolism unrelated to the energy substrate levels.[15–17]

However, since fatty acid is a major energy source for the normal myocardium in the fasting condition, fatty acid utilization has the potential to be a sensitive marker for the detection of cardiac abnormalities. Thus, it should be of utmost importance to provide a simple and reliable index for the estimation of fatty acid metabolism *in vivo* with PET. The present study indicates that the slope and fraction of the early clearance component of C-11 palmitate related well with cardiac work in normal subjects. Dobutamine infusion decreased the clearance half time by 30–40% and the residual fraction by 10–15%. Similar responses were observed in the regional myocardium. Thus, there was a significant metabolic reserve in the normal myocardium. In addition, the rate of β-oxydation seems to be homogeneous within the left ventricular myocardium without regional differences either at control or during dobutamine infusion. These studies in normal subjects will help to understand the pathophysiology and to identify impaired metabolic reserve in patients with various cardiac disorders in the near future.

Dobutamine increases both the cardiac workload and the coronary blood flow. Thus, the clearance of C-11 palmitate may possibly be augmented due to the increase in the coronary blood flow as well. However, Schon et al[6] demonstrated that the size of the early rapid phase of C-11 palmitate clearance was independent of the myocardial blood flow in his experimental studies with various drug interventions.

The monoexponential fitting technique was applied in this study instead of biexponential curve fitting. We have previously used the biexponential fitting technique in a C-11 palmitate kinetic study.[18] However, since C-11 palmitate clearance was slower in man than in the dog, the late slow clearance phase may not be so accurately identified as the canine experiment. Thus, the slope of the early component and the residual fraction were measured using monoexponential fitting in this study. This approach may provide reasonably accurate estimates of the frac-

tional distribution of the tracer between the two major metabolic pools in the myocardium.[10]

Physical exercise is considered to be the most suitable means to increase in cardiac work. However, maintaining a constant level of exercise for the entire imaging period would be difficult. Grover-McKay et al[10] first used atrial pacing to identify the impaired metabolic reserve assessed by PET and C-11 palmitate in patients with coronary artery disease. Although cardiac pacing takes it possible to maintain the optimal cardiac work load, it seems to be rather invasive which may not be practical to apply it to out-patients or normal volunteers. Dobutamine, a cathecolamine, which increases cardiac contractility[19,20] is often used in treating patients with congestive heart failure[20,21] and as a non-invasive alternative to exercise testing in patients with coronary artery disease.[13,14,21,22] It seems to be relatively safe with little potential for inducing severe arrhythmia. We considered it a most suitable alternative to assessing the metabolic reserve with PET and C-11 palmitate.

The cardiac state should be maintained for 30–40 minutes during the PET study. Each subject was studied in the fasting condition to enhance fatty acid utilization and to maintain the steady state during the study, as compared to the postprandial condition. Venous glucose, insulin and NEFA levels showed that each subject was kept in the fasting condition, and the levels were expected to be constant during the study. In addition, the heart rate and the systolic blood pressure were constant during the PET study under dobutamine infusion.

In conclusion, this preliminary study indicates that β-oxydation of fatty acid assessed by a C-11 palmitate kinetic study may be considered to be homogeneous and uniformly increased during dobutamine infusion in relation to the increase in the cardiac work load in the normal subjects. Thus, a PET study with C-11 palmitate at control and dobutamine infusion is a suitable means for assessing metabolic reserve. This technique is expected to be applied to patients with various cardiac disorders.

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