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*Department of Nuclear Medicine, **Third Department of Internal Medicine,
Kyoto University Faculty of Medicine, Kyoto, Japan

Experimental studies indicated the clearance rate constant of ^{11}C-acetate as an index of regional myocardial oxygen consumption. To assess the response of the clearance rate from the left ventricular (LV) myocardium to the change in plasma substrate levels and to the increase in the cardiac work load in normal subjects, a total of 18 dynamic positron emission tomographic studies were performed at rest in the fasting state (control) (n=7), after oral glucose administration (n=4), and during dobutamine infusion (n=7) in 7 normal volunteers. The clearance rate constant (Kmono) was similar in the control (0.065 ± 0.017 min^{-1}) and glucose loading states (0.059 ± 0.008 min^{-1}), whereas a significant increase in Kmono was observed during dobutamine infusion (0.106 ± 0.018 min^{-1}) ($p<0.01$) in relation to the increase in the pressure-rate product with a correlation coefficient of 0.873 ($p<0.01$). When the LV myocardium was divided into 6 segments, there were no significant differences among the segments in Kmono values in any condition. These normal responses should be valuable for assessing oxidative metabolic reserve and regional changes in oxidative metabolism in patients with coronary artery disease.

Key words: Positron emission tomography, ^{11}C-acetate, myocardial metabolism, dobutamine, oxygen consumption

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with various physiological substrates facilitates the evaluation of regional myocardial metabolism in vivo.[1,2] Fatty acid and exogenous glucose utilizations have been fully investigated by means of PET with ^{11}C-palmitate and ^{18}F-2-fluoro-2-deoxyglucose (FDG).[3-8] However, quantitative measurement of energy metabolism in a kinetic study with these tracers largely

depends on substrate availability and plasma substrate levels. Completely different substrate utilization in the myocardium may be observed in fasting and postprandial conditions.[9]

[11]C-acetate permits the evaluation of flux through the tricarboxylic acid (TCA) cycle, and thus the evaluation of myocardial oxygen consumption.[10-13] Experimental studies suggested that the rapid clearance phase corresponded closely to the release of ^{11}C-carbon dioxide from the myocardium, and thus, to the rate of oxidation of ^{11}C-acetate in the TCA cycle, reflecting oxygen consumption following intravenous administration of ^{11}C-acetate.[10-13] In addition, the clearance rate of ^{11}C-acetate was independent of different plasma substrate levels.[14] Furthermore, recent preliminary studies suggest the value of PET with ^{11}C-acetate in normal subjects and patients with coronary artery disease.[15-18] In addition, in order to estimate the capacity of the

left ventricular (LV) myocardium to augment oxidative metabolism, Henes et al.[16] measured the changes in the clearance rate of ^{11}C-acetate during dobutamine infusion as a marker of oxidative metabolic reserve. To validate the clinical utility of this tracer and to assess normal response to various conditions, dynamic PET following intravenous administration of ^{11}C-acetate was performed in normal volunteers with different substrate levels and work loads.

The present study was designed to assess the clearance rate constant of ^{11}C-acetate from the LV myocardium in normal subjects in fasting and glucose loading conditions, as well as dobutamine infusion in order to evaluate (1) regional heterogeneity of its clearance kinetics, (2) the potential effect of glucose loading on its clearance, and (3) the oxygen metabolic reserve by comparing the clearance rate constant under control and dobutamine infusion in the normal subjects.

METHODS

Subjects studied
We studied 7 male normal volunteers with ages ranging from 23 to 41 years old and a mean of 34.7 years. None of them had a history of cardiac diseases, hypertension or any apparent cardiac symptoms. Each subject gave written informed consent approved by Kyoto University Human Study Committee.

Preparation of ^{11}C-acetate
[11]C-acetate was synthesized according to the procedures reported by Pike et al.[19] with a slight modification. ^{11}C-carbon dioxide was produced from the proton bombardment of nitrogen gas by the $^{14}N(p,a)$ [11]C reaction in an ultra-compact cyclotron (Sumitomo, Model-325), and reacted with methyl magnesium bromide purchased from Tokyo Chemical Industry, Co., Ltd. Following acidic hydrolysis of the reaction mixture with HCl and separation of the HCl layer, the ether layer was extracted with NaOH solution. Ether elimination from the aqueous layer was followed by neutralization with HCl and filtration through a $0.22~\mu$ millipore filter for injection.

Stucy protocol
A total of 18 PET studies were performed. In the control study, each subject fasted for at least 5 hours at rest before the administration of ^{11}C-acetate. In the glucose loading study, four subjects took 75 g of glucose following at least 5 hour fasting approximately 30–50 minutes before the administration of ^{11}C-acetate. Infusion of dobutamine was used instead of physical exercise to increase the myocardial work load constantly over 20 minutes of dynamic

PET acquisition. Intravenous infusion of dobutamine was given to 7 fasted subjects starting at 5 μg/kg/min and increased by 5 μg/kg/min every 5 minutes with cardiac monitoring.[20,21] When the heart rate reached 120 bpm or the systolic blood pressure reached 180 mmHg, ^{11}C-acetate was administered intravenously and serial PET scans were acquired. The dobutamine was constantly infused during the PET study to maintain steady hemodynamic conditions while monitoring the heart rate, blood pressure and ECG. Each study was separated by at least 4 hours to minimize the effects of the previous studies. The order of these three studies (fasting control state, glucose loading state, and dobutamine infusion state) was randomly selected in each subject to eliminate the effects of training on cardiac function.

The PET study was performed with a whole body PET camera (Positologica III or PET 3600 W, Hitachi Medico, Co., Tokyo, Japan). The Positologica III 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.[22] The PET 3600W has 8 rings providing 15 tomographic slices at 7 mm intervals and the intrinsic resolution was 4.6 mm FWHM. Each subject was positioned on the PET camera by the ultrasound technique. A transmission scan was performed to accurately correct photon attenuation. Before each study, the heart rate and the blood pressure were measured to estimate the cardiac work load. Venous blood was drawn to measure plasma glucose, insulin and non-esterified fatty acid (NEFA) levels at the time of ^{11}C-acetate injection.[21] Immediately after intravenous administration of 185 to 370 MBq (5 to 10 mCi) of ^{11}C-acetate, serial dynamic scan was performed, collecting twenty 60 second frames for a period of 20 minutes.

Data analysis
One middle transverse slice where the size of the LV cavity was largest among all the images was selected for analysis. Six square regions of interest (0.75 by 0.75 cm each) were assigned in the posteroseptal, anteroseptal, anterior, anterolateral, lateral and posterolateral regions of the LV myocardium (Fig. 1).

Regional myocardial time activity curves in the total of 6 myocardial segments were generated from the serial PET images after the correction of dead time and physical decay of ^{11}C activity. Using the iterative least-square fitting technique, regional time activity curves were fitted monoexponentially to calculate the clearance rate constant (Kmono). The linear portion of the first exponential fitting was selected visually from semilogarithmic plots of the

data for the whole plane. Since the clearance of blood pool activity was rapid, the spillover activity from the blood pool to the myocardium was considered minimal and was not corrected in this study.
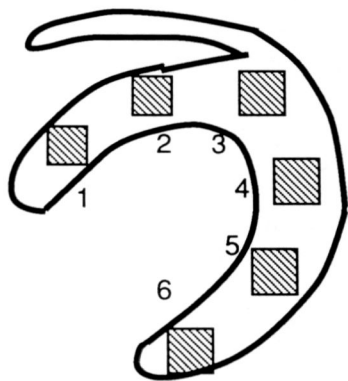
Fig. 1 Schematic presentation of a mid-transverse slice with 6 myocardial regions of interest. 1=posteroseptal, 2=anteroseptal, 3=anterior, 4=anterolateral, 5=lateral, and 6=posterolateral region.

Table 1 Plasma substrate levels in the control, during glucose loading and during dobutamine infusion

	Control(7)	Glucose load(4)	Dobutamine(7)
Glucose (mg/dl)	98±5	133±12*	not measured
NEFA (μEq/L)	848±241	300±67*	not measured
Insulin (μU/ml)	8.6±1.6	58.7±25.9*	not measured

NEFA=nonesterified fatty acid   (*p<0.01)

Monoexponential fitting of the summed time activity curves for the 6 myocardial regions was used to obtain the mean rate constant for the LV myocardium.

Statisticalanalysis
Mean values were given with standard deviations. A paired Student t test was used to compare observations within the same patient. Analysis of variance (ANOVA) was used to compare differences in Kmono values among the segments. There was considered to be significant difference when the p value was less than 0.05.

RESULTS

Plasma substrate levels
The plasma substrate levels in the fasting and glucose loading conditions are shown in Table 1. Oral glucose loading increased plasma glucose from 98±5 mg/dl to 133±12 mg/dl and insulin levels from 8.6±1.6 μU/ml to 58.7±25.9 μU/ml (p<0.01 each). On the other hand, NEFA decreased from 848± 241 μEq/L to 300±67 μEq/L (p<0.01) after glucose loading.

^{11}*C-acetate kinetics in the LV myocardium*
Figure 2 shows serial dynamic images obtained at a midventricular slice following intravenous administration of ^{11}C-acetate at rest and during dobutamine infusion. While the first images showed biventricular
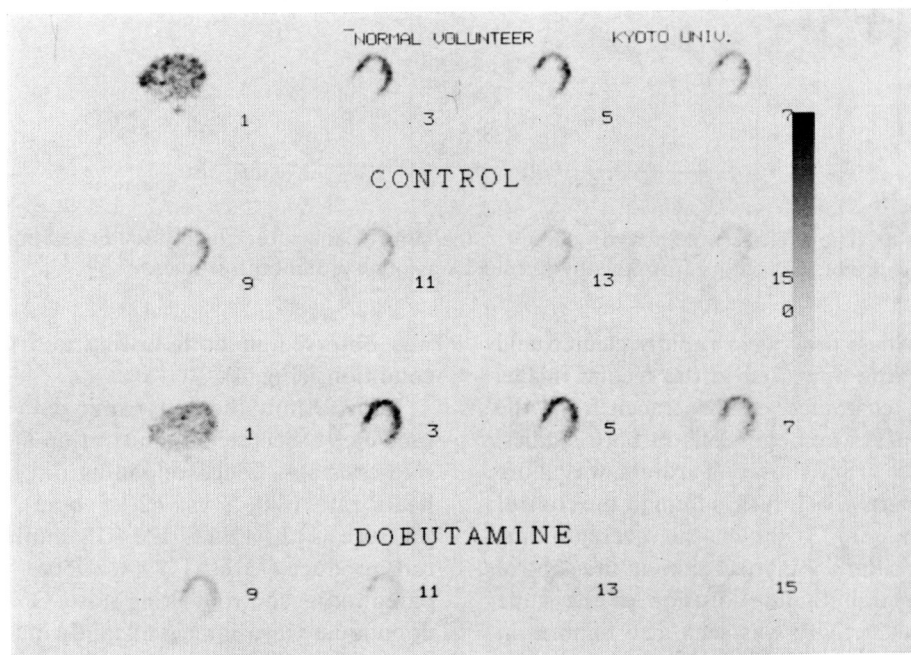
Fig. 2 A serial 2 minute-dynamic images in a midventricular slice following intravenous administration of ^{11}C-acetate at rest (top) and during dobutamine infusion (bottom). The activity gradually decreased from the myocardium in each study, but the clearance was more rapid during dobutamine infusion.
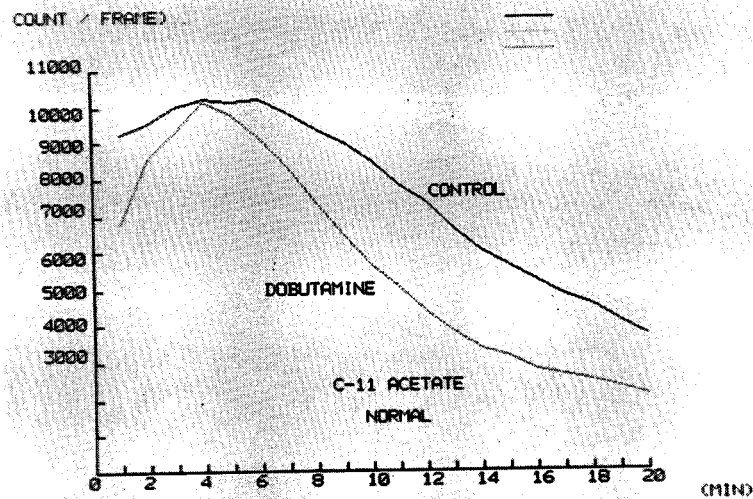
Fig. 3 The average time activity curves in the control and during dobutamine infusion for the same subject. More rapid clearance from the myocardium is noted during dobutamine infusion.
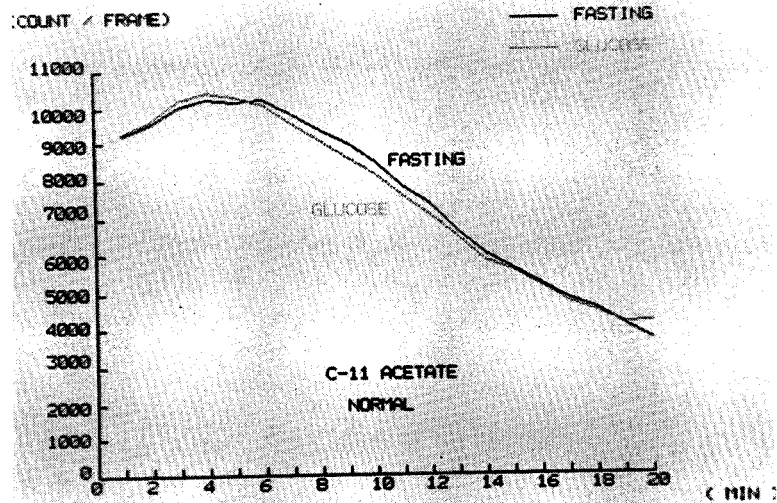

Fig. 4 The average time activity curves in the control and after glucose loading. Similar clearance of the activity from the myocardium was observed in both studies.

blood-pool activities, they were rapidly cleared and the LV myocardium appeared in the second image. The subsequent clearance of the tracer from the myocardium appears homogeneous in both studies. But the clearance from the myocardium was more rapid during dobutamine infusion than in the control resting study. Figure 3 shows the average time activity curves for the LV myocardium in the control state and during dobutamine infusion of the same subject. The peak activity was seen at 6 minutes in the control and 4 minutes during dobutamine infusion. The clearance was more rapid in the dobutamine study than that in the control study. On the other hand, a similar clearance rate for the tracer

was observed in both fasting and glucose loading conditions (Fig. 4).

Table 2 shows hemodynamic data obtained at the time of ^{11}C-acetate administration and the clearance rate constant. Glucose loading did not increase the heart rate (64 ± 5 vs. 62 ± 5 bpm), systolic blood pressure (117 ± 12 vs. 120 ± 12 mmHg) or pressure rate product (7516 ± 1189 vs. 7506 ± 1264), as compared to the control fasting state. On the other hand, dobutamine infusion significantly increased the heart rate (81 ± 14 bpm) by 31% and the systolic blood pressure (165 ± 10 mmHg) by 37%. The pressure-rate product also increased by 77% (13296 ± 2622) during dobutamine infusion.

Table 2 The hemodynamic data and the clearance rate constant (Kmono) in the left ventricular myocardium in the control, during glucose loading and during dobutamine infusion

	Control	Glucose	Dobutamine
Heart rate (bpm)	62 ± 5	64 ± 5	81 ± 14
Systolic blood pressure (mmHg)	120 ± 12	117 ± 12	$165\pm10^*$
Pressure-rate product	7500 ± 1260	7520 ± 1190	$13300\pm2620^*$
Kmono (min^{-1})	0.065 ± 0.017	0.059 ± 0.008	$0.106\pm0.018^*$

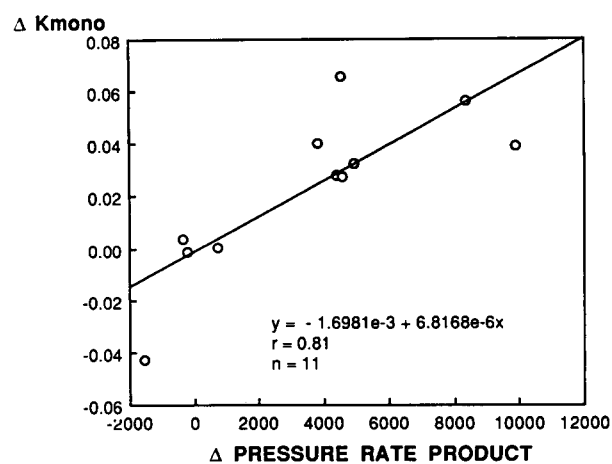(*p<0.01 dobutamine vs. control and glucose loading state)

Table 3 Kmono values (min^{-1}) in individual segments in control, during glucose loading and during dobutamine infusion (min^{-1})

	Control(7)	Glucose(4)	Dobutamine(7)
Posteroseptal	0.0674 ± 0.0181	0.0588 ± 0.0110	0.1784 ± 0.0170
Anteroseptal	0.0638 ± 0.0182	0.0584 ± 0.0058	0.1123 ± 0.0256
Anterior	0.0584 ± 0.0156	0.0639 ± 0.0118	0.0867 ± 0.0232
Anterolateral	0.0645 ± 0.0143	0.0478 ± 0.0103	0.1074 ± 0.0232
Lateral	0.0623 ± 0.0183	0.0676 ± 0.0037	0.1114 ± 0.0222
Posterolateral	0.0646 ± 0.0153	0.0533 ± 0.0093	0.1114 ± 0.0222
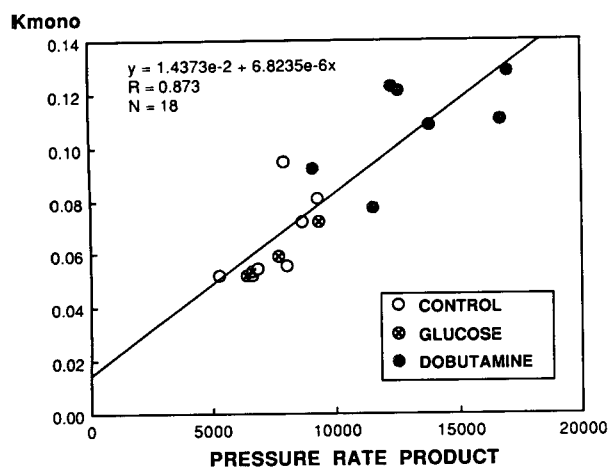
Fig. 5 Correlation of the clearance rate constant (Kmono) with pressure-rate product in the control, during glucose loading and during dobutamine infusion.

Fig. 6 Correlation of the changes in the clearance rate constant (Kmono) with the changes in the pressure-rate product during glucose loading and during dobutamine infusion.

The clearance rate constant (Kmono) of the global LV myocardium was measured twice by the same observer in the 7 normal subjects at control. The intraobserver variance was $10.8\pm4.2\%$. Kmono was 0.065 ± 0.017 min^{-1} at control, 0.059 ± 0.008 min^{-1} under glucose loading and 0.106 ± 0.018 min^{-1} during dobutamine infusion (p<0.01: dobutamine vs. both control and glucose loading conditions, respectively) (Table 2). In the 4 subjects who received ^{11}C-acetate both at fasting and glucose loading states, Kmono was also similar in the control $(0.069\pm0.016$ $min^{-1})$ and glucose loading states $(0.059\pm0.008$ $min^{-1})$. When the value of Kmono was compared with the pressure-rate product, a high positive

correlation was observed between these two parameters with a correlation coefficient of 0.873 (p<0.01) (Fig. 5). When the changes in Kmono was compared to the changes in the pressure-rate product, a high positive correlation was also observed (r=0.81) (p<0.01) (Fig. 6).

[11]C-acetate kinetics in regional myocardium
The Kmono values in individual myocardial segments are shown in Table 3. There was no regional differences in the LV myocardium in the control or glucose loading state. They were uniformly increased under dobutamine infusion without regional differences.

DISCUSSION

The results obtained in this study of normal volunteers confirmed the potential clinical value of dynamic PET and ^{11}C-acetate for assessing oxidative metabolism *in vivo*. The clearance rate constant of ^{11}C-acetate (Kmono) as an index of oxidative metabolism was unchanged after glucose loading but it significantly increased in relation to the increase in the pressure-rate product without regional differences.

Previous animal experiments showed that the clearance kinetics of ^{11}C-acetate from the myocardium was related to the flux of the TCA cycle and myocardial oxygen consumption.[10-13] The early component has been shown to reflect direct oxidation of ^{11}C-acetate via the TCA cycle,[10-13] whereas the late component is considered to represent activity in equilibrium with the amino acid pool via transamination of the TCA cycle intermediate.[23] However, in the human study, the estimates of the clearance rate for the second exponential curve component seem to be rather unreliable.[16] We therefore performed monoexponential curve fitting of the clearance curve of ^{11}C-acetate from the myocardium to calculate Kmono as a marker of oxidative metabolism in the myocardium. This technique seems to be simple, requiring only a relatively short acquisition time (20 minutes) with little fluctuation in the values. The spillover of the residual blood pool activity into the myocardium may potentially modify the Kmono values. However, since the clearance of ^{11}C-acetate from the blood pool was rapid, the spillover activity from the blood pool was not corrected. Our Kmono values were similar to those reported previously.[15,16]

The pressure-rate product is considered to be a simple and reliable noninvasive index of myocardial oxygen consumption.[24,25] The present study showed high correlation of the Kmono with the pressure-rate product, indicating that Kmono can be used as a marker of myocardial oxidative metabolism.

In the postprandial state, glucose is preferentially used in the normal myocardium, while in the fasting state glucose is used only in ischemic myocardium.[9,26] On the other hand, fatty acid is a major energy source in the normal myocardium in the fasting state but fatty acid oxidation is suppressed in the postprandial state.[8,26] Thus, one should be aware of this physiological changes when studying cardiac metabolism by means of PET. This study showed no significant change in Kmono under glucose loading, compared to fasting state, indicating that myocardial oxygen consumption is independent of the difference in plasma substrate levels. The present data indicate the ease of the metabolic study with ^{11}C-acetate unrelated to the plasma substrate levels. Such a metabolic study can be performed in patients with diabetes or similar patients who responded abnormally to oral glucose, where glucose utilization may be rather difficult to interpret.[27,28]

The experimental studies showed a slight increase in oxidative metabolism following a predominantly carbohydrate than in fatty acid meal.[13] Ambrecht et al. in the normal volunteer study showed that oral glucose only slightly decreased the Kmono in association with a mild decrease in the pressure-rate product.[15] In our study, on the other hand, the oral glucose did not change either the pressure-rate product or the clearance rate constant of ^{11}C-acetate. Myocardial oxidative metabolism may be easily influenced by a fluctuation in the heart rate and blood pressure due to mental stress and anxiety of the test. To eliminate training effects, the order of the study was selected randomly in this study. A further experience in more patients may be required to confirm our findings.

Dobutamine is a potent inotropic agent which activates beta-1, beta-2, and alpha-1 adrenoreceptors.[29] This agent has been used for pharmacological stress testing by increasing the myocardial oxygen demand associated with an increase in both the heart rate and systolic blood pressure without an increase in the incidence of cardiac arrhythmia.[30-32] Our preliminary data showed an increase in the clearance of ^{11}C-palmitate in relation to the increase in the pressure-rate product after dobutamine infusion in normal subjects.[21] In addition, Henes et al.[16] showed an increase in Kmono in proportion to the increase in the pressure-rate product and indicated a PET study with ^{11}C-acetate under dobutamine infusion as a valuable means of assessing the myocardial oxidative metabolic reserve. Our data support their findings. Thus, the ^{11}C-acetate kinetic study at control and during dobutamine infusion is a safe and valuable alternative for assessing the oxidative metabolic reserve in patients with various cardiac disorders.

The assessment of regional myocardial metabolism is of the utmost importance in identifying regional ischemia in patients with coronary artery disease. Heterogeneous utilization of glucose has been reported in normal subjects, particularly in the fasting condition.[6] Regional kinetic analysis of ^{11}C-acetate, on the other hand, showed homogeneous clearance of activities following the administration of ^{11}C-acetate in any condition and this evidently supports the previous findings.[15,16] The present findings may be helpful in assessing regional differences in oxidative metabolism by PET with ^{11}C-acetate in patients with ischemic heart disease at control and under various drug interventions as well.

It may be useful to relate the regional clearance rate constant with the regional cardiac work load.[33] Unfortunately, there seems to be no reliable index of the regional work load or tension to compare with Kmono at present. In this respect, the Kmono value in individual segment is considered to be a single and most reliable parameter of regional cardiac work measured noninvasively.

We used one midventricular slice to obtain six regions of interest in order to minimize the partial volume effect, but the present study did not include the analysis of anterior or inferior regions. However, regional analysis of clearance should be performed with three-dimensional tomographic images from a series of contiguous slices using appropriate software.

Recently, Buck et al.[34] developed three-compartment model for the accurate measurement of oxygen consumption in dogs to correct metabolites in blood and recirculation. However, it remains unknown whether this complicated model may reflect oxidative metabolism in man more accurately than the simple monoexponential model.

In conclusion, the calculation of the clearance rate constant of the monoexponetial clearance curve (Kmono) in the myocardium after intravenous administration of ^{11}C-acetate may facilitate accurate measurement of regional as well as global oxygen consumption over a wide range of hemodynamic and metabolic conditions. In the normal subjects, while the Kmono did not change after glucose loading state, it significantly increased in relation to the increase in the pressure-rate product. The regional curve analysis indicated a homogeneous value of Kmono in fasting and glucose loading states with uniformly increase in Kmono under dobutamine infusion. These normal studies should be useful for assessing regional changes of oxidative metabolism in patients with ischemic heart disease and cardiomyopathy.

ACKNOWLEDGMENTS

REFERENCES

1. Schelbert HR, Henze E, Phelps ME: Emission tomography of the heart. Semin Nucl Med 10: 355–373, 1980
2. Bergmann SR, Fox KAA, Geltman EM, et al: Positron emission tomography of the heart. Prog Cardiovasc Dis 28: 165–194, 1985
3. Schon HR, Schelbert HR, Robinson G, et al: C-11 labeled palmitic acid for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron computed tomography. I. Kinetics of C-11 palmitic acid in normal myocardium. Am Heart J 103: 532–547, 1982
4. Grover-McKay M, Schelbert HR, Schwaiger M, et al: Identification of impaired metabolic reserve by atrial pacing in patients with significant coronary artery stenosis. Circulation 74: 281–292, 1986
5. Marshall RC, Tillisch JH, Phelps ME, et al: Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, ^{18}F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation 67: 766–788, 1983
6. Tillisch J, Brunken R, Marshall R, et al: Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Eng J Med 314: 884–888, 1986
7. Tamaki N, Yonekura Y, Yamashita K, et al: Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol 64: 860–865, 1989
8. Schelbert H, Henze E, Sochor H, et al: Effect of substrate availability on myocardial C-11 palmitate kinetics by positron emission tomography in normal subjects and patients with ventricular dysfunction. Am Heart J 111: 1055–1064, 1986
9. Berry JJ, Baker JA, Pieper KS, et al: The effect of metabolic milieu on cardiac PET imaging using fluorine-18-deoxyglucose and nitrogen-13-ammonia in normal volunteers. J Nucl Med 32: 1518–1525, 1991
10. Brown M, Marshall DR, Sobel BE, et al: Delineation of myocardial utilization with carbon-11-labeled acetate. Circulation 76: 687–696, 1987
11. Buxton DB, Schwaiger M, Nguyen A, et al: Radiolabeled acetate as a tracer of myocardial tricarboxylic acid cycle flux. Circ Res 63: 628–634, 1988
12. Brown MA, Myears DW, Bergmann SR: Noninvaive assessment of canine myocardial oxidative metabolism with carbon-11 acetate and dynamic positron emission tomography. JACC 12: 1054–1063, 1988
13. Buxton DB, Nienaber CA, Luxen A, et al: Noninvasive quantitation of regional myocardial oxygen consumption in vivo with 1-^{11}C acetate and dynamic positron emission tomography. Circulation 79: 134–142, 1989
14. Brown MA, Myears DW, Bergmann SR: Validity of estimates of myocardial oxidative metabolism with carbon-11 acetate and positron emission tomography despite altered patterns of substrate utilization. J Nucl Med 30: 187–193, 1989
15. Ambrecht JJ, Buxton DB, Brunken RC, et al: Regional myocardial oxygen consumption determined noninvasively in humans with [1-^{11}C] acetate and dynamic positron tomography. Circulation 80: 863–872, 1989
16. Henes CG, Bergmann SR, Walsh MN, et al: Assessment of myocardial oxidative metabolic reserve with positron emission tomography and carbon-11 acetate. J Nucl Med 30: 1489–1499, 1989

17. Walsh MN, Geltman EM, Brown MA, et al: Non-invasive estimation of regional myocardial oxygen consumption by positron emission tomography using carbon-11 acetate in patients with myocardial infarction. *J Nucl Med* 30: 1798–1808, 1989

18. Gropler RJ, Siegel BA, Geltman EM: Myocardial uptake of carbon-11-acetate as an indirect estimate of regional myocardial blood flow. *J Nucl Med* 32: 245–251, 1991

19. Pike VW, Eakins MN, Allan RM et al: Preparation of [1 ¹¹C]acetate as agent for the study of myocardial metabolism by positron emission tomography. *Int J Appl Radiat Isot* 33: 505–512, 1982

20. Stratmann HG, Kennedy H: Evaluation of coronary artery disease in the patients unable to exercise: alternatives to exercise stress testing. *Am Heart J* 117: 1344–1365, 1989

21. Tamaki N, Kawamoto M, Takahashi N, et al: Metabolic reserve in normal myocardium assessed by positron emission tomography with C-11 palmitate. *Ann Nucl Med* 5: 53–58, 1991

22. Senda M, Tamaki N, Yonekura Y, et al: Performance characteristics of Positologica III, a whole body positron emission tomograph. *J Comput Assist Tomogr* 9: 940–946, 1985

23. Randle PJ, England PJ, Denton RM: Control of the tricarboxylate cycle and its interaction with glycolysis during aceta e ut lization in rat heart. *Biochem J* 117: 677–695, 1970

24. Nelson RR, Gobel FL, Jorgensen CR, et al: Hemodynami cprediction of myocardial oxygen consumption during static and dynamic exercise *Circulation* 50: 1179–1189, 1974

25. Rooke GA, Feigl EO: Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. *Circ Res* 50: 273–286, 1982

26. Neely JR, Rovetto MJ, Oran JF: Myocardial utilization of carbohydrate and lipids. *Prog Cardiovasc Dis* 15: 89–301, 1972

27. Tamaki N, Yonekura Y, Kawamoto M, et al: Simple quantification of regional myocardial uptake of fluorine-18-deoxyglucose in the fasting condition. *J Nucl Med* 32: 2152–2157, 1991

28. Hicks RJ, Herman WH, Kalff et al: Quantitative evaluation of regional substrate metabolism in the human heart by positron emission tomography. *JACC* 18: 101–111, 1991

29. Tuttle RR, Millis J: Dobutamine. Development of new catecholamine to selectively increase cardiac contractility. *Circ Res* 36: 185–196, 1975

30. Meyer SL, Curry GC, Donsky MS, et al: Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease. *Am J Cardiol* 8: 103–108, 1976

31. Mason JR, Palac RT, Freeman ML, et al: Thallium-201 scintigraphy during dobutamine infusion: non-exercise-dependent screening test for coronary disease. *Am Heart J* 107: 481–485, 1984

32. Berthe C, Pierard LA, Hiernaux M, et al: Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dubutamine infusion. *Am J Cardiol* 58: 1167–1172, 1986

33. Wolpers HG, Nguyen N, Buck A, et al: Relationship of C-11 acetate kinetics and hemodynamic performance in the canine heart (abstr). *J Nucl Med* 31: 785, 1990

34. Buck A, Wolpers HG, Hutchins GD, et al: Effects of carbon-11-acetate recirculation on estimates of myocardial oxygen consumption by PET. *J Nucl Med* 32: 1950–1957, 1991