Myocardial Oxidative Metabolism in Hyperthyroid Patients Assessed by PET with Carbon-11-Acetate

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Hyperthyroid patients often complain of cardiovascular symptoms because of increased metabolism. This study was designed to quantitatively evaluate myocardial oxidative metabolism in these patients. **Methods:** Dynamic PET with ^{11}C-acetate was performed in 19 patients who had not undergone treatment for hyperthyroidism. Eight were restudied 2 wk after oral administration of propranolol. The clearance rate constant of ^{11}C-acetate (Kmono) was calculated with monoexponential fitting of tracer washout from the myocardium as a marker of myocardial oxidative metabolism. The results were compared with those in nine normal subjects both at rest and during dobutamine infusion. **Results:** Kmono in our patients (0.109 ± 0.028 min^{-1}) was significantly increased compared to normal subjects (0.066 ± 0.016 min^{-1}) ($p < 0.05$). After propranolol treatment, Kmono decreased (0.082 ± 0.014 min^{-1}) but remained significantly higher in eight patients than normal subject levels ($p < 0.05$), while the rate pressure product decreased significantly (7500 ± 1700) toward the normal range (7900 ± 1500). **Conclusion:** These results suggest the possibility of excessive myocardial oxygen consumption in hyperthyroid patients. The clearance rate of ^{11}C-acetate is a new and valuable index to assess myocardial oxidative metabolism not closely related to the pressure rate product or thyroid hormones in these patients.

Key Words: hyperthyroidism; propranolol treatment; myocardial oxidative metabolism; carbon-11-acetate; positron emission tomography

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Patients with hyperthyroidism are known to have increased cardiovascular metabolism and often complain of cardiac symptoms such as tachycardia, increased pulse pressure and palpitation (*1–3*). To immediately reduce these cardiac symptoms, a beta-sympathetic blocker agent, propranolol, has been used because of its rapid effectiveness (*2–6*). Therefore, assessment of myocardial metabolism may be important to monitor therapeutic effects in these patients.

In experimental and clinical studies, myocardial clearance of ^{11}C-acetate is considered a marker of myocardial oxidative metabolism (*7–19*). These studies have shown that the ^{11}C-acetate clearance rate of the rapid first phase correlates closely with myocardial oxygen consumption in animals and with the rate-pressure product as an indirect marker of myocardial oxygen consumption in humans. Recently, regional oxidative metabolism in ischemic or infarcted myocardium was evaluated noninvasively by PET with ^{11}C-acetate (*13–16*). To estimate the metabolic response of normal myocardium to increase cardiac work, the ^{11}C-acetate clearance rate was measured by PET in normal subjects at rest and during dobutamine infusion (*10,11*). The results indicated that the clearance rate constant of ^{11}C-acetate increased proportionally to the increase in the rate-pressure product during dobutamine infusion.

This study was designed to assess myocardial oxidative metabolism in patients with hyperthyroidism, before and after treatment with propranolol, by analyzing the clearance rate constant of ^{11}C-acetate from the myocardium. To characterize oxidative metabolism in these patients, the results were compared with those in normal subjects at rest and during dobutamine infusion.

MATERIALS AND METHODS

Patients

Nineteen untreated hyperthyroid patients (5 men, 14 women; mean age 40 yr, range 16–58 yr) were studied. They were diagnosed as having hyperthyroidism based on clinical findings and endocrinological data. Eighteen patients had primary hyperthyroidism (Graves' disease) and the remaining patient had secondary hyperthyroidism and a high serum TSH (8.9 μU/ml). No patient had left ventricular hypertrophy on chest radiograph or EKG. Eight patients, including the one with secondary hyperthyroidism, were restudied after treatment with oral administration of propranolol (20 mg/day) for 2 wk. As a reference, nine normal volunteers (mean age 36 yr, range 23–42 yr) were also studied. No volunteer had a history of thyroid or cardiac disease or any cardiac risk factors. Our previously reported data about normal subjects (*11,20*) are included in this article. Each subject gave written

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TABLE 1
Hemodynamic Data and Clearance Rate Constant (Kmono) in Myocardium: Hyperthyroid Patients before Treatment and Normal Subjects at Rest and during Dobutamine Infusion

	Hyperthyroid patients before treatment (n = 19)	Normal subjects	
		Rest (n = 9)	Dobutamine (n = 9)
Heart rate (bpm)	92 ± 16*	66 ± 9	89 ± 19*
Systolic blood pressure (mmHg)	122 ± 18†	120 ± 12	166 ± 9*
Rate-pressure product (RPP)	11400 ± 3200*†	7900 ± 1500	14800 ± 3500*
Kmono (min^{-1})	0.109 ± 0.028*	0.066 ± 0.016	0.113 ± 0.020*
Kmono/RPP ($\times 10^{-6}$)	9.98 ± 2.16†	8.54 ± 1.68	7.85 ± 1.5

*$p < 0.05$ vs. normal at rest.
†$p < 0.05$ vs. normal during dobutamine infusion.

informed consent and the study was approved by the Kyoto University Human Study Committee.

Preparation of Carbon-11-Acetate

Carbon-11-acetate was synthesized according to the procedures reported by Pike et al. (*21*) with a slight modification (*11,20*).

Study Protocol

PET scans were obtained at rest for the hyperthyroid patients before and after treatment. Nine normal subjects were examined both at rest and during dobutamine infusion. Infusion of dobutamine was used instead of physical exercise to increase myocardial work constantly over the 20-min period acquisition dynamic PET, as shown in our previous studies (*11,20*). Intravenous infusion of dobutamine was given μg/kg/min initially and was increased by 2–5 μg/kg/min every 5 min with cardiac monitoring (*22*). When the heart rate reached 120 bpm or systolic blood pressure reached 180 mmHg, ^{11}C-acetate was administered intravenously and serial dynamic PET scans were acquired. Dobutamine was constantly infused during the PET study to maintain steady hemodynamics while heart rate, blood pressure and EKG were monitored. Ultimately, dobutamine was given 7 μg/kg/min in three subjects, 10 μg/kg/min in five subjects and 15 μg/kg/min in one subject.

The PET study was performed with a whole-body PET camera (Positologica III or PCT 3600W, Hitachi Medico Co., Tokyo, Japan). The Positologica III has four rings providing seven tomographic slices at 16-mm intervals. Intrinsic spatial resolution in the tomographic plane was 7.6 mm FWHM at the center and the axial resolution was 12 mm FWHM (*23*). The PCT 3600W has 8 rings providing 15 tomographic slices at 7-mm intervals and the intrinsic resolution was 4.6 mm FWHM. The axial field of view was 11.2 cm in the Positologica III and 10.5 cm in the PCT 3600W. Each subject was positioned on the PET camera using the ultrasound technique so that the heart was included in the field of view. Transmission scans were performed for accurate correction of photon attenuation and, before each study, heart rates and blood pressures were measured to estimate the myocardial work. Immediately after intravenous administration of 185–370 MBq of ^{11}C-acetate, serial dynamic scanning was performed and 20 frames of 60 sec each for 20 min were collected.

Data Analysis

Three transverse slices of the left ventricular (LV) myocardium were selected for analysis. The middle slice included the largest portion of the LV cavity among all the images. Six regions of interest (ROIs) (0.75 × 0.75 cm each) were placed over the posteroseptal, anteroseptal, anterior, anterolateral, lateral and posterolateral regions in the middle slice. In addition, two ROIs were placed over the anterior region in the cranial slice and the posterior region in the caudal slice, respectively.

Regional myocardial time-activity curves in the eight myocardial segments were generated from serial PET images after correction for deadtime and physical decay of ^{11}C activity. By using an iterative least squares fitting technique, regional time-activity curves were fitted monoexponentially to calculate the clearance rate constant (Kmono). The linear portion of the first exponential fit was selected visually from semilogarithmic plots of the data for the whole plane. Since the clearance of blood-pool activity was rapid, spillover activity from the blood pool to the myocardium was considered minimal and was not corrected in this study. Because the blood activity was low and unchanged 6 min after tracer injection, monoexponential fitting was performed between 6 and 15 min postinjection. In each subject, the mean Kmono obtained from the eight regional time-activity curves was used to determine the rate constant for the global LV myocardium (*20*). In addition, the ratio of the Kmono-to-rate pressure product (Kmono/RPP ratio) was calculated.

Statistical Analysis

Mean values are given with s.d. Significant differences between groups were assessed with paired or unpaired Student's t-tests. Analysis of variance (ANOVA) was used to compare differences in Kmono values among the myocardial segments. Differences were significant when p was less than 0.05.

RESULTS

Hemodynamic Findings

Hemodynamic data are shown in Tables 1 and 2. Compared with normal controls, the patients had significantly increased heart rates (92 ± 16 versus 66 ± 9 bpm at rest) and rate-pressure products (11400 ± 3200 versus 7900 ± 1500 at rest) ($p < 0.05$, each), whereas there was similar systolic blood pressure (122 ± 18 versus 120 ± 12 mmHg at rest, ns) for both subjects and patients. In eight patients, propranolol treatment significantly decreased heart rate (86 ± 12 to 71 ± 10 bpm), systolic blood pressure (119 ± 18 to 105 ± 12 mmHg) and the rate-pressure product (10300 ± 2600 to 7500 ± 1700) ($p < 0.05$, each). The heart rate and rate-pressure product were similar to those of the

TABLE 2
Hemodynamic Data and Clearance Rate Constant (Kmono) in Myocardium: Hyperthyroid Patients before and after Treatment and Normal Subjects at Rest

	Hyperthyroid patients		Normal subjects at rest (n = 9)
	Before treatment (n = 8)	After treatment (n = 8)	
Heart rate (bpm)	86 ± 12*	71 ± 10	66 ± 9
Systolic blood pressure (mmHg)	119 ± 18*	105 ± 12	120 ± 12*
Rate pressure product (RPP)	10300 ± 2600*	7500 ± 1700	7900 ± 1500
Kmono (min^{-1})	0.111 ± 0.026*	0.082 ± 0.014	0.066 ± 0.016*
Kmono/RPP ($\times 10^{-6}$)	10.92 ± 1.86	11.4 ± 2.22	8.54 ± 1.68*

*$p < 0.05$ vs. after treatment.

control subjects. In the normal subjects, dobutamine infusion significantly increased the hemodynamic data (*20*).

Endocrinological Data

Serum free T3 values (6.4–25.5 pg/ml, normal range; 2.2–5.0) and free T4 (1.78–10.4 ng/dl, normal range; 0.99–1.92) were elevated in all patients. The values of serum TSH were less than 0.03 μU/ml (normal range; 0.3–3.9) in 18 with primary hyperthyroidism but the value was 8.9 μU/ml in one patient with secondary hyperthyroidism. These hormone values did not significantly change after propranolol treatment (data not shown).

Myocardial Uptake and Clearance of Carbon-11-Acetate

The LV myocardium of the patients was clearly visible and appeared homogeneous. No regional differences were observed in the myocardium of these patients before and after treatment or in the normal subjects (Table 3).

Time-activity curves were obtained from a patient before treatment and a normal subject both at rest and during dobutamine infusion from the cross-sectional ROIs in the lateral segment of the myocardium (Fig. 1). More rapid tracer clearance was observed in the patient before treatment and in the normal subject with dobutamine infusion compared with that in the normal subject at rest.

Figure 2 shows the time-activity curves obtained from the same patient, before and after treatment, and the same normal subject at rest, as shown in Figure 1. Clearance became slower after treatment but remained more rapid than in the normal subject at rest.

Clearance Rate Constant of Carbon-11-Acetate

The Kmono of global LV myocardium increased significantly in patients (0.109 ± 0.028 min^{-1}) and in the normal subjects during dobutamine infusion (0.113 ± 0.020 min^{-1}) compared to normal subjects at rest (0.066 ± 0.016 min^{-1}) ($p < 0.05$, each) (Table 1). The Kmono/RPP ratio of the hyperthyroid patients ($9.98 \pm 2.16 \times 10^{-6}$) was significantly higher than that of the dobutamine-administered normal subjects ($7.85 \pm 1.50 \times 10^{-6}$) ($p < 0.05$), although there was no significant difference in the Kmono/RPP ratio between normal subjects at rest ($8.54 \pm 1.68 \times 10^{-6}$) and during dobutamine infusion. No high correlation was observed between Kmono and serum thyroid hormone values: observed $r = 0.567$ ($p < 0.05$, versus free T3) and $r = 0.404$ (ns, versus free T4).

TABLE 3
Regional Kmono Values (min^{-1}) in Individual Segments: Hyperthyroid Patients before and after Treatment and Normal Subjects at Rest and during Dobutamine Infusion

	Hyperthyroid patients		Normal subjects	
	Before treatment (n = 19)	After treatment (n = 8)	Rest (n = 9)	Dobutamine (n = 9)
Anterior (cranial)	0.111 ± 0.027	0.085 ± 0.014	0.068 ± 0.019	0.116 ± 0.02
Posteroseptal	0.109 ± 0.025	0.079 ± 0.009	0.07 ± 0.016	0.114 ± 0.02
Anteroseptal	0.108 ± 0.028	0.082 ± 0.013	0.069 ± 0.017	0.112 ± 0.021
Anterior	0.108 ± 0.029	0.085 ± 0.013	0.062 ± 0.016	0.114 ± 0.022
Anteroseptal	0.108 ± 0.027	0.087 ± 0.013	0.067 ± 0.015	0.108 ± 0.022
Lateral	0.112 ± 0.029	0.077 ± 0.016	0.064 ± 0.019	0.115 ± 0.025
Posterolateral	0.109 ± 0.029	0.081 ± 0.019	0.068 ± 0.015	0.112 ± 0.021
Posterior (caudal)	0.111 ± 0.028	0.082 ± 0.012	0.067 ± 0.017	0.113 ± 0.015
COV (%)	6.77 ± 2.29	6.95 ± 3.49	9.04 ± 4.15	6.95 ± 1.67

COV = coefficient of variation.

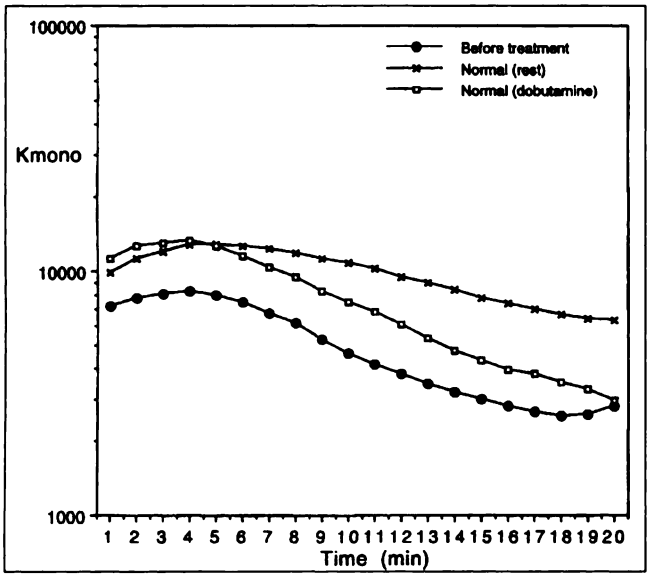

FIGURE 1. Time-activity curves in the semi-log plot obtained from a patient before treatment and a normal subject at rest and during dubutamine infusion. Compared with the normal subject at rest, more rapid clearance from the myocardium was observed in the patient before treatment and during dobutamine infusion.

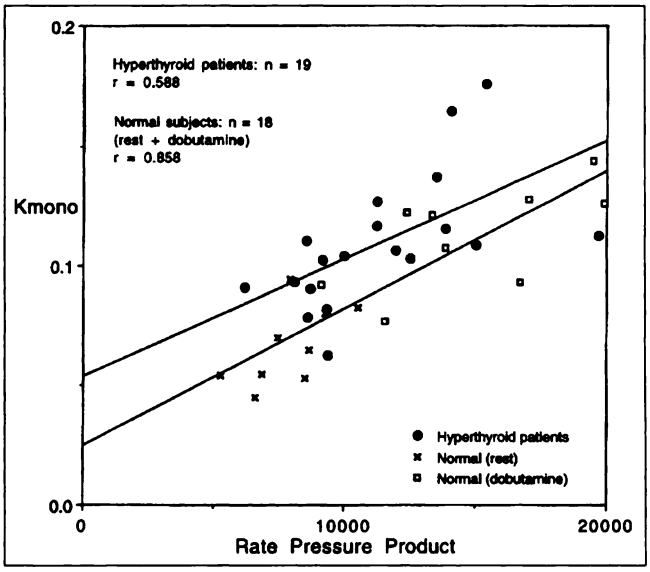

FIGURE 3. Correlation of the clearance rate constant (Kmono) with the rate-pressure product obtained from 19 patients and 9 subjects at rest and during dobutamine infusion.

After propranolol treatment, Kmono decreased significantly (0.111 ± 0.026 to 0.082 ± 0.014 min^{-1}) but remained significantly higher than the normal range (0.066 ± 0.016 min^{-1}) ($p < 0.05$) (Table 2). In addition, the Kmono/RPP ratio after treatment ($11.4 \pm 2.22 \times 10^{-6}$) also remained significantly higher than the normal range ($8.54 \pm 1.68 \times 10^{-6}$) ($p < 0.05$).

The correlation between Kmono and the rate-pressure product in patients was significant ($r = 0.588$) but was scattered even more in the normal subjects ($r = 0.858$) (Fig. 3). The increases in Kmono in these patients tended to be more excessive compared with normal subjects during dobutamine infusion. In addition, after treatment with propranolol, Kmono remained elevated but the rate-pressure product decreased toward the normal range (Fig. 4).

DISCUSSION

Our results indicate that the Kmono of ^{11}C-acetate as an index of oxidative myocardial metabolism was significantly increased in untreated hyperthyroid patients compared to normal subjects. The increase in Kmono was greater than

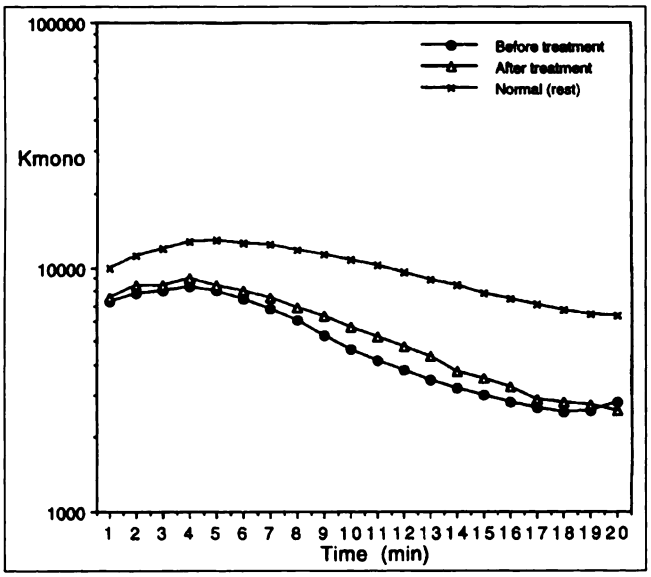

FIGURE 2. Time-activity curves in the semi-log plot obtained from the same patient and the subject in Figure 1. The clearance in the patient became slower after treatment but remained more rapid than that in the subject at rest.

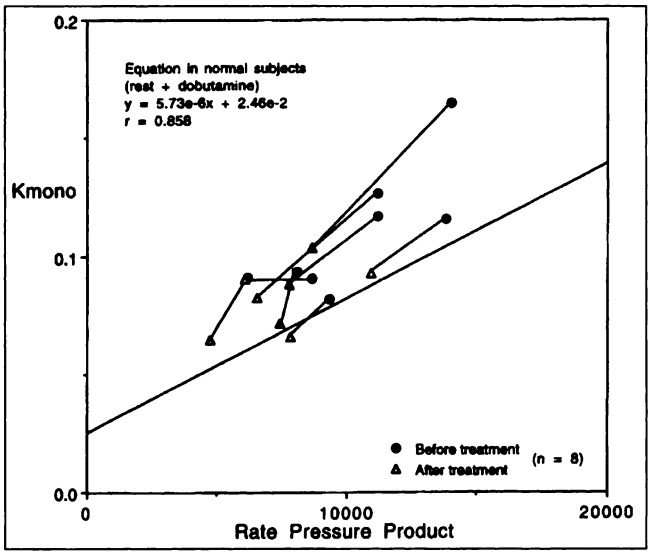

FIGURE 4. Correlation of the clearance rate constant (Kmono) with the rate-pressure product from eight patients before and after propranolol treatment.

that in the rate-pressure product and was not closely related to serum thyroid hormone levels. After propranolol treatment, Kmono was reduced but remained higher than the normal range, while the rate-pressure product decreased toward the normal range. These findings suggest the possibility of myocardial oxygen wasting in hyperthyroid patients.

Previous studies have demonstrated the potential value of ^{11}C-acetate and dynamic PET for noninvasive measurement of regional oxidative metabolism (*7–19*). In their study of normal subjects, Henes et al. (*10*) described that the ^{11}C-acetate clearance rate increased in proportion to the increase in the rate-pressure product during dobutamine infusion. Our results for the slope between Kmono and the rate-pressure product in normal subjects (Fig. 4) were similar to the findings presented in these previous studies: 12.4×10^{-6} during dobutamine infusion (*10*) and 5.89×10^{-6} during exercise (*12*).

In hyperthyroidism, the cardiovascular response to epinephrine is accelerated by thyroid hormones (thyroid-sympathoadrenal interactions) (*1–4,24*). Previous experiments showed that alterations in cardiovascular function seen in hyperthyroid dogs were ameliorated after spinal epidural procaine blockade (*25*). In addition, propranolol generally decreases heart rate, pulse pressure and cardiac output toward normal levels in hyperthyroidism in vivo (*4*), suggesting that these cardiovascular manifestations of hyperthyroidism may be attributable to enhanced thyroid-sympathoadrenal interactions.

In this study, we evaluated myocardial oxidative metabolism in hyperthyroid patients with dynamic PET and compared the results with those in normal subjects at rest and during dobutamine infusion. Before propranolol treatment, there was significant correlation ($r = 0.588$) between the Kmono and the rate-pressure product (Fig. 3). In patients, the Kmono/RPP ratios were greater than those in normal subjects, suggesting excessive myocardial oxygen consumption in hyperthyroid patients. In addition, the increased Kmono did not correlate highly with the serum free T3 values ($r = 0.567$, $p < 0.05$) or free T4 ($r = 0.404$, ns).

Previous studies have demonstrated that thyroid hormones may exert a direct effect on the heart. These effects are complex and may include increased synthesis of myosin as well as alteration in the structure of myosin and have better contractile properties (*5,26*). Thyroid hormones have also been shown to increase the activity of sarcoplasmic calcium ATPase in the myocardium (*3*). In studies of hyperthyroid animals (*27*) and humans (*28,29*), the effect of thyroid hormone on increased myocardial contractility could not be altered by beta-adrenagic blockade. Our PET results after propranolol treatment support these findings and suggest the possibility that increased myocardial contractility in hyperthyroid patients may be associated with excessive myocardial oxidative metabolism.

Propranolol has been successful in rapidly ameliorating the sympathomimetic features of hyperthyroidism (*2,6*). There seems little rationale, however, for its long-term use as the sole therapeutic agent because it incompletely corrects increased myocardial metabolism and does not ensure progression of thyrotoxicosis (*4*). Myocardial oxidative metabolism is expected to decrease to the normal range after effective antithyroid treatment, although our results did not determine whether the thyroid-sympathoadrenal interaction was fully suppressed by propranolol treatment. To clarify these problems, another patient study using PET after antithyroid treatment is warranted.

CONCLUSION

We used ^{11}C-acetate and PET and found that Kmono, as an index of myocardial oxidative metabolism, was significantly increased in untreated hyperthyroid patients. This increase was not closely related to either the rate-pressure product or serum thyroid hormone levels. After propranolol treatment, Kmono decreased but remained higher than the normal range while the rate-pressure product was considerably decreased, suggesting the possibility of myocardial oxygen wasting in hyperthyroid patients. Therefore, Kmono calculated in PET ^{11}C-acetate studies is a new and valuable index with which to assess myocardial oxidative metabolism in these patients.

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