# Myocardial Oxidative Metabolism in Remote Normal Regions in the Left Ventricles with Remodeling After Myocardial Infarction: Effect of β-Adrenoceptor Blockers

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In patients with myocardial infarction (MI), an expansion of the remote normal regions of the left ventricle is often observed. However, the characteristics of such regions are not fully understood. Thus, we investigated this issue from the standpoint of myocardial oxidative metabolism using $^{11}$C-acetate PET. **Methods:** In 33 patients with recent MI (24 not receiving β-blockers, 9 receiving β-blockers) and 12 age-matched normal control subjects, $^{11}$C-acetate dynamic myocardial PET scanning was performed at rest. Time–activity curves of $^{11}$C-acetate in 5–7 regions of interest (ROIs) on the midventricular transaxial image in each subject were generated, and the clearance rate constant ($K_{mono}$) in each ROI was calculated by monoexponential fitting as an index of myocardial oxidative metabolism. The left ventricular (LV) end-diastolic volume index as an index of LV remodeling and the heart rate · pressure product were obtained in all subjects. **Results:** The LV end-diastolic volume index was significantly larger in patients with MI without β-blockers than in normal control subjects (101 ± 22.5 vs. 61.6 ± 12.8 mL · m$^{-2}$; $P <$ 0.001). There was no significant difference in the heart rate · pressure product between the patients with MI without β-blockers and the normal control subjects (8,229 ± 1,503 vs. 8,311 ± 1,311 mm Hg · min$^{-1}$). The $K_{mono}$ in remote normal regions was significantly greater in patients with MI without β-blockers even when compared with the highest $K_{mono}$ on the anteroseptal wall of the left ventricle in normal control subjects (0.078 ± 0.022 vs. 0.065 ± 0.007 min$^{-1}$; $P < 0.01$). In contrast, the heart rate · pressure product (6,911 ± 1,135 mm Hg · min$^{-1}$) and the $K_{mono}$ (0.054 ± 0.009 min$^{-1}$) in remote normal regions were significantly less in patients with β-blockers than in those without β-blockers ($P <$ 0.001). No significant difference in the LV end-diastolic volume index was found between the MI patients with and without β-blockers. Multivariate regression analysis showed that β-blockers significantly and directly decreased the $K_{mono}$ in remote normal regions after adjusting the effect of the heart rate · pressure product, although the prime determinant of the $K_{mono}$ in such regions was the heart rate · pressure product. **Conclusion:** Myocardial oxidative metabolism in remote normal regions is accelerated in the left ventricles with remodeling after acute MI. Therapy using β-blockers normalizes the myocardial oxidative metabolism in such regions through the reduction of the heart rate · pressure product and their direct effect on the myocardium.

**Key Words:** acetate; β-blocker; myocardial infarction; PET; remodeling

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As a consequence of acute myocardial infarction (MI), the changes in the left ventricular (LV) size, shape, and thickness involving the infarct and the noninfarct (remote normal) regions of the left ventricle are observed, referring to LV remodeling (*1–3*). A combination of alterations in LV dilatation and hypertrophy of residual remote normal myocardium is a substantial cause of remodeling (*1–3*). The LV remodeling is a sign of impaired LV function and of poor prognosis (*1–3*). On the other hand, it has been shown that the patients who began to receive β-adrenoceptor blockers in the convalescent phase of acute MI showed a reduction in long-term mortality (*3,4*). The mortality benefit from chronic administration of β-blockers after acute MI is seen in patients with baseline risks (i.e., those with compromised ventricular function and ventricular arrhythmias) (*4*). From these points of view, a clinical study to examine the pathologic conditions of the myocardium in remote normal regions may be an important issue. Accordingly, we investigated the metabolic change in the remote normal regions from the standpoint of myocardial oxidative metabolism using $^{11}$C-acetate PET and the effect of β-blockers on oxidative metabolism in such regions.

## MATERIALS AND METHODS

### Subjects

Subjects consisted of 33 patients suffering from recent MI who underwent exercise stress $^{201}$Tl SPECT, cardiac catheterization,

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**TABLE 1**
Medication in Patients With and Without β-Blockers

| Medication | MI patients | | |
|---|---|---|---|
| | Without β-blockers | With β-blockers | *P* |
| *n* | 24 | 9 | |
| Aspirin | 24 (100) | 9 (100) | NS |
| ACEIs | 9 (37.5) | 4 (44.4) | NS |
| Dihydropiridine derivatives | 11 (45.8) | 6 (66.7) | NS |
| Diltiazem | 6 (25.0) | 2 (22.2) | NS |
| Long-acting nitrates | 10 (41.7) | 6 (66.7) | NS |
| Diuretics | 2 (8.3) | 1 (11.1) | NS |
| Statins | 10 (41.7) | 5 (55.6) | NS |

MI = myocardial infarction; NS = not significant; ACEIs = angiotensin-converting enzyme inhibitors.
Values in parentheses are percentage.

and $^{11}$C-acetate PET 4–12 wk after the onset of acute MI. $^{201}$Tl SPECT and cardiac catheterization were performed within 1 wk. The $^{11}$C-acetate PET study was then accomplished within 2 wk after completion of these examinations. MI was diagnosed by the presence of typical chest pain, a depression or elevation in the ST segment on a standard 12-lead electrocardiogram, and an increase in the MB fraction of creatine kinase. Patients in whom the peak creatine kinase concentrations were >1,000 IU/L at the acute phase were enrolled in this study. With the clinical requirements to treat sinus tachycardia, supraventricular premature contractions, or angina pectoris, 9 of 33 patients began to receive β-blockers (metoprolol, 120 mg/d [5 patients]; atenolol, 50 mg/d [4 patients]) 2–3 wk after the onset of the MI and continued taking them at least until the end of the test period. The mean interval of administration of β-blockers until the PET study was 7.8 ± 2.0 wk. Medication other than β-blockers is shown in Table 1. Twelve healthy volunteers also participated in this study as normal control subjects. Their electrocardiograms and echocardiograms were normal; they did not have a history of cardiac disease or hypertension. Only the PET examination was performed on these normal control subjects. Clinical characteristics of the patients and the normal control subjects are summarized in Table 2.

All individuals provided written informed consent for participation in the study. Procedures were performed according to the protocol approved by the Ethical Guideline Committees of the Nagoya City University Medical School and the Nagoya City Rehabilitation and Sports Center.

### Exercise $^{201}$Tl SPECT

Patients were imaged using a 3-head rotating gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator (MULTISPECT 3; Siemens Medical Systems, Hoffman Estates, IL) at 10 min, 3 h, and 24 h after $^{201}$Tl injection (*5,6*). The regions with reverse redistribution as well as redistribution on 3- and 24-h delayed images had reduced glucose and oxidative metabolism, which indicated that these regions were apparently abnormal (*5,6*). Thus, in this study, we defined the regions with normal $^{201}$Tl uptake on stress imaging and without reverse redistribution on 3- and 24-h delayed images as those of remote normal (noninfarct).

### Cardiac Catheterization and Echocardiography

Diagnostic cardiac catheterization was performed on all MI patients. Before the injection of contrast material into the LV cavity, the LV pressure was recorded and the LV end-diastolic

**TABLE 2**
Clinical Characteristics in 3 Groups

| Characteristic | Normal control subjects | MI patients | |
|---|---|---|---|
| | | Without β-blockers | With β-blockers |
| *n* | 12 | 24 | 9 |
| Age (y) | 57.1 ± 13.7 | 60.8 ± 10.2 | 58.6 ± 7.4 |
| Male/female | 9/3 | 20/4 | 7/2 |
| Heart rate (beats/min) | 66.1 ± 9.2 | 66.7 ± 8.1 | 56.0 ± 7.7*† |
| Systolic BP (mm Hg) | 126 ± 10.4 | 121 ± 13.1 | 124 ± 10.2 |
| Diastolic BP (mm Hg) | 76.3 ± 7.1 | 71.0 ± 7.3 | 70.6 ± 9.4 |
| Mean BP (mm Hg) | 92.8 ± 7.3 | 88.0 ± 7.8 | 88.3 ± 7.7 |
| Heart rate · pressure product (mm Hg/min) | 8,311 ± 1,311 | 8,229 ± 1,503 | 6,911 ± 1,135‡§ |
| LV end-diastolic volume index (mL/m$^2$) | 61.6 ± 12.8 | 101 ± 22.5¶ | 91.9 ± 19.4¶ |
| LV end-systolic volume index (mL/m$^2$) | 17.3 ± 4.7 | 42.6 ± 18.7¶ | 38.3 ± 13.0¶ |
| LV ejection fraction (%) | 71.7 ± 6.0 | 58.9 ± 11.2¶ | 58.6 ± 9.9¶ |
| LV end-diastolic pressure (mm Hg) | | 16.7 ± 5.2 | 15.2 ± 3.9 |
| Anterior MI/inferior MI | | 19/5 | 7/2 |
| PCI at admission (yes/no) | | 14/10 | 5/4 |

*$P < 0.05$ vs. normal control subjects.
†$P < 0.01$ vs. without β-blockers.
‡$P < 0.01$ vs. normal control subjects.
§$P < 0.05$ vs. without β-blockers.
¶$P < 0.001$ vs. normal control subjects.
MI = myocardial infarction; BP = blood pressure; PCI = percutaneous coronary intervention.
Data represent mean ± SD.

pressure was computed by a polygraph system (RMC-2000; Nihon Kohden Inc., Tokyo, Japan). Biplane contrast left ventriculography and selective coronary angiography were then performed. LV end-systolic and end-diastolic volumes were calculated by a cardiac image analyzer (Cardio-500; Kontron, Munich, Germany) using the method of Chapman et al. (*7*) Both volumes were divided by the body surface area of each patient, being expressed as the LV end-systolic and end-diastolic volume indices. The LV ejection fraction was then determined. The LV end-diastolic volume index was used as an index of LV remodeling after MI. The normal range of the angiographic LV end-diastolic volume index in our institute, which was obtained from the patients suffering from atypical chest pain, was 70 ± 14 mL · $m^{-2}$. Echocardiography was performed in normal control subjects to obtain the LV volumes using the method of Teichholz et al. (*8*). The LV volumes calculated by this method in subjects without LV asynergy, such as our control subjects, were reported to be accurately and closely correlated with the angiographic LV volumes (echocardiographic volume = 0.91 × angiographic volume + 14; $r = 0.97$; $P < 0.001$) (*8*).

### $^{11}$C-Acetate PET

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 tomographic images at 7-mm intervals and an in-plane resolution of 12 mm as full width at half maximum. After obtaining a 20-min transmission scan to correct for attenuation, 400 MBq $^{11}$C-acetate were administered intravenously. A dynamic PET scan was started 2 min after injection, with acquisition of 20 image frames over 23 min. A total of 20 frames of $^{11}$C-acetate PET imaging was reconstructed as follows: The first 6 frames were from a 30-s acquisition during the first 3 min, and the succeeding 8 frames were from a 60-s acquisition for 8 min (3–11 min after starting the scanning). The last 6 frames were from a 120-s acquisition during the last 12 min (11–23 min). On the midventricular transaxial image of each subject, 5 square ROIs (10 × 10 mm) in the normal control subjects and 6 or 7 square ROIs (10 × 10 mm) in the patients were placed on the LV wall. Time–activity curves of $^{11}$C-acetate in these ROIs were generated from serial PET values after corrections of dead time and physical decay. Just before PET scanning, the heart rate and blood pressure were measured in each subject, and the heart rate · pressure product was then calculated. From the generated time–activity curves of $^{11}$C-acetate, a clearance rate constant ($K_{mono}$) in each ROI was calculated as an index of the regional myocardial oxidative metabolism by applying a monoexponential fitting of the least-squares method in the decreasing phase of the $^{11}$C-acetate activity curve after reaching its peak counts (*9–14*).

### Statistical Analysis

Results are presented as mean ± SD. Parameters between 2 groups were compared using the Student unpaired *t* test and between 3 groups were compared using ANOVA with Bonferroni adjustment. Differences in incidence between 2 groups were compared using the $\chi^2$ test. Differences in $K_{mono}$ values between 5 ROIs in normal control subjects were also compared using ANOVA with repeated measures and Bonferroni adjustment. Using multivariate regression analysis by the SAS General Linear Models procedure (*15*), the effects of β-blockers on the LV end-diastolic volume index and the $K_{mono}$ in remote normal regions were evaluated after adjusting for the influences of the location of the MI, age, heart rate · pressure product, LV end-diastolic pressure, and LV end-systolic volume index (*15*). The adjusted LV end-diastolic volume indices and $K_{mono}$ values in remote normal regions in patients with and without β-blockers were presented as least-squares mean ± SEM. $P < 0.05$ was considered to be significant.

## RESULTS

In normal control subjects, $K_{mono}$ values in the anteroseptal and lateral regions were significantly higher than those in the apical region on the midventricular level of transaxial images. The highest $K_{mono}$ value was observed in the anteroseptal region (0.065 ± 0.007 $min^{-1}$) (Table 3).

No significant differences were found in age or mean blood pressure between the normal control subjects and the

**TABLE 3**
$K_{mono}$ Values in Normal Control Subjects

| Volunteer no. | Apex | Anteroseptal | Anterior | Lateral | Inferolateral |
|---|---|---|---|---|---|
| 1 | 7.12 | 8.13 | 8.05 | 8.06 | 7.03 |
| 2 | 4.75 | 6.02 | 6.99 | 6.06 | 7.20 |
| 3 | 6.12 | 6.17 | 5.33 | 6.59 | 5.27 |
| 4 | 6.61 | 6.80 | 7.34 | 6.92 | 6.15 |
| 5 | 4.56 | 5.78 | 5.22 | 5.98 | 6.15 |
| 6 | 5.06 | 5.60 | 6.29 | 5.87 | 5.70 |
| 7 | 4.46 | 5.85 | 4.94 | 4.82 | 4.43 |
| 8 | 6.74 | 6.78 | 6.40 | 6.66 | 5.92 |
| 9 | 5.06 | 6.04 | 4.69 | 6.45 | 6.40 |
| 10 | 5.94 | 6.47 | 5.67 | 6.38 | 6.47 |
| 11 | 6.15 | 6.62 | 7.25 | 6.12 | 6.04 |
| 12 | 5.93 | 7.34 | 7.51 | 6.36 | 6.47 |
| Mean ± SD ($min^{-1}$) | 5.71 ± 0.90 | 6.47 ± 0.73* | 6.31 ± 1.13 | 6.36 ± 0.76* | 6.10 ± 0.75 |

*$P < 0.01$ vs. apex.
Data are expressed as mean ± SD × 0.01.

MI patients receiving or not receiving β-blockers. Heart rate was significantly less in the MI patients receiving β-blockers than in normal control subjects and patients without β-blockers. The LV end-diastolic volume index (101 ± 22.5 vs. 61.6 ± 12.8 mL · $m^{-2}$; $P < 0.001$) and the LV end-systolic volume index (42.6 ± 18.7 vs. 17.3 ± 4.7 mL · $m^{-2}$; $P < 0.001$) were significantly larger in the MI patients without β-blockers than in normal control subjects. There was no significant difference in the heart rate · pressure product between the MI patients without β-blockers and the normal control subjects (8,229 ± 1,503 vs. 8,311 ± 1,311 mm Hg · $min^{-1}$). The $K_{mono}$ in remote normal regions was significantly greater in the MI patients without β-blockers compared with the highest $K_{mono}$ observed on the anteroseptal wall of the left ventricle in normal control subjects (0.078 ± 0.022 vs. 0.065 ± 0.007 $min^{-1}$; $P < 0.01$) (Fig. 1).

In contrast, the heart rate · pressure product was significantly less in the MI patients receiving β-blockers than in those not receiving β-blockers (6,911 ± 1,135 vs. 8,229 ± 1,503 mm Hg · $min^{-1}$; $P < 0.001$). The $K_{mono}$ in the remote normal regions was significantly less in patients with β-blockers than in those without β-blockers (0.054 ± 0.009 vs. 0.078 ± 0.022 $min^{-1}$; $P < 0.001$) (Fig. 1). No significant differences in the LV end-diastolic volume index (91.9 ± 19.4 vs. 101 ± 22.5 mL · $m^{-2}$) or the LV end-systolic volume index (38.3 ± 13.0 vs. 42.6 ± 18.7 mL · $m^{-2}$) were found between the MI patients with and without β-blockers.

Multivariate regression analysis using the SAS General Linear Models procedure showed that the LV end-systolic volume index, which is a substantial parameter of LV systolic function, was a prime determinant of the LV end-diastolic volume index ($P < 0.0001$). It also indicated that administration of β-blockers did not significantly affect the LV end-diastolic volume index (97.0 ± 7.3 vs. 101 ± 4.3 mL · $m^{-2}$; not significant) (with β-blockers vs. without β-blockers) after adjusting the effects of the LV end-systolic volume index and other parameters. In contrast, β-blockers significantly and directly decreased the $K_{mono}$ in remote normal regions after adjusting the effects of the heart rate · pressure product and other factors (0.061 ± 0.004 vs. 0.078 ± 0.002 $min^{-1}$; $P < 0.01$), although the prime determinant of the $K_{mono}$ in such regions was the heart rate · pressure product ($P < 0.0001$).

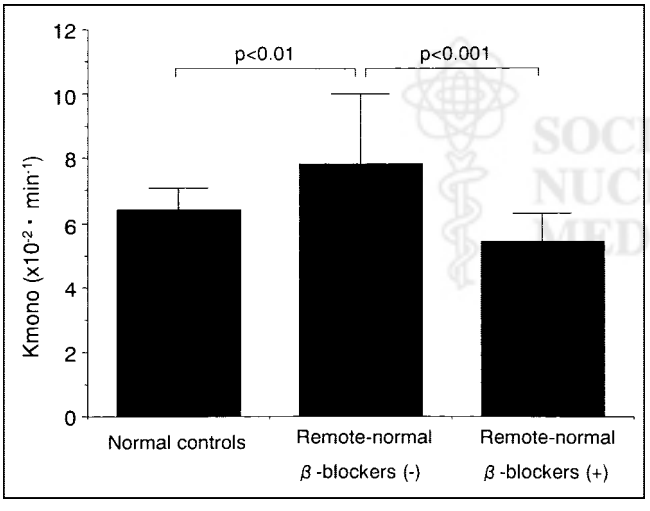


**FIGURE 1.** Comparison of $K_{mono}$ values in remote normal regions in patients with (+) and without (−) β-blockers and highest $K_{mono}$ observed on anteroseptal wall in normal control subjects. $K_{mono}$ in remote normal regions in patients without β-blockers was significantly higher than that in normal control subjects. In patients with β-blockers, $K_{mono}$ is reduced to normal range.

## DISCUSSION

This study shows that in patients with recent MI, the myocardial oxidative metabolism in remote normal regions is accelerated in the left ventricles with remodeling compared with that in normal left ventricles. Furthermore, myocardial oxidative metabolism in remote normal regions is significantly reduced to the normal range in patients receiving β-blockers.

It has been shown that the clearance rates of $^{11}$C-acetate in normal and ischemic myocardium correlate closely with overall myocardial oxygen consumption in corresponding segments (*9–14*). In a clinical setting, the $K_{mono}$ calculated by applying a monoexponential fitting to the clearance curve of $^{11}$C-acetate has been used as an index of the regional myocardial oxidative metabolism (*11*). In contrast to myocardial $^{18}$F-FDG uptake, the clearance of $^{11}$C-acetate is independent of heterogeneous substrate utilization (*12,13*). Thus, we investigated the pathologic status in the noninfarct or remote normal regions from the standpoint of myocardial oxidative metabolism using the $K_{mono}$.

We found that a heterogeneity in the myocardial oxidative metabolism existed on the LV wall in normal control subjects. Similar to our finding, slow $^{11}$C-acetate clearance has been reported in the apex and inferior wall in previous studies (*16–18*). We adopted the highest mean $K_{mono}$ observed on the anteroseptal wall as the $K_{mono}$ value in the normal control subjects.

Increased LV end-diastolic volume and eccentric hypertrophy in recent MI have been revealed in humans and animal models, referring to LV remodeling (*1–3*). The remodeling process is secondary to lengthening of noninfarct segments, which are free of significant fibrosis (*1–3*). Olivetti et al. (*19,20*) showed that compensated reactive ventricular hypertrophy develops chronically after MI, and growth processes in myocytes are inadequate for normalization of wall stress in a large MI. Thus, in remote normal regions of the LV wall in the hearts with remodeling, an elevated myocardial load persisted and caused a vicious cycle of LV volume increase and elevation of the load to the left ventricle. The remote normal regions work against the persistently elevated myocardial load should consume a larger amount of energy sources with oxygen compared

with that of the normal myocardium, resulting in an accelerated myocardial oxidative metabolism (*21*).

Walsh et al. (*22*) examined the differences in the clearance rates of $^{11}$C-acetate among the regions with central infarct, infarct, periinfarct, and noninfarct in patients with acute MI who were treated conservatively. In contrast with our data, they showed that the $K_{mono}$ in remote normal regions in 6 patients with acute MI was not significantly different from the values in the myocardium observed in 5 normal volunteers. They performed the PET examination within 48 h after the onset of acute MI; however, our study was done on patients with proven remodeling 4–12 wk after the onset of MI. This may be the main reason for the discrepancy between the 2 studies. In addition, the relatively small numbers of patients and normal subjects enrolled in their study may also have affected the discrepancy between the 2 studies because the local myocardial oxidative metabolism is very dependent on the global myocardial work in each subject (*11*). The global myocardial work also depends heavily on the heart rate and blood pressure in each subject, which is easily alterable according to the individual inconstant autonomic status. Thus, in the study evaluating the $^{11}$C-acetate clearance from the myocardium, the small number of subjects might be a potential risk for the statistical analysis of the local differences in the oxidative metabolism. In contrast, Kalff et al. (*23*) showed that the $K_{mono}$ in remote normal regions in patients with an acute MI was significantly greater compared with that in young normal control subjects, being similar to our finding although the age of the normal control subjects was different. In their study, however, the heart rate · pressure product was significantly higher in the MI patients than that in the normal control subjects, suggesting that not only the remodeling process of the LV myocardium but also the increased heart rate · pressure product was accountable for the enhanced myocardial oxidative metabolism in the remote normal regions. On the contrary, our study indicated that without the increase of the heart rate · pressure product, the remodeling process of the left ventricles apparently affected the accelerated oxidative metabolism in remote normal regions.

The poor prognosis of patients with LV remodeling after MI is widely acknowledged (*1–3*). The pathologic conditions including accelerated myocardial oxidative metabolism in the remote normal regions may be responsible. In contrast, administration of β-blockers has been shown to improve the prognosis of MI patients (*3,4*). Thus, we investigated the effect of β-blockers on the oxidative metabolism in remote normal regions, showing that a direct effect of β-blockers on the myocardium as well as a reduction of the heart rate · pressure product by β-blockers diminished the $K_{mono}$ in the remote normal regions. This finding is comparable with the report by Kalff et al. (*23*). We believe that the reduction of the oxidative metabolism in remote normal regions by β-blockers may serve to improve the prognosis.

Whether β-blockers affected the LV remodeling process in acute MI patients needs to be addressed, although this study was not a prospective randomized trial for this purpose. Multivariate regression analysis indicated that an increased LV end-systolic volume index—in other words, a decline of LV systolic function—was a prime determinant of the LV remodeling. This result is consistent with the findings that deterioration of the LV systolic function preceded the increase in the LV end-diastolic volume and caused the LV remodeling in dogs with pacing-induced heart failure (*24*). We were unable to show that β-blockers had a potential for preventing the LV remodeling.

## CONCLUSION

The myocardial oxidative metabolism in remote normal regions is accelerated in the left ventricles with remodeling. β-Blockers decrease the myocardial oxidative metabolism in such regions through the reduction of the heart rate · pressure product and their direct effect on the myocardium, by which they may exert beneficial effects on the left ventricles with remodeling after MI.

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