Heterogeneous cardiac sympathetic innervation in heart failure after myocardial infarction of rats

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Igawa, Akihiko, Takashi Nozawa, Naohiro Yoshida, Nozomu Fujii, Minoru Inoue, Shusaku Tazawa, Hidetsugu Asanoi, and Hiroshi Inoue. Heterogeneous cardiac sympathetic innervation in heart failure after myocardial infarction of rats. Am J Physiol Heart Circ Physiol 278: H1134–H1141, 2000.—We examined cardiac neuronal function and β-receptor with a dual-tracer method of [131I]meta-iodobenzylguanidine (MIBG) and [125I]iodocyanopindolol (ICYP) in rat heart failure after myocardial infarction (MI). In rats with MI, left ventricular (LV) systolic function decreased, and LV dimension and right ventricular (RV) mass increased gradually. MIBG accumulations of the noninfarcted LV (remote region) and RV decreased by 15% at 1 wk compared with sham-operated rats, and these accumulations were restored by 71% and 56%, respectively, at 24 wk compared with age-matched sham rats despite sustained depletion of myocardial norepinephrine contents in these regions. ICYP accumulation of the remote region and of the RV did not decrease at any stages. Myocardial MIBG distribution was heterogeneous at 1 wk when it was lower in the peri-infarcted region than in the remote region, associated with reduced ICYP accumulation in the peri-infarcted region. The heterogeneous distribution of both isotopes disappeared at 12 wk. Thus cardiac sympathetic neuronal alteration was coupled with downregulation of β-receptors in rat heart failure after MI. The abnormal adrenergic signaling occurred heterogeneously in terms of ventricular distribution and time course after MI.

autonomic nervous system; β-receptors; radioisotopes; dual-tracer method

AN INCREASED SYMPATHETIC NERVE activity after myocardial infarction (MI) may contribute to the progression of cardiac remodeling and heart failure and, consequently, increased mortality. Many studies have demonstrated that plasma catecholamine concentrations increase (17, 30) and norepinephrine (NE) contents of the noninfarcted myocardium are depleted after MI (16, 31, 45), suggesting an increased sympathetic nerve activity. However, an impaired cardiac sympathetic neuronal function seen in heart failure may also affect cardiac adrenergic signaling, because synaptic NE levels depend on circulating NE, the amount of neuronal release, and subsequent inactivation by neuronal uptake. The increased sympathetic activity and/or impaired neuronal function after MI would promote an impairment of cardiac response to β-adrenergic stimulation (42) and also a decrease in β-receptor density (4, 7, 15). Thus alterations of cardiac adrenergic signaling might contribute to the progression of heart failure. However, there is little information of a relationship between cardiac neuronal function and β-receptors during the progression of heart failure after MI.

Recently, we established a dual-tracer method to assess sympathetic neuronal function with [131I]meta-iodobenzylguanidine (MIBG), an analog of NE, and β-receptors with [125I]iodocyanopindolol (ICYP) in rats (24). Using this method, we designed the present study to elucidate serial changes in cardiac sympathetic neuronal function and β-receptor density from an early stage after MI to a chronic stage with cardiac remodeling in rats.

METHODS

The present study was undertaken in accordance with the guideline for animal experiment at Toyama Medical and Pharmaceutical University.

Experimental animals. Male Wistar rats weighing 300–350 g were used for induction of MI. MI was produced by ligating the left coronary artery while the rats were under ether anesthesia as described by Pfeffer et al. (26). Briefly, a left thoracotomy was performed to exteriorize the heart rapidly. The left coronary artery was ligated ~2 mm from its origin with a suture of 6–0 silk. With this method, the 24-h survival rate was 57% in the infarcted rats. Control rats were sham operated by using a similar procedure without coronary ligation. All rats were fed standard rat chow and given water ad libitum throughout the experiment. Rats were divided into three groups. The first group was used for hemodynamic study and for measurements of plasma and cardiac tissue catecholamine levels. The second group was used for the assessment of myocardial MIBG and ICYP accumulation. The third group was used for cardiac autoradiography to evaluate ventricular distribution of MIBG and ICYP. Data were collected at 1, 4, 12, and 24 wk after the operation in the first two groups and at 1 and 12 wk in the third group.

MI size was determined using a technique described by Chien et al. (3). Briefly, the right ventricle (RV) and left ventricle (LV) including the interventricular septum (IVS) were dissected, separated, and weighed. Incisions were made in the LV so that the LV tissue could be pressed flat. The
therefore we neglect the cross talk between 125I and 131I. To a cross talk from ICYP to MIBG window was later following the decay of MIBG. In our previous study (24), noninfarcted LV (remote region) and RV counts of MIBG and RV were dissected. After the determination of infarct size, injection. The heart was removed from the chest, and LV and given intravenously. Rats were killed at 1 h after the ICYP jugular vein with the rat under anesthesia with pentobarbital (24). Briefly, a 20-µCi of MIBG was injected via the external carotid artery for an analysis of plasma catecholamines. The chest was opened and the heart was quickly removed from the chest, and the heart was quickly removed. After the decay of MIBG activity and required 21 days for adequate image quality. A myocardial section at a level of papillary muscle was used for quantification of myocardial distribution of MIBG and ICYP. As shown in Fig. 1, four regions of interest (ROIs) were determined, i.e., the infarcted region (left ventricular (LV) free wall), remote region (noninfarcted interventricular septum (IVS)), peri-infarcted region (noninfarcted region adjacent to the infarcted region) and right ventricle (RV). B: similar ROIs were determined in sham-operated rats (SHAM), i.e., LV free wall, IVS, “peri-infarcted” region (region between LV free wall and IVS) and RV. Myocardial accumulation at two peri-infarcted regions were averaged. Ventricular distribution was expressed as relative accumulation of each region to RV.

Table 1. Ventricular weight and infarct size

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>BW, g</th>
<th>LV/BW, mg/g</th>
<th>RV/BW, mg/g</th>
<th>Infarct Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wk</td>
<td>MI</td>
<td>12</td>
<td>318 ± 19</td>
<td>2.09 ± 0.1</td>
<td>0.69 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>12</td>
<td>341 ± 21</td>
<td>1.98 ± 0.16</td>
<td>0.46 ± 0.03</td>
</tr>
<tr>
<td>4 Wk</td>
<td>MI</td>
<td>12</td>
<td>401 ± 21</td>
<td>1.91 ± 0.15</td>
<td>0.78 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>12</td>
<td>398 ± 26</td>
<td>1.88 ± 0.13</td>
<td>0.42 ± 0.05</td>
</tr>
<tr>
<td>12 Wk</td>
<td>MI</td>
<td>12</td>
<td>464 ± 19</td>
<td>2.06 ± 0.20*</td>
<td>0.81 ± 0.25</td>
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<tr>
<td></td>
<td>Sham</td>
<td>11</td>
<td>488 ± 22</td>
<td>1.84 ± 0.09</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td>24 Wk</td>
<td>MI</td>
<td>11</td>
<td>523 ± 47</td>
<td>2.00 ± 0.16*</td>
<td>0.89 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>10</td>
<td>526 ± 40</td>
<td>1.71 ± 0.11</td>
<td>0.38 ± 0.04</td>
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<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td>0.711</td>
<td>0.7144</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = number of rats. MI, rats with myocardial infarction; Sham, sham-operated rats; BW, body weight; LV, left ventricular weight; RV, right ventricular weight. *P < 0.05 vs. age-matched sham-operated rats. †P < 0.05 vs. Sham 1 week.

The hemodynamic study was performed on ether-anesthetized rats. A 2-Fr. micromanometer-tipped catheter (Millar Instruments) was inserted into the right carotid artery and advanced into the LV to determine LV pressure. With the rat anesthetized lightly and breathing spontaneously, LV pressure and electrocardiograms were recorded on a multichannel thermal recorder (WR3151, Nihon Kohden, Tokyo, Japana). These signals were digitized on-line at 2-ms intervals and analyzed with a signal-processing computer system (7T-18, NEC San-Ei, Tokyo, Japana).

After the hemodynamic study, blood was drawn from the carotid artery for an analysis of plasma catecholamines. Pentobarbital sodium (70 mg/kg) was then injected intraperitoneally. The chest was opened and the heart was quickly removed. After the RL and LV were dissected, rinsed in ice-cold saline, and weighed, infarcted size was determined by the method described above. The remaining noninfarcted LV (remote region) was cut and prepared free of both scar tissue and peri-infarcted regions for measurement of tissue catecholamines. Plasma and noninfarcted LV and RV tissue samples were stored at −80°C for later analyses. Catecholamines were determined by an automated high-performance liquid chromatography as described previously (24).

MIBG and ICYP accumulation. The method for determining MIBG and ICYP accumulation was reported previously (24). Briefly, a 20-µCi of MIBG was injected via the external jugular vein with the rat under anesthesia with pentobarbital sodium (30 mg/kg ip). Two hours later a 10-µCi of ICYP was given intravenously. Rats were killed at 1 h after the ICYP injection. The heart was removed from the chest, and LV and RV were dissected. After the determination of infarct size, noninfarcted LV (remote region) and RV counts of MIBG and ICYP were obtained with a gamma counter (ARC 2000, Arokajapan). The ICYP counts were determined 60 days later following the decay of MIBG. In our previous study (24), a cross talk from ICYP to MIBG window was <3% and therefore we neglect the cross talk between 125I and 131I. To normalize MIBG and ICYP accumulation for differences in animal weight, tissue accumulations of MIBG and ICYP were expressed in percent kilogram dose per gram of tissue wet weight (%kg dose/g).

Dual-tracer autoradiography. Dual-tracer autoradiography was performed as described previously (24). Briefly, rats were injected intravenously with 50 µCi of MIBG and 2 h later with an injection of 5 µCi of ICYP. The heart was removed 1 h after the second injection. Serial 20-µm thick transverse sections of the heart were obtained after freezing the specimens. The first autoradiographic exposure on an imaging plate (BAS-UR, Fuji, Japana) was carried out for 6 h to reveal MIBG distribution. The second exposure was initiated 60 days later following the decay of MIBG activity and required 21 days for adequate image quality. A myocardial section at a level of papillary muscle was used for quantification of myocardial distribution of MIBG and ICYP. As shown in Fig. 1, four regions of interest (ROIs) were determined, i.e., the infarcted region, the peri-infarcted region (noninfarcted region adjacent to the infarcted region), the remote region.
**RESULTS**

Hemodynamic and LV geometry. Infarct size ranged from 31 to 50% of LV and was similar among groups with different post-MI weeks (Table 1). There was no significant difference in body weight between MI and age-matched, sham-operated rats. RV mass indexed for body weight (RV/BW) was significantly greater in MI rats than in sham-operated rats at each age.

Hemodynamic data are shown in Table 2. LV systolic pressure was lower in MI rats than in sham-operated rats. LV end-diastolic pressure was not different between MI and sham-operated rats at 1 wk, and thereafter it elevated significantly in MI rats. A maximum value of the rate of change in LV pressure (dP/dt max) and a minimum value of dP/dt (dP/dt min) decreased significantly in MI rats throughout the study period.

LV end-diastolic dimension was larger in MI rats than in sham-operated rats and gradually increased during the study period in MI rats (Table 2). LV fractional shortenings decreased significantly in MI rats at each age.

Myocardial NE contents. Plasma NE levels tended to be higher in MI rats compared with the levels in the sham-operated rats, but the differences did not reach statistical significance (1.1 ± 0.8 vs. 0.6 ± 0.2 ng/ml at 1 wk, 0.8 ± 0.3 vs. 0.6 ± 0.2 ng/ml at 4 wk, 1.5 ± 0.4 vs. 0.9 ± 0.2 ng/ml at 12 wk, and 1.1 ± 0.4 vs. 0.8 ± 0.4 ng/ml at 24 wk). Markedly decreased myocardial NE contents in the noninfarcted LV (remote region) and RV in MI rats at the early stage after MI continued to the chronic stage (Fig. 2).

Cardiac MIBG accumulation and distribution. Figure 3 shows MIBG accumulation of the noninfarcted LV (remote region) and RV in MI and sham-operated rats.

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**Table 2. Hemodynamic and echocardiographic data**

<table>
<thead>
<tr>
<th>n</th>
<th>HR, beats/min</th>
<th>LVSP, mmHg</th>
<th>LVEDP, mmHg</th>
<th>dP/dt max, ×10^4 mmHg/s</th>
<th>dP/dt min, ×10^4 mmHg/s</th>
<th>LVDD, mm</th>
<th>FS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>415 ± 16</td>
<td>85 ± 2*</td>
<td>4 ± 2</td>
<td>6.1 ± 0.7*</td>
<td>7.9 ± 0.1*</td>
<td>19 ± 2*</td>
</tr>
<tr>
<td>Sham</td>
<td>6</td>
<td>394 ± 23</td>
<td>111 ± 11</td>
<td>3 ± 1</td>
<td>10.8 ± 2.1</td>
<td>7.1 ± 1.3</td>
<td>6.3 ± 0.2</td>
</tr>
<tr>
<td>4 Wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>389 ± 22</td>
<td>96 ± 5</td>
<td>16 ± 6†</td>
<td>6.5 ± 0.7†</td>
<td>3.9 ± 0.4*</td>
<td>9.5 ± 0.2†</td>
</tr>
<tr>
<td>Sham</td>
<td>6</td>
<td>402 ± 17</td>
<td>114 ± 14</td>
<td>3 ± 2</td>
<td>11.1 ± 2.1</td>
<td>6.9 ± 1.7</td>
<td>6.5 ± 0.2</td>
</tr>
<tr>
<td>12 Wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>355 ± 24</td>
<td>108 ± 6†</td>
<td>17 ± 5†</td>
<td>7.1 ± 1.3†</td>
<td>4.8 ± 1.0*</td>
<td>10.0 ± 0.3†</td>
</tr>
<tr>
<td>Sham</td>
<td>5</td>
<td>398 ± 40</td>
<td>119 ± 6</td>
<td>3 ± 1</td>
<td>12.0 ± 2.1</td>
<td>9.0 ± 0.4</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td>24 Wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>393 ± 7</td>
<td>113 ± 9†</td>
<td>17 ± 6†</td>
<td>7.4 ± 2.2†</td>
<td>4.6 ± 1.0*</td>
<td>10.2 ± 0.3†</td>
</tr>
<tr>
<td>Sham</td>
<td>5</td>
<td>367 ± 33</td>
<td>116 ± 3</td>
<td>3 ± 2</td>
<td>11.4 ± 1.2</td>
<td>8.4 ± 0.5</td>
<td>6.9 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of rats. HR, heart rate; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt max and dP/dt min, maximum and minimum value of rate of change in LV pressure; LVDD, LV end-diastolic dimension; FS, fractional shortening. *P < 0.05 vs. age-matched sham-operated rats. †P < 0.05 vs. MI 1 wk. ‡P < 0.05 vs. MI 4 wk.

**Fig. 2. Myocardial norepinephrine (NE) contents of noninfarcted LV remote region (A; i.e., IVS) and RV (B).** Filled bars, rats with MI (n = 5 at each week). Open bars, sham-operated rats (n = 6 at 1 and 4 wk, n = 5 at 12 and 24 wk). Values are means ± SD. *P < 0.05 vs. age-matched sham-operated rats.
LV infarct size was similar among four groups with different post-MI stages (38 ± 7% at 1 wk, 32 ± 3% at 4 wk, 36 ± 7% at 12 wk, and 35 ± 5% at 24 wk). In MI rats, the decreases in MIBG accumulation were prominent at 1 wk (15% of sham-operated rats) in both the LV and RV. The accumulation was gradually restored at chronic stages and was 71% (LV) and 56% (RV) in the sham-operated rats at 24 wk. The reduced differences in MIBG accumulation between MI and sham-operated rats at chronic stages were partially due to gradual decreases in the MIBG accumulation with age in sham-operated rats (Fig. 3).

The MIBG distribution of LV was homogeneous in sham-operated rats but was heterogeneous in MI rats (Fig. 4). A quantitative analysis of MIBG distribution showed that the accumulation of the peri-infarcted region was significantly lower than that of the remote region at 1 wk but was restored at 12 wk (Fig. 5). In sham-operated rats, the MIBG accumulation of the LV including the ventricular septum was homogeneous at 1 and 12 wk.

Cardiac ICYP accumulation and distribution. ICYP accumulation of the noninfarcted LV (remote region) and RV was not significantly different between MI and sham-operated rats at all stages, although ICYP accumulation of RV tended to be lower in rats with MI (Fig. 6). Ventricular distribution of ICYP in MI rats showed that the accumulation was significantly lower in the peri-infarcted region than in the RV remote region at 1 wk and became homogeneous except the infarcted region at 12 wk (Figs. 7 and 8). The ICYP accumulation was homogeneous in the sham-operated rats.

**DISCUSSION**

The major findings of the present study are as follows. First, a marked decrease in MIBG accumulation of the LV remote region and RV occurred at the early stage after MI and was gradually restored at the chronic stage despite a sustained depletion of myocardial NE and a gradual ventricular enlargement. Second, a heterogeneous MIBG distribution at the early stage, i.e., lower accumulation in the peri-infarcted region, became homogeneous except for the infarcted region at the chronic stage. Third, markedly reduced MIBG accumulation in the peri-infarcted region in the early stage was associated with reduced ICYP accumulation, a phenomenon of downregulation of β-receptors. MIBG and ICYP accumulations were, however, restored at the chronic stage. Thus a cardiac sympathetic neuronal function was coupled with β-receptor density, and the neuronal alteration and downregulation of β-receptors occurred heterogeneously in terms of ventricular distribution and the time course after MI.

Heart failure after MI in rats was characterized by reduced LV systolic function, increased LV filling pressure and volume, and increased RV mass (5, 26), all observed in the present study. Despite reduced LV systolic function at the early stage, there was no increase in ventricular filling pressure, a consistent finding with the previous report (10). At the chronic stage after MI, markedly increased LV end-diastolic pressure and LV systolic dysfunction were associated with gradual increases in LV dimension and RV mass in the present study, suggesting a progressive ventricular remodeling in both ventricles after MI.

A decrease in myocardial NE is commonly observed in heart failure (2, 28). Depletion of myocardial NE in the noninfarcted LV and RV was reported at both acute and chronic stages after MI in experimental animals (6, 12, 31, 45). This depletion could be attributed to an...
increase in cardiac sympathetic discharge and NE release from the nerve terminal in heart failure (19, 35). A magnitude of increased sympathetic activation after MI depends on the extent of cardiac damage and hemodynamic consequences (17, 30). In the present study, depleted cardiac NE was seen at the early stage and was sustained until the chronic stage, at which a reduction of stroke volume due to MI could be compensated by an enlargement of ventricular volume. The present results suggest that increased cardiac sympathetic activity after MI might be sustained throughout the study periods and contribute to further ventricular remodeling (25), in association with increased wall stress due to an enlargement of ventricular volume and increased filling pressure.

MIBG is an analog of NE and shares neuronal transport and storage mechanisms with NE (23, 34). Decreased cardiac MIBG uptake has been reported in both clinical (9) and experimental heart failure (29, 32). Several mechanisms for decreased MIBG accumulation in heart failure could be proposed. Among them are increased neuronal release of MIBG by sympathetic activation, impaired cardiac neuronal uptake of MIBG, and decreased adrenergic neuron density.

Nonneuronal MIBG accumulation has been reported to reach 30–50% of the total cardiac accumulation in rats, hamsters, and dogs studied 3–4 h after MIBG injection (23, 29, 40). A magnitude of nonneuronal accumulation was assessed using neuronal uptake-1 blocker in most studies. However, Sisson et al. (34) reported 69% or more neuronal uptake in rats, in which 6-hydroxydopamine was used to impair function of the nerve terminals, although the selective uptake-1 blocker desmethylimipramine reduced MIBG accumulation only to 50% of the control. Cardiac MIBG accumulation is also influenced by the specific activity, and it markedly decreases following a high MIBG dose. In the present study, MIBG with high specific activity (65 Ci/mmol) was used at a low dose. A recent rat experiment, using MIBG with a high specific activity, revealed an accumulation of 80–90% of MIBG in cardiac sympathetic neurons 3 h after injection and a storage of 70–80% of MIBG in adrenal vesicles (M. Inoue, unpublished data). In the present study, it is unlikely that reduced MIBG accumulation in the LV remote region and RV would be due to sympathetic denervation with the operative procedure because the accumulation did not decrease in the sham-operated rats. Therefore, cardiac MIBG accumulation in the present study can be regarded as a reflection of cardiac sympathetic neuronal function, although some amount of MIBG injected would be taken up by nonneuronal tissue in the heart.

In our previous study, cardiac washout rate of MIBG, an index of sympathetic activity, increased significantly in noninfarcted myocardium after MI compared with sham-operated rats (unpublished data). An acute hemodynamic deterioration and subsequent activation of cardiac sympathetic nerve and/or impaired cardiac neuronal uptake function would lead to a decrease in cardiac MIBG accumulation at the early stage after MI.
In the chronic stage (12–24 wk), however, an improvement of cardiac MIBG accumulation was not associated with a restoration of cardiac NE. Along with hemodynamic stabilization, cardiac neuronal uptake function might be improved and cardiac MIBG accumulation recovered gradually. The sustained decreases in cardiac NE at the chronic stage may be due to an increased sympathetic activity and insufficient NE synthesis in the nerve (27). The discrepancy between cardiac MIBG accumulation and NE contents was observed in earlier studies (24, 36).

In patients with MI, the area of reduced cardiac MIBG uptake is often greater than that of a myocardial perfusion defect with thallium-201 chloride (18, 37). In the present study of cardiac autoradiography, the MIBG accumulation was significantly less in the peri-infarcted region than in the remote region at the early stage, although the accumulation decreased even in the remote region compared with the sham-operated rats. The reduced accumulation in the peri-infarcted region was restored at the chronic stage, a consistent finding with the previous observations (8, 20).

Sisson et al. (33) reported that an intravenous injection of ICYP bound predominantly to β-receptors and nonspecific binding was 10–20% of total bindings. In our previous study (24), the amount of cardiac ICYP accumulation was comparable to the maximal binding capacity of β-receptors assessed by radioligand receptor assay in a membrane preparation in rats. Because a 20-µm transverse section of heart for autoradiography was fixed on the slide glass, a 60-day delay could not affect ICYP densities in each region of the heart. Therefore, we consider that the present method would reasonably reflect changes in distribution and density of β-receptors in a heart.

In the present study, there were no significant changes in ICYP accumulation in both the LV remote region and RV after MI, which is consistent with the earlier study (1) in which membrane preparation was used for measurement of β-receptor density. In contrast, a significant reduction of β-receptor density was reported in the noninfarcted myocardium (31, 44). These differences may be attributed to the MI size and the period examined after MI.

In the present autoradiographic study, markedly reduced MIBG accumulation in the peri-infarcted region was accompanied with reduction in ICYP accumulation at the early stage. Similar findings of decreased β-receptor density in the peri-infarcted region were observed in previous studies (13, 38). A peri-infarcted myocardium, in which MIBG accumulation is reduced but coronary flow is preserved, is considered to be “denervated but viable” (18, 37). A direct influence of ischemia by the coronary occlusion might contribute to the reduced MIBG and ICYP accumulations in the peri-infarcted region. Acute myocardial ischemia has been reported to lead to an increase in β-receptor density (21). A cardiac sympathetic denervation would be associated with an increased (41) or unchanged density of β-receptors (11). Delehanty et al. (4) reported that synaptic NE levels were inversely related with β-receptor densities in heart failure. Therefore, our data suggest that reduction of MIBG accumulation in the peri-infarcted region at the early stage after MI might not be induced by the sympathetic denervation. An increased synaptic NE due to increased NE releases...
and/or impairs its reuptake, which might induce the downregulation of β-receptors in the peri-infarcted region at the early stage, a consistent finding with our previous observations in hypertensive heart failure rats (24).

The relative MIBG accumulation of the remote region (IVS to RV) was lower at 12 wk than at 1 wk in MI rats (Fig. 5). A similar finding was observed in ICYP accumulation (Fig. 8). However, the "absolute accumulation (\%kg dose/g)" of both isotopes, especially MIBG accumulation, in the remote region increased from week 1 to week 12 (Figs. 3 and 6). Therefore, it is unlikely that the homogenized distribution of isotopes in the remote and peri-infarcted regions at 12 wk may be due to the reduced accumulation in the remote region.

Some methodological limitations deserve comments in interpreting the present results. First, myocardial blood flow that would influence MIBG and ICYP accumulation was not evaluated in the present study. However, markedly decreased MIBG accumulation was found even in the remote region of LV and RV. Recently, Kramer et al. (14) reported that MIBG accumulation was reduced in the peri-infarcted region relative to the remote region, in which blood flow was preserved. Some amount of MIBG injected may be taken up by nonneuronal tissue in the heart. Takatsu et al. (39) reported that the reduced MIBG accumulation in the infarcted region after coronary occlusion followed by the reperfusion might result from a deficit in nonneuronal accumulation. The influence of the nonneuronal accumulation in the present results was not evaluated, although the present study was performed without the reperfusion after the coronary occlusion. The influence of regional blood flow and nonneuronal MIBG accumulation requires further study. Second, we did not determine the infarct size with the standard histological method but determined with macroscopic boundary of scar as described by Chien et al. (3). This method may underestimate the infarct size compared with the histological method (6). Because rats with MI were compared with rats without MI, this underestimation might not seriously affect the present results. Finally, blood sampling for NE measurement was performed with the animals under anesthesia, which could affect the level of plasma NE. In the study by Musch and Zelis (22), the plasma NE in conscious unrestrained rats without MI is lower than that found in the present study. The influence of anesthesia might account for the lack of the significant differences in plasma NE between sham-operated and MI rats in the present study.

Although limited for these reasons, the present method of dual tracers with MIBG and ICYP is useful for an in vivo evaluation of changes in the cardiac adrenergic signaling after MI. The present results suggest that the increased sympathetic activity accompanied with the neuronal dysfunction in the early stage after MI might cause the downregulation of β-receptors. In the chronic stage after hemodynamic stabilization, an increased wall stress as well as the sustained neural activity might contribute to further ventricular enlargement despite a restoration of the neuronal function. Cardiac sympathetic alteration and downregulation of β-receptors occur heterogeneously in terms of ventricular distribution and periods after MI.

This study was supported by a grant-in-aid for Scientific Research from the Japanese Ministry of Education, Science, and Culture (6670701).

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Received 9 April 1999; accepted in final form 19 October 1999.

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