# Effects of Extrinsically Elevated Plasma Norepinephrine Concentration on Myocardial $^{123}$I-MIBG Kinetics in Rats

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Rapid $^{123}$I-metaiodobenzylguanidine (MIBG) washout and high plasma norepinephrine (NE) levels are frequently observed in patients with congestive heart failure, and high plasma NE levels are not necessarily induced by increased cardiac NE spillover. The purpose of this study was to assess the effect of extrinsically elevated plasma NE levels on myocardial MIBG kinetics. **Methods:** MIBG was injected into the femoral vein in 47 adult male Wister rats. In the first study, normal saline solution or NE (0.3, 1.0 and 3.0 μg/kg/min) was administered to each group of 6 or 7 rats continuously from 30 min before to 30 min after MIBG injection. In the second study, NE was administered at 3.0 μg/kg/min to each group of 7 rats continuously from 30 min before to 2 h after or from 30 to 60 min after MIBG injection, and NE was not administered to a control group of 7 rats. For 2 or 4 h after MIBG injection, scintigrams were acquired using a gamma camera with a pinhole collimator, after which myocardial MIBG uptake (percentage injected dose normalized for the difference in rat weight per tissue weight) was determined in isolated heart with a gamma counter. **Results:** In the first study, the MIBG washout rate from the heart was significantly increased during high-dose NE infusion (1.0 and 3.0 μg/kg/min) compared with that during saline infusion, whereas the washout rate was not increased during low-dose NE infusion. In the second study, the MIBG washout rate from the heart during NE infusion was significantly increased compared with that of the control but was not increased during discontinuation of NE infusion. **Conclusion:** Extrinsically induced high levels of plasma NE may accelerate MIBG washout from the heart.

**Key Words:** metaiodobenzylguanidine; rat; norepinephrine; myocardium

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Noninvasive evaluation of cardiac sympathetic nerve activity uses $^{123}$I-metaiodobenzylguanidine (MIBG), an analog of guanethidine with neuronal uptake, storage and release mechanisms that are similar to those of norepinephrine (NE) (*1–4*). Patients with congestive heart failure (CHF) show increased washout of MIBG (*5–8*), for which some mechanisms have been proposed. An activated sympathetic nervous system or the increased release of NE at cardiac nerve terminals in CHF has been suggested to promote MIBG washout from the heart (*6,9,10*). On the other hand, the plasma NE level is often increased in patients with CHF (*11–13*), which is another possible mechanism of the increased MIBG washout (*14*). Nakajo et al. (*15*) found an increased plasma NE concentration accompanied by a decreased myocardial MIBG uptake in patients with pheochromocytoma. In CHF patients, a significant correlation between the plasma NE concentration and the myocardial washout rate has also been reported (*8*). However, this correlation has been refuted by other studies (*6,7*), and, therefore, opinions are divided.

In pheochromocytoma, enhanced NE release from the tumor tissue has been suggested to increase the plasma NE concentration, resulting in a decrease in myocardial MIBG uptake (*15*). In CHF, the high plasma NE concentration is not entirely associated with an increased NE release from the heart alone but is caused by enhanced NE release from organs in the entire body, including the heart, and a delay in NE disappearance (*16*). In CHF and pheochromocytoma, an increased plasma NE concentration associated with factors other than increased NE release from the heart may secondarily affect myocardial MIBG kinetics. Therefore, we evaluated the possible effects of an exogenous increase in the plasma NE concentration after NE administration on myocardial MIBG kinetics in normal rat hearts originally without increased NE release.

## MATERIALS AND METHODS

### Animals

Adult male Wistar rats (n = 65; age 14.7 ± 1.9 wk; body weight 0.31 ± 0.03 kg) were used in the experiments. Cannulas were inserted into the bilateral femoral veins under anesthesia with intraperitoneal sodium pentobarbital (40 mg/kg).

In the first study, 4 mL normal saline solution (NSS) or NE (0.3, 1.0 and 3.0 μg/kg/min) was administered to each group of 6 or 7 rats continuously from 30 min before to 30 min after MIBG injection (Fig. 1).

In the second study, NE at 3.0 μg/kg/min was administered to each group of 7 rats continuously from 30 min before to 2 h after, from 30 min before to 30 min after or from 30 to 60 min after

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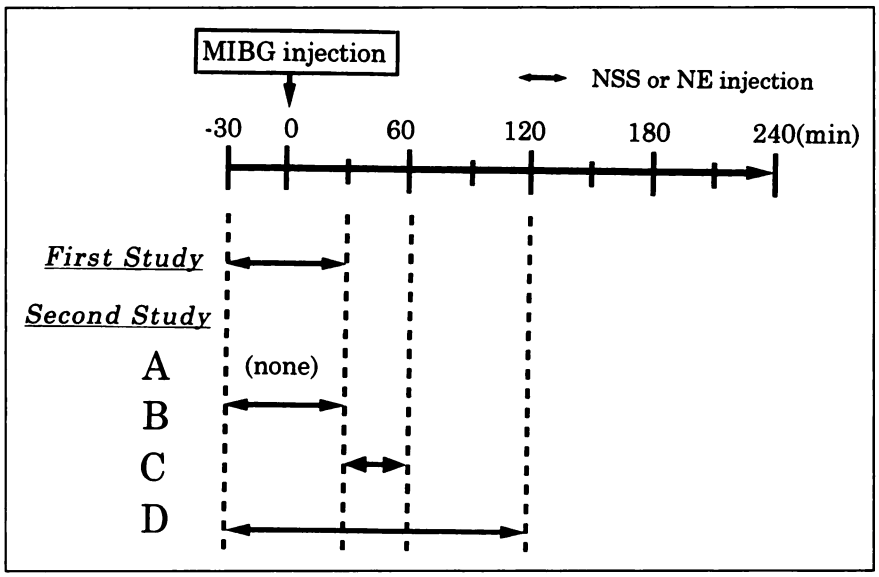


**FIGURE 1.** Study protocols. In first study, 0.3, 1.0 or 3.0 μg/kg/min (4 mL) $^{123}$I-metaiodobenzylguanidine (MIBG) or 4 mL normal saline solution (NSS) were administered from 30 min before to 30 min after MIBG injection. In second study, A depicts no norephinephrine (NE) administration, and B, C and D depict administration of NE at 3.0 μg/kg/min from 30 min before to 30 min after MIBG injection, from 30 to 60 min after MIBG injection and from 30 min before to 120 min after MIBG injection, respectively.

MIBG injection. The control group of 7 rats was not administered NE (Fig. 1).

In addition, changes in the plasma NE concentration, heart rate and arterial blood pressure after NE administration were examined in groups consisting of 3–5 adult male Wistar rats (n = 18; age 12.0 ± 0.5 wk; body weight 0.284 ± 0.02 kg).

### $^{123}$I-MIBG Study

In each group, MIBG (mean dose 9.51 ± 0.99 MBq; specific activity 1.1–3.7 GBq/mg; Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan) was injected through a cannula into a femoral vein.

While the rats were restrained by tapes on a small board with additional administration of pentobarbital, static imaging was performed for 5 min/frame on a gamma camera with a pinhole collimator. Images were obtained 5, 10, 15, 30, 60, 90 and 120 min after MIBG injection. In the group injected with NE at 3.0 μg/kg/min in the first study, additional images were obtained 180 and 240 min after MIBG injection.

In a region of interest manually drawn around the heart, the average counts/pixel were measured. The myocardial MIBG washout rate (percentage) was calculated using the following equation: (initial heart count − delayed heart count)/initial heart count × 100. Two or 4 h after the injection, the animals were killed under deep pentobarbital anesthesia. The heart was removed and weighed, and its radioactivity was counted with an auto-well gamma counter. The myocardial MIBG uptake was expressed as percentage injected dose normalized for the difference in rat weight per tissue weight (%kg dose/g) (*10*). Each time after MIBG injection, the myocardial MIBG uptake was calculated from the value measured using the gamma counter and the washout rate obtained by scintigraphy.

In the first study, we attempted to assess whether the increase in the plasma NE concentration influences the myocardial MIBG uptake and washout. In the second study, NE administration was initiated 30 min before MIBG injection or 30 min after MIBG administration so that the effects of the increased plasma NE concentration on myocardial MIBG washout could be evaluated separately from its effects on myocardial MIBG uptake.

### Plasma Norepinephrine Level, Peripheral Blood Pressure and Heart Rate

The plasma NE concentration was determined 1 h after initiation of continuous intravenous injection of NE at 0.3, 1.0 and 3.0 μg/kg/min to 5, 4, and 3 rats, respectively. On the other hand, the arterial blood pressure and heart rate were measured before and 30 min after initiation of continuous intravenous injection of NE at 0.3 or 3.0 μg/min to 3 rats each. Hemodynamic data were recorded on a BSM-3201 multichannel recorder (Nihon Koden, Tokyo, Japan) after insertion of a cannula into a carotid artery.

### Statistical Analysis

The mean data for each group were compared using analysis of variance followed by a multiple comparison test. Data are expressed as mean ± SD. $P < 0.05$ was considered significant.

## RESULTS

In the first study, the age, body weight, heart weight and injected MIBG dose were not significantly different in the

**TABLE 1**
Background of Each Group in First Study

| Parameter | NSS | NE infusion (μg/kg/min) 0.3 | 1.0 | 3.0 |
|---|---|---|---|---|
| n | 7 | 6 | 6 | 7 |
| Age (wk) | 13.9 ± 0.4 | 14.0 ± 0.9 | 12.3 ± 0.5 | 13.7 ± 1.5 |
| Body weight (kg) | 0.30 ± 0.01 | 0.32 ± 0.02 | 0.30 ± 0.02 | 0.29 ± 0.02 |
| Heart weight (g) | 0.65 ± 0.03 | 0.68 ± 0.04 | 0.68 ± 0.07 | 0.64 ± 0.04 |
| Injected MIBG dose (MBq) | 9.13 ± 0.59 | 8.67 ± 0.94 | 8.46 ± 1.31 | 10.0 ± 0.81 |

NE = norepinephrine; NSS = normal saline solution; MIBG = $^{123}$I-metaiodobenzylguanidine.
Data are expressed as mean ± SD.

four groups indicated in Table 1. In this study, rats continuously injected with NSS from 30 min before to 30 min after MIBG injection served as a control group. The MIBG uptake was significantly lower in the group injected with NE at 1.0 μg/kg/min from 30 min before to 30 min after MIBG injection than that in the control group 30, 60, 90 and 120 min after MIBG injection (Table 2). Similarly, 15, 30, 60, 90 and 120 min after MIBG injection, the myocardial MIBG uptake was significantly lower in the group injected with NE at 3.0 μg/kg/min from 30 min before to 30 min after MIBG injection than that in the control group (Table 2). The myocardial MIBG washout rate from 5 to 30 min after MIBG injection was significantly higher in the group injected with NE at 1.0 or 3.0 μg/kg/min from 30 min before to 30 min after MIBG injection than that in the control group (Table 3)..

In the second study, the age, body weight, heart weight and MIBG dose did not significantly differ in the four groups (Table 4). In this study, rats injected with MIBG but not with NE served as a control group. The myocardial MIBG washout rate from 5 to 30 min after MIBG injection was significantly higher in the group injected with NE at 3.0 μg/kg/min from 30 min before to 30 min after MIBG injection than that in the control group (Table 5). Similarly, the myocardial MIBG washout rate from 30 to 60 min after MIBG injection was significantly higher in the group injected with NE at 3.0 μg/kg/min from 30 to 60 min after MIBG injection than that in the control group. The group injected with NE at 3.0 μg/kg/min from 30 min before to 120 min after MIBG injection showed a significantly higher myocardial MIBG washout rate from 5 to 120 min after MIBG injection than that in the control group (Table 5). Thus, the washout rate during NE administration alone was increased in each NE administration group compared with that in the control group.

The plasma NE concentration was 1434 ± 596 pg/mL during NE infusion at 0.3 μg/kg/min (n = 5), 2808 ± 1369 pg/mL during NE infusion at 1.0 μg/kg/min (n = 4) and 8687 ± 1328 pg/mL during NE infusion at 3.0 μg/kg/min (n = 3). The heart rate did not significantly change after continuous administration of NE at 0.3 μg/kg/min (380 ± 34 to 420 ± 60 beats/min, $P > 0.05$) or NE at 3.0 μg/kg/min (430 ± 17 to 450 ± 30 beats/min, $P > 0.05$). The systolic blood pressure did not significantly change after continuous administration of NE at 0.3 μg/kg/min (101 ± 34 to 127 ±

**TABLE 2**
Myocardial MIBG Uptake in First Study

| Time after MIBG injection (min) | Myocardial MIBG uptake (%kg dose/g) | | | |
|---|---|---|---|---|
| | | NE infusion (μg/kg/min) | | |
| | NSS | 0.3 | 1.0 | 3.0 |
| 5 | 1.33 ± 0.1 | 1.26 ± 0.28 | 1.16 ± 0.28 | 1.18 ± 0.21 |
| 10 | 1.23 ± 0.13 | 1.19 ± 0.27 | 1.08 ± 0.26 | 1.09 ± 0.20 |
| 15 | 1.23 ± 0.14 | 1.16 ± 0.25 | 1.00 ± 0.25 | 0.99 ± 0.18* |
| 30 | 1.12 ± 0.13 | 1.05 ± 0.28 | 0.87 ± 0.23* | 0.82 ± 0.18† |
| 60 | 0.98 ± 0.10 | 0.92 ± 0.22 | 0.75 ± 0.21* | 0.72 ± 0.15† |
| 90 | 0.88 ± 0.11 | 0.79 ± 0.18 | 0.66 ± 0.19* | 0.64 ± 0.16† |
| 120 | 0.79 ± 0.08 | 0.69 ± 0.16 | 0.56 ± 0.16† | 0.57 ± 0.12† |
| 180 | | | | 0.47 ± 0.11 |
| 240 | | | | 0.40 ± 0.10 |

*$P < 0.05$ vs. NSS.
†$P < 0.01$ vs. NSS.
MIBG = $^{123}$I-metaiodobenzylguanidine; %kg dose/g = percentage injected dose normalized for difference in rat weight per tissue weight; NE = norepinephrine; NSS = normal saline solution.
Data are expressed as mean ± SD.

**TABLE 3**
Myocardial MIBG Washout Rate in First Study

| MIBG injection | Myocardial MIBG washout rate (%) | | | |
|---|---|---|---|---|
| | | NE infusion (μg/kg/min) | | |
| | NSS | 0.3 | 1.0 | 3.0 |
| From 5 min before to 30 min after | 15.6 ± 3.8 | 17.4 ± 2.5 | 25.9 ± 2.6* | 31.0 ± 5.9* |
| From 30 min before to 60 min after | 12.0 ± 2.5 | 12.0 ± 1.7 | 14.3 ± 2.8 | 11.4 ± 4.1 |
| From 60 min before to 90 min after | 10.6 ± 3.9 | 13.6 ± 3.3 | 12.1 ± 3.6 | 12.1 ± 4.0 |
| From 90 min before to 120 min after | 10.0 ± 4.0 | 12.6 ± 4.9 | 14.4 ± 4.6 | 10.6 ± 3.4 |

*$P < 0.01$ vs. NSS.
MIBG = $^{123}$I-metaiodobenzylguanidine; NE = norephinephrine; NSS = normal saline solution.
Data are expressed as mean ± SD.

**TABLE 4**
Background of Each Group in Second Study

| Parameter | No NE infusion | NE infusion (3.0 μg/kg/min) | | |
|---|---|---|---|---|
| | | From 30 min before to 30 min after MIBG injection | From 30 min before to 60 min after MIBG injection | From 30 min before to 120 min after MIBG injection |
| n | 7 | 7 | 7 | 7 |
| Age (wk) | 14.9 ± 2.4 | 13.7 ± 1.5 | 13.3 ± 1.1 | 16.3 ± 1.0 |
| Body weight (kg) | 0.32 ± 0.04 | 0.29 ± 0.02 | 0.29 ± 0.02 | 0.34 ± 0.02 |
| Heart weight (g) | 0.70 ± 0.06 | 0.64 ± 0.04 | 0.68 ± 0.04 | 0.75 ± 0.05 |
| Injected MIBG dose (MBq) | 9.87 ± 0.53 | 10.0 ± 0.81 | 9.34 ± 1.30 | 8.75 ± 0.57 |

NE = norepinephrine; MIBG = $^{123}$I-metaiodobenzylguanidine.
Data are expressed as mean ± SD.

**TABLE 5**
Myocardial MIBG Washout Rate in Second Study

| MIBG injection | Myocardial MIBG washout rate (%) | | | |
|---|---|---|---|---|
| | | NE infusion (3.0 μg/kg/min) | | |
| | No NE infusion | From 30 min before to 30 min after MIBG injection | From 30 min before to 60 min after MIBG injection | From 30 min before to 120 min after MIBG injection |
| From 5 min before to 30 min after | 19.1 ± 2.2 | 31.0 ± 5.9* | 17.6 ± 5.5 | 31.4 ± 4.6* |
| From 30 min before to 60 min after | 11.2 ± 2.6 | 11.4 ± 4.1 | 27.9 ± 1.6* | 24.4 ± 6.0* |
| From 60 min before to 90 min after | 14.4 ± 4.6 | 12.1 ± 4.0 | 18.9 ± 6.4 | 23.8 ± 6.2† |
| From 90 min before to 120 min after | 11.3 ± 3.8 | 10.6 ± 3.4 | 15.3 ± 7.6 | 17.1 ± 4.3* |

*$P < 0.01$ vs. group with no NE infusion.
†$P < 0.05$ vs. group with no NE infusion.
MIBG = $^{123}$I-metaiodobenzylguanidine; NE = norepinephrine.
Data are expressed as mean ± SD.

31 mm Hg, $P > 0.05$) but significantly increased after administration of NE at 3.0 μg/kg/min (104 ± 20 to 191 ± 9 mm Hg, $P < 0.05$).

## DISCUSSION

In this study, the marked increase in the plasma NE concentration after NE administration did not affect the myocardial MIBG uptake in the early phase but significantly increased the myocardial MIBG washout during NE infusion.

### $^{123}$I-MIBG Uptake and Plasma Norepinephrine

Nakajo et al. (*15*) reported a decrease in the myocardial MIBG uptake after 24 and 48 h in patients with a markedly high plasma NE concentration (≥1500 pg/mL). On the other hand, Schofer et al. (*17*) found that the heart-to-mediastinum ratio of MIBG 2 h after MIBG administration, which may reflect both uptake and washout, was significantly correlated with the myocardial NE content but not with the plasma NE concentration in patients with dilated cardiomyopathy. Henderson et al. (*7*) found that the myocardial MIBG uptake in patients with congestive cardiomyopathy showing a normal plasma NE concentration did not differ from that in the healthy control 15 min after MIBG administration but was significantly decreased after 85 min and 4 h, suggesting a decrease in the myocardial MIBG uptake regardless of the plasma NE concentration in CHF patients. However, the effects of the increased plasma NE concentration on myocardial MIBG kinetics cannot be excluded by the findings in the studies by Schofer et al. (*17*) and Henderson et al. (*7*) because the possible effects of drugs for heart failure, enhanced sympathetic activity associated with heart failure in organs other than the heart or delayed excretion of plasma NE (*18*) may complicate the possible relationship between plasma NE and myocardial MIBG kinetics (in human studies). In this study, which evaluated the direct relationship between plasma NE and MIBG uptake, an increase in the plasma NE concentration did not affect the myocardial MIBG uptake in the early phase. However, there was a trend toward lower initial MIBG activity at 5 and 10 min after injection that might be significant with larger study groups.

In in vitro systems, NE was reported to competitively block MIBG uptake (*14,19*). One study showed that NE at 1700 and 17,000 pg/mL inhibited the MIBG uptake by the human NE transporter by 24% and 87%, respectively (*14*). However, in this study, the myocardial MIBG uptake 5 min after MIBG injection was not decreased by NE administration at 3 μg/kg/min (plasma NE concentration 8687 ± 1328 pg/mL). Even at a concentration that affected the in vitro MIBG uptake, no effects were observed in vivo, perhaps because the increase in the NE concentration in the synaptic cleft at the sympathetic nerve terminal is slight compared with the increase in the plasma NE concentration in vivo.

### $^{123}$I-MIBG Washout and Plasma Norepinephrine

In patients with CHF, the plasma NE concentration is increased (1000 ~ 2000 pg/mL) (*11–13,20*), and the myocardial MIBG washout is enhanced (*6,7,10–18,21–25*). Imamura et al. (*8*) found a significant correlation between plasma NE and myocardial MIBG washout in CHF patients, although the correlation was not as high. In addition, in patients with chronic renal failure, a correlation between myocardial MIBG washout and plasma NE was reported (*26*). However, these studies evaluated the relationship between the plasma NE concentration and myocardial MIBG washout in pathologic conditions. Therefore, even if a correlation was observed between the two factors, the finding might have been a result of the effects of other factors associated with the pathologic condition on the plasma NE concentration and myocardial MIBG washout. In other words, the finding does not always represent the effects of the increase in the plasma NE concentration on myocardial MIBG washout.

These results show that a slight increase in the plasma NE concentration (1434 ± 596 pg/mL) does not affect myocardial MIBG washout. Therefore, in patients with heart failure, unlike pheochromocytoma, an increase in the plasma NE concentration may not affect myocardial MIBG washout. On the other hand, a marked increase in the plasma NE concentration (2808 ± 1369 pg/mL) significantly increased not only the myocardial MIBG washout from 5 to 30 min after MIBG injection but also that after MIBG incorporation into the sympathetic nerve (from 30 to 60 min after injection). Therefore, the myocardial MIBG washout appears to be affected by a marked increase in the plasma NE concentration.

### Possible Mechanisms for Increased $^{123}$I-MIBG Washout

Three mechanisms have been proposed for the increased washout from the heart in patients with CHF. First, because the MIBG efflux from extraneuronal sites is more rapid than that from intraneuronal sites, decreased neuronal uptake of MIBG enhances MIBG washout (*10*). Second, promotion of MIBG release from cardiac sympathetic neurons increases MIBG washout from the heart, which is caused by impairment in the vesicular storage (*21*) or increased cardiac sympathetic nerve activity (*6*). Third, an increased plasma NE concentration associated with increased NE release from organs other than the heart or delayed NE excretion in CHF (*16*) affects myocardial MIBG kinetics (*22*). Our results support the third possibility, i.e., the effects of a marked increase in the plasma NE concentration itself on myocardial MIBG kinetics.

### Limitations

This study has several limitations. The first is evaluation of cardiac MIBG kinetics under pentobarbital anesthesia. Pentobarbital may have affected the cardiac sympathetic system, thus altering cardiac MIBG kinetics. However, under pentobarbital anesthesia, changes in MIBG kinetics associated with an increase in the plasma NE concentration could be observed.

The second limitation is observation of MIBG kinetics by exogenously increasing the plasma NE concentration over a short period by NE administration in healthy rats. The decrease in the myocardial NE content in patients with CHF might be a result of a chronic increase in NE turnover and a chronic decrease in the NE reuptake and storage efficiency (*27*). Therefore, the changes in myocardial MIBG uptake associated with an acute increase in the plasma NE concentration observed in this experiment do not always occur in states of a chronically increased plasma NE concentration such as CHF.

The third limitation is administration of NSS at 4 mL/h for continuous NE administration. Fluid administration may possibly alter hemodynamics, thus affecting myocardial MIBG uptake. However, no significant difference was observed in myocardial MIBG uptake or washout between the rats that received NSS from 30 min before to 30 min after MIBG injection in the first study and the rats not treated with NSS before or after MIBG administration in the second study. This finding suggests negligible effects of fluid administration in this study.

The fourth limitation is administration of MIBG with a specific activity $\geq$1.85 MBq/μg at a mean dose of 9.51 MBq to rats with a mean weight of 0.31 kg. The mean loading dose was 16.3 μg/kg. However, Mock and Tuli (*28*) observed a significant decrease in radiolabeled MIBG associated with antagonism to unlabeled MIBG at an MIBG loading dose of 42 μg/kg or more in an animal experiment. Although the dose used in this study is the upper limit that allows analysis of original MIBG kinetics, we administered a relatively high dose of MIBG to increase the reliability of the measurement of cardiac MIBG accumulation (*29*).

The fifth limitation is differences in neuronal uptake and myocardial MIBG uptake between animal species (*2,6,24*). About half of the myocardial uptake of MIBG in rats is nonneuronal by uptake 2 (*10*), the passive transport system, but nonneuronal uptake in humans is <10% (*6*). Therefore, myocardial MIBG washout observed in this study may be related to nonneuronal uptake. Thus, the result of this study may not be completely blocked by desipramine. Therefore, the results of this study may not necessarily be applicable to humans.

The sixth limitation is the possibility that an increase in blood pressure by NE administration alters hemodynamics, affecting MIBG kinetics. Further experiments using phenylephrine or other drugs may elucidate how changes in hemodynamics influence myocardial MIBG kinetics.

## CONCLUSION

We evaluated changes in myocardial MIBG kinetics in intact rats using a gamma camera and gamma counting. A marked increase in the plasma NE concentration significantly increased the washout rate of MIBG from the heart in the initial and delayed stages. However, a slight increase in the plasma NE concentration induced no changes in the washout rate of MIBG from the heart. These results show the effects of a marked increase in the plasma NE concentration itself on cardiac MIBG kinetics.

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