# Effect of Specific Activity on Cardiac Uptake of Iodine-123-MIBG

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Radioiodinated meta-iodobenzylguanidine (MIBG), an analog of norepinephrine, has been used to assess myocardial sympathetic innervation. Recent in vivo studies predict enhanced cardiac uptake of this radiopharmaceutical with high specific activity. **Methods:** To clarify the effect of specific activity on cardiac uptake of radioiodinated MIBG, the distribution and kinetics of no-carrier-added [$^{123}$I]MIBG (≥7.4 TBq/μmol) were compared with those of commercial [$^{123}$I]MIBG (~74 MBq/μmol) in three healthy volunteers by serial imaging and blood sampling. **Results:** Higher specific activity result in higher uptake of radioiodinated MIBG in all volunteers in the heart ($p < 0.05$) and liver ($p < 0.05$) but not in the lung ($p = 0.26$). Due to rapid deiodination, a more pronounced accumulation of radioactivity was present in plasma after no-carrier-added MIBG than commercial [$^{123}$I]MIBG, resulting in higher background and thyroid activity after administration of the former. Calculated heart-to-liver ($p = 0.96$) and heart-to-lung ($p = 0.42$) count ratios in all volunteers revealed no significant improvement in cardiac imaging with no-carrier-added [$^{123}$I]MIBG compared to commercial [$^{123}$I]MIBG. **Conclusion:** This study highlights the appreciably higher in vivo deiodination of no-carrier-added [$^{123}$I]MIBG compared to commercial preparation of [$^{123}$I]MIBG in humans. Cardiac images acquired with no-carrier-added [$^{123}$I]MIBG do not seem to be superior to those obtained with commercial MIBG.

**Key Words:** no-carrier-added iodine-123-MIBG; cardiac imaging; deiodination

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Radioiodinated meta-iodobenzylguanedine (MIBG) has been used for the management of neuroendocrine tumors such as neuroblastomas and pheochromocytomas (*1–3*) and in the diagnosis of abnormalities of cardiac sympathetic innervation (*4–6*). Wieland et al. (*7*) reported that the cardiac uptake of this radiopharmaceutical was relatively constant over a wide range of specific activity, and the highest uptake was observed with the lowest specific activity. In another study of rats, Mock and Tuli (*8*) found that heart uptake of [$^{123}$I]MIBG was dependent on specific activity, with a constant uptake up to a certain loading dose, after which it started to decline with increasing doses. There has been increased interest in no-carrier-added (n.c.a.) MIBG to improve cardiac uptake in heart studies because of recent in vivo studies in animals that demonstrated a correlation between the specific activity and cardiac uptake of radioiodinated MIBG (*9,10*). In an aninmal study of nude mice, we observed a threefold higher cardiac uptake with n.c.a. MIBG (>2.6 TBq/μmol) compared to those of lower specific activity of 37 MBq/μmol (*3*). These results in animals predict remarkable improvement of this imaging techniqe using higher specific activity.

To evaluate the effect of specific activity on cardiac uptake of radioiodinated MIBG, we investigated the distribution and kinetics of [$^{123}$I]MIBG with two different specific activities in three volunteers by serial imaging and blood sampling.

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## MATERIALS AND METHODS

### Subjects

Three male nuclear medicine department staff members, aged 39, 41 and 50 yr, participated in this study. All volunteers were considered healthy according to medical history, physical examination, ECG, routine blood and urine analysis. All subjects were free of medication and had fasted 6 hr before the study. Each volunteer underwent the first study with n.c.a.[$^{123}$I]MIBG and 3 wk later (in one case 10 days later) with commerically available [$^{123}$I]MIBG.

### Radiochemistry

Iodine-123 was supplied from the Forschungszentrum Karlsruhe (KFK). Meta-iodobenzylguanidine as nonradioactive chromatographic standard was obtained from SIGMA-Aldrich Chemie GmbH, Deisenhofen, Germany. Meta-bromobenzylguanidine was prepared according to the method described by Wieland et al. (*11*), using a mixture of cyanamide and 3-bromobenzylamine. No-carrier-added [$^{123}$I]MIBG was synthesized by Cu(I)-assisted, nonisotopic exchange from meta-bromobenzylguanidine (*12*). HPLC separations for preparation and quality control of the labeled compounds were performed with a Purospher RP-18 5μ 244 × 4 mm column (Merck), a Rheodyne injection port, a SPD-10AT UV detector at 254 and 230 nm, a LC-10AT pump (Shimadzu) and a Geiger-Müller tube for online detection of radioactivity. The mobil phase was $CH_3CN$/0,01 M $NaH_2PO_4$ (4/96) with a flow rate of 1.5 ml/min. The detection limit of MIBG at 230 nm was 0.015 nmol. n.c.a. [$^{123}$I]MIBG formulated in isotonic phosphate buffer and achieved a specific activity of 7.4 ± 0.4 TBq/μmol (85% of the theoretical value).

Commercial [$^{123}$I]MIBG was purchased from Amersham Buchler (Braunschweig). The specific activity, determined by HPLC, was 74 ± 0.025 MBq/μmol.The radiochemical purity of both commercial and n.c.a.[$^{123}$I]MIBG, determined just before the administration, was >98%. HPLC chromatograms revealed no impurities within n.c.a. and commercial MIBG.

### Application

An activity of 200 MBq of n.c.a. and commercial [$^{123}$I]MIBG was administered as a bolus injection through an antecubital vein. Heart rate, blood pressure and ECG were continuously monitored during and for 30 min after the injections. All subjects were interviewed regarding any abnormal subjective findings after the injection of [$^{123}$I]MIBG with both specific activities.

### Imaging

We used a large field of view gamma camera equipped with a high-resolution collimator for simultaneous imaging of the heart, liver and lungs. The biodistribution of the compound was studied after an initial dynamic acquisition of 70 min. In addition, several dynamic and static datasets were acquired up to 5 hr after injection. Irregular regions of interest were drawn on the heart, liver and

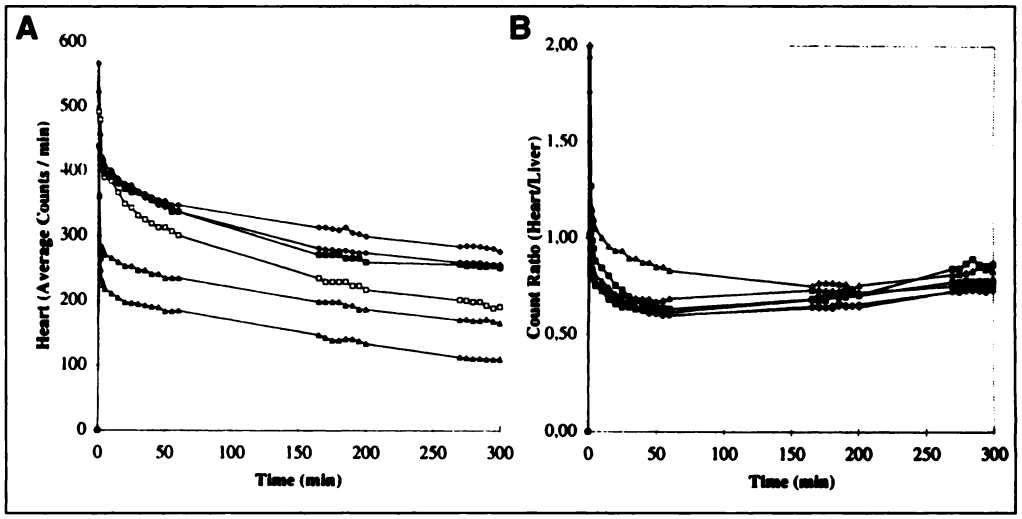


**FIGURE 1.** (A) Comparison of cardiac kinetic curves between n.c.a. (filled symbols) and commercial (open symbols) [$^{123}$I]MIBG for three volunteers. Symbols represent the average counts per minute in the heart. (B) Comparison of heart-to-liver count ratios between n.c.a. (filled symbols) and commercial (open symbols) [$^{123}$I]MIBG for three volunteers.

lungs in all planar images. Average counts of each organ per minute were plotted against the acquisition time to generate time-activity curves. For each subject, the average counts of the heart were divided by the average counts of the liver to obtain the heart-to-liver count ratio.

SPECT studies were performed using the same large field of view gamma camera equipped with a high-resolution collimator at 2 and 4 hr postinjection. Thirty-two images, 30 sec each, were obtained over 180° arc. From the raw projection data, transaxial tomograms with a slice thickness of 6 mm were reconstructed by filtered backprojection using a Butterworth filter.

To visualize whole-body distribution of the radiopharmaceutical, anterior and posterior whole-body scans were obtained at 1, 2, 3, 5 and 24 hr after injection with a dual-head gamma camera equipped with low-energy, high-resolution collimators.

### Blood Kinetics

Radioactivity clearance from the blood was determined by serial blood sampling up to 5 hr postinjection and once at 24 and 48 hr postinjection from 10-ml venous blood samples from the antecubital vein contralateral to the injection site. By using differential centrifugation, platelet-rich plasma, platelet-poor plasma and platelet pellet were separated (*13*). The activity in each sample was measured by a well scintillation counter and the radioactivity was expressed as becquerels per milliliter.

### Dosimetry

The dosimetric study was performed on one of the volunteers using two dual-head gamma cameras (Siemens Body Scan and Diacam cameras) equipped with low-energy, high-resolution collimators. For calibration of images acquired with the DIACAM, we constructed a phantom consisting of two perspex containers with volumes of 500 and 1000 ml, respectively. Each phantom was filled with $^{99m}$Tc with a specific activity of 10 kBq/ml. To simulate organ activities, the containers were immersed in water. At a constant camera-to-water surface distance, the immersion depth of the containers in the water was varied. Organ volumes of 500, 1000 and 1500 ml were simulated. The phantom images were quantitatively evaluated by drawing appropriate regions of interest around the phantom. A set of calibration data for different organ sizes and depths was derived. By applying the calibration data to the subject's images, absolute organ activities for liver, heart, thyroid and bladder were calculated. Activity retention in the remainder of the body was determined using conjugate whole-body images at 1, 2, 3, 5 and 24 hr after injection. After 3 and 7 days, the whole-body activity was determined with a whole-body counter. All datasets were normalized to the injected activity to calculate the residence times for the liver, heart, thyroid and whole body. We used the MIRDOSE computer code (*14*) to determine the organ doses and effective doses from the residence times.

### Urinary Excretion

To assess the rate of urinary loss of activity, urine collections were obtained at 2, 4 and 6 hr postinjection. Each subject's urinary activity was determined from a 1-ml sample with a well scintillation counter and expressed as becquerels per milliliter.

### Statistical Analysis

Student's t-test for paired variables was used to compare intraindividual alteration MIBG organ uptake. A p value of less than 0.05 was considered significant.

## RESULTS

### Hemodynamic Parameters

Two volunteers reported dizziness immediately after the bolus injection of commercial [$^{123}$I]MIBG, whereas no abnormality was reported after the injection of n.c.a. MIBG. However, we observed no signs of abnormalities in the ECG, blood pressure or heart rate after bolus injection up to 30 min postinjection with both specific activities.

### Imaging

Cardiac uptake of [$^{123}$I]MIBG (Fig. 1A) rapidly decreased from a peak value after the injection initially and more slowly thereafter. In comparison to the lower specific activity, the uptake of n.c.a. MIBG was significantly higher in the heart ($p < 0.05$) (Fig. 1A) and liver ($p < 0.05$) but not in the lungs ($p = 0.26$). Calculated heart-to-liver (Fig. 1B) and heart-to-lung count ratios revealed no significant difference between both specific activities (heart-to-liver, $p = 0.96$; heart-to-lung, $p = 0.42$). Similarly, the whole-body scans did not reveal any remarkable difference in isotope incorporation in the heart, salivary glands, liver, lungs and bowel between n.c.a. (Fig. 2) and commercial [$^{123}$I]MIBG (Fig. 3) at 1 (Figs. 2A and 3A), 2, 3, 5 and 24 hr (Figs. 2B and 3B). In the whole-body scans, the background radioactivity observed with n.c.a. MIBG was higher than that with commercial MIBG (Figs. 2 and 3).

At 24 hr, thyroid uptake was higher with n.c.a. than commercial [$^{123}$I]MIBG (Figs. 2B and 3B). This difference was much less pronounced in the early images (Figs. 2A, 3A).

Cardiac SPECT images at 1 (not shown here) and 4 hr postinjection (Fig. 4) were not remarkably different with n.c.a. and commercial [$^{123}$I]MIBG.

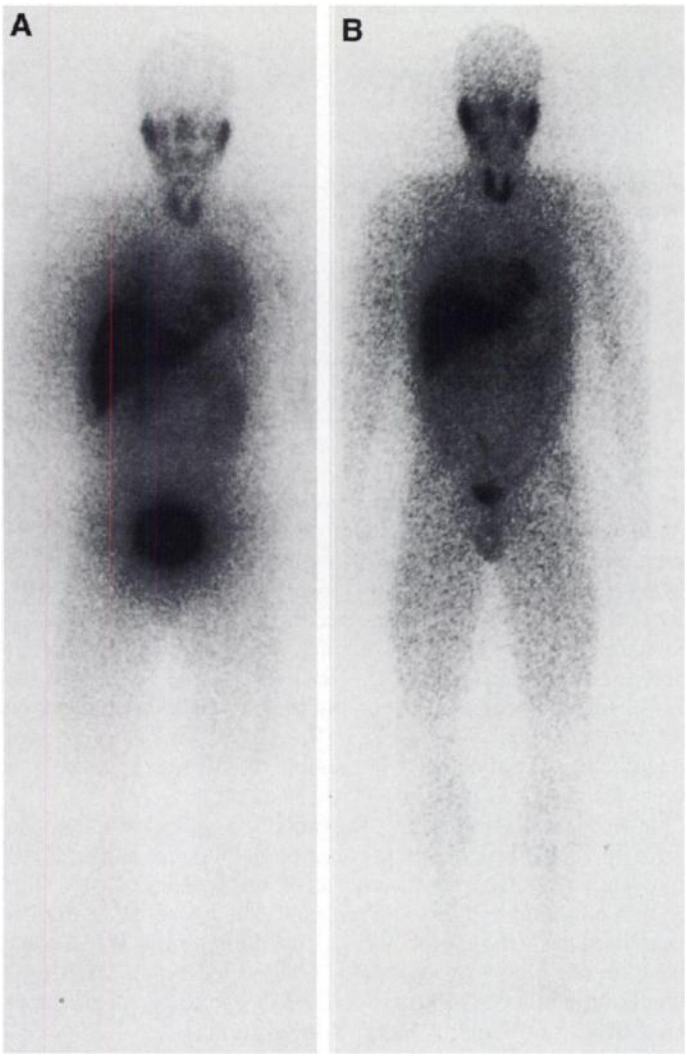


**FIGURE 2.** Anterior whole-body scans of the first volunteer with n.c.a. [$^{123}$I]MIBG at (A) 1 and (B) 24 hr postinjection.

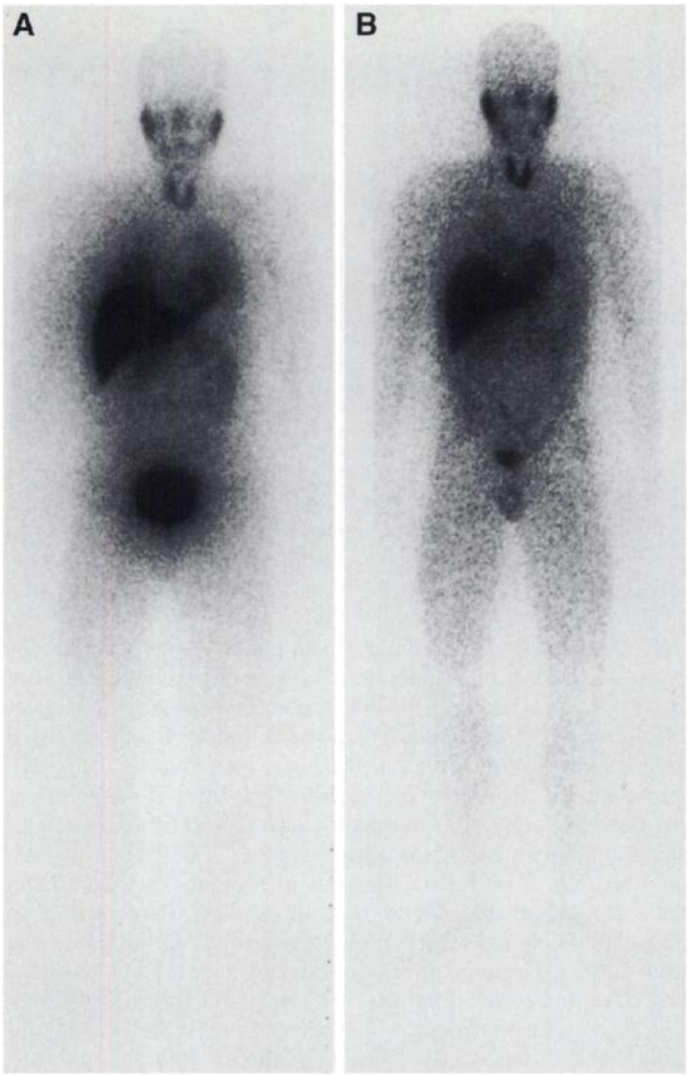


**FIGURE 3.** Anterior whole-body scans of the first volunteer with commercial [$^{123}$I]MIBG at (A) 1 and (B) 24 hr postinjection.

### Blood Kinetics

After bolus injection of radiolabeled MIBG, radioactivity cleared from the blood after biexponential kinetics (Fig. 5A). The first component was more rapid with commercial than n.c.a. [$^{123}$I]MIBG. The mean of injected activity remaining in platelet-poor plasma at 60 min amounted to 4% (3%–5%) with commercial [$^{123}$I]MIBG and 30% (25%–40%) with n.c.a. [$^{123}$I]MIBG. The subsequent loss of activity was monoexponential up to 48 hr.

The initial biodistribution of commercial and n.c.a. [$^{123}$I]MIBG in the platelet pellet was quite similar with both compounds (Fig. 5B). After a rapid initial uptake into platelets during the first 4 hr, the uptake curves plateaued.

### Dosimetry

In general, radiation exposure for all organs was slightly higher after n.c.a. than commercial [$^{123}$I]MIBG (Table 1). This was probably due to n.c.a. [$^{123}$I]MIBG having a higher residence time of activity in the heart, liver and thyroid than commercial MIBG (Table 1).

### Urinary Excretion

There was no remarkable difference in the urinary excretion of radioactivity between both types of [$^{123}$I]MIBG. Twenty-six to 33% of the injected dose was excreted in urine during the first 2 hr, 36%–41% during 4 hr and 42%–51% during 6 hr.

## DISCUSSION

There have been several reports on animal experiments which predicted higher cardiac uptake of n.c.a. in comparison to commercial [$^{123}$I]MIBG (*3,9,10*). In this study, we compared the biodistribution and clearance of a commercial preparation of [$^{123}$I]MIBG (~74 MBq/$\mu$mol) with that of n.c.a. [$^{123}$I]MIBG (~7.4 TBq/$\mu$mol) in three healthy volunteers. There was significantly higher uptake in the heart with the higher specific activity. However, the calculated heart-to-liver and heart-to-lung ratios revealed no significant difference between both

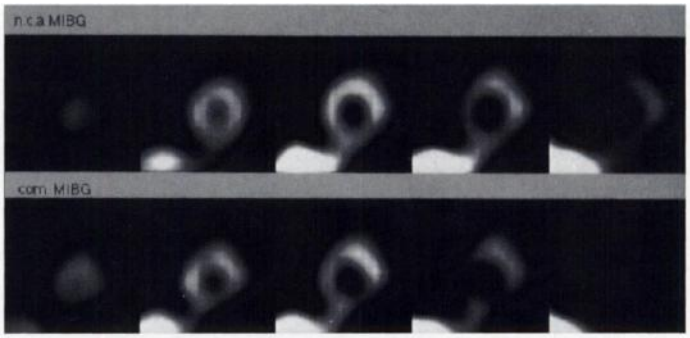


**FIGURE 4.** Cardiac SPECT images in a volunteer. Short-axis slices show normal pattern of distribution in all regions of left ventricle from apex to base with n.c.a. and commercial MIBG 4 hr postinjection.

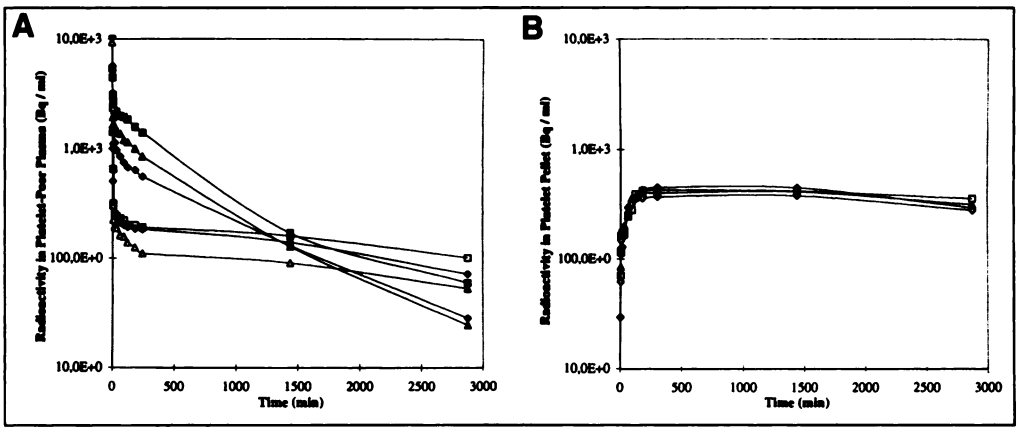


**FIGURE 5.** Time-activity curve of n.c.a. MIBG (filled symbols) and commercial MIBG (open symbols) in platelet-poor plasma (A) and platelet pellet (B) for three volunteers.

specific activities. In agreement with this observation, the urinary excretion of radioactivity was also quite similar in both groups. Due to the longer residence time of the radioactivity in the heart, liver and thyroid, the radiation exposure was generally slightly higher with n.c.a. than with commercial [$^{123}$I]MIBG.

Because of the high radiochemical purity of both compounds before injection, we conducted the study without thyroid blockade. A considerable difference was observed with respect to radioactivity accumulation in the thyroid, which increased after administration of n.c.a. but not commercial [$^{123}$I]MIBG. Although, we did not control the chemical form of radioactivity in plasma or urine, the most likely explanation for radioactivity accumulation in the thyroid after n.c.a.[$^{123}$I]MIBG is in vivo deiodination. Presumably, the loss of radioactive iodine from the intact component leads to accumulation of free iodine in plasma, which results in pronounced thyroidal uptake. The time-activity curve of plasma in humans supports the assumption of rapid degradation of n.c.a.[$^{123}$I]MIBG after its injection.

Although little is known about dehalogenases that are responsible for the degradation of iodine-labeled radiopharmaceuticals, it can be assumed that radioiodinated MIBG also serves as a substrate of this enzyme. Because both the radioactive and nonradioactive substituted compounds compete for the same number of available dehalogenases, it is apparent why n.c.a. [$^{123}$I]MIBG is more affected than commercial [$^{123}$I]MIBG.

There have been several in vivo studies on the specific activity of radioiodinated MIBG (*3,9,10*). However, none of these studies investigates in vivo deiodination. In a study of nude mice, we observed threefold higher cardiac uptake of n.c.a. MIBG compared to a lower specific activity of 37 MBq/$\mu$mol. We observed no significant difference of radioactivity in plasma with both specific activities at 4 hr after injection. However, at 24 hr, there was significantly higher activity in plasma with n.c.a. MIBG compared to that with the lower specific activity. Concordant in vivo results were reported by Vaidyanathan and Zalutsky (*9*). These findings suggest a degradation of radiolabeled compound to a lesser extent even in mice as compared to humans.

Indeed, less information is available about deiodinases in mice (*15*). However, several studies in humans and animals indicate an interspecies difference of deiodinases (*15,16*). For example, human type I iodothyronine deiodinase has a significantly higher affinity for 3,3,',5'-triiodothyronine (rT3) compared to dog type I deiodinase (*16*). Thus, different n.c.a. MIBG uptake in humans and mice could be due to different interspecies affinity of deiodinases for this substrate.

Slow injection of MIBG is recommended because a postulated release of endogenous norepinephrine could precipitate a hypertensive crisis. To assess any drug effect, the [$^{123}$I]MIBG was administered as a bolus injection. As mentioned in the Results section, two volunteers reported dizziness after bolus injection of commercial [$^{123}$I]MIBG. However, no changes in heart rate, blood pressure and ECG recordings could be moni-

**TABLE 1**
Estimated Radiation Dose for the Reference Adult for No-Carrier-Added and Commercial Iodine-123-MIBG

| | n.c.a.MIBG | | com.MIBG | |
|---|---|---|---|---|
| Target organ | Absorbed dose (mGy/MBq) | Residence time (hr) | Absorbed dose (mGy/MBq) | Residence time (hr) |
| Adrenals | 1.51E−02 | | 1.38E−02 | |
| Bladder wall | 5.93E−02 | | 3.40E−02 | |
| Bone surfaces | 1.88E−02 | | 1.82E−02 | |
| Breast | 8.34E−03 | | 8.04E−03 | |
| Heart | 3.74E−02 | 3.60E−01 | 2.96E−02 | 2.70E−01 |
| Kidneys | 1.29E−02 | | 1.20E−02 | |
| Liver | 4.23E−02 | 1.85E+00 | 3.08E−02 | 1.29E+00 |
| Lungs | 1.25E−02 | | 1.17E−02 | |
| Ovaries | 1.40E−02 | | 1.31E−02 | |
| Pancreas | 1.54E−02 | | 1.42E−02 | |
| Red marrow | 1.02E−02 | | 9.77E−03 | |
| Spleen | 1.15E−02 | | 1.12E−02 | |
| Testes | 1.02E−02 | | 9.64E−03 | |
| Thyroid | 1.21E−01 | 1.10E−01 | 8.18E−02 | 7.20E−02 |
| Total body | 1.20E−02 | 1.18E+01 | 1.12E−02 | 1.18+E01 |
| Effective dose (mSv/MBq) | 2.24E−02 | | 1.76E−02 | |

tored during and for 30 min postinjection of both n.c.a. and commercial [$^{123}$I]MIBG. In isolated perfused rabbit hearts, MIBG induced a dose-dependent norepinephrine release, but, when compared with tyramine, behaved as a weakly acting indirect sympathomimetic amine (Graefe et al., unpublished observations). Thus, especially high amounts of MIBG, as in the therapy of neuroblastoma or pheochromocytoma, should be injected slowly to prevent possible side effects induced by released norepinephrine.

## CONCLUSION

In inter- and intraindividual comparison of n.c.a. MIBG and commercial MIBG in three volunteers, we observed significantly higher cardiac uptake with n.c.a. MIBG as compared to commercial MIBG. However, presumably due to in vivo deiodination in humans which results in higher background activity, heart images with n.c.a.[$^{123}$I]MIBG were not superior to those acquired with commercial [$^{123}$I]MIBG.


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# Effects of Active Chronic Cocaine Use on Cardiac Sympathetic Neuronal Function Assessed by Carbon-11-Hydroxyephedrine


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Cardiac toxicity of cocaine has been linked to its inhibitory effect on norepinephrine reuptake by sympathetic nerve terminals of the heart. Carbon-11-hydroxyephedrine is a positron-emitting tracer that has been validated as a highly specific marker for norepinephrine transporter activity of the sympathetic nerve terminals and thus makes possible in vivo assessment of the effect of cocaine on norepinephrine reuptake and storage in the cardiac sympathetic nerve terminals. The aim of the study was to use the catecholamine analog $^{11}$C-hydroxyephedrine with PET to determine whether active chronic use of cocaine in women modifies the function of sympathetic nerve terminals of the heart. **Methods:** Six normal female volunteers and nine female active chronic cocaine users were studied. Cardiac regional $^{11}$C-hydroxyephedrine uptake and blood flow, as assessed with $^{13}$N-ammonia, were determined using semiquantitative polar map analysis of myocardial tracer distribution. Carbon-11-hydroxyephedrine cardiac retention was quantified using dynamic data acquisition and kinetic analysis of blood and tissue activity. **Results:** Active chronic cocaine users showed small areas of abnormal blood flow and $^{11}$C-hydroxyephedrine retention in the heart in comparison with normal volunteers. The extent of abnormalities expressed as a percent of the total polar map area averaged 2.0% ± 2.6% and 2.5% ± 2.7% for blood flow and $^{11}$C-hydroxyephedrine uptake, respectively. Myocardial $^{11}$C-hydroxyephedrine retention was significantly reduced by 22% in active cocaine users (0.109 ± 0.017 $min^{-1}$), as compared to normal controls (0.140 ± 0.027 $min^{-1}$). **Conclusion:** PET imaging with $^{11}$C-hydroxyephedrine permits quantitative assessment of cardiac norepinephrine transporter function in active chronic cocaine users. The results of this study suggest prolonged reduction of norepinephrine uptake and storage capacity in the cardiac sympathetic nerve terminals which may reflect the effect of repetitive elevation of norepinephrine levels induced by cocaine exposure.



**Key Words:** PET; carbon-11-hydroxyephedrine; cardiac sympathetic nerve function; cocaine abuse

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Cocaine use has reached epidemic proportion in the United States, and drug-related neurologic and cardiac toxicities have become social and medical problems (*1,2*). The acute effect of cocaine is principally due to its inhibitory action on the presynaptic reuptake of catecholamines (norepinephrine and dopamine), which results in an increase of neurotransmitter concentration at the postsynaptic receptor sites (*3,4*). Animal


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