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release, but, when compared with tyramine, behaved as a weakly acting indirect sympathomimetic amine (Graefe et al., unpublished observations).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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TABLE 1
Clinical Characteristics of Study Subjects

Cocaine users	Age (yr)	Heart rate (bpm)	Blood pressure (mmHg)	History of cocaine use (yr)	Last use of cocaine before PET (hr)	NE plasma level (pg/ml)	Urine drug screening	
							Gas chromatography	Immunoassay
1	38	77	90/60	6	8	223	Chlorphenidramine, codeine	Cocaine, opiate
2	36	65	130/90	3	36	307	—	Cocaine
3	32	69	105/70	7	8	NA	—	Cocaine
4	26	61	130/90	3	36	196	Methadone	Cocaine, opiate
5	35	73	100/70	3	12	129	—	Cocaine
6	30	62	130/85	6	8	230	—	Cocaine
7	29	70	105/85	3	5	719	Benzocaine	Cocaine
8	25	75	120/70	4	33	NA	—	Cocaine, cannabinoids
9	36	67	190/120	6	5	NA	Diphenhydramine	Cocaine, opiate
Volunteers								
1	33	60	80/55					
2	38	75	125/70					
3	33	59	125/80					
4	35	64	100/60					
5	28	50	105/80					
6	32	64	120/95					

NA = nonavailable; NE = norepinephrine.

and clinical studies have shown that chronic exposure to cocaine caused a depletion of dopamine in the brain which may have been implicated to its toxicity (*5,6*). Since the heart is richly innervated by sympathetic nerve fibers (*7,8*), it may be hypothesized that chronic cocaine use may also alter the functional integrity of the presynaptic nerve terminals of the heart. Technical difficulties in the clinical assessment of the sympathetic nerve function of the heart have impeded research aimed at assessing the effects of chronic cocaine use on cardiac norepinephrine uptake and storage. Until recently, the assessment of the cardiac sympathoneural function has required the determination of arteriovenous differences in catecholamine plasma concentration during complicated invasive procedures (*9*). With the advent of new radiolabeled catecholamine analogs, medical imaging methods have permitted the noninvasive assessment of the integrity of the sympathetic nervous system in various cardiac diseases. Radioiodinated metaiodobenzylguanidine was first used with conventional nuclear medicine techniques to evaluate the integrity of the sympathetic nervous system in patients with congestive heart failure (*10*). More recently, our laboratory introduced ^{11}C-hydroxyephedrine, a positron-emitting radiopharmaceutical, which has been validated as a highly specific marker for norepinephrine transporter function of the sympathetic nerve terminals (*11*). Quantitative assessment of neuronal retention of this new tracer in the living heart may be provided by the use of PET (*12*).

Therefore, the aim of this study was to use ^{11}C-hydroxyephedrine with PET to determine whether active chronic cocaine use in humans modifies norepinephrine transporter function of cardiac sympathetic nerve terminals.

METHODS

Study Population

All the participants in this study gave informed consent as approved by the Committee for Clinical Research at the University of Michigan.

Cocaine Users. Nine black female cocaine users with a mean age of 31.0 ± 5.2 yr were included in the study. They were selected from subjects who participated in a research project funded by the National Institute on Drug Abuse at the University of Michigan. All nine females were currently chronic "crack" cocaine smokers and had been using crack for approximately 4.7 ± 1.7 yr without any changes in their cocaine consumption habit during the 6 mo prior to the study. The mean daily cocaine consumption was ≥1.5 g. Other drugs were also sporadically used by some of the women, but none of them stated they were addicted to these drugs.

Control Group. Six healthy female volunteers with mean age of 34.5 ± 5.2 yr constituted the control group. None had a past history of drug abuse.

For both groups of women, the presence of cardiac and systemic diseases was excluded by history, physical examination and resting electrocardiogram. None of the cocaine users and volunteers were taking any cardiac or noncardiac medication at the time of the study.

PET Imaging

Radiochemistry of Carbon-11-Hydroxyephedrine. A detailed description of the synthesis of ^{11}C-hydroxyephedrine has been published (*11*). Briefly, ^{11}C-hydroxyephedrine was produced by direct N-methylation of metaraminol with ^{11}C-methyl iodide in dimethyl formamide/dimethyl sulfoxide and purified by reverse-phase, high-performance liquid chromatography in an isotonic aqueous buffered system. The specific activity was >37,000 MBq/mmole at the end of synthesis; radiochemical and chemical purities were >95%.

Data Acquisition. Studies were performed with a Siemens 931-12 (Siemens Gammasonics, Des Plaines, IL) whole-body tomograph. This device allows simultaneous acquisition of 15 cross-sectional images (eight direct planes and seven cross planes) with a spatial resolution of 6–8 mm. A ^{13}N-ammonia scout scan of 5 min was used for positioning the subject correctly in the field of view of the tomograph. Transmission scans were acquired for 20 min using a retractable ^{68}Ge ring source for correction of the emission scans. The imaging protocol consisted of a cardiacd ynamic positron emission tomographic imaging after ^{11}C-hydroxyephedrine administration followed by a myocardial blood flow study. Carbon-11-hydroxyephedrine (740 MBq) was injected

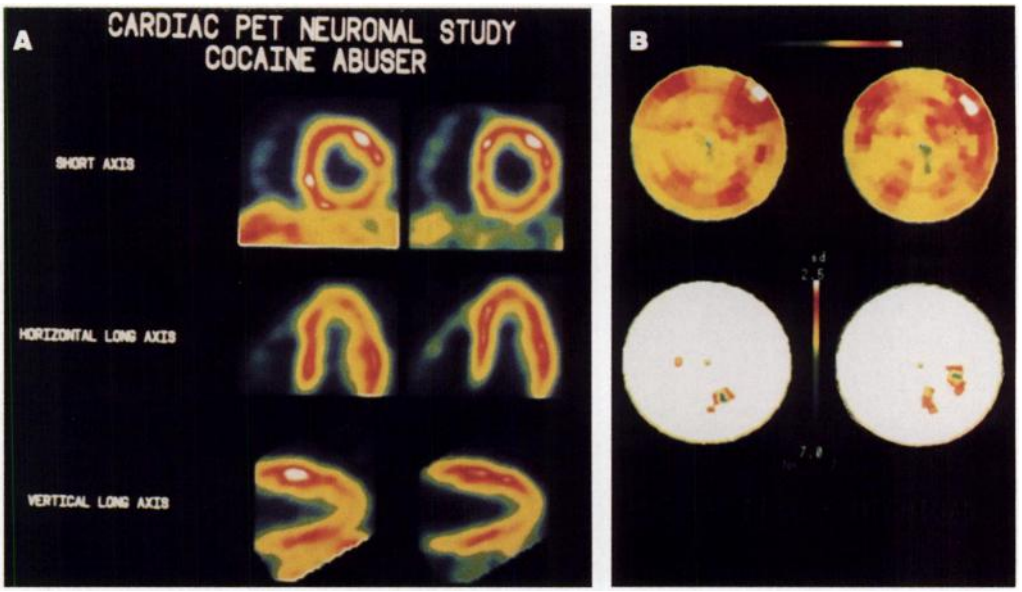

FIGURE 1. (A) PET heart images of an active chronic cocaine abuser, a 38-yr-old woman with a 6-yr history of crack smoking. Representative short-axis and long-axis images of blood flow (left) and ^{11}C-hydroxyephedrine (right) of PET scan performed 8 hr after the last drug consumption. (B) Polar maps corresponding to images in (A). Top: relative count distribution. Bottom: maps where pixels 2.5 s.d. outside the normal database range are shown in color—2.5% of blood polar map is abnormal and 6% of ^{11}C-hydroxyephedrine polar map area is abnormal. Blood flow is at left and ^{11}C-hydroxyephedrine is at right.

intravenously as a slow bolus over 30 sec. At the beginning of the tracer injection, a dynamic PET acquisition with various time frames (six 30-sec frames, two 60-sec frames, two 150-sec frames, two 300-sec frames, two 600-sec frames and one 1200-sec frames) was initiated for 60 min. After allowing for ^{11}C decay for 60 min, 740 MBq ^{13}N-ammonia were injected intravenously to determine blood flow. A 10-min static scan was started 3 min after tracer administration.

Data Processing and Analysis

Homogeneity of Relative Myocardial Tracer Retention. Transaxial images of the heart were reoriented to the short and long axis of the left ventricle using a SUN workstation (SUN Microsystems Inc., Mountainview, CA). The polar maps of relative tracer activity were generated from the reoriented short-axis images using a circumferential profile analysis with maximum search algorithm developed at our institution (*13*). Map pixel values of ^{13}N-ammonia and ^{11}C-hydroxyephedrine activity obtained from each subject of the control group were averaged and used to construct normal database values. Cocaine abuser map pixels >2.5 s.d. below normal database values were defined as abnormal. These data were displayed on a separate polar map for each study, and the extent of abnormal tracer activity was expressed in percent of the total polar map area.

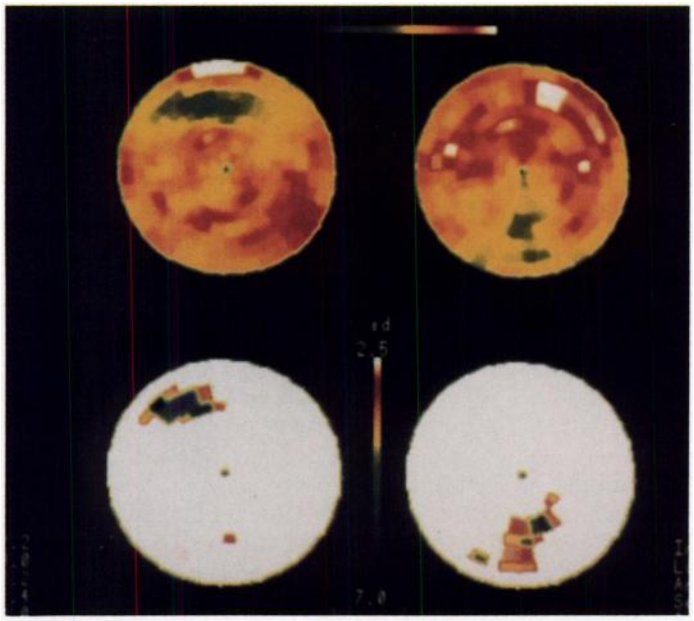

FIGURE 2. Cocaine abuser No. 9 blood flow images are at left and ^{11}C-hydroxyephedrine images are at right. Top: Polar maps of relative distribution of ^{13}N-ammonia and ^{11}C-hydroxyephedrine images. Bottom: 3.9% of blood flow polar map area is abnormal and 5.3% of ^{11}C-hydroxyephedrine polar map is abnormal. There were large areas of abnormal blood flow and ^{11}C-hydroxyephedrine retention that were localized in the anterior and inferior regions of the left ventricle, respectively.

Absolute Myocardial Carbon-11-Hydroxyephedrine Retention Fraction. Cardiac ^{11}C-hydroxyephedrine retention fraction was used as an index of norepinephrine uptake and storage into the sympathetic nerve terminals (*14*). Carbon-11-hydroxyephedrine retention fraction was determined by placing large regions of interest (ROIs) on proximal, mid and distal short-axis images of the heart. The arterial input function for the tracer was obtained by drawing a region of interest over the left ventricular blood pool. Selected ROIs were automatically propagated for the entire sequence of scans, and time-activity curves for blood and myocardium were generated. The retention fraction of ^{11}C-hydroxyephedrine, having the unit of inverse minutes, was calculated for each myocardial ROI by dividing the tissue ^{11}C concentration (counts/pixel) measured 30–40 min post-tracer injection by the integral of ^{11}C-hydroxyephedrine concentration in the blood (counts/pixel) from 0 to 40 min. Values of proximal, mid and distal regions were then averaged to obtain an average retention value for each heart.

Urine and Plasma Analysis

A comprehensive urine drug screen was performed at the time of the PET study to confirm active cocaine use and to identify other drugs. Methadone, propoxyphene, tricyclic antidepressants, phenylpropanolamine, pseudoephedrine, meprobamate, diphenhydramine, methaqualone, meperidine, lidocaine and ibuprofen were systematically screened by gas chromatography. Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates were screened by immunoassay. A threshold cutoff level of 300 ng/ml was used for detection of cocaine and opiates.

At the end of transmission image acquisition, blood was withdrawn and plasma was immediately frozen for norepinephrine plasma level measurements by high-performance liquid chromatography.

Statistical Analysis

All values are given as mean ± 1 s.d. Differences in heart rate, blood pressure and ^{11}C-hydroxyephedrine retention fraction between controls and cocaine abusers were tested by the unpaired t-test. A p value of less than 0.05 was considered statistically significant.

TABLE 2
Extent of Carbon-11-Hydroxyephedrine and Nitrogen-13-Ammonia Abnormalities Expressed in Percent of Total Polar Map Area in Active Chronic Cocaine Users

Cocaine user no.	Extent of abnormality (%)	
	^{11}C-hydroxyephedrine	^{13}N-ammonia
1	6	2.5
2	2.3	0.5
3	1.9	0
4	0	0
5	0.9	0
6	0	0
7	0	7.2
8	6.3	3.9
9	5.3	3.9
Mean ± s.d.	2.5 ± 2.7	2.0 ± 2.6

TABLE 3
Carbon-11-Hydroxyephedrine Retention Fraction (min^{-1}) in Normal Control Subjects and Active Chronic Cocaine Users

No.	Controls	Cocaine users
1	0.114 ± 0.009	0.095 ± 0.009
2	0.153 ± 0.011	0.100 ± 0.007
3	0.134 ± 0.014	0.128 ± 0.005
4	0.187 ± 0.006	0.086 ± 0.000
5	0.135 ± 0.008	0.128 ± 0.020
6	0.115 ± 0.049	0.127 ± 0.013
7		0.122 ± 0.009
8		0.106 ± 0.008
9		0.093 ± 0.008
Mean ± s.d.	0.140 ± 0.027	0.109 ± 0.017*

*$p < 0.02$ values of retention in cocaine users versus controls.

RESULTS

Subject Characteristics

Table 1 summarizes demographic and clinical characteristics of cocaine users and control subjects. Heart rate and arterial blood pressure were not statistically different between the two groups. In the cocaine users' group, the time interval between the last use of cocaine and the PET study ranged from 5 to 36 hr (mean 19 ± 14 hr). Detection of cocaine in the urine of each cocaine user confirmed recent use of the drug.

An example of a cocaine user PET study is depicted in Figure 1A. This study was performed in a 38-yr-old woman with a 6-yr history of "crack" cocaine smoking. PET imaging was performed 8 hr after the last consumption of cocaine. Figure 1B shows corresponding heart polar maps of myocardial tracer retention of this cocaine user compared with the normal database, indicating that 2.5% of the blood flow map area is abnormal, and 6% of the ^{11}C-hydroxyephedrine map is abnormal. It is noteworthy that the ^{13}N-ammonia and ^{11}C-hydroxyephedrine abnormal areas were unmatched.

Extent of Nitrogen-13-Ammonia and Carbon-11-Hydroxyephedrine Abnormalities

Table 2 summarizes the extent of blood flow and ^{11}C-hydroxyephedrine uptake abnormalities of total polar map area for each cocaine user. Two of the cocaine users did not show any abnormalities in the distribution of both tracers as compared to normals. Other cocaine abusers had small areas of abnormal ^{11}C-hydroxyephedrine and ^{13}N-ammonia uptake as compared to controls (as depicted in Fig. 1B). For one subject (cocaine user #9), small areas of abnormal tracer uptake were associated with larger regions of abnormal ^{11}C-hydroxyephedrine and ^{13}N-ammonia uptake in the anterior and inferior wall of the myocardium, respectively (Fig. 2).

Carbon-11-Hydroxyephedrine Absolute Retention Fraction

Table 3 presents individual values of ^{11}C-hydroxyephedrine retention fraction, which represent the uptake and storage capacity of myocardial neurons for norepinephrine. The cardiac retention fraction of the tracer was significantly reduced by 22% in cocaine users as compared to controls ($p < 0.02$). As shown in Figure 3, there was no correlation between values of cardiac ^{11}C-hydroxyephedrine retention fraction and the time elapsed since the last cocaine use or the duration of cocaine addiction.

Plasma norepinephrine level measured in cocaine users varied from 129 to 719 pg/ml, with reference values from the laboratory for control population ranging from 125 to 300 pg/ml (Table 1). Figure 4 shows that cardiac ^{11}C-hydroxyephedrine retention fraction was not correlated with plasma norepinephrine levels.

DISCUSSION

Previous PET studies that assessed the effects of chronic cocaine use in humans concentrated mainly on the brain dopaminergic system since it has been demonstrated to be essential in the drug's reinforcing properties (*15–17*). Although numerous cocaine-related adverse cardiac events have been reported among long-term users, investigations examining the effects of chronic cocaine exposure on the sympathetic nerve terminals of the human heart have not yet been performed. Previous experimental work performed in our laboratory evaluated the effects of an acute dose of cocaine on cardiac norepinephrine transporter activity in dogs using ^{11}C-hydroxyephedrine and PET (*18*). Our findings suggested severe and prolonged inhibitory action of a single dose of drug on cardiac norepinephrine transporters. The present study examines the effect of long-term cocaine exposure on norepinephrine transporter activity of the sympathetic nerve terminals in human heart. Among cocaine users, the values of ^{11}C-hydroxyephedrine retention fraction were not correlated with the duration of active chronic drug abuse or time elapsed since the last drug exposure at the time of the PET study. In comparison with normal controls, active cocaine abusers showed a significant reduction of ^{11}C-hydroxyephedrine retention by the cardiac sympathetic nerve terminals. However, there was an overlap between tracer retention fraction values of the active cocaine abusers and controls. These results suggest that, if chronic cocaine use has a significant effect on cardiac sympathetic nerve function, it is quite variable between individuals and may reflect different degrees of sensitivity of the cardiac sympathetic nerve terminals to chronic cocaine exposure. The exact mechanisms responsible for the reduction of ^{11}C-hydroxyephedrine uptake and accumulation in the heart of active chronic cocaine users remain to be determined. It could be hypothesized that repetitive excess of synaptic and interstitial norepinephrine concentration caused by long-term use of cocaine may determine a reduction of concentration of norepinephrine transporters and/or sympathetic neuron loss. In an experimental dog model of right heart failure characterized by elevated plasma and cardiac tissue norepinephrine concentration, Liang et al. (*19*) found a significant decrease of then umber of norepinephrine uptake-1 transporters in the right

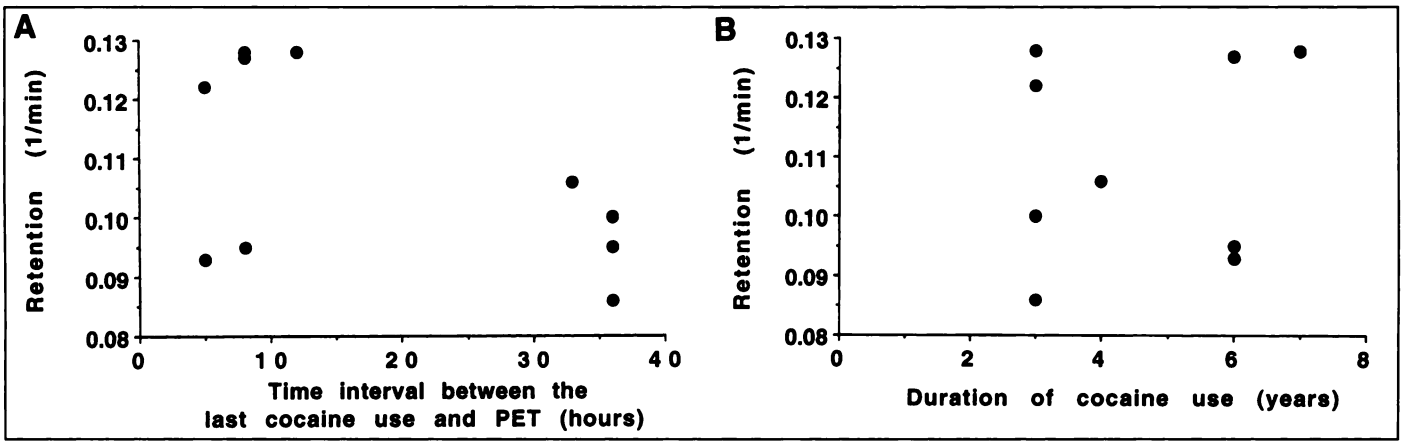

FIGURE 3. Carbon-11-hydroxyephedrine retention values for active chronic cocaine abusers in relation to (A) time since last drug use and (B) duration of cocaine addiction.

heart. More recently, in rats having chronically elevated circulating norepinephrine levels obtained by intravenous infusion of the neurotransmitter, Mardon et al. (*20*) reported decreased norepinephrine cardiac uptake that was correlated with decreased cardiac uptake-1 transporter concentration. In dogs chronically infused with norepinephrine, Himura et al. (*21*) also showed depressed cardiac norepinephrine uptake associated with lesions of sympathetic nerve terminals as assessed by catecholaminergic histofluorescence and immunoreactive tyrosine hydroxylase. These findings suggest that chronic elevation of norepinephrine concentration in the plasma and at the synaptic level as determined by cocaine use could cause not only functional impairment but also anatomic destructions of cardiac sympathetic nerve terminals. Future studies measuring norepinephrine transporters and sympathetic nerve terminals concentration in tissue samples will be necessary to confirm these hypotheses. The role of the sympathetic nervous system has been recognized in the pathophysiology of various cardiac diseases such as congestive heart failure and dysrhythmias (*22*). Since the uptake and storage of norepinephrine in the presynaptic nerve terminals is an important mechanism for regulating the stimulation of postsynaptic receptors by the neurotransmitter, the dysfunction of the presynaptic nerve terminals observed in active chronic cocaine users may play a role in the cardiac toxicity of this drug.

Our data were obtained using ^{11}C-hydroxyephedrine, a norepinephrine analog that shares a common pathway for neuronal uptake and storage with endogeneous catecholamines. Following intravenous administration, the tracer produces metabolites in the blood (*11*). For data analysis, it was hypothesized that ^{11}C-hydroxyephedrine metabolization was not different in cocaine abusers from that in normals. Since Degrado et al. (*23*) have previously shown that increasing concentration of norepinephrine in the perfusate of the isolated working heart decreased the cardiac retention of ^{11}C-hydroxyephedrine, it might be hypothesized that the reduction in cardiac ^{11}C-hydroxyephedrine retention observed in our study may result from increased competition by endogenous norepinephrine for neuronal uptake and storage. However, such a mechanism is unlikely to explain the reduced cardiac retention of ^{11}C-hydroxyephedrine observed in our study because norepinephrine plasma concentrations and hemodynamic parameters, reflecting sympathetic tone, were not significantly different in cocaine abusers compared to normal controls at the time of the PET study.

Myocardial ischemia represent the most frequent cardiovascular event reported in cocaine users (*2*). It has been related to cocaine-induced sympathetic potentiation of vascular smooth muscle which causes sustained vasoconstriction of normal and diseased coronary arteries (*24–26*). In this study, quantitative analysis of ^{13}N-ammonia data was used to quantify regional blood flow abnormalities in active cocaine abusers' hearts. In comparison with normal controls, small areas of decreased ^{13}N-ammonia uptake were observed in cocaine users, which may reflect regional reduction of myocardial blood flow resulting from cocaine-induced small coronary vessel vasoconstriction. In regard to regional blood-flow abnormalities, the regional heterogeneity of cardiac ^{11}C-hydroxyephedrine uptake in active chronic cocaine users may indicate neuronal dysfunction provoked by ischemic episodes. Using a canine reperfusion model, Wolpers et al. (*27*) have previously demonstrated decreased cardiac retention of ^{11}C-hydroxyephedrine in the territory of ischemically injured myocardium. Their work provides evidence for the sensitivity of the sympathetic nerve terminals to episodes of reversible ischemia. However, a direct toxic effect of cocaine on the sympathetic neurons cannot be excluded.

Study Limitations

The limitation of this study is that only a small number of cocaine abusers were evaluated. This in part is due to the difficulties in obtaining cooperation of cocaine abusers for medical investigations. Moreover, our intention was to recruit subjects with fully documented histories of cocaine abuse. It has only been possible to achieve our objectives by recruiting

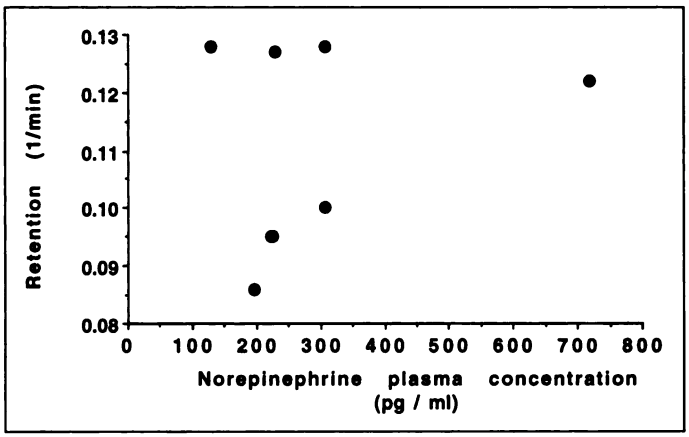

FIGURE 4. Carbon-11-hydroxyephedrine retention values for active chronic cocaine abusers in relation to norepinephrine plasma concentration.

female crack smokers who were part of a large National Institute on Drug Abuse funded research project, "Factors Related to Female Cocaine Abuse." This explains why our study consisted only of female subjects. Thus, the selective recruitment of subjects may have contributed to the nature of our results.

Another limitation is that our study only evaluated the function of sympathetic nerve terminals during active chronic cocaine use. Since the cocaine abusers were not enrolled in a detoxification program, our study did not permit assessment of the reversibility of the observed abnormalities in sympathetic nerve terminal function after a period of drug abstinence. Furthermore, "street cocaine" may contain various amounts of contaminants or may be associated with other stimulants (as detected for several cocaine abusers in this study), which also may have contributed to alterations in the sympathetic neuronal function. Lastly, the cutoff threshold of 2.5 s.d. of tracer uptake below reference database values for the detection of regional abnormalities of blood flow and ^{11}C-hydroxyephedrine uptake was selected arbitrarily and did not have any physiological basis. However, this approach provided rigid criteria for the identification of significant regional abnormalities in cardiac blood flow and presynaptic nerve function.

CONCLUSION

PET imaging in combination with the norepinephrine analog ^{11}C-hydroxyephedrine permits quantitative assessment of cocaine effects on cardiac neuronal function during active, chronic drug use. The results of the current 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.

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