

Cocaine Alters Heart Rate Dynamics in Conscious Ferrets

BRUCE S. STAMBLER, M.D., JAMES P. MORGAN, M.D., Ph.D.,
JOSEPH MIETUS, B.S., GEORGE B. MOODY, AND
ARY L. GOLDBERGER, M.D.

*Cardiovascular Division, Beth Israel Hospital and Harvard Medical School, Boston,
Massachusetts*

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This study was designed to test the hypothesis that cocaine intoxication induces distinctive alterations in sinus rhythm heart rate dynamics. Time-series and spectral analysis techniques were used to examine the effects of lethal doses of cocaine on heart rate variability in conscious, restrained ferrets. In all animals ($n = 5$), cocaine administration resulted in a marked decrease in sinus rhythm heart rate variability prior to sudden death. Heart rate variability (coefficient of variation of heart rate) just prior to death (0.018 ± 0.005) was significantly ($p < 0.02$) decreased compared to that at baseline prior to cocaine administration (0.061 ± 0.022). There was also a significant ($p < 0.02$) decrease in total spectral power prior to death compared to baseline. Transient low-frequency (0.04–0.10 Hz) oscillations in heart rate were also noted in three of the five animals following cocaine administration. There were, however, no significant changes in mean heart rate in response to cocaine. Alterations in heart rate dynamics were not seen in three saline-treated controls. Lethal effects of cocaine included ventricular arrhythmias ($n = 2$) and seizures ($n = 3$). One animal developed transient ST segment elevations that were consistent with coronary vasospasm. In conclusion, lethal doses of cocaine in the conscious ferret induce characteristic alterations in heart rate dynamics. These abnormalities (loss of heart rate variability and the appearance of low-frequency heart rate oscillations) are similar to those reported previously in certain patients at high risk of sudden cardiac death due to organic heart disease.

Recreational cocaine use has been associated with ventricular arrhythmias, myocardial infarction, and sudden death [1–6]. Sympathetic nervous system hyperactivity mediated by both central and peripheral stimulation is thought to be primarily responsible for cocaine's cardiovascular toxicity [7]. Characteristic markers of increased risk of sudden death due to cardiac instability from cocaine have, however, thus far not been identified.

There has been considerable interest recently in the assessment of heart rate variability as an independent prognostic marker in certain clinical conditions. Reduced sinus rhythm heart rate variability has been correlated with increased

Abbreviation: ECG: electrocardiogram

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Address reprint requests to Ary L. Goldberger, M.D., Cardiovascular Division (GZ-435), Beth Israel Hospital, 330 Brookline Ave., Boston, MA 02215

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mortality after acute myocardial infarction and with increased risk of sudden death in patients with high-grade ventricular ectopy [8,9]. Time-series and spectral (Fourier) analysis of heart rate dynamics have been used to characterize the mechanisms involved in heart rate variability. Spectral analysis of heart rate variability in healthy subjects reveals a broadband pattern with superimposed peaks corresponding to respiration, baroreceptor regulation, and other physiologic control mechanisms [9,10]. It has been reported recently that certain patients at high risk of sudden cardiac death exhibit characteristic alterations in this physiologic broadband spectrum [9]. These changes in heart rate dynamics include a flat, low-amplitude spectral pattern, associated with a loss of physiologic sinus rhythm heart rate variability, and a sharply peaked spectrum, associated with sustained low-frequency heart rate oscillations. It has been postulated that these abnormalities in heart rate dynamics reflect perturbations in the neuroautonomic control of heart rate [9].

Based on these findings, this study was designed to test the hypothesis that cocaine intoxication would be associated with distinctive alterations in heart rate dynamics. Heart rate dynamics were examined in conscious, restrained ferrets given lethal doses of cocaine. The results of this study suggest that time-series and spectral analysis of cardiovascular dynamics may offer a novel approach to monitoring patients with drug toxicity.

METHODS

Experimental Protocol

Twelve- to fourteen-week-old ferrets of either sex (weight, approximately one kilogram) were lightly sedated with ketamine (10–15 mg/kg, intramuscular). The animals were placed in a restraining cage and were allowed to acclimate and recover from the anesthetic. The surface electrocardiogram (ECG) was monitored continuously in a single lead (usually lead II), displayed on an oscilloscope, and recorded on magnetic tape. The baseline ECG was recorded for 30 to 45 minutes, and then five animals were given serial intramuscular injections of cocaine hydrochloride every 15 minutes until death. Cocaine injections were initially 2 to 4 mg/kg. If the animal survived beyond a cumulative cocaine dose of 20 mg/kg, then the dose of each cocaine injection was increased to 10 mg/kg. In a separate group of three control animals, saline was substituted for cocaine, and animals were given serial intramuscular injections every 15 minutes for 60 to 90 minutes. The experimental protocol conformed to the "Position of the American Heart Association on Research Animal Use," adopted November 11, 1984.

Data Analysis and Statistics

The electrocardiographic data from magnetic tape were digitized at 250 Hz. An arrhythmia detector analyzed the digitized ECG and labeled each beat as normal sinus, premature ventricular, or supraventricular. The output of the arrhythmia detector and the electrocardiographic beats were visually scanned and verified. Mean heart rate, sinus rhythm heart rate variability (defined as the coefficient of variation of heart rate), and frequency spectra were determined from a continuous one-minute section of ECG, of at least 250 beats, obtained immediately prior to each dose of cocaine and just prior to the terminal event. The ECG sections chosen for analysis were free of artifacts due to movement or electrical noise and of premature

ventricular beats. Frequency spectra in the frequency band from 0.02 to 4.0 Hz were computed from the heart rate time series sampled at 8 Hz with a 2,048-point fast Fourier transform. Total spectral power was computed as the area under the frequency spectra in the frequency band from 0.02 to 0.6 Hz. Spectral power was determined at baseline before cocaine and just prior to death, following the last cocaine injection. Oscillations in heart rate were noted by visually scanning the time series. The frequencies of these oscillations were determined from the peaks in the frequency spectra (Fig. 1).

A two-tailed Student's *t*-test for paired data was used to compare differences in heart rate, heart rate variability, and spectral power at baseline versus just prior to sudden death. Values were expressed as mean \pm standard deviation. Statistical significance was defined as $p < 0.05$.

RESULTS

Baseline Heart Rate Dynamics

At baseline, the heart rate time series from all the conscious ferrets (five experimental, three control) demonstrated considerable beat-to-beat sinus rhythm heart rate variability. The frequency spectra were broadband with a 1/*f*-like distribution (Fig. 1). The term 1/*f*-like applies to broadband spectra of this type, in which there is an inverse relationship between spectral amplitude and frequency [10].

Effects of Cocaine on Heart Rate Variability and Spectral Power

Cocaine administration was associated in four of the five ferrets with a biphasic response in heart rate variability. There was an increase in heart rate variability at low doses of the drug, followed by a progressive decrease at higher doses until death. All five animals demonstrated a marked decrease in sinus rhythm heart rate variability prior to sudden death (Fig. 2). The coefficient of variation of heart rate just prior to death (0.018 ± 0.005) was significantly less than at baseline prior to cocaine administration (0.061 ± 0.022), ($p < 0.02$). The marked decrease in heart rate variability in the pre-terminal stage was visually apparent by comparing the heart rate time series at baseline to that just prior to sudden death. The decreased variability was associated in all animals with a relatively flat, low-amplitude spectral pattern before sudden death, in contrast to the broad pattern at baseline (Fig. 1). The decrease in amplitude of the frequency spectrum, quantitated as spectral power in arbitrary units, was significantly ($p < 0.02$) reduced just prior to sudden death (0.56 ± 0.28) compared to baseline (8.26 ± 4.63), (Fig. 3).

Effects of Cocaine on Heart Rate Oscillations

Subtle low-frequency (0.04 to 0.10 Hz) oscillations in sinus heart rate were noted in the time series of three of the five animals after cocaine administration. An example of these oscillations from one animal is given in Fig. 1. These oscillatory patterns were less than 60 seconds in duration and were not seen at baseline prior to cocaine administration.

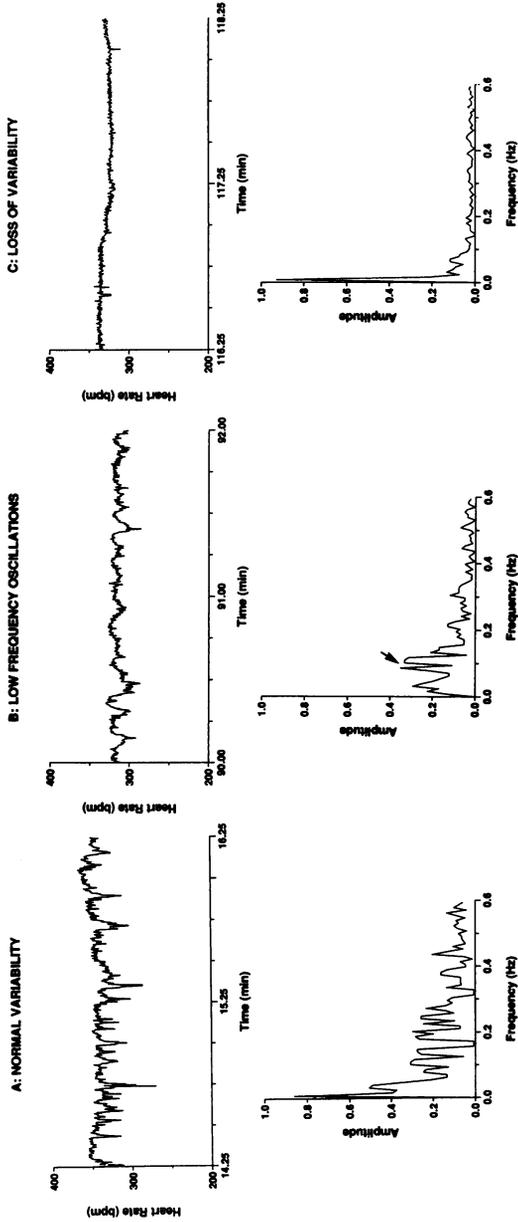


FIG. 1. Heart rate time-series (*upper diagrams*) and corresponding spectral frequency plots (*lower diagrams*) from a single ferret experiment. In panel A, at baseline prior to cocaine administration, there is considerable beat-to-beat variability in heart rate dynamics with a broadband, $1/f$ -like frequency spectrum. In panel B, after a cumulative cocaine dose of 16 mg, low-frequency heart rate oscillations appear in the time series with a corresponding frequency peak (*arrow*) at approximately 0.09 Hz. In panel C, after a cumulative cocaine dose of 28 mg, just prior to death from seizure and ventricular tachycardia (VT), there is marked loss of heart rate variability, visually apparent from the heart rate time series, and a corresponding relatively flat, low-amplitude frequency spectrum. Spectral amplitude is expressed in arbitrary linear units.

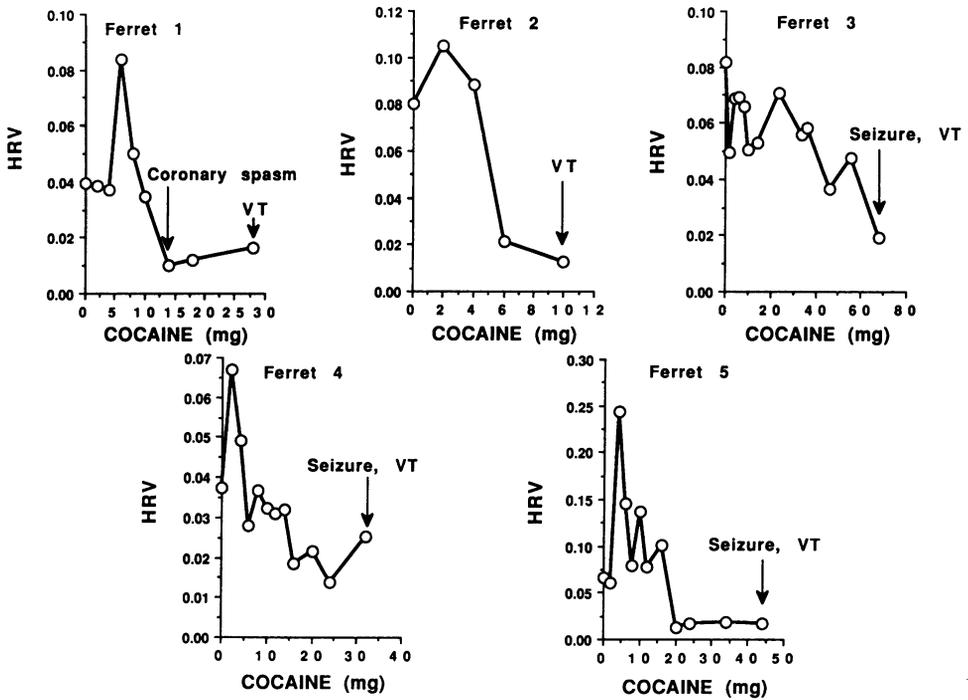


FIG. 2. Heart rate variability (coefficient of variation of heart rate) plotted against cumulative cocaine dose (mg) in each of the experimental animals. Cocaine administration results in a progressive decrease in heart rate variability. HRV = heart rate variability, VT = ventricular tachycardia. Coronary spasm was indicated by transient ST segment elevation.

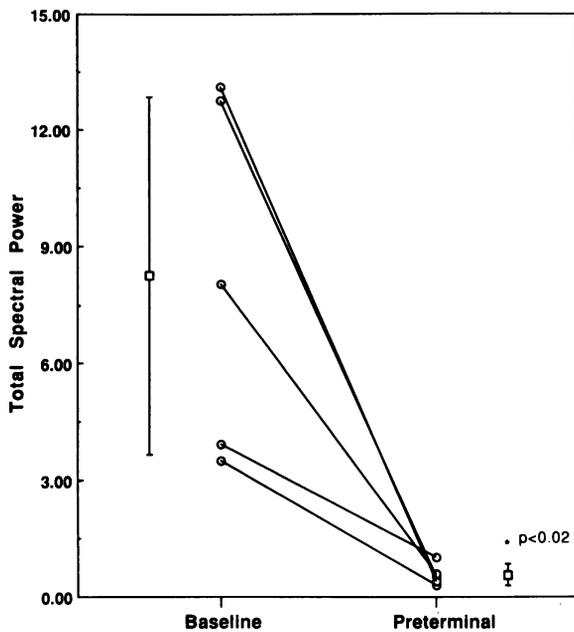


FIG. 3. Total spectral power at baseline and prior to the terminal event in each of the experimental animals. Total spectral power in the frequency band from 0.02 to 0.6 Hz is given in arbitrary units. See text and Fig. 2 for details of cocaine dosage. Cocaine administration is associated with a marked loss of spectral power in each animal.

Effects of Cocaine on Mean Heart Rate

Cocaine did not produce a consistent change in mean heart rate (Fig. 4). Mean heart rate (beats/minute) just prior to death (309 ± 39) was not significantly different from baseline (305 ± 35).

Toxic Effects of Cocaine

Mean cumulative dose of cocaine (mg/kg) prior to death was 36 ± 21 , with a range of 10 to 68. Clinical events that led to death included ventricular arrhythmias (ventricular tachycardia and fibrillation) in two animals and generalized tonic-clonic seizures followed by ventricular tachycardia in three animals. There was no difference in the pattern of heart rate variability between animals dying of arrhythmias and those dying of seizures (Fig. 1). In one animal that developed sustained ventricular tachycardia after 10 mg of cocaine, several four- to five-beat premonitory salvos of ventricular tachycardia were noted after 6 mg of cocaine. In two animals that died of seizures, ventricular premature beats increased in frequency from 0 to 1 per minute at baseline prior to cocaine, up to a maximum of 10 to 20 per minute after cocaine. In the remaining two animals, one of which died of seizure and the other of ventricular tachycardia, ventricular premature beats did not increase following cocaine. Finally, one animal developed marked ST segment elevations after 14 mg of cocaine (Fig. 5). The ST elevation lasted six minutes, resolved spontaneously, and did not recur despite continued administration of cocaine. This animal developed ventricular tachycardia that resulted in death after 28 mg of cocaine.

Saline-Treated Controls

Control animals ($n = 3$) demonstrated broadband frequency spectra with beat-to-beat fluctuations in heart rate that were not altered following multiple serial injections of saline. These animals did not develop significant changes in either mean heart rate or heart rate variability in response to saline injections. Mean heart rate (beats/minute) and heart rate variability (coefficient of variation) in the control group at baseline were 353 ± 29 and 0.053 ± 0.024 , respectively, compared to 320 ± 64 and 0.087 ± 0.021 following the last saline injection ($p = \text{NS}$). The low-frequency oscillations in heart rate observed after cocaine were not seen in the time series of any animal in the saline-treated control group.

DISCUSSION

This study demonstrates that lethal doses of cocaine administered to the conscious ferret induce characteristic alterations in sinus rhythm heart rate dynamics prior to sudden death. Time-series and spectral analysis techniques were used to detect and quantify these alterations in heart rate variability. The heart rate patterns observed after high doses of cocaine were similar to the sinus rhythm dynamics that have been reported recently in patients at high risk of sudden cardiac death due to organic heart disease [9]. These pathologic patterns include: (1) a marked overall reduction in heart rate variability and (2) the appearance of relatively low-frequency heart rate oscillations.

Effects of Cocaine on Heart Rate Dynamics

Heart rate dynamics from conscious ferrets have not been previously reported. Under resting conditions, the time-series and frequency spectra of sinus rhythm

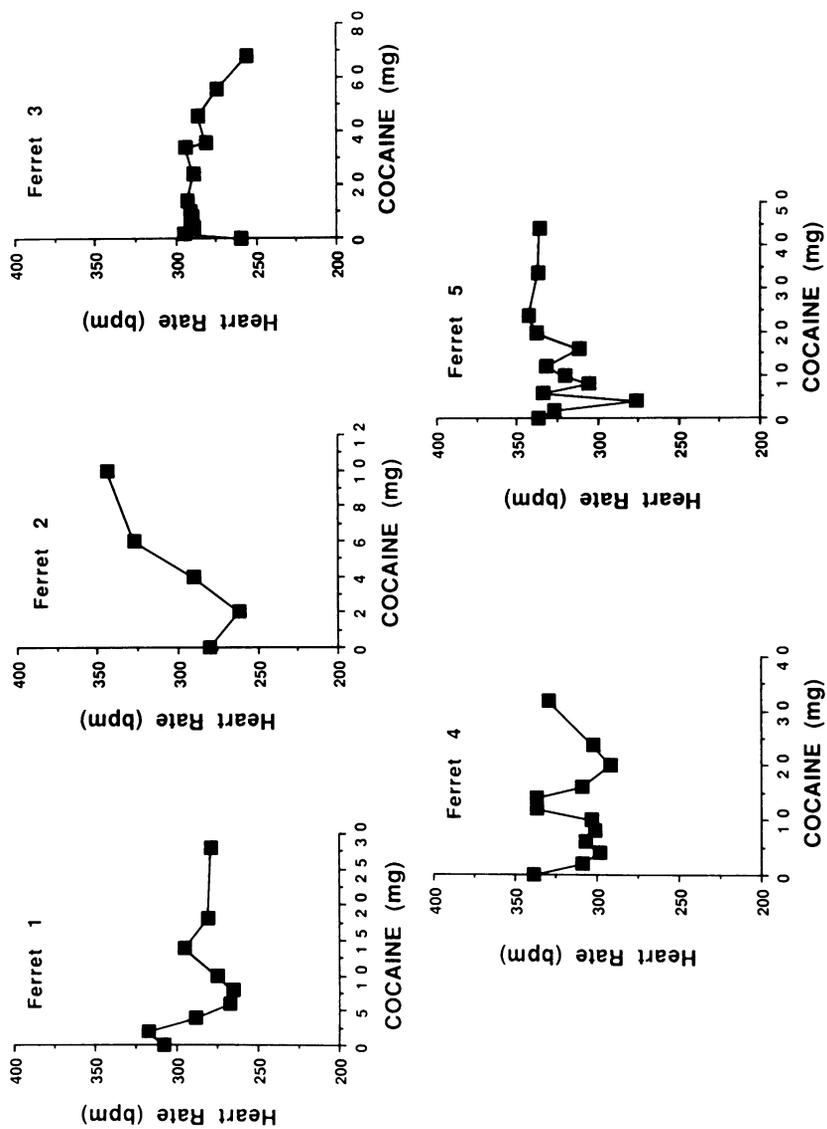


FIG. 4. Mean heart rate plotted against cumulative cocaine dose (mg) in each of the experimental animals. Cocaine administration did not produce a consistent change in mean heart rate.



FIG. 5. Single lead (II) electrocardiographic recording from a ferret immediately before (*top tracing*), during (*middle tracing*), and after (*bottom tracing*) an episode of probable coronary vasospasm with marked ST segment elevations.

dynamics in these animals are similar to those observed in conscious dogs and in healthy humans [9–14]. In these species, there is considerable beat-to-beat heart rate variability. The frequency spectrum of these fluctuations is broadband with a $1/f$ -like distribution [10].

The effects of cocaine on these physiologic sinus rhythm heart rate dynamics have not been described previously in any species. This study was designed to examine the hypothesis that cocaine administration would induce marked changes in physiologic heart rate dynamics. A conscious, restrained animal model was used in order to avoid the well-recognized confounding effects of anesthetic agents. A marked loss of heart rate variability prior to morbid events (seizure, ventricular tachycardia, and presumed coronary vasospasm) was observed in all ferrets treated with cocaine but in none of the saline-treated controls. The loss of variability was apparent on visual inspection of the time-series plots and was quantitated by analysis of the coefficient of variation of heart rate and by spectral analysis (Figs. 1 to 3).

The mechanism of the loss of heart rate variability secondary to cocaine is not certain, but is probably more complex than a simple linear combination of autonomic influences. At higher doses of cocaine, prior to sudden death, increased sympathetic tone alone, or in combination with decreased vagal tone, would have been expected both to increase heart rate and to decrease heart rate variability. Mean heart rate prior to death, however, was similar to baseline heart rate, in contrast to heart rate variability, which was markedly reduced. The local anesthetic properties of high doses of cocaine may have played a role in these dynamics by causing direct toxic effects on both neural and cardiac tissue [7]. Alternatively, since generalized tonic-clonic seizures were a frequent morbid event in these animals, cocaine-induced seizure activity may have directly modified central neural influences on heart rate

control. The appearance of low-frequency (0.04–0.10 Hz) oscillations in heart rate patterns following cocaine administration provides further evidence for a nonlinear mechanism underlying heart rate control [9]. Loss of heart rate variability or low-frequency oscillatory patterns in heart rate have been described in other pathologic conditions, including severe congestive heart failure [9,15,16], myocardial infarction [8,17], heart transplantation [18], and prior to sudden cardiac death [9,19].

Although an increase in heart rate in response to cocaine has been noted previously in some reports, this study's finding that cocaine did not produce a consistent change in mean heart rate is in agreement with a number of other studies [20–23]. Species differences and use of anesthesia, as well as differences in the dose and route of administration of cocaine, might account for the different findings among these various reports.

Coronary Vasospasm

There has been recent interest in the possibility that coronary vasospasm is one mechanism responsible for myocardial infarction associated with recreational use of cocaine [1,3,4]. In this study, one of the ferrets spontaneously developed marked ST segment elevations following a cumulative dose of 14 mg of cocaine (Fig. 5). The ST segment elevation lasted six minutes and, paradoxically, did not recur despite repeated cocaine administration. This electrocardiographic pattern of acute transmural ischemia is consistent with coronary vasospasm and has not been described previously in a cocaine-treated animal model. Since only a single ECG lead (lead II) was monitored continuously, coronary spasm may not have been detected in all animals studied.

Limitations

A possible confounding factor in this study is the high doses of cocaine that were administered, along with the sevenfold range in lethal dose. This study was designed to examine lethal effects of the drug on heart rate dynamics in a conscious animal model. Animals were given serial intramuscular injections of cocaine until death. Serum cocaine levels were not obtained in this study. Assuming rapid and complete absorption, these doses are much greater than those employed in most other experimental studies on the effects of cocaine and are probably much greater than the recreational doses of the drug. These doses are comparable, however, to the lethal doses of the drug previously reported in the dog (22 ± 2 mg/kg, intravenous) and in the rat (146 ± 66 mg/kg, intra-arterial) [24,25]. Whether similar heart rate dynamics would be associated with smaller non-lethal doses requires further study. The marked variability in lethal dose in the ferret is similar to that seen in the rat and is also consistent with the clinical observation in humans that the cardiovascular toxicity of cocaine is not clearly related to the administered dose or to the serum cocaine level [1,5,6,25].

Marked agitation caused by higher doses of cocaine in this conscious animal model precluded accurate measurement of physiologic variables other than heart rate, including blood pressure and respiration. The possible role of reflex changes in the pathogenesis of reduced heart rate variability associated with cocaine requires further study.

Clinical Implications and Future Studies

Clinical predictors of the cardiovascular toxicity associated with cocaine use have not been identified. This study demonstrates an association between lethal doses of cocaine and abnormal heart rate dynamics in ferrets prior to death. The observed toxic effects of cocaine in ferrets (ventricular arrhythmias, seizures, presumed coronary spasm) were quite similar to those previously described in humans and animals suffering from acute cocaine poisoning [1,4,5,26]. Furthermore, despite the variety of clinical toxicities from cocaine, all animals developed a marked loss of heart rate variability prior to these toxic effects. The findings of this study suggest, therefore, that time-series and spectral analysis of electrocardiographic data from patients with cocaine intoxication may provide new diagnostic information not otherwise available and may offer new indicators of high risk associated with cocaine use. Further studies will be required to assess systematically this possibility in humans using cocaine.

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