Mechanism of Cocaine-Induced Myocardial Depression in Dogs

Theodore D. Fraker Jr., MD, Peter N. Temes-Armos, MD, Pamela S. Brewster, MA, and R. Douglas Wilkerson, PhD

Cocaine causes pronounced depression of left ventricular function in conscious dogs immediately after intravenous administration. To examine this effect, 14 mongrel dogs were anesthetized with pentobarbital sodium (32 mg/kg) and instrumented with arterial and venous catheters and a Doppler blood flow transducer on the left circumflex coronary artery. Two weeks later, heart rate, blood pressure, coronary blood flow, and regional left ventricular ejection fraction (by two-dimensional echocardiography) were measured before and 1, 2, 5, and 10 minutes after cocaine (4 mg/kg i.v.), while the animals were fully conscious. Heart rate, blood pressure, and coronary blood flow were increased significantly at each time after cocaine. Regional ejection fraction, however, was depressed by 50±7%, 35±4%, and 21±4% at 1, 2, and 5 minutes after cocaine treatment, respectively. Ten minutes after cocaine treatment, regional ejection fraction had recovered to a level not significantly different from baseline. Because the observed myocardial depression after cocaine was accompanied by a large increase in the rate-pressure product, and presumably, myocardial oxygen consumption, this depression could have been secondary to increased myocardial oxygen demand not appropriately matched by an increase in coronary blood flow. To minimize the effects of cocaine on myocardial oxygen demand, a subset of six dogs received cocaine (4 mg/kg i.v.) while sedated with pentobarbital (25 mg/kg). In these dogs, cocaine did not significantly alter heart rate or blood pressure; however, regional ejection fraction was significantly depressed by 44±5% and 36±6% at 1 and 2 minutes after cocaine treatment, respectively. Significant depression of canine left ventricular function, in the absence of changes in major determinants of myocardial oxygen consumption, is consistent with a direct myocardial depressant action of cocaine. (Circulation 1990;81:1012–1016)

Numerous clinical reports of cardiovascular toxicity in humans have led to speculation that cocaine causes myocardial ischemia, infarction, or both.1–4 Potential mechanisms for cocaine-induced myocardial ischemia might include vasospasm in a large epicardial coronary artery or a diffuse increase in coronary vascular resistance, leading to a decrease in coronary blood flow, in conjunction with a marked, cocaine-induced, increase in myocardial oxygen consumption. Because it is well established that cocaine increases sympathetic tone, while at the same time blocking the neuronal reuptake of norepinephrine, heightened sympathetic activity and associated elevation of myocardial oxygen consumption is to be expected after cocaine administration.5 These actions of cocaine provide a potential milieu for myocardial ischemia that can result in depressed ventricular function as a result of an imbalance between oxygen demand and supply. A direct myocardial depressant action of cocaine has previously been suggested.6–8

In this study, we report an acute transient depression of myocardial function in dogs after intravenous cocaine treatment. Additionally, we provide evidence supporting the hypothesis that the observed myocardial depression is not secondary to myocardial ischemia but is the result of a direct myocardial depressant action of cocaine.

Methods

Animal Preparation

Fourteen conditioned mongrel dogs weighing 15–25 kg were trained to lie quietly on a nylon mesh elevated platform as described herein. After 2–3 weeks of training, they were anesthetized with sodium pentobarbital intravenously (32 mg/kg initially, with supplementation as needed), intubated, and ventilated with a Harvard respirator (Harvard
Experimental Protocol

During the conditioning time before surgery and during the 2 weeks of recovery after surgery, each dog was trained to lie quietly on its right side on an elevated platform fabricated from nylon mesh. Access to the dog's right parasternal area for echocardiographic examination was obtained from below the platform through a 6×6-in. hole in the nylon mesh. After the dog was positioned on the mesh support stand and allowed to accommodate to the dim light surroundings in the laboratory (necessary for optimal visualization of the echocardiographic image on a monitor), the study commenced.

Studies in Conscious Dogs

Continuous electrocardiographic, arterial blood pressure, and coronary blood flow recordings were performed using a Gould (model TA-2000, Gould Electronics, Cleveland, Ohio) physiological recorder. Two-dimensional echocardiographic images of the left ventricle in a short-axis view at the midpapillary muscle level were recorded on a Hewlett-Packard model 77020A Ultrasound system (Hewlett-Packard, Waltham, Massachusetts). Images were recorded continuously and stored on 1/2-in. videotape for later playback and analysis. The echocardiographic system was triggered to obtain end-diastolic and end-systolic frames that were used to calculate end-diastolic cavity area and end-systolic cavity area, from which regional ejection fractions were calculated. End diastole was determined from the peak of the R wave of the electrocardiogram, and end systole was determined from aortic valve closure as determined by pulsed Doppler examination.

After baseline recordings of heart rate, blood pressure, coronary blood flow, and left ventricular function by echocardiography, these conscious dogs received 4 mg/kg cocaine intravenously, and all of the parameters previously listed were recorded continuously for the next 10 minutes. At the conclusion of this recording period, the dogs were returned to a quiet, low-light environment until the effects of the cocaine had dissipated. There were no episodes of convulsions in these studies.

Studies in Sedated Dogs

A subset of six consecutive dogs from the original 14 was studied a second time, 1 week after the conscious experiment. Other than the flush solution used to keep indwelling arterial and venous catheters patent and sterile, these dogs received no drugs between studies. The dogs were then sedated with intravenous sodium pentobarbital 25 mg/kg and allowed to breathe spontaneously. Dogs were positioned on the nylon mesh elevated platform as in the conscious experiment. All dogs breathed spontaneously without respiratory assistance. Arterial blood pressure, heart rate, coronary blood flow, and echocardiographic images were recorded continuously as previously described. After a period of stable baseline recording, each dog received 4 mg/kg cocaine intravenously. Recording was continued for the next 10 minutes as in the conscious experiment. At the end of the study, each dog was returned to its pen to recover. All dogs tolerated the experiment without incident. There was no episode of seizure activity at this dose of cocaine.

Determination of Plasma Cocaine Concentration

Blood samples (5 ml) were obtained 1, 2, 5, and 10 minutes after intravenous administration of 4 mg/kg cocaine to these same dogs, while conscious, on a different day during the course of another study. Samples were placed immediately into vacutainers containing potassium oxalate and sodium fluoride, and they were gently mixed before centrifugation. After centrifugation, plasma was collected and frozen at −40°C until time of assay.

Plasma cocaine concentration was determined by the Medical College Hospital Toxicology Laboratory by a modification of the gas chromatography–mass spectroscopic procedure previously described.\textsuperscript{10} Deuterated cocaine (0.25 μg/ml) and deuterated benzylocgonine (0.25 μg/ml) (Radian Pharmaceuticals, Austin, Texas) were added to each sample as internal standards. The sensitivity of the assay for cocaine in this laboratory is 0.02 mg/l, and it is linear over a range of 0.02–10.0 mg/l.

Echocardiographic Protocol

Two-dimensional echocardiographic images were recorded continuously throughout each experiment on 1/2-in. videotape. During the baseline phase and at
TABLE 1. Response to 4 mg/kg Cocaine Administered Intravenously

<table>
<thead>
<tr>
<th></th>
<th>Conscious dogs (n=14)</th>
<th>Sedated dogs (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>103±5</td>
<td>163±9</td>
</tr>
<tr>
<td>p value*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate</td>
<td>116±6</td>
<td>164±8</td>
</tr>
<tr>
<td>p value*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Rate-pressure product (×100)</td>
<td>168±14</td>
<td>329±24</td>
</tr>
<tr>
<td>p value*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary flow</td>
<td>70±7</td>
<td>96±11</td>
</tr>
<tr>
<td>p value*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td>1.7±1</td>
<td>2.0±2</td>
</tr>
<tr>
<td>p value*</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>53±3</td>
<td>25±3</td>
</tr>
<tr>
<td>p value*</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*pComparison of cocaine response at each time to baseline for that state (conscious or sedated). p values are calculated using Dunnett’s test for multiple comparisons where repeated measures analysis of variance was significant (p<0.05).

1, 2, 5, and 10 minutes after cocaine administration, five triggered end-diastolic and end-systolic images were selected for determination of area and calculation of regional ejection fraction. End-diastolic area (EDA) and end-systolic area (ESA) were determined by planimetry of the endocardial border of still-frame images at the midpapillary level of the left ventricle. The average value of each set of five areas was then used to calculate regional ejection fraction using the formula: Regional ejection fraction = ( [EDA - ESA] / EDA ) × 100.

Statistical Analysis

Results are expressed as the mean±SEM for the number of dogs (n) in each study. Overall significance levels for changes in heart rate, blood pressure, rate-pressure product, coronary blood flow, coronary resistance, and regional ejection fractions from before to after cocaine were determined by repeated measures analysis of variance (ANOVA). Post hoc multiple-comparison analysis using Dunnett’s test was used to compare baseline values with changes at each time after cocaine for all parameters. For making the comparison of cocaine responses between conscious and sedated animals, multivariate analysis of variance was used to test for independent and interaction effects of time and conscious versus sedated state.

Results

Effects of cocaine, 4 mg/kg i.v., on blood pressure, heart rate, rate-pressure product, coronary flow, coronary resistance, and regional ejection fraction in conscious and sedated dogs are shown in Table 1. Mean blood pressure, heart rate, coronary blood flow, and rate-pressure product increased significantly after cocaine in conscious dogs but, with the exception of coronary blood flow, did not change significantly in sedated dogs. Coronary vascular resistance, which would be expected to decline in response to increased myocardial oxygen demand resulting from the increase in blood pressure and heart rate induced by cocaine, actually increased significantly in conscious dogs in response to cocaine.

After sedation with pentobarbital (25 mg/kg i.v.), this same dose of cocaine did not significantly alter blood pressure, heart rate, or rate-pressure product. Coronary blood flow, however, was decreased at 2 and 5 minutes after cocaine administration in these sedated dogs.

In contrast to the very dissimilar hemodynamic responses to cocaine in conscious versus sedated dogs, regional ejection fraction was significantly decreased, whether the dogs were conscious or sedated (Table 1). The baseline regional ejection fraction was lower in each dog during the sedated phase of the study as compared with the conscious state, presumably because of depressant effects of pentobarbital on left ventricular function. Table 2 presents all data as percentages of change from baseline. The statistical comparison in Table 2 is between cocaine responses in conscious versus sedated dogs at each time. This comparison indicates that the effect of cocaine on regional ejection fraction was not different in conscious versus sedated dogs, whereas the hemodynamic variables (excluding coronary resistance) did respond differently in conscious versus sedated states.

The change in regional ejection fraction from before to after cocaine treatment in these dogs was because of a dramatic increase in end-systolic area and a modest increase in end-diastolic area. In conscious dogs, end-systolic area increased by 81±25% (mean±SEM) (p<0.01) 1 minute after cocaine treatment, whereas end-diastolic area increased by 13±7% (p<0.05). In sedated dogs, the increase in end-systolic area was 54±11% (p<0.01) 1 minute after cocaine treatment, whereas the end-diastolic area was increased by only 15±6% (p<0.01). Thus, significant ventricular dilation occurs in response to intravenous cocaine administration.
The time course of the hemodynamic responses and the changes in regional ejection fraction in conscious dogs given 4 mg/kg cocaine intravenously can be seen in Table 2. These same relations are shown in sedated dogs. While regional left ventricular ejection fraction decreased similarly in both conscious and sedated states, the hemodynamic variables showed very little change in sedated dogs after cocaine treatment.

The relation between rate-pressure product, an index of myocardial oxygen consumption, and coronary vascular resistance in conscious dogs given 4 mg/kg cocaine also can be seen in Table 2. The change in coronary vascular resistance observed after cocaine administration is paradoxical, that is, coronary vascular resistance would be expected to decline in response to an elevated myocardial oxygen demand if normal metabolic vasoregulatory mechanisms were intact; however, after cocaine treatment, metabolic coronary vasodilation seems not to occur. In sedated dogs, there was no significant change in either rate-pressure product or coronary vascular resistance after intravenous administration of 4 mg/kg cocaine. The decrement in coronary blood flow observed in sedated dogs is consistent with a decrease in myocardial oxygen demand associated with depressed myocardial function.

The effects of cocaine on the relation between rate-pressure product and ejection fraction in conscious and sedated dogs are presented in Table 2. Cocaine significantly increased the rate-pressure product at all times in conscious dogs (p<0.01) but did not change rate-pressure product in sedated dogs. The effect of cocaine on the rate-pressure product was, therefore, significantly different in conscious versus sedated dogs (p<0.0003). The decrease in regional ejection fraction after cocaine, however, was remarkably similar in both conscious and sedated dogs (p<0.51). This suggests that the myocardial depression observed after cocaine treatment was not related to the increase in myocardial oxygen consumption induced by cocaine.

Plasma cocaine concentrations at 1, 2, 5, and 10 minutes after a 4 mg/kg intravenous dose of cocaine were determined in each dog, in a separate study, at least 1 week before studies of the effects of this drug on myocardial function. Plasma cocaine concentrations (µg/ml) were 4.1±0.4, 3.0±0.2, 2.3±0.2, and 1.2±0.1 at 1, 2, 5, and 10 minutes after cocaine administration, respectively.

Discussion

Three important findings with regard to the cardiovascular actions of cocaine have been demonstrated by this study, and they are as follows: 1) cocaine caused severe transient depression of myocardial function in dogs at an intravenous dose of 4 mg/kg, 2) the hemodynamic effects of cocaine were significantly different in conscious versus sedated dogs, and 3) the depressant effect of cocaine on left ventricular function seems not to be secondary to myocardial ischemia. This conclusion is supported by the persistence of this myocardial depression in sedated dogs in which major determinants of myocardial oxygen consumption were not significantly affected by cocaine treatment. These findings support the hypothesis that the myocardial depressant effect of cocaine is primarily because of a direct action of this drug on the myocardium, as opposed to being secondary to cocaine-induced myocardial ischemia.

The possibility of direct myocardial depression by cocaine has been suggested previously. Wilson et al6 studied pentobarbital-anesthetized open-chest dogs in which arterial pressure and heart rate were controlled. Intravenous cocaine in doses greater than 100 mg caused a decline in left ventricular dP/dt that was followed by a decrease in circumflex coronary artery blood flow, coronary sinus blood flow, and myocardial oxygen consumption. This study suggested that myocardial depression is unrelated to an ischemic mechanism. Herman et al7 examined the effects of cocaine in an isolated blood-perfused–dog Langendorff preparation. Low-dose cocaine resulted in an increased force of myocardial contraction,
whereas high-dose cocaine caused prolonged depression of myocardial contractile force. Hale et al examined hemodynamic effects and echocardiographic changes in pentobarbital-anesthetized dogs before and 15 minutes after cocaine (10 mg/kg). Left ventricular dP/dt was depressed, and chamber dimensions increased after cocaine. These preliminary reports using a wide variety of experimental models are in agreement with data presented in the present study.

Previous studies from our laboratory have documented the diverse hemodynamic responses to cocaine in conscious versus anesthetized dogs. The present study confirms these observations. Conscious dogs given 4 mg/kg cocaine showed a marked increase in heart rate, blood pressure, and, hence, rate-pressure product. Although coronary blood flow increased in response to these hemodynamic effects of cocaine, calculated coronary resistance did not decrease, as would be expected in response to an increase in myocardial oxygen consumption but, rather, increased significantly. This suggests that cocaine might either cause coronary vasoconstriction as suggested by several investigators or that it might interfere with metabolic vasoregulatory mechanisms.

In distinct contrast to the pronounced variability in hemodynamic effects of the same dose of cocaine in conscious versus sedated dogs, the effect of cocaine to depress left ventricular function, as assessed by echocardiography, was remarkably similar in both conscious and sedated dogs. Specifically, the pronounced decline in left ventricular regional ejection fraction observed in conscious dogs was also present in sedated dogs despite modest changes in heart rate, blood pressure, and coronary blood flow. The decrease in coronary blood flow measured after cocaine administration in sedated dogs was probably secondary to a decrease in myocardial oxygen demand, as a result of the depression in myocardial function without significant change in other determinants of myocardial oxygen consumption, namely, heart rate and arterial blood pressure.

The plasma cocaine concentrations associated with the observed myocardial depression in this study were less than those reported in numerous autopsy reports of humans whose deaths were attributed to cocaine overdose. For example, Wettl and Wright reported 24 patients who apparently died from acute cocaine overdose, and they found that plasma cocaine concentrations measured at autopsy were in the range of 0.3–12.8 μg/ml. It should be noted that the plasma cocaine concentrations reported in all these studies were measured at the time of autopsy; thus, the peak plasma cocaine concentration was undoubtedly much higher because cocaine is biotransformed by plasma esterases, a reaction that can continue even after death.

Intravenous cocaine, 4 mg/kg, caused a pronounced depression in left ventricular function in conscious and sedated dogs that peaked within the first minute after administration. By 10 minutes after cocaine treatment, myocardial function had recovered significantly. The observation that cocaine-induced myocardial depression occurred in sedated dogs, where changes in indexes of myocardial oxygen consumption were absent, suggests that myocardial ischemia resulting from an oxygen supply-demand mismatch was not responsible for the dramatic decline in myocardial function. This clearly suggests that the myocardial depression produced by cocaine is the result of its local anesthetic effects on the myocardium, and this depressant effect occurs even in the presence of intense adrenergic stimulation.

References

Key Words: myocardial depression • coronary blood flow • cocaine
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