Effect of Cocaine on the Coronary Circulation and Systemic Hemodynamics in Dogs

FREDERICK E. KUHN, MD, MICHAEL N. JOHNSON, MD, RICHARD A. GILLIS, PHD, MARC S. VISNER, MD, FACC, GARY L. SCHAER, MD, FACC, WITH THE TECHNICAL ASSISTANCE OF CRAIG GOLD, BA, SVEA K. WAHLSTROM, BS

Washington, D.C.

This study investigated the effect of intravenous cocaine (0.5 to 2 mg/kg body weight) on the coronary circulation and systemic hemodynamics in closed chest sedated dogs. The role of alpha- and beta-adrenoceptor stimulation in mediating these effects was also investigated. Cocaine produced dose-dependent increases in mean arterial pressure and rate-pressure product. Although the lower doses of cocaine had no significant effect on the coronary circulation, the 2 mg/kg dose produced a 55 ± 1.1% increase in coronary vascular resistance (p < 0.05 versus baseline) and a 19 ± 3% reduction in diameter of the left anterior descending coronary artery (p < 0.05 versus baseline). Despite these potentially deleterious effects on the coronary circulation (occurring at a time of markedly increased myocardial oxygen demand), the electrocardiogram did not demonstrate ischemic changes and there was no myocardial lactate production.

Cocaine-induced coronary vasoconstriction was abolished by pretreatment with the alpha-adrenoceptor antagonist phentolamine, but not by pretreatment with the beta-adrenoceptor antagonist propranolol. The findings that cocaine did not change systemic vascular resistance in dogs without adrenergic blockade, reduced systemic vascular resistance in dogs after alpha-blockade (p < 0.05) and increased systemic vascular resistance in dogs after beta-blockade (p = 0.06) suggest that epinephrine (rather than norepinephrine) is primarily responsible for the peripheral vascular actions of cocaine.

Thus, in this canine preparation with normal coronary arteries, cocaine produced vasoconstriction of both epicardial and coronary resistance vessels that was not associated with evidence of myocardial ischemia. The pharmacologic mechanism for the effect of cocaine on the coronary circulation is alpha-adrenoceptor stimulation, whereas systemic hemodynamic effects are mediated by combined alpha- and beta-adrenoceptor stimulation.

The incidence of cocaine abuse has reached epidemic proportions in numerous communities throughout the United States. It is estimated that 30 million Americans have used cocaine at some time and 5 million use it regularly (1). Over the past 5 years, numerous cases of myocardial ischemia and infarction have been reported to be associated with the recreational use of cocaine (2-16). It has been postulated that cocaine-induced myocardial ischemia results from coronary vasospasm or a marked imbalance between myocardial oxygen supply and demand (2,3); however, few clinical or experimental data exist in support of these postulates. We therefore investigated the effect of cocaine on the coronary circulation (epicardial and coronary resistance vessels) and on systemic hemodynamics.

The lack of understanding of the mechanisms responsible for cocaine-induced cardiovascular complications has severely limited a rational approach to prevention and treatment of these serious problems. To clarify the pharmacologic mechanism whereby cocaine produces its effects on the coronary circulation and on systemic hemodynamics, we investigated the role of alpha- and beta-adrenoceptor stimulation in mediating these actions.
Methods

This study conformed to the guidelines specified in the National Institutes of Health Guide for Care and Use of Laboratory Animals and was approved by the Animal Care and Use Committee of the Georgetown University School of Medicine.

Experimental preparation. Adult male mongrel dogs (25 to 30 kg) received the short-acting anesthetic thiopental sodium (25 mg/kg body weight intravenously) and were intubated with a cuffed endotracheal tube and ventilated with a Harvard respirator (Harvard Instruments). Adequacy of ventilation was assessed by periodic arterial blood gas determinations; pH was maintained at 7.40 ± 0.05. The potent short-acting narcotic sufentanil was given as a bolus injection (2 µg/kg intravenously) followed by a continuous intravenous infusion (1 µg/kg per h) to achieve a constant level of sedation throughout the experiment. Pancuronium bromide (0.1 mg/kg intravenously) was given as needed to provide continuous skeletal muscle relaxation. A bipolar V2 chest lead (addressing the anterior wall of the left ventricle supplied by the left anterior descending coronary artery) was placed to provide electrocardiographic (ECG) and arrhythmia monitoring.

Animals were then positioned supine on the catheterization table and both femoral arteries and the right femoral vein were cannulated percutaneously with introducer sheaths. A 7F micromanometer-tipped pigtail catheter (model SPC474-A, Millar Instruments) was advanced under fluoroscopic guidance to the apex of the left ventricle to measure left ventricular pressure and perform microsphere injections. A second micromanometer-tipped catheter (model MPC500, Millar Instruments) was placed in the aortic root for measurement of aortic pressure. The micromanometers were driven with a direct current preamplifier (Gould Electronics) and zero referenced and balanced at 38°C immediately before each study. The zero drift did not exceed 0.5 mm Hg during the course of any study. The left main coronary artery was intubated with a 6F Judkins catheter (type 3.5 left) for subsequent coronary angiography. A 7F thermodilution pulmonary artery catheter (American Edwards Laboratories) was advanced into the main pulmonary artery. Cardiac output was determined by the thermodilution technique with use of a cardiac output computer (model 9520, American Edwards Laboratories) and recorded as the average of three determinations obtained with hand injections of saline solution (10 ml, 0° to 5°C). All tracings were recorded on an eight channel recorder (model TA2000, Gould Electronics) for subsequent analysis.

Study protocol. After 20 to 30 min of stable hemodynamics after instrumentation, baseline hemodynamic measurements (heart rate, cardiac output and left ventricular and aortic pressures), coronary angiography and myocardial blood flow determinations (by microsphere injection) were performed. Dogs were assigned to receive one of three doses of cocaine hydrochloride by intravenous bolus injection. The first group of eight dogs received 2 mg/kg of cocaine. Hemodynamic measurements and coronary angiography were performed 2, 5, 10, 15, 30 and 60 min after cocaine administration. Microsphere injections (to assess myocardial blood flow) were performed 2, 5 and 10 min after cocaine administration. In four of these eight dogs, a control study was performed before cocaine administration to evaluate the coronary angiographic and hemodynamic effects of repeated contrast injections. This study was identical to the subsequent cocaine protocol except that a saline solution placebo was administered instead of cocaine and microsphere injections were not performed. The subsequent responses to cocaine in these four dogs were similar to those observed in the other four dogs in this group. Two additional groups of four dogs each were studied to determine the dose response to cocaine. The study protocol was identical to that of the group receiving 2 mg/kg of cocaine, except that cocaine doses of either 0.5 or 1 mg/kg were administered.

To assess the role of alpha-adrenoceptors in mediating the cardiovascular effects of cocaine, a fourth group of six dogs was pretreated with the alpha-adrenoceptor antagonist phentolamine (2.5 mg/kg intravenously) 10 min before administration of cocaine (2 mg/kg intravenously). This dose has been shown to fully antagonize the alpha-adrenoceptor-mediated effects of norepinephrine (17). Hemodynamic measurements, coronary angiography and myocardial blood flow determinations were performed 5 min after phentolamine administration, and these values served as the precocaine baseline data. After cocaine administration, hemodynamic status and myocardial blood flow were determined and coronary angiography was performed according to the protocol described for the first three groups.

The role of beta-adrenoceptors in mediating the cardiovascular effects of cocaine was assessed in a final group of six dogs pretreated with propranolol (0.75 mg/kg intravenously) 10 min before administration of cocaine (2 mg/kg). This dose of propranolol has been shown to fully antagonize the beta-adrenoceptor-mediated effects of isoproterenol (18). The remainder of the study protocol was otherwise identical to the protocol in the group with alpha-adrenoceptor blockade.

Hemodynamic data were used to derive the following variables: SV = (CO x 1,000)/HR, RPP = (HR x LVPSP)/1,000 and SVR = [(MAP - CVP)/CO] x 80, where SV is stroke volume (ml/min), CO is cardiac output (liters/min) and HR is heart rate (beats/min); RPP is rate-pressure product (beats/min x mm Hg x 10⁻³) and LVPSP is left ventricular peak systolic pressure (mm Hg); SVR is systemic vascular resistance (dyne·s·cm⁻⁴·m²), MAP is mean arterial pressure (mm Hg) and CVP is central venous pressure (mm Hg).
Myocardial blood flow determinations. Transmural myocardial blood flow was determined using the colored microsphere technique (19). Approximately 5 to 8 x 10⁶ color-labeled 11.9 ± 1.9 µm polystyrene microspheres (yellow, orange, red, green, blue or black, E-Z Trac, SRP) were thoroughly mixed by vortex agitation for 1 min and then hand-injected through the central lumen of the pigtail catheter into the apex of the left ventricle. Microsphere injections into the left ventricular apex have been shown to compare favorably with left atrial injections (20). Reference arterial samples were withdrawn from the femoral artery at a constant rate (13.9 ml/min) using a withdrawal pump (model 901, Harvard Instruments), beginning 5 s before microsphere injection and continuing for 90 s after injection.

At the conclusion of each experiment, dogs were sacrificed with an overdose of potassium chloride (40 mEq intravenously), and a transmural sample of myocardium (2 to 4 g) was excised from the anterior wall of the left ventricle supplied by the left anterior descending coronary artery. Blood and tissue samples were processed with digestive reagents by methods previously described (19). Final aliquots from the blood and tissue samples were counted with a hemocytometer, and four to eight chambers were counted for each sample.

Myocardial blood flow (MBF [ml/min per g]) was then calculated by the following equation: MBF = (Cm x Q,)/ (C, x WT), where Cm is the total number of microspheres in the tissue sample, Q, is the rate of reference blood withdrawal (ml/min), C, is the total number of microspheres in the reference blood sample and WT is the weight of the tissue sample (in g).

Coronary vascular resistance (CVR) was calculated as CVR = MAP/MBF, where MAP is mean arterial pressure (mm Hg) and MBF is myocardial blood flow (ml/min per g).

Coronary angiography. This was always performed in a 30° right anterior oblique position using hand injections (3 to 5 ml) of nonionic contrast medium (iopamidol 76%, Squibb) and recorded on cinefilm at 30 frames/s. Nonionic contrast medium was chosen because it produces less alteration in cardiovascular variables than ionic agents (21). Coronary angiograms were performed during brief periods (10 s) while the respirator was not cycling. For subsequent quantitative analysis, angiograms were projected on a viewing screen and traced at end-diastole by an observer who had no knowledge of the experimental intervention. The proximal 1.5 cm of the left anterior descending coronary artery was divided into three 0.5 cm segments, and the diameter at the midpoint of each segment was measured using calipers. The final diameter of the proximal vessel was then taken as the mean of these three segments and was corrected for image magnification using the known diameter of the angiographic catheter. Pincushion distortion was minimized by keeping the area of interest within the central third of the image intensifier. The maximal distortion within this field was determined by using standardized grids and was found to be <1%. Throughout the experiment, care was taken to avoid changes in animal or camera position that might affect image projection or magnification.

Myocardial lactate determinations. To assess whether cocaine (2 mg/kg intravenously) results in metabolic changes consistent with myocardial ischemia, myocardial lactate extraction was determined in a separate group of three dogs. The coronary and systemic hemodynamic effects of cocaine in these dogs were similar to those observed in the other group that received 2 mg/kg. The right internal jugular vein was cannulated percutaneously and a 7F multipurpose catheter was advanced into the coronary sinus, with its tip positioned in the great cardiac vein. Correct catheter placement was confirmed by contrast injection and oximetric study of blood samples. Lactate extraction was determined at baseline and 5 min after cocaine administration by collecting simultaneous blood samples from the ascending aorta and the great cardiac vein. Serum lactate concentration was determined spectrophotometrically with a Dupont AutoAnalyzer.

Percent lactate extraction was calculated as: (Lact, - Lact, / Lact, x 100 / Lact, where Lact, is aortic lactate concentration and Lact, is great cardiac vein lactate concentration.

Serum cocaine levels. In five dogs from the group receiving 2 mg/kg cocaine, venous blood (10 ml) was drawn into chilled Vacutainer tubes (Beckton-Dickinson) containing sodium fluoride and calcium oxalate at 5, 10, 15, 30 and 60 min after cocaine administration. Serum concentrations of cocaine were subsequently measured with gas chromatography-mass spectroscopy using selected ion monitoring (22) (American Medical Laboratories).

Statistical analysis. Data are presented as mean values ± SEM. Statistical analysis of the changes from the cocaine baseline study to peak effects was performed using Student's t test for paired samples (two-tailed). Analysis of variance was used to assess differences between study groups. When significant differences were found, a multiple comparisons procedure (Tukey's test) was used to determine at which time points the groups differed. A linear regression analysis was performed to assess the relation between cocaine dose and several cardiovascular variables. A p value <0.05 was considered significant.

Results

Effect of cocaine on systemic hemodynamics (Table 1). The hemodynamic effects of three doses of cocaine (0.5, 1 and 2 mg/kg intravenously) are shown in Table 1. Cocaine (0.5 mg/kg) had minimal effects on hemodynamics except for a small but statistically significant reduction in left ventricular end-diastolic pressure and a borderline significant (p = 0.07) increase in stroke volume. Cocaine (1 mg/kg) produced
Kuhn ETA. Coronary and Hemodynamic Effects of Cocaine. Te6fe t.Bertof Intravenous Cocaine on Several Indexes of Cardiovascular Function in 16 Dogs

'a significant increase in heart rate and a modest increase in mean arterial pressure of borderline statistical significance (p = 0.06). The 2 mg/kg dose of cocaine resulted in pronounced hemodynamic changes, including a significant increase in heart rate, mean arterial pressure, left ventricular end-diastolic pressure and cardiac output. The increase in mean arterial pressure was associated with a comparable increase in systolic (127 ± 6 to 199 ± 25 mm Hg, p < 0.01) and diastolic (88 ± 7 to 137 ± 13 mm Hg, p < 0.001) arterial pressures. This pressor effect occurred in the absence of any significant effect of cocaine on systemic vascular resistance.

Although the 0.5 mg/kg cocaine dose had no significant effect on rate-pressure product, the 1 and 2 mg/kg doses produced significant increases in this variable (Table 2), with a maximal increase of 129 ± 51% observed 5 min after the 2 mg/kg dose. Two minutes after this dose, coronary vascular resistance increased 55 ± 14% (p < 0.015 versus baseline) despite a 50 ± 16% increase in rate-pressure product (p < 0.05 versus baseline). The two lower doses of cocaine (0.5 and 1 mg/kg intravenously) also resulted in an increase in coronary vascular resistance at 2 min, but these changes were of smaller magnitude and did not reach statistical significance.

Five minutes after the 2 mg/kg dose of cocaine, coronary vascular resistance returned to near baseline values in association with further increases in rate-pressure product. Five and 10 min after cocaine administration in the 1 mg/kg group, coronary vascular resistance was significantly reduced from the precocaine baseline value.

**Table 1. Effect of Intravenous Cocaine on Several Indexes of Cardiovascular Function in 16 Dogs**

<table>
<thead>
<tr>
<th>Cocaine Dose (mg/kg)</th>
<th>No. of Dogs</th>
<th>Experimental Condition</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>SV (ml)</th>
<th>SYR (dynes-cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>4</td>
<td>Baseline</td>
<td>89 ± 7</td>
<td>101 ± 8</td>
<td>5.0 ± 2.9</td>
<td>4.00 ± 1.10</td>
<td>94.4 ± 3.4</td>
<td>2.038 ± 2.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak</td>
<td>87 ± 15</td>
<td>101 ± 9</td>
<td>3.5 ± 1.0*</td>
<td>4.74 ± 1.30</td>
<td>55.0 ± 3.2</td>
<td>1.835 ± 2.04</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>Baseline</td>
<td>96 ± 14</td>
<td>110 ± 5</td>
<td>4.3 ± 2.9*</td>
<td>3.87 ± 0.45</td>
<td>66.0 ± 4.5</td>
<td>2.232 ± 3.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak</td>
<td>112 ± 16*</td>
<td>121 ± 12</td>
<td>4.3 ± 0.6</td>
<td>4.83 ± 0.25</td>
<td>48.5 ± 3.9</td>
<td>1.664 ± 2.46</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Baseline</td>
<td>80 ± 9</td>
<td>104 ± 6</td>
<td>3.0 ± 0.6</td>
<td>3.66 ± 0.61</td>
<td>47.0 ± 6.0</td>
<td>2.478 ± 3.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak</td>
<td>116 ± 15*</td>
<td>156 ± 12*</td>
<td>8.6 ± 1.6*</td>
<td>6.06 ± 1.40*</td>
<td>48.0 ± 6.2</td>
<td>2.516 ± 4.26</td>
</tr>
</tbody>
</table>

*p < 0.05 versus baseline values. Data are mean values ± SEM. CO = cardiac output; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; SV = stroke volume; SYR = systemic vascular resistance.

**Table 2. Effect of Cocaine on Coronary Hemodynamics in 16 Dogs**

<table>
<thead>
<tr>
<th>Cocaine Dose (mg/kg)</th>
<th>No. of Dogs</th>
<th>Time (min)</th>
<th>MBF (ml/min per g)</th>
<th>CVR (dynes-cm⁻²·mmHg)</th>
<th>RPP (beats/min × mm Hg × 10⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>4</td>
<td>Baseline</td>
<td>0.84 ± 0.12</td>
<td>1.37 ± 0.12</td>
<td>310 ± 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.73 ± 0.03</td>
<td>1.51 ± 0.12</td>
<td>90 ± 14</td>
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<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.83 ± 0.08</td>
<td>1.23 ± 0.33</td>
<td>106 ± 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>1.28 ± 0.19</td>
<td>0.96 ± 0.24</td>
<td>105 ± 15</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>Baseline</td>
<td>1.18 ± 0.18</td>
<td>1.00 ± 0.17</td>
<td>111 ± 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>1.07 ± 0.19</td>
<td>1.41 ± 0.34</td>
<td>335 ± 22*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>1.56 ± 0.19</td>
<td>0.67 ± 0.08*</td>
<td>123 ± 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>1.82 ± 0.27</td>
<td>0.67 ± 0.17*</td>
<td>134 ± 22</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Baseline</td>
<td>1.35 ± 0.18</td>
<td>1.06 ± 0.17</td>
<td>98 ± 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>1.03 ± 0.20</td>
<td>1.51 ± 0.17*</td>
<td>158 ± 26*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>2.54 ± 0.97</td>
<td>1.16 ± 0.33</td>
<td>274 ± 62*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>2.05 ± 0.68</td>
<td>1.23 ± 0.29</td>
<td>206 ± 55*</td>
</tr>
</tbody>
</table>

*p < 0.05 versus baseline values. Data are mean values ± SEM. CVR = coronary vascular resistance; MBF = myocardial blood flow; RPP = rate-pressure product.
Effect of cocaine on coronary artery diameter (Fig. 2). Baseline diameter of the left anterior descending coronary artery was 3.4 ± 0.3 mm for the group that received cocaine and 3.1 ± 0.2 mm for the control group (saline solution placebo). Cocaine resulted in a 19 ± 3% reduction in left anterior descending coronary artery diameter (p < 0.05 versus baseline) 2 min after drug administration, with a return to baseline dimension by 15 min. This was in contrast to the small increase in epicardial vessel diameter observed in the control group, probably resulting from contrast-induced vasodilation. Cocaine-induced left anterior descending coronary artery narrowing was observed to be a diffuse phenomenon because focal vasospasm was not observed in any experiment. Epicardial vasoconstriction occurred in association with a significant increase in coronary vascular resistance, despite a marked increase in rate-pressure product. The two lower doses of cocaine (0.5 and 1 mg/kg intravenously) had no significant effect on the diameter of the left anterior descending coronary artery.

Effect of cocaine on the ECG. No ischemic ECG changes or ST segment shifts were observed in response to cocaine in any of the dogs studied. In addition, no significant ventricular arrhythmias were seen.

Effect of cocaine on myocardial lactate extraction. Myocardial lactate extraction was 63 ± 1% at baseline study and 55 ± 7% 5 min after intravenous administration of 2 mg/kg of cocaine (p = NS). Net myocardial lactate production was not observed in any of the dogs studied.

Serum cocaine levels. Mean serum concentrations of cocaine obtained during a 1 h period after the 2 mg/kg dose of cocaine are shown in Figure 3. The peak level obtained 5 min after cocaine administration was 1,142 ± 115 ng/ml. Serum levels declined in an exponential fashion over the 60 min period of measurement; the serum half-life was 50 min.

Effects of Adrenergic Blockade

Alpha-adrenoceptor blockade and coronary hemodynamics (Table 3). The effect of alpha-adrenoceptor blockade on cocaine-induced changes in coronary hemodynamics, epicardial coronary artery diameter and rate-pressure product are shown in Table 3. Administration of phentolamine (2.5 mg/kg) produced significant increases in rate-pressure...
product and myocardial blood flow compared with prephentolamine baseline values. Subsequent administration of cocaine (2 mg/kg intravenously) produced vasodilation in the left anterior descending coronary artery (p < 0.05 at 2 min) and a decrease in coronary vascular resistance (p < 0.05 at 10 min), but no significant changes in myocardial blood flow or rate-pressure product.

When compared with findings in control dogs without adrenergic blockade (Fig. 4), alpha-adrenergic blockade dramatically altered the vasoconstrictive effect of cocaine (2 mg/kg) on the coronary circulation (2 min after cocaine). Specifically, pretreatment with phentolamine abolished both the cocaine-induced increase in coronary vascular resistance and the reduction in left anterior descending artery diameter.

In addition, this intervention prevented the increase in rate-pressure product produced by cocaine, thereby greatly limiting cocaine-induced increases in myocardial oxygen demand.

**Beta-adrenergic blockade and coronary hemodynamics (Table 3).** As expected, pretreatment with propranolol (0.75 mg/kg) significantly reduced the rate-pressure product and

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**Table 3. Effect of Adrenergic Receptor Blockade on Cocaine-Induced (2 mg/kg) Changes in Coronary Hemodynamics and Left Anterior Descending (LAD) Coronary Artery Diameter**

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>No. of Dogs</th>
<th>Experimental Condition</th>
<th>MBF (mL/min per g)</th>
<th>CVR (mm Hg x 10^{-1} min/g)</th>
<th>RPP (beats/min x mm Hg x 10^{-2})</th>
<th>LAD Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentolamine</td>
<td>6</td>
<td>Baseline</td>
<td>1.03 ± 0.06</td>
<td>1.08 ± 0.14</td>
<td>112 ± 15</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>(2.5 mg/kg)</td>
<td></td>
<td>Baseline</td>
<td>1.72 ± 0.36*</td>
<td>0.87 ± 0.71</td>
<td>174 ± 17*</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-cocaine</td>
<td>1.54 ± 0.33</td>
<td>0.75 ± 0.16</td>
<td>192 ± 22</td>
<td>3.5 ± 0.2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 min</td>
<td>1.76 ± 0.28</td>
<td>0.64 ± 0.15</td>
<td>184 ± 23</td>
<td>3.3 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 min</td>
<td>1.87 ± 0.20</td>
<td>0.53 ± 0.09†</td>
<td>184 ± 27</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 min</td>
<td>1.01 ± 0.16</td>
<td>1.18 ± 0.17</td>
<td>124 ± 12</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>Propranolol</td>
<td>6</td>
<td>Baseline</td>
<td>0.73 ± 0.06*</td>
<td>1.41 ± 0.12*</td>
<td>89 ± 7*</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>(0.75 mg/kg)</td>
<td></td>
<td>Baseline</td>
<td>0.62 ± 0.25</td>
<td>1.94 ± 0.21†</td>
<td>128 ± 11†</td>
<td>3.3 ± 0.2</td>
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<tr>
<td></td>
<td></td>
<td>Post-cocaine</td>
<td>1.15 ± 0.22†</td>
<td>1.56 ± 0.23</td>
<td>136 ± 20†</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 min</td>
<td>1.02 ± 0.16</td>
<td>1.67 ± 0.27</td>
<td>120 ± 21†</td>
<td>3.4 ± 0.3</td>
</tr>
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<td></td>
<td></td>
<td>5 min</td>
<td>1.15 ± 0.22†</td>
<td>1.56 ± 0.23</td>
<td>136 ± 20†</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 min</td>
<td>1.02 ± 0.16</td>
<td>1.67 ± 0.27</td>
<td>120 ± 21†</td>
<td>3.4 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.05 versus baseline pre-adrenergic blockade; †p < 0.05 versus baseline post-adrenergic blockade. Data are mean values ± SEM. Abbreviations as in Table 2.
myocardial blood flow, with a concomitant increase in coronary vascular resistance. No significant change in epicardial coronary artery diameter was observed. Subsequent administration of cocaine to these beta-blocked dogs resulted in a significant increase in coronary vascular resistance (p < 0.05 at 2 min) and a trend toward reduced epicardial coronary artery diameter, despite significant increases in rate-pressure product (p < 0.05 at 2, 5 and 10 min). A transient increase in myocardial blood flow was also observed (p < 0.05, at 5 min).

When compared with findings in dogs without beta-adrenergic blockade (2 min after cocaine administration), prior beta-adrenoceptor blockade did not alter the increase in rate-pressure product or coronary vascular resistance produced by cocaine (Fig. 4). Although the cocaine-induced reduction in left anterior descending artery diameter was less striking in dogs with beta-adrenergic blockade, this response was not statistically different from that in dogs without beta-adrenergic blockade.

Alpha-adrenoceptor blockade and hemodynamic response (Table 4). Pretreatment with phentolamine (2 mg/kg) resulted in a significant increase in heart rate as well as significant reductions in mean arterial pressure, left ventricular end-diastolic pressure and systemic vascular resistance. Stroke volume and cardiac output were not significantly affected. In contrast to the marked pressor effect of cocaine (2 mg/kg) in dogs without alpha-adrenergic blockade, mean arterial pressure was not significantly increased by cocaine in these dogs with alpha-adrenergic blockade. Cocaine produced a significant reduction in systemic vascular resistance in phentolamine-pretreated dogs, even though alpha-adrenoceptor blockade alone had significantly reduced systemic vascular resistance. In addition, alpha-adrenoceptor blockade prevented the increase in heart rate normally observed with cocaine; however, this effect may have been related to the positive chronotropic effect of alpha-adrenoceptor blockade itself, thereby blunting any additional cocaine-induced increase in heart rate. Similar to the results observed in dogs without alpha-adrenergic blockade, cocaine administration caused significant increases in left ventricular end-diastolic pressure and cardiac output in dogs pretreated with phentolamine. Although increased cardiac output in dogs without alpha-adrenergic blockade was due to a positive chronotropic effect of cocaine, the increase in cardiac output in phentolamine-pretreated dogs was primarily related to a reduction in systemic vascular resistance, although small increases in heart rate, left ventricular end-diastolic pressure (preload) and stroke volume also may have contributed to this effect.

Beta-adrenoceptor blockade and hemodynamic response (Table 4). As expected, beta-adrenoceptor blockade with propranolol resulted in a significant reduction in heart rate. Administration of cocaine (2 mg/kg) to these dogs with beta-adrenergic blockade resulted in significant increases in heart rate, mean arterial pressure and left ventricular end-diastolic pressure. These effects were not statistically different from those produced by the same dose of cocaine in dogs without beta-adrenergic blockade. A trend toward increased systemic vascular resistance was also observed in this group (p = 0.06).

Discussion

These experiments demonstrate that doses of cocaine ranging from 0.5 to 2 mg/kg produce dose-dependent increases in mean arterial pressure and rate-pressure product. More important, they demonstrate that although low doses of cocaine (0.5 and 1 mg/kg) have minimal effect on the
Cocaine and systemic hemodynamics. The findings that cocaine produces increases in heart rate, mean arterial pressure and rate-pressure product are consistent with prior experimental (23,24) and clinical (25) reports. The pressor effect of cocaine observed in dogs without adrenergic receptor blockade was primarily due to its effect on increasing cardiac output, as systemic vascular resistance was not significantly increased. Because cocaine inhibits the re-uptake of norepinephrine at sympathetic nerve terminals (26), it might have been expected to increase systemic vascular resistance through alpha-adrenoceptor-mediated vasoconstriction. However, our results suggest that cocaine stimulates both alpha- and beta-adrenoceptors in the peripheral vasculature, thereby producing a balance between peripheral vasoconstriction and vasodilation. This view is supported by our finding that cocaine administration did not significantly change systemic vascular resistance in dogs without adrenergic receptor blockade but did produce a significant reduction in systemic vascular resistance in the presence of alpha-blockade and resulted in a trend toward increased systemic vascular resistance in the presence of beta-blockade (p = 0.06).

The systemic vascular resistance response to cocaine in dogs without adrenergic receptor blockade, and dogs with alpha- or beta-adrenoceptor blockade is best explained by the predominant action of epinephrine, a potent stimulator of beta-2-adrenoceptors (in addition to alpha- and beta-1-adrenoceptors). Indeed, Chiueh and Kopin (27) demonstrated that cocaine results in a fivefold increase in the adrenal release of epinephrine in the conscious rat. Thus, the cocaine-induced decrease in systemic vascular resistance in dogs with alpha-adrenoceptor blockade is due to the predominant peripheral vasodilating effect of beta-2-adrenoceptor stimulation by epinephrine, and the cocaine-induced increase in systemic vascular resistance observed in dogs with beta-blockade is due to predominant alpha-1-mediated peripheral vasoconstriction in the setting of beta-2-adrenoceptor blockade by propranolol. Although catecholamine levels were not measured in our study, the hemodynamic findings strongly support a role for cocaine-induced epinephrine release. These findings cannot be explained by the action of norepinephrine alone because norepinephrine has minimal activity at beta-2-adrenoceptors, which predominate in the peripheral vasculature.

Cocaine and the coronary circulation. We showed that cocaine produces a marked increase in rate-pressure product, a major determinant of myocardial oxygen demand (28). Such increases in myocardial oxygen demand normally lead to metabolically induced coronary vasodilation (29) with a concomitant decrease in coronary vascular resistance. In contrast, cocaine induces transient vasoconstriction of both coronary epicardial and resistance vessels at a time when myocardial oxygen demand is greatly increased. Although these results suggest that cocaine leads to an imbalance in myocardial oxygen supply and demand, myocardial ischemia was not evident from the ECG tracings and myocardial lactate production was not observed (5 min after cocaine administration). Although we cannot exclude the possibility that transient lactate production occurred 2 min after cocaine administration (at the time of peak increase in coronary vascular resistance), no lactate production was identified at the time of significant epicardial coronary vasoconstriction and peak increase in myocardial oxygen demand (5 min after cocaine). Thus, in this animal model with normal coronary arteries, cocaine produces coronary vasoconstriction that does not appear to be of sufficient magnitude or duration to cause myocardial ischemia.

Our findings regarding the effect of cocaine on coronary vascular resistance are consistent with studies in dogs (30) and humans (31). In the study of Wilkerson (30), as in our own, the administration of $1 \text{ mg/kg}$ of cocaine increased coronary vascular resistance, although not significantly. Lange et al. (31) administered $2 \text{ mg/kg}$ of cocaine intranasally and demonstrated a $33 \pm 29\%$ increase in coronary vascular resistance, which is similar to the $55 \pm 14\%$ increase in coronary vascular resistance observed in our study after a $2 \text{ mg/kg}$ intravenous dose of cocaine.

Our finding of cocaine-induced epicardial coronary vasoconstriction is also consistent with human data obtained by Lange et al. (31). They demonstrated a $10 \pm 5\%$ reduction in the diameter of the proximal left anterior descending coronary artery in response to a $2 \text{ mg/kg}$ intranasal dose of cocaine. In contrast, Bedotto et al. (32) found no constrictive effect of cocaine on epicardial coronary arteries in a canine model. Their finding may have been due to the dosing regimen employed (a constant infusion of $0.5 \text{ mg/kg per min}$), which would not be expected to produce the same rate of rise in cocaine serum concentration as that achieved with an intravenous bolus injection. In addition, this constant infusion may have caused tachyphylaxis, thereby reducing the effect of cocaine on the coronary arteries (25).

Although diffuse epicardial coronary vasoconstriction was noted in our experiments with the $2 \text{ mg/kg}$ dose of cocaine, focal vasospasm was never observed. Several investigators (2,3,5-7) have postulated that coronary vasospasm may be responsible for cocaine-induced ischemic
events especially in patients with normal or minimally diseased coronary arteries; however, only two cases of angiographically documented coronary artery spasm have been reported (7,8). In both cases, spasm was not documented until several days after admission and last presumed cocaine use. The substantial delay between cocaine use and documented coronary spasm casts doubt on a causal relation between these events. Furthermore, ergonomics challenge has yielded negative results in all cases in which it has been performed (2-7). Although it is difficult to extrapolate from a relatively small number of animals, our results combined with the absence of convincing clinical reports suggest that cocaine-induced coronary vasospasm is not a common event.

Mechanism of cocaine-induced coronary vasospastic. Cocaine is known to inhibit the uptake of norepinephrine into postganglionic sympathetic nerve endings (26) and may release stored norepinephrine from sympathetic nerve terminals (33). In addition, cocaine stimulates catecholamine release from the adrenal medulla (27). Kopka et al. (34) demonstrated that alpha1- and alpha2-adrenoceptors are present on coronary epicardial and resistance vessels in dogs and both subserve coronary vasospastic. Thus, cocaine may cause coronary vasospasm by means of catecholamine-mediated stimulation of alpha1- and alpha2-adrenoceptors. Our finding that the nonselective alpha-adrenoceptor antagonist phentolamine abolishes the coronary vasospastic effects of cocaine supports the hypothesis that these effects are mediated by alpha-adrenoergic receptor stimulation. This hypothesis is also supported by human data from Lange et al. (31), who demonstrated that cocaine-induced coronary epicardial and resistance vessel vasospasm was abolished by alpha-blockade with phentolamine.

In contrast to the effects of alpha-adrenoceptor blockade, the nonselective beta-adrenoceptor antagonist propranolol did not significantly alter cocaine-induced coronary vasospasm. Because beta-adrenoceptor stimulation produces coronary vasodilation, beta-adrenoceptor blockade might have been expected to potentiate the coronary vasospastic effects of cocaine by resulting in unopposed alpha-adrenoceptor-mediated coronary vasospasm. Indeed, this theoretical concern led Olson et al. (33) to suggest that these agents should not be employed in the treatment of cocaine-induced cardiovascular complications.

Our finding that beta-adrenoceptor blockade did not potentiate the coronary vasospastic effects of cocaine is that adequate beta-blockade was not achieved with the propranolol dose administered. For example, a small but significant increase in heart rate was observed in dogs after beta-blockade in response to cocaine (Table 4). However, we believe beta-blockade was adequate for several reasons. First, propranolol (0.75 mg/kg) resulted in changes consistent with beta-blockade, including a significant decrease in heart rate, rate-pressure product and myocardial blood flow and a significant increase in coronary vascular resistance (Tables 3 and 4). Second, prior work from our laboratory (18) demonstrated that this dose of propranolol abolishes the chronotropic response to intravenous isoproterenol in dogs. Third, the increase in heart rate observed after cocaine administration in dogs after beta-blockade may be related to an anticholinergic effect of cocaine (37).

Potential study limitations. The potential limitations of our study include those inherent in any animal model of human disease. It is possible that a species difference in vasoreactivity to cocaine may exist. The relative concentration and physiologic importance of adrenergic receptors may be different in dogs and humans. In addition, this study was performed in dogs with normal nonatherosclerotic coronary arteries. Shimokawa et al. (38) suggested that coronary atherosclerosis is a major predisposing factor for coronary spasm. Thus, it is possible that the presence of atherosclerosis with concomitant loss of endothelial-derived relaxing factors may potentiate the effects of cocaine, although preliminary data from our laboratory (39) suggest that endothelial injury does not potentiate cocaine-induced coronary vasospasm.

Our model may not accurately simulate the dosing regimen employed recreationally. The lower doses (0.5 and 1 mg/kg) used in this study were similar to those reported by Javaid et al. (40) to reproduce the psychotropic effects of recreational cocaine doses in human volunteers. The serum cocaine levels obtained with the 2 mg/kg dose are higher than those reported by Javaid et al. (40) but are similar to those reported in several postmortem studies (41-43) of cocaine-related deaths. In addition, use of a single intravenous dose may not accurately reproduce the cardiovascular effects of different patterns of cocaine use, in particular, the common practice of repeated dosing or “hinging.”

Our studies were performed in sufentanil-sedated dogs. Anesthetics are known to blunt cardiovascular reflexes, which may confound experimental results (44). In a recent study Willkerson (23) found that pentobarbital anesthesia blunted the cardiovascular response to cocaine (1 mg/kg intravenously) and concluded that a conscious animal is the only appropriate model in which to study the cardiovascular effects of cocaine. Fints et al. (45) also showed that pentobarbital blunts the effects of cocaine; however, in their study, urethane-anesthetized animals had hemodynamic re-
...sponses to cocaine similar to those of animals in the conscious state. Thus, the confounding effects of pentobarbital anesthesia do not necessarily extend to all anesthetic agents. Indeed, the increase in heart rate and blood pressure produced by cocaine (2 mg/kg) in our sufentanil-sedated dogs was very similar to that observed by Wilkerson (23) in conscious dogs, suggesting that our anesthetic regimen did not greatly alter the cardiovascular responses to cocaine.

Clinical implications. This study demonstrates that cocaine produces vasoconstriction of both coronary epicardial and resistance vessels at a time when heart rate and systolic blood pressure are markedly increased, but these effects are not associated with myocardial ischemia in this animal model. However, we cannot exclude the possibility that cocaine-induced coronary vasoconstriction may result in myocardial ischemia in patients who have atherosclerotic coronary artery disease or who are concomitantly using other drugs with potent coronary vasoconstrictive properties, such as nicotine (46) and ethanol (47).

Therapy of cocaine-induced myocardial ischemia and infarction has been largely empirical. Various agents have been employed despite a lack of experimental evidence to support their use (48). Our study provides a more rational basis for treatment. The finding that alpha-adrenoceptor blockade abolishes the coronary vasoconstrictive effects of cocaine suggests that alpha-adrenoceptor antagonists may be useful in the treatment of cocaine-induced myocardial ischemia and infarction. To be clinically effective these agents should possess both alpha-1 and alpha-2 antagonist properties because both receptor subtypes are known to subserve coronary vasconstriction. In addition, our study demonstrates that the beta-blocker propranolol does not potentiate the vasoconstrictive effects of cocaine on the coronary circulation. Although this suggests that propranolol need not be omitted from the treatment of cocaine-induced hypertension or supraventricular tachycardia, human studies are warranted to prove the safety of this approach.

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References


