Acute Intravenous Cocaine Causes Transient Depression Followed by Enhanced Left Ventricular Function in Conscious Dogs

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Background. Prior studies in experimental canine models have demonstrated that intravenous cocaine administration causes myocardial depression. The purpose of the present study was to establish the mechanisms of cocaine's actions on myocardial and left ventricular performance after single intravenous bolus doses in conscious, chronically instrumented dogs, in which the full autonomic influences of cocaine would be manifest.

Methods and Results. In the intact state, cocaine (1 mg/kg) caused a transient decrease in left ventricular dP/dt (baseline; 3,086±107 mm Hg/sec; 2.5 minutes, 2,649±114 mm Hg; p<0.05) followed by a 25±4% increase in left ventricular dP/dt that peaked at 15 minutes (left ventricular dP/dt, 3,751±127 mm Hg/sec, p<0.01) and remained elevated during the 30-minute period of observation. Both the initial depression and the sustained increase in left ventricular contractile response were dose related. The increase in left ventricular dP/dt persisted under circumstances in which the responses were normalized for changes in heart rate and preload that accompanied cocaine administration. The positive inotropic effects were abolished by full autonomic or selective β-adrenergic blockades. Finally, both cardiac output (baseline, 2,461±142 min/mL; peak [5 minutes], 3,434±218 mL/min; p<0.05) and left ventricular stroke work (baseline, 39±5 g·m; peak, 49±6 g·m; p<0.05) were increased at all times after cocaine administration, suggesting that pump performance was enhanced, despite early reductions in myocardial contractility. Similarly, indexes of early diastolic filling were enhanced despite transient early prolongation in isotropic relaxation.

Conclusions. Acute intravenous cocaine administration (0.1–2 mg/kg) has a biphasic effect on myocardial and left ventricular function with a transient depression followed by significant sustained increases in left ventricular contractility. The results are in keeping with an early local effect followed by significant adrenergic stimulation, which may be obscured by anesthesia or masked by changes in loading conditions. (Circulation 1993;87:1687–1697)

KEY WORDS • cocaine • left ventricular function • autonomic blockade • β-blockade

Despite increased awareness of the cardiovascular toxicities of cocaine, the mechanisms underlying the specific clinical syndromes remain incompletely understood. For example, although cocaine use has been associated with the development of myocardial ischemia and infarction,1–6 the effects of cocaine on the coronary circulation in experimental models have been inconsistent, with some studies showing increases in coronary blood flow7,8 and others failing to observe changes9–11 or demonstrating frank decreases in coronary blood flow.12–14 In contrast, most experimental studies have shown impaired myocardial function in response to acute cocaine administration, including depressed cardiac output,9,13,14 and impaired isovolumic13,15 and ejection phase indexes8,9 of myocardial contractility, yet there are few clinical reports of documented myocardial dysfunction attributable to cocaine.16,17 The depression in myocardial and ventricular performance has been ascribed to associated myocardial ischemia or to direct myocardial depressant effects of cocaine. However, these experimental observations are contrary to the predicted acute pharmacological actions of cocaine of increasing sympathetic nervous system activity as well as the effects of cocaine of blocking neuronal reuptake of norepinephrine.18 These discrepancies probably are reconciled by the fact that the full manifestations of cocaine's cardiovascular effects are dependent on the integrity of the autonomic nervous system.19 The majority of prior experimental studies have been conducted with the animals under anesthesia or sedation, thereby blunting the full auto-
nomic influences. Furthermore, the presence of sedation or anesthesia may necessitate larger doses of cocaine to elicit comparable hemodynamic effects.\textsuperscript{19}

Accordingly, the purpose of the present study was to establish the acute left ventricular and systemic hemodynamic effects of cocaine in chronically instrumented conscious dogs. Cocaine was administered as single intravenous bolus over 1 minute in doses of 0.1–2.0 mg/kg. We focused on the hemodynamic responses and mechanisms of cocaine’s effects on left ventricular performance and myocardial contractility in response to 1 mg/kg, which is a dose comparable to that used in acute studies in humans of cocaine’s hemodynamic effects.\textsuperscript{20–24}

\textbf{Methods}

\textbf{Instrumentation}

Twenty-seven mongrel dogs of either sex weighing 23–28 kg were sedated with xylazine (2 mg/kg i.v.) and anesthetized with halothane (1 vol\%). With sterile technique and insertion through an incision in the fifth intercostal space, Tygon catheters (Norton Plastics and Synthetics Division, Akron, Ohio) were implanted in the descending thoracic aorta and left atrium. In addition, a solid-state miniature pressure transducer (model P22, Konigsberg Instruments, Inc., Pasadena, Calif.) was implanted in the apex to measure left ventricular pressure in all dogs. In 15 dogs, a Transonic aortic flow probe (Transonic Systems, Inc., Ithaca, N.Y.) was placed around the ascending aorta to measure aortic flow. An additional six animals were instrumented with piezoelectric ultrasonic dimension crystals implanted on opposing anterior and posterior endocardial surfaces of the left ventricle to measure the internal short axis and on opposing endocardial and epicardial surfaces in the same equatorial plane as the internal short-axis diameter crystal to measure wall thickness. Endocardial wall thickness crystals were implanted obliquely to avoid damage to the myocardium between two wall thickness crystals. Ultrasonic transducers also were implanted at the basal epicardial surface and apical endocardial surfaces to measure left ventricular long axis. This scheme is based on a prolate ellipsoidal model of left ventricular geometry\textsuperscript{22} and has been used previously in our laboratory to measure changes in left ventricular volume.\textsuperscript{26,27} After instrumentation, catheters and wires were externalized infrascapularly, and the thoracotomy was closed. The dogs used in the study were maintained in accordance with the “Guidance for the Care and Use of Laboratory Animals” of the Institute of Laboratory Animal Resources, National Council (Department of Health and Human Services publication No. [NIH] 85-23, revised 1985) and the Harvard Medical School Standing Committee on Animal Care.

Aortic and left atrial pressures were sampled from chronically implanted catheters and measured with strain-gauge manometers (model P23 ID, Statham Instruments, Oxnard, Calif.), which were calibrated with a mercury manometer. Left ventricular pressure was measured using solid-state miniature pressure gauges calibrated in vitro with a mercury manometer and in vivo using left atrial and aortic catheters and Statham strain-gauge manometers. An ultrasonic dimension gauge was used to measure left ventricular dimensions. The dimension gauge generates a voltage linearly proportional to the time transit of ultrasonic impulses traveling at the velocity of $1.58 \times 10^7$ m/sec between the crystals. At constant room temperature, the thermal drift of the instrument is minimal. The position of all transducers was confirmed at autopsy.

\textbf{Protocols}

Hemodynamic measurements were made in all dogs while the dogs were lying quietly on an examining table in the unrestrained state. Experiments were conducted when the dogs were healthy and had recovered completely from surgery. In all dogs, intravenous cocaine was administered over a 1-minute period. In six dogs, dose–response relations (0.1–2 mg/kg) were established for left ventricular and systemic hemodynamics. After these initial studies, the dose of 1 mg/kg was chosen to study in detail the effects of cocaine on myocardial and left ventricular systolic and diastolic function. The dose was chosen based on preliminary experiments in which higher doses (2 mg/kg) produced unpredictable agitation and restlessness in the unrestrained animals. Hemodynamic recordings were made continuously with analysis performed at 30 seconds and 1, 2.5, 5, 10, 20, and 30 minutes after administration of the drug. Ten dogs were studied in the intact state in which systemic and left ventricular hemodynamics and myocardial contractility (left ventricular $dP/dt$) were assessed. As mentioned above, a separate group of six dogs instrumented specifically to measure left ventricular volumes was studied in the intact state to assess the effects of cocaine on ejection phase indexes and indexes of diastolic function.

In a subset of seven dogs, the intravenous response to cocaine (1 mg/kg) on systolic function was assessed after autonomic blockade with hexamethonium (30 mg/kg) and atropine methyl bromide (0.1 mg/kg). The efficacy of autonomic blockade was established by the absence of a heart rate response to a 20–mm Hg reduction in mean arterial pressure induced by 120 $\mu$g nitroglycerin i.v. On a separate occasion, cocaine (1 mg/kg) was administered after $\beta$-adrenergic blockade with propranolol (2 mg/kg) in a subset of seven dogs. The efficacy of $\beta$-blockade was established by demonstrating the absence of a heart rate, contractile, or vasodepressor response to isoproterenol (0.1 $\mu$g/kg). In a subset of five dogs, the contractile response to cocaine was compared with that of the local anesthetic lidocaine (2 mg/kg).

The data were recorded on a multichannel tape recorder (model 101, Honeywell, Denver, Colo.) and a direct writing oscillograph (Mark 200, Gould-Brush, Cleveland, Ohio). A cardiochometer (model 8557B, Beckman Instruments, Inc., Fullerton, Calif.) triggered by left ventricular pressure provided a continuous recording of heart rate. Continuous recordings of left ventricular $dP/dt$ and left ventricular $dV/dt$ were derived from left ventricular pressure and short-axis dimension signals, respectively, using Philbrick operational amplifiers (Teledyne Philbrick, Dedham, Mass.), which were operated as differentiators and had a frequency response of 700 Hz. A triangular wave signal was substituted for the pressure and dimension signals to calibrate directly the differentiator. Left ventricular end-diastolic dimensions were measured immediately before the onset of left ventricular contraction. The left ventricular end-systolic dimensions were measured at
the time of maximum negative \(\frac{dp}{dt}\). Ejection time was taken as the interval between maximum and minimum left ventricular \(\frac{dp}{dt}\).

Left ventricular shortening fraction was determined using end-diastolic (EDD) and end-systolic (ESD) short-axis dimensions and was calculated as:

\[
\text{Left ventricular shortening fraction} = \text{EDD} - \text{ESD}/\text{EDD} (\%)
\]

The velocity of circumferential shortening (Vcf) was determined as follows:

\[
\text{Vcf} = \text{shortening fraction}/\text{ejection time}
\]

Cavity volume was calculated using a prolate ellipsoidal model:

\[
\begin{align*}
\text{EDV} &= \frac{\pi}{6}(\text{EDD})^3(\text{EDL} - 0.55 \times \text{EDW})/1,000 \\
\text{ESV} &= \frac{\pi}{6}(\text{ESD})^3(\text{ESL} - 0.55 \times \text{ESW})/1,000
\end{align*}
\]

where EDV is end-diastolic volume, ESV is end-systolic volume, EDD is the end-diastolic short axis, and ESD is the end-systolic short axis, EDL is the end-diastolic long axis, ESL is the end-systolic long axis, EDW is end-diastolic wall thickness, and ESW is end-systolic wall thickness. Note that a wall thickness factor is subtracted from the measured long axis because one of the long axis crystals is endocardial and the other is epicardial.

End-systolic wall stress (Esc) was calculated using a cylindrical model:

\[
\text{Esc} = 1.36 \times [(\text{AP}_w \times \text{ESD})/(2 \times \text{ESW})]
\]

where AP\(_w\) is aortic pressure at end systole, ESD is the short-axis dimension at end systole, and ESW is wall thickness at end systole.

Left ventricular ejection fraction was calculated as:

\[
\text{Left ventricular ejection fraction} = \text{EDV} - \text{ESV}/\text{EDV} (\%)
\]

Left ventricular stroke work (SW) was calculated as:

\[
\text{SW} = 0.0136 \times \text{LVP}_{\text{peak}} \times \text{SV} \text{ (g} \cdot \text{m)}
\]

Systemic vascular resistance was equal to mean arterial pressure divided by cardiac output (dyne \cdot sec \cdot cm\(^{-2}\)).

**Indexes of Diastolic Function**

The time constant of isovolumic left ventricular pressure decay (\(\tau\)) was calculated using pressure data from peak negative \(\frac{dp}{dt}\) to a pressure equal to left ventricular end-diastolic pressure plus 5 mm Hg. \(\tau\) was calculated assuming a variable asymptote \((P_0)\) for left ventricular pressure decay and taking into account the effect of extramural forces (pleural pressure, interventricular dependence, or baseline shifts) using the formula:

\[
\text{LVP} = (P_0 - P_b)e^{-(t/T_D)} + P_b
\]

where LVP is left ventricular intracavity pressure, \(P_0\) is left ventricular pressure at the start of decay, \(t\) is time, and \(T_D\) is the time constant of isovolumic relaxation.

Positive left ventricular \(\frac{dD}{dt}\), the peak velocity of internal diameter lengthening, was used as an index of early filling. The derivatives were normalized for variations in left ventricular diameter among dogs by dividing positive \(\frac{dD}{dt}\) by the internal diameter at the point of maximal lengthening velocity and was expressed as

\[\frac{(+\text{dD/dt})/D}.\]

The lengthening of the minor axis has been shown to correlate closely with changes in early diastolic volume.

Plasma norepinephrine and epinephrine levels were determined at baseline and at 5 minutes after cocaine administration using the radioenzymatic assay of Peuler and Johnson. Plasma renin activity was determined by radioimmunnoassay by a method adapted from the method of Haber et al.

**Statistical Analyses**

The temporal response of the hemodynamic variables to cocaine was assessed using repeated-measures ANOVA. ANOVA was used to compare baseline levels with early and late responses, and where required, groups were compared by Student's t test with Bonferroni's correction. Significance was set at a value of \(p<0.05\).

**Results**

**Effects of Intravenous Cocaine on Systemic and Left Ventricular Hemodynamics in the Intact State**

The effects of increasing doses (0.1–2.0 mg \cdot kg\(^{-1}\) \cdot min\(^{-1}\)) of intravenous cocaine on selected left ventricular and systemic hemodynamic variables are summarized in Figure 1. There were dose-related increases in left ventricular systolic pressure, mean arterial pressure, and heart rate. A more detailed account of the effects of cocaine (1 mg/kg) on left ventricular and systemic hemodynamics is provided in Table 1. Left ventricular systolic pressure increased by 46±5% \((p<0.01)\) within the first minute and returned to baseline within 45 minutes. Left ventricular end-diastolic pressure increased from 10±1 to 17±2 mm Hg \((p<0.01)\) within the first 2.5 minutes and returned to baseline within 20 minutes of cocaine administration (Figure 2). There was a prompt (43±4%, \(p<0.01\)) and sustained increase in mean arterial pressure but only a transient increase in systemic vascular resistance, which increased by 25±9%
Table 1. Effects of Cocaine (1 mg/kg) on Left Ventricular and Systemic Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Early (2.5 minutes)</th>
<th>Late (15 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>123±5</td>
<td>164±6*</td>
<td>146±3*</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>114±6</td>
<td>116±5†</td>
<td>114±6†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>131±5</td>
<td>163±5*</td>
<td>147±5*</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>10±1</td>
<td>17±2*</td>
<td>12±1</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>5±1</td>
<td>5±1†</td>
<td>6±1†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>9±1</td>
<td>15±2*</td>
<td>11±2</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>92±3</td>
<td>132±5*</td>
<td>113±3*</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>96±5</td>
<td>99±6†</td>
<td>95±6†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>92±3</td>
<td>139±5*</td>
<td>118±5*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>82±6</td>
<td>122±9*</td>
<td>105±7*</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>128±3</td>
<td>131±3†</td>
<td>132±3†</td>
</tr>
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<td>β-Blockade (n=7)</td>
<td>80±3</td>
<td>95±3*†</td>
<td>78±4†</td>
</tr>
<tr>
<td>Cardiac output (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>2,461±142</td>
<td>3,061±149*</td>
<td>3,018±184*</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>1,962±143</td>
<td>1,825±173†</td>
<td>1,937±186†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>2,017±213</td>
<td>2,007±150†</td>
<td>1,861±144†</td>
</tr>
<tr>
<td>Stroke work (g · m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>39±5</td>
<td>45±6*</td>
<td>49±8*</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>18±3</td>
<td>17±2†</td>
<td>17±2†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>33±3</td>
<td>34±2†</td>
<td>34±3†</td>
</tr>
<tr>
<td>Systemic peripheral resistance (dyne · sec · cm⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n=10)</td>
<td>3,106±218</td>
<td>3,822±279*</td>
<td>3,114±214</td>
</tr>
<tr>
<td>Hexamethonium (n=7)</td>
<td>4,053±444</td>
<td>4,412±444†</td>
<td>4,135±429†</td>
</tr>
<tr>
<td>β-Blockade (n=7)</td>
<td>3,889±365</td>
<td>5,825±687*†</td>
<td>5,192±472*†</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.  
*p<0.01 compared with baseline.  
†p<0.01 change from baseline compared with the intact state.

(p<0.02) within the first minutes from 3,106±218 to 3,822±279 dyne · sec · cm⁻¹ (Figure 3). Thus, the major mechanism by which arterial pressure increase was the prompt and significant increase in cardiac output (Figure 4), which peaked within 5 minutes (+41±7%, p<0.01) at 3,434±218 mL/min from a baseline value of 2,461±142 mL/min. There was a 47±5% increase in heart rate from 82±6 to 122±9 beats per minute, whereas stroke volume was maintained despite the increase in heart rate after a transient decline from 31±3 to 26±3 mL (p<0.05) at 1 minute. Left ventricular stroke work increased significantly from 39±5 to 49±8 g · m (p<0.02).

Figure 5 summarizes the effects of increasing doses of cocaine (0.1–2.0 mg/kg) on left ventricular dP/dt as an index of myocardial contractility. There was an initial depression in left ventricular dP/dt that was evident within the first minute after cocaine administration, the magnitude of which was significant at 1- and 2-mg/kg doses. However, the response was followed rapidly by increases in left ventricular dP/dt within 5 minutes, which were significantly greater at higher doses (0.5, 1.0, and 2.0 mg/kg). Thus, there was a transient early depression in left ventricular dP/dt that quickly was replaced by a sustained significant increase in left ventricular contractility. The magnitude of the transient early depression was most evident at higher doses, whereas the sustained positive inotropic effects clearly were dose dependent.

Table 2 illustrates the peak effects of intravenous cocaine (1 mg/kg) on isovolumic and ejection phase indexes of myocardial contractility in dogs studied in the intact state. There was a transient depression in left ventricular dP/dt within the first minute after intravenous cocaine. However, left ventricular dP/dt returned to baseline levels by 2.5 minutes (3,167±96 mm Hg/sec), and there followed a significant (p<0.01) 25±3% increase in left ventricular dP/dt that peaked at 15 minutes and remained elevated to 30 minutes (Figure 6). Of importance, the peak left ventricular dP/dt response to cocaine occurred when left ventricular end-diastolic volume was not elevated (Table 2). In addition, the biphasic pattern of response of left ventricular dP/dt was maintained under conditions in which heart rate was held constant by atrial pacing (Table 2).

In the group of six dogs instrumented specifically to study the indexes of left ventricular ejection, the pattern of response to 1 mg/kg cocaine included an initial significant decline followed by a gradual return to baseline over 30 minutes. The marked early depression in left ventricular ejection occurred at a time of peak increase in afterload (Table 2). Overall, the pattern of velocity of
Effect of intact response with enhanced left ventricular autonomic blockade.

FIGURE 2. Plots of the effects of cocaine (1 mg/kg) on left ventricular peak systolic and end-diastolic pressures in the intact state (n=10) and after pretreatment with β-adrenergic blockade (n=7) or full autonomic blockade (n=7). The response in the intact group (p<0.01) and the β-blockade group (p<0.05) differed significantly from the combined autonomic blockades.

FIGURE 3. Plots of the effects of cocaine (1 mg/kg) on mean arterial pressure and systemic vascular resistance in the intact state and after full autonomic or β-adrenergic blockades. The mean arterial pressure response was significantly altered (p<0.01) in the presence of complete autonomic blockade compared with intact and β-blockade. The systemic vascular resistance response was enhanced (p<0.01) significantly in the presence of β-blockade.

circumferential shortening mirrored that of left ventricular end-systolic stress (Figure 7). Notably, both indexes of left ventricular ejection returned to or exceeded baseline values when left ventricular end-systolic stress remained significantly increased (Table 2), consistent with enhanced left ventricular function. In addition, preload recruitable stroke work increased significantly both initially and later after cocaine administration.

Effect of Combined and Selective Autonomic Blockade on Systemic and Left Ventricular Hemodynamics and Myocardial Contractility

To establish the mechanism of cocaine’s effects on systemic and left ventricular hemodynamics, the 1-mg/kg dose was repeated in the presence of β-adrenergic blockade with propranolol. The peak left ventricular systolic (+32±6 mm Hg) and end-diastolic pressure (+6±2 mm Hg) responses were similar to those observed in the intact state, as was the time course of the response (Figure 2). In contrast, the systemic vasoconstrictor response to cocaine was enhanced in the presence of β-blockade with significantly greater (intact, +716±246 dyne·sec·cm⁻⁵; β-blockade, +1,817±249 dyne·sec·cm⁻⁵, p<0.01) and more sustained (Figure 3) increases in systemic vascular resistance. However, there was no significant increase in cardiac output in response to cocaine in the presence of β-blockade (Figure 4) compared with the significant increase observed in the intact state. There was a transient but significant (+15±4 beats per minute, p<0.01) increase in heart rate within the first 2.5 minutes in the presence of β-blockade that was less than that observed in the intact state (+38±4 beats per minute, p<0.01).

The increase in left ventricular dP/dt observed in the intact state in response to cocaine was abolished completely by β-blockade, suggesting that sympathetic stim-
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**Figure 4.** Plots of the effects of cocaine (1 mg/kg) on cardiac output and heart rate in the intact state and after full autonomic or β-adrenergic blockade. The cardiac output response was blunted significantly (p<0.01) in the presence of both blockades. In addition, the heart rate response was altered significantly (p<0.01) in the presence of both blockades.

Cardiac output was the mechanism of enhanced contractility. However, the initial transient depression in left ventricular dP/dt was not altered by β-blockade, suggesting that a nonadrenergic mechanism was responsible for the first phase of cocaine’s action (Figure 6).

The effect of cocaine on left ventricular and systemic hemodynamics also was examined in the presence of full autonomic blockade to determine if neural mechanisms were responsible for cocaine’s cardiovascular effects. Combined autonomic blockade with hexamethonium and atropine methyl bromide abolished completely the left ventricular (Figure 2) and systemic pressor (Figure 3) effects of cocaine. Furthermore, both the chronotropic response and the increases in cardiac output were abolished (Figure 4). Finally, combined autonomic blockade prevented the positive isotropic effects of cocaine, suggesting that neural adrenergic mechanisms were involved. However, autonomic blockade did not alter the transient depression in left ventricular dP/dt (Figure 6) observed within the first 2.5 minutes after cocaine administration, suggesting a distinct, nonneural mechanism for the early negative inotropic response to cocaine.

In further support of the role of sympathetic activation as the mechanism responsible for the increase in contractility after cocaine is the doubling in plasma norepinephrine and epinephrine levels (Table 3) observed in the intact state and in the presence of β-blockade. However, the increase in plasma catecholamines was blunted in the presence of complete autonomic blockade, which is consistent with neural influences mediating cocaine’s adrenergic effects. In addition, there was a small increase in plasma renin activity in response to cocaine that was abolished completely by both selective β- and combined autonomic blockades.

To clarify the mechanism for the early pattern of contractile response, the initial depression in left ventricular dP/dt observed in response to cocaine under all conditions was compared with the administration of the local anesthetic lidocaine (2 mg/kg). The initial depression in left ventricular dP/dt was observed with the local anesthetic and was of a magnitude comparable to that observed with cocaine (Figure 6). **Effects of Cocaine on Diastolic Function in the Intact State**

Table 4 depicts the effect of intravenous cocaine (1 mg/kg) on diastolic function. The time constant of isovolumic relaxation was prolonged transiently (1–2 minutes) after cocaine administration but rapidly returned to baseline levels. The early depression in isovolumic relaxation persisted when heart rate was held constant. In contrast, early diastolic filling was enhanced significantly both early (first 1–2 minutes) and later after cocaine administration and was independent of heart rate. The findings of early enhanced filling were consistent with normal ventricular relaxation and an enhanced gradient to ventricular filling associated with elevated left atrial pressures (+8±2 mm Hg, p<0.05). The enhanced early filling is consistent with the main-
tendance of left ventricular end-diastolic volume despite increases in heart rate.

Figure 8 reveals that the end-diastolic pressure–volume relation during cocaine administration (1 mg/kg) was comparable to that observed during an infusion of norepinephrine designed to affect a similar increase in mean arterial pressure. Both agents produced greater increases in end-diastolic pressure relative to volume as the dogs were operating on the steep portion of the relation.

**Discussion**

In the present study, we observed that the myocardial contractile response to acute intravenous cocaine followed a biphasic pattern, i.e., brief initial depression in left ventricular dp/dt observed within the first 2.5 minutes after drug administration followed by significant increases in myocardial contractility that remained elevated during the 30-minute period of observation. The effects were dose dependent. Second, ejection phase indexes of myocardial performance revealed a similar pattern of brief, initial depression within the first 2.5 minutes followed by a return to baseline values over the ensuing 20–25 minutes after 1 mg/kg cocaine. The pattern of ejection phase response closely mirrored the marked changes in afterload associated with acute cocaine administration to which such ejection phase indexes are known to be exquisitely sensitive. The later observation that ejection phase indexes increased in the presence of residual significant afterload is consistent with enhanced ventricular function. In addition, at no time were the indexes of global left ventricular performance, i.e., cardiac output and stroke work, depressed, but rather they demonstrated prompt and sustained increases over the entire period of observation after cocaine administration (1 mg/kg). These increases in both myocardial contractility and left ventricular performance were either abolished completely or markedly attenuated by pretreatment with full autonomic blockade using hexamethonium and atropine methylbromide or β-adrenergic antagonists. However, although the positive inotropic effects of cocaine were abolished by β-blockade, the left ventricular and sys-

| Table 2. Effects of Intravenous Cocaine (1 mg/kg) on Left Ventricular Contractile Function |
|-----------------------------------------------|---|---|---|
| Index                                      | No. of dogs | Baseline | Time after cocaine |
|                                            |              |          | Minimum (early) | Maximum (late) |
| Isovolumic                                 |              |          |                |                |
| LV dp/dt (mm Hg/sec)                       | 10           | 3,086±107 | 2,649±114*     | 3,751±127*     |
| LV dp/dt (mm Hg/sec) (heart rate constant) | 6            | 3,309±172 | 2,830±172†     | 3,708±196†     |
| LV dp/dt/V\text{ed} (mm Hg \cdot \text{sec}^{-1} \cdot \text{mL}^{-1}) | 6            | 56±2     | 49±3†          | 64±3†          |
| Ejection phase                             |              |          |                |                |
| Ejection fraction (%)                      | 6            | 54±2     | 43±3†          | 54±2          |
| Vcf (sec\textsuperscript{-1})              | 6            | 1.49±0.08| 1.25±0.07†     | 1.56±0.08     |
| Stroke work/EDV (g \cdot m/mL)            | 6            | 0.81±0.08| 1.00±0.84†     | 1.07±0.25†    |
| Loading conditions                         |              |          |                |                |
| LV end-systolic stress (g/cm\textsuperscript{2}) | 6           | 133±5    | 221±17*        | 168±11†       |
| LV end-diastolic volume (mL)               | 6            | 50±2     | 54±3           | 51±3          |

LV, left ventricular.

*\textsuperscript{p}<0.01 compared with control.

†\textsuperscript{p}<0.05 compared with control.

**Figure 6.** Plot of the contractile response to intravenous cocaine (1 mg/kg) in the intact state and after full autonomic and β-adrenergic blockades and compared with intravenous lidocaine. The contractile response was significantly (*\textsuperscript{p}<0.01) greater in the intact group than in the other groups. LV, left ventricular.

**Figure 7.** Plot of the temporal relation between the increase in left ventricular (LV) end-systolic wall stress and the velocity of circumferential shortening (Vcf). The peak decline in LV Vcf occurred at the point of the largest increase in end-systolic wall stress. Later, the ejection phase index returned to baseline when end-systolic stress remained elevated.
temic hemodynamic responses persisted. Thus, in conscious chronically instrumented dogs, acute intravenous cocaine (0.1–2 mg/kg) caused transient depression in contractile performance followed by a sustained positive inotropic effect, and at no time was depressed ventricular pump performance observed.

The findings of a positive inotropic effect were in contrast to prior studies in which left ventricular dP/dt was depressed during the administration of much larger (5–15 mg/kg) doses of cocaine.9,12,13 These differences probably were related to our use of chronically instrumented dogs studied in the conscious, unrestrained state in which the full effects of the autonomic nervous system were manifest. Wilkerson19 has shown that pentobarbital anesthesia, which was used frequently in prior studies,9,11–13 dramatically alters the cardiovascular profile of cocaine. In support of this important autonomic influence was the observation in the present study that in response to cocaine the enhanced myocardial contractility was abolished by pretreatment with autonomic blocking agents. Notably, the transient depression in myocardial contractility, which has been observed by others,8,9,12–15 was unaffected by autonomic blockade, consistent with a direct myocardial depressant effect probably related to cocaine’s local anesthetic properties.18 In support of this as the mechanism of the transient myocardial depression was our observation that the time course and extent of impaired contractility were mimicked closely by lidocaine (Figure 6). It is possible that when larger doses of cocaine (5–15 mg/kg) were used in anesthetized experimental models, the local anesthetic effects predominate, as evidenced by global depression in both left ventricular and systemic hemodynamics in these studies.11–14 However, the presence of anesthesia probably biases these prior studies against the positive inotropic effects that we observed. Furthermore, doses of more than 2 mg/kg may be associated with altered elimination kinetics, resulting in much higher, more prolonged plasma cocaine levels.35

With respect to ejection phase indexes, Fraker et al.8 found a significant depression in echocardiographically derived area ejection fraction, which peaked at 1 minute and returned to baseline values within 10 minutes in conscious dogs. These authors concluded that cocaine (4 mg/kg) had a direct myocardial depressant effect. However, they failed to consider that such ejection phase indexes need to be interpreted in the light of profound changes in afterload, which peaked simultaneously with the impaired ejection fraction. Our data demonstrated that a component of the depressed ejection phase indexes observed in the early phase after cocaine administration was related to afterload mismatch. When the ejection phase–afterload relation was examined later (i.e., 5–30 minutes after cocaine), the relation is found to have shifted upward, consistent with enhanced ventricular function. In contrast, Hale et al.12 reported no change in echocardiographically derived estimates of changes in cavity area in anesthetized dogs exposed to large doses of cocaine, but they also observed a decrease in mean arterial pressure. Thus, dose, use of anesthetic, and the load dependence of ejection phase indexes accounted for the differences between the findings and interpretations of these prior studies and the current observations.

We also observed consistent evidence that in contrast to prior studies, cocaine enhanced ventricular performance as assessed by cardiac output and stroke work.9,13,14 The cardiac output response to cocaine was abolished by both selective β- and full autonomic blockades, again suggesting that adrenergic mechanisms were

### Table 3. Effects of Cocaine (1 mg/kg) on Plasma Catecholamines and Renin Activity

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Intact</th>
<th>β-Blockade</th>
<th>Autonomic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5 Minutes</td>
<td>Baseline</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>170±14</td>
<td>299±15*</td>
<td>189±19</td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>109±29</td>
<td>327±51*</td>
<td>142±18</td>
</tr>
<tr>
<td>Plasma renin activity (ng/mL/hr)</td>
<td>0.6±0.2</td>
<td>1.2±0.4</td>
<td>0.6±0.2</td>
</tr>
</tbody>
</table>

*p<0.05 compared with baseline.
†p<0.05 response compared with intact.

### Table 4. Effects of Intravenous Cocaine (1 mg/kg) on Left Ventricular Diastolic Function

<table>
<thead>
<tr>
<th>Index</th>
<th>No. of dogs</th>
<th>Baseline</th>
<th>Minimum (early)</th>
<th>Maximum (late)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time constant isovolumic relaxation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>τ (msec)</td>
<td>6</td>
<td>28.9±1.6</td>
<td>34.5±2.6*</td>
<td>28.0±1.6</td>
</tr>
<tr>
<td>τ (msec) (heart rate constant)</td>
<td>6</td>
<td>26.5±1.4</td>
<td>34.4±3.9*</td>
<td>25.6±1.6</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic stress (g/cm²)</td>
<td>6</td>
<td>114±5</td>
<td>201±17†</td>
<td>153±10†</td>
</tr>
<tr>
<td>End-systolic stress (g/cm²) (heart rate constant)</td>
<td>6</td>
<td>110±7</td>
<td>190±23†</td>
<td>140±9†</td>
</tr>
<tr>
<td>Early diastolic filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+dD/dt (mm/sec)</td>
<td>6</td>
<td>104±14</td>
<td>150±26*</td>
<td>139±13*</td>
</tr>
<tr>
<td>(+dD/dt)/D (sec⁻¹)</td>
<td>6</td>
<td>3.23±0.47</td>
<td>4.30±0.73*</td>
<td>3.97±0.41*</td>
</tr>
<tr>
<td>(+dD/dt)/D (sec⁻¹) (heart rate constant)</td>
<td>6</td>
<td>3.79±0.34</td>
<td>4.26±0.35*</td>
<td>4.13±0.50*</td>
</tr>
</tbody>
</table>

*p<0.05 compared with control.
†p<0.01 compared with control.
tricular filling rate also was consistent with the effects of increases in heart rate and contractility, and probably was important in the maintenance of left ventricular end-diastolic volume and stroke volume in the presence of heart rate increases observed during cocaine administration. Finally, the observation that left ventricular end-diastolic pressure increased to a greater extent than did end-diastolic volume probably is a consequence of the fact that the conscious dog operated on the steep or exponential portion of the diastolic pressure–volume relation. In support of this interpretation was the finding that equippressor doses of norepinephrine resulted in similar diastolic pressure–volume relations, arguing against any significant change in chamber stiffness. Thus, the effects of cocaine on indexes of diastolic function parallel closely the effects on myocardial and left ventricular systolic performance with the dominant effect being enhanced diastolic responses.

The biphasic response to intravenous cocaine administration is in keeping with the multiple pharmacological effects of this drug, including local anesthetic properties, its sympathetic stimulating effects, and its action to prevent presynaptic reuptake of norepinephrine. However, the relative contribution of each of these mechanisms may vary with dose. Perreault et al. have shown that cocaine exerts positive inotropic effects in ferret papillary muscles and that these were associated with increases in intracellular calcium transients that were blocked by β-adrenergic blockade. In contrast, larger doses of cocaine (i.e., >10⁻⁵ M) had negative inotropic effects. Our data demonstrated that the effects of cocaine (1 mg/kg) on contractile indexes were observed even when these indexes were corrected for associated changes in preload to which both dP/dt and stroke work are known to be sensitive. In addition, the peak inotropic effects of cocaine were associated with a marked increase in both plasma norepinephrine and epinephrine, adding further evidence of the role of sympathetic stimulation in the observed response. The greater increase in plasma epinephrine suggested an adrenal medullary contribution to the observed responses. These findings are consistent with similar evidence in rats and monkeys and prior studies in conscious dogs, although results were observed at lower doses. The abolition of both the positive inotropic effects and the plasma catecholamine responses by pretreatment with hexamethonium and atropine suggested that the inotropic effects were mediated primarily by neural adrenergic stimulation. Furthermore, the slight increase in plasma renin activity that we observed was dependent on sympathetic stimulation as the response was inhibited by β - or full autonomic blockade. The findings that the hemodynamic and inotropic responses were abolished by ganglionic blockade are in contrast to the effects in rats and monkeys — where persistent heart rate and blood pressure effects were noted. This difference may be due to species difference, the use of smaller doses in our conscious dogs, or the fact that we used both hexamethonium and atropine to affect complete autonomic blockade. Our findings were supported by the fact that cocaine-induced increases in plasma catecholamines also were blocked by ganglionic blockade. If the observed increases in plasma catecholamines in response to cocaine were a consequence of peripheral reuptake blockade alone, these markers of...
adrenergic stimulation should not have been abolished by ganglionic blockade. However, we cannot conclude from the present studies whether the primary effect of cocaine was due to influences on afferent central nervous system input or direct central nervous system effects but only that autonomic neural influences were an essential mechanism in hemodynamic manifestations of cocaine's cardiovascular effects at moderate doses. In this regard, it is interesting to note that Gillis et al.\textsuperscript{52} have shown that direct injection of cocaine into the central nervous system resulted in sympathetic inhibition, which argues that peripheral mechanisms dominate. However, an equally plausible mechanism may involve interruption of tonic sympathetic inhibition by arterial baroreceptors.\textsuperscript{53,54} Further study will be required to determine the contribution of afferent versus central mechanisms.

**Study Limitations**

In the present investigation, we focused on the contractile and relaxation responses to moderate doses of cocaine rather than on higher doses that have been studied extensively in anesthetized or sedated experimental preparations. Specifically, we were interested in the acute effects of cocaine using single intravenous bolus doses. However, it must be noted that chronic cocaine users characteristically use larger doses administered over several hours rather than single intravenous doses. The doses used in the present study are similar to those that have been used in other acute studies of chronic cocaine users\textsuperscript{22-24} or normal human subjects.\textsuperscript{20,21} It is possible that in the presence of anesthesia, where higher doses of cocaine were required to elicit comparable hemodynamic effects, the relative contributions of local anesthetic and neural adrenergic stimulatory effects of cocaine were altered in favor of its anesthetic properties. Thus, our results are not generalizable to these experimental conditions, nor should the results be extrapolated to conditions in which cocaine has been used or is administered chronically. We did not study the pharmacokinetics of cocaine in these conscious dogs and therefore cannot comment on the association between physiological responses observed and plasma levels of cocaine. However, the time course and the dose-response data reported in the present study are qualitatively similar to prior reports in conscious dogs using comparable doses.\textsuperscript{19,35} In addition, the administration of cocaine by intravenous infusion minimizes absorption differences, and the doses used also were in a range in which first-order elimination kinetics were applicable.\textsuperscript{35} Plasma catecholamines were measured as a correlate of sympathetic stimulation and in conjunction with selective and combined autonomic blockades were consistent with neural adrenergic mechanisms of cocaine's contractile response.

**Acknowledgment**

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