Cholinergic Modulation of the Coronary Vasoconstriction Induced by Cocaine in Conscious Dogs

Richard P. Shannon, MD; Bruce S. Stambler, MD; Kazuo Komamura, MD; Tadashi Ihara, PhD; and Stephen F. Vatner, MD

Background. The effects of cocaine on the coronary circulation were examined in conscious dogs chronically instrumented to measure arterial and left ventricular pressures, coronary blood flow, and arterial and coronary sinus oxygen content.

Methods and Results. With heart rate held constant, the peak effects of cocaine (1 mg/kg i.v.) occurred within 2 minutes, when mean arterial pressure increased by 42±5 mm Hg, coronary blood flow increased by 13±3%, and coronary vascular resistance increased by 24±3%. The arterial oxygen content increased significantly (by 2.8±0.3 vol%), the arterial-coronary sinus oxygen difference increased by 2.5±0.6 vol%, and myocardial oxygen consumption increased by 41±9%. The increase in coronary vascular resistance induced by cocaine was attenuated (p<0.05) in the presence of cholinergic blockade (12±3%) despite a similar increase in MVO$_2$ (49±8%). The increase in coronary vascular resistance was enhanced (p<0.05) in the presence of $\beta$-adrenergic receptor blockade (46±8%), whereas the MVO$_2$ response was less (28±3%). Again, the addition of cholinergic blockade to $\beta$-blockade attenuated the increase in coronary vascular resistance (23±6%) without affecting the increase in MVO$_2$ (25±4%). Combined $\alpha$, $\beta$-, and cholinergic blockades abolished the systemic hemodynamic and coronary vasoconstrictor response to cocaine.

Conclusions. In conscious dogs, cocaine induces coronary vasoconstriction, which competes with coronary vasodilator responses to increases in myocardial oxygen consumption. The mechanisms of cocaine’s coronary vascular effects are mediated via adrenergic stimulation, and the intensity of the vasoconstrictor effects was reduced significantly by cholinergic blockade, in both the presence and absence of $\beta$-adrenergic receptor blockade. (Circulation 1993;87:939–949)

Key Words • myocardial oxygen tension • parasympathetic • coronary vascular tone

The recognition that cocaine causes myocardial ischemia and infarction in otherwise healthy individuals has led to an intense investigation to identify the mechanisms of cocaine’s cardiovascular effects. Previous studies have identified increases in epicardial coronary artery diameter or

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increases in coronary vascular resistance in response to acute challenges with cocaine. These findings have been interpreted to indicate that cocaine predisposes to myocardial ischemia in the face of increases in heart rate and blood pressure. However, these studies have failed to measure myocardial oxygen consumption directly or to examine the effects of cocaine on myocardial oxygen content. As such, the observed effects of cocaine on coronary vascular resistance were probably the sum of competing influences of $\beta$-adrenergically mediated increases in myocardial metabolic demand and direct $\alpha$-adrenergic influences on coronary smooth muscle. However, relative contributions of adrenergic vasoconstriction versus adrenergically mediated increases in metabolic vasodilation have not been investigated. In addition, it is important to consider the influence of parasympathetic withdrawal on the coronary vascular response to cocaine on the basis of previous studies in conscious dogs in which a component of the increase in heart rate in response to cocaine is blocked by atropine. Parasympathetic influences may not only contribute to the metabolic effects of cocaine but also exert direct influence on coronary vascular tone. However, this potential contribution to the coronary vascular effects of cocaine has not been examined and has probably been obscured in experiments conducted under anesthesia. In addition, the magnitude of the parasympathetic effect may be inapparent unless cholinergic blockade is administered in the presence and absence of $\beta$-blockade to control metabolic determinants.
Accordingly, the purpose of the present study was to identify the autonomic influences, both sympathetic and parasympathetic, whereby cocaine exerts its acute coronary vasomotor effects. A secondary goal was to distinguish the competing influences of metabolic vasodilation from direct autonomic influences on coronary vascular tone using combined and selective adrenergic and cholinergic blocking agents. A third goal was to interpret the effects of cocaine on the coronary circulation in the context of cocaine's effects on myocardial oxygen content and consumption. Finally, the effects of intravenous cocaine were compared with those of equiressor doses of norepinephrine to contrast the coronary vascular profile, because it is through norepinephrine that cocaine is thought to exert its primary coronary vascular effects. Importantly, these studies were conducted in conscious, chronically instrumented dogs in which both autonomic influences of cocaine would be manifest. Previous studies that used anesthetized experimental models have required large doses, i.e., 5–15 mg/kg, of intravenous cocaine to elicit significant hemodynamic and coronary vasoconstrictor effects,11,14,17–20 which obscured important autonomic influences.12,21 The use of conscious, chronically instrumented dogs allows the use of much smaller doses of cocaine, which are physiologically and pharmacologically more relevant to those used in acute human studies.15,16,27,28

Methods

Surgical Preparation and Instrumentation

Ten mongrel dogs of either sex (weight, 17–27 kg) were sedated with xylazine (10 mg/kg) and anesthetized with halothane (1–1.5 vol%). By sterile technique and through a left lateral thoracotomy, Tygon catheters were implanted in the descending thoracic aorta and left atrium, and a Silar catheter was implanted in the coronary sinus.29,30 A solid-state miniature pressure transducer (Konigsberg Instruments, Pasadena, Calif.) was implanted in the apex to measure left ventricular (LV) pressure. A Doppler ultrasonic flow transducer was placed around the left circumflex coronary artery for measurement of coronary blood flow. Bipolar pacing electrodes were sutured to the surface of the left atrium as well as the right ventricular free wall. The catheters and wires were tunneled subcutaneously and externalized infrascapularly. The thoracotomy was closed. Dogs received Keuffin for 2–3 days after surgery, during which time catheters were flushed regularly with saline and heparin. Dogs were allowed to recover for 2 weeks after surgery, during which time they were trained to lie quietly on a table. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of Harvard Medical School and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Department of Health and Human Services Publication No. [NIH] 85-23, revised 1985).

Experimental Measurements

Measurements were made according to methods described in References 29 and 31. Aortic and left atrial pressures were measured from the chronically implanted catheters with Statham strain-gauge manometers, which were calibrated with a mercury manometer. The LV pressure was measured with the solid-state miniature pressure gauge (model P22, Konigsberg Instruments) calibrated in vitro with a mercury manometer and in vivo with the left atrial and aortic catheters and Statham strain-gauge manometers. Left circumflex coronary artery blood flow was measured with a Doppler ultrasonic flowmeter that measured velocity in kilohertz. Measurements of arterial and coronary sinus oxygen content were made with a Lex O2 Con (Lexington Instruments, Waltham, Mass.) oxygen analyzer.

Experimental Protocols

Experiments were conducted in conscious dogs 2–3 weeks after surgery. The effects of three doses of cocaine hydrochloride (0.1, 0.5, and 1 mg/kg) were examined. Each dose of cocaine was administered on a separate day by intravenous infusion over 1 minute. Larger doses of cocaine, e.g., 2 mg/kg i.v., resulted in agitation in these conscious, unrestrained dogs; therefore, doses >1 mg/kg were not studied in detail. The effects of cocaine were studied in the intact state with intrinsic heart rate and with heart rate held constant by atrial pacing under the following conditions: 1) with autonomic nervous system intact; 2) after β-adrenergic receptor blockade with propranolol (2 mg/kg); 3) after cholinergic receptor blockade with atropine methylbromide (0.1 mg/kg); 4) after combined β- and cholinergic receptor blockades; and 5) after combined α- and β-adrenergic and cholinergic receptor blockades. A combination of prazosin (1 mg/kg) and phentolamine (2 mg/kg bolus followed by 0.1–0.2 mg·kg⁻¹·min⁻¹ infusions) was used for α-adrenergic receptor blockade. The adequacy of β-adrenergic, cholinergic, and α-adrenergic receptor blockades was assessed by acute challenges with isoproterenol (0.2 μg/kg), acetylcholine (5 μg/kg), and norepinephrine (0.2 μg/kg), respectively. Adequacy of the block was established before and after the administration of cocaine. In a separate series of experiments, the effects of cocaine (1 mg/kg) were compared with equiressor doses of norepinephrine (0.2–0.4 μg·kg⁻¹·min⁻¹) under conditions in which heart rate was held constant. Under all circumstances, changes in myocardial oxygen consumption were measured by simultaneous collection of arterial and coronary sinus blood samples at baseline and 3–5 minutes after the initiation of the respective infusions, during the peak steady-state responses. In a subset of five animals, additional samples for the determination of myocardial oxygen consumption were obtained at 10, 20, and 30 minutes after the infusion of cocaine in the intact state.

Data Analysis

The hemodynamic data were recorded continuously on a multichannel magnetic tape recorder and strip-chart recorder. Mean pressures and mean left circumflex coronary blood flow were derived by use of electronic filters with 2-second time constants. The mean left circumflex coronary resistance was calculated as the quotient of mean aortic pressure and mean left circumflex coronary artery blood flow. A cardiographometer triggered from the aortic or ventricular pressure pulse provided instantaneous and continuous records of heart rate. Continuous records of LV dp/dt were derived from LV pressure signals with operational amplifiers connected as differentiators. A triangular wave signal with
a known slope was substituted for the pressure signal for direct calibration of the differentiator. An index of myocardial oxygen consumption was calculated as the product of oxygen extraction across the heart (i.e., arterial–coronary oxygen difference) and left circumflex coronary blood flow.29 The coronary blood flow measurements by ultrasonic flowmeters were measured in kilohertz and were subsequently converted to measurements of flow (in milliliters per minute) by multiplying the velocity (in kilohertz) times the cross-sectional area of the left circumflex coronary artery obtained at the time of postmortem examination. Segments of the left circumflex coronary artery immediately distal to the implanted flowmeter were used as the reference sample.

Peak coronary vascular responses to both cocaine and norepinephrine were measured at the time of the maximal increase in mean arterial pressure (±1–3 minutes) after the infusion. The peak response was compared with baseline in the same dogs by a Student’s t test for paired comparisons. Differences between the responses of the animals obtained in the intact state and after the combined and selective autonomic blockades were compared by ANOVA and, where required, Bonferroni test to compare groups.32

The time course of the response after intravenous cocaine administration was compared between the intact state and after cholinergic blockade and between β-adrenergic blockade and β- plus cholinergic blockade by repeated-measures ANOVA. All data are reported as mean±SEM. Statistical significance was accepted at p<0.05.

**Results**

**Dose–Response Relation**

The peak effects of three doses of intravenous cocaine (0.1, 0.5, and 1 mg/kg) on systemic, LV, and coronary hemodynamics are detailed in Table 1. There were significant dose-related increases in LV systolic and end-diastolic pressures, heart rate, and mean arterial pressure. LV dP/dt did not change significantly. Left circumflex coronary blood flow and coronary vascular resistance both increased in a dose-related fashion, as did myocardial oxygen consumption.

Figure 1 illustrates the phasic waves during acute infusion of cocaine (1 mg/kg). In the 10 dogs studied in the conscious, unrestrained state, cocaine caused a significant (27±3%, p<0.01) increase in coronary blood flow from 38±3 ml/min that peaked within the first 2 minutes. Coronary vascular resistance increased (p<0.01) promptly by 16±2% and remained significantly elevated during the 30-minute period of observation. Myocardial oxygen consumption increased by 59±5% (p<0.01), consistent with the observed 46±7% (p<0.01) increase in heart rate and blood pressure (47±3%, p<0.01). Of particular interest was the finding that cocaine caused a significant increase (+2.6±0.2 vo2%, p<0.05) in arterial oxygen content from 15.7±0.5 vo2%, which, when coupled with increases in coronary blood flow, contributed to enhanced oxygen delivery (+48±5%, p<0.01). Thus, in the fully intact state, cocaine caused dose-related increases in coronary vasocostriction and significant increases in myocardial oxygen consumption and oxygen delivery associated with increased arterial oxygen content.

**Table 1. Dose–Response Effects of Intravenous Cocaine on Systemic and Coronary Hemodynamics and Myocardial Oxygen Consumption**

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<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Baseline</th>
<th>Change</th>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
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<td>96±7</td>
<td>17±5*</td>
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<tr>
<td>0.5 (n=6)</td>
<td>100±7</td>
<td>32±6*</td>
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<tr>
<td>1.0 (n=6)</td>
<td>90±6</td>
<td>46±2*</td>
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<tr>
<td>Mean coronary blood flow (ml/min)</td>
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<tr>
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<td>33.4±2.6</td>
<td>3.3±1.3*</td>
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<tr>
<td>0.5 (n=6)</td>
<td>33.3±2.7</td>
<td>5.7±1.4*</td>
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<tr>
<td>1.0 (n=6)</td>
<td>33.1±3.1</td>
<td>9.8±1.7*</td>
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<tr>
<td>Mean coronary resistance (mm Hg·ml⁻¹·min⁻¹)</td>
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<td>0.24±0.06*</td>
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<td>0.5 (n=6)</td>
<td>3.06±0.22</td>
<td>0.40±0.10*</td>
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<td>1.0 (n=6)</td>
<td>2.80±0.19</td>
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<tr>
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<td>LV systolic pressure (mm Hg)</td>
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<td>15.7±4*</td>
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<td>LV end-diastolic pressure (mm Hg)</td>
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<td>0.5 (n=6)</td>
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<td>5.0±1.2*</td>
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<td>1.0 (n=6)</td>
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<td>10.1±1.6*</td>
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<tr>
<td>Myocardial oxygen consumption (ml O₂/min)</td>
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<tr>
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<td>1.0 (n=6)</td>
<td>3.90±0.47</td>
<td>2.43±0.35*</td>
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bpm, Beats per minute; LV, left ventricular.

*p<0.05 compared with baseline.

**Mechanisms of the Coronary Vasconstrictor Effects of Cocaine**

Given the marked heart rate response to cocaine in the intact state, subsequent studies to identify the mechanisms of the coronary vasconstrictor effects were conducted with heart rate held constant by atrial pacing. Table 2 depicts the effects of cocaine (1 mg/kg) on coronary hemodynamics in the intact state and after selective and combined autonomic blockades. In the intact state, with heart rate held constant, cocaine caused a peak systemic pressor effect (+41±5%) within 1 minute after infusion with an associated 13±5% (p<0.05) increase in left circumflex coronary blood flow from 45±4 ml/min and a 24±3% increase (p<0.01) in coronary vascular resistance from 23±1 mm Hg·ml⁻¹·min⁻¹. LV dP/dt was unchanged, whereas myocardial oxygen consumption increased by 41±9% (p<0.05) from 4.82±0.63 ml O₂/min.

There was a significant increase in the arterial–coronary sinus oxygen content from 10.4±0.5 to 12.9±0.6 vo2% in response to cocaine. Notably, this
occurred as a consequence of a significant increase in arterial oxygen content, from 15.0±0.6 to 17.8±0.5 vol% (p<0.05), without a significant change in coronary sinus oxygen content.

In contrast, in the presence of cholinergic receptor blockade alone, the left circumflex coronary blood flow response to cocaine (+28±6% increase from 49±5 ml/min) was greater (p<0.01) than that observed in the intact state (+13±3%), whereas the coronary vasoconstric- tor response (+12±3% from 2.5±0.2 mm Hg·ml⁻¹·min⁻¹) was blunted compared with the response in the intact state (+24±3%) (Table 2). The increase in arterial oxygen content (+2.7±0.3 vol% from 14.9±0.6 vol%, p<0.05) was similar to that observed in the intact state, whereas there was a significant increase in coronary sinus oxygen content from 3.9±0.2 to 4.6±0.2 vol% (p<0.05), consistent with the attenuated coronary vasoconstrictor response to cocaine observed in the presence of cholinergic blockade.

To clarify the importance of cholinergic modulation of the coronary vasoconstrictor effects of cocaine, the time course of the changes in mean arterial pressure and coronary vascular resistance was studied in the intact state and after cholinergic blockade alone (Figure 2). Whereas the mean arterial pressure response did not differ significantly over time, the coronary vasoconstrictor response was significantly (p<0.05) more intense in the intact state than the response to the same dose of cocaine after cholinergic blockade. At comparable increases in coronary blood flow in response to cocaine (+25 mm Hg; intact, 20 minutes; with cholinergic blockade, 10 minutes), coronary vascular resistance was significantly greater (p<0.05) in the intact state (+25±6%) than the response observed in the presence of cholinergic blockade (+7±5%) (Figure 3). The greater vasoconstrictor response in the intact state was not attributed to differences in arterial oxygen content or myocardial oxygen consumption responses (Figure 4).

In the presence of β-adrenergic blockade, the systemic pressor response to cocaine tended to be greater (+51±6% increase from 103±6 mm Hg) than the response in the intact state, whereas the increase in left circumflex coronary blood flow tended to be less (+4±3% increase from 43±3 ml/min). However, the coronary vasoconstrictor response to cocaine was significantly enhanced (p<0.05) in the presence of β-blockade (+46±8% increase from 2.5±0.2 mm Hg/ml/min) compared with the response in the intact state (+24±3%). The LV dP/dt response was unchanged.

**Figure 1.** Representative recordings taken from an experiment during which cocaine (1 mg/kg) was administered during a 1-minute period.
The myocardial oxygen consumption response tended to be less in the presence of β-blockade (+28±3% increase from 4.98±0.29 ml O2/min) compared with the intact state. However, whereas the arterial oxygen content increased similarly in response to cocaine (+2.1±0.4 vol% from 15.5±0.5 vol%, p<0.05), coronary sinus oxygen content fell significantly (by 0.6±0.1 vol%) from a baseline of 4.2±0.3 vol% (p<0.05) compared with the response in the intact state, in keeping with the greater coronary vasoconstriction observed in response to cocaine after β-blockade.

In the presence of combined β-adrenergic and cholinergic receptor blockades, the enhanced coronary vasoconstrictor response to cocaine seen in the presence of β-blockade alone was again attenuated (Table 2), despite similar increases in myocardial oxygen consumption. In the presence of combined β- plus cholinergic blockades, the arterial oxygen content increased
FIGURE 2. Graphs showing time course of the mean arterial pressure and coronary vascular resistance (CVR) responses to intravenous cocaine (1 mg/kg) with heart rate held constant in the intact state and after cholinergic blockade (Chol). The CVR response after cholinergic blockade was significantly less (p<0.05) than in the intact state.

by 2.2±0.3 vol%, similar to the increase observed in the presence of β-blockade alone. However, there was no significant change in coronary sinus oxygen content, in contrast to the significant reduction in coronary sinus oxygen content observed in the presence of β-blockade alone. This difference in the response of the coronary sinus oxygen content reflected the fact that the increase in coronary vascular resistance was significantly less in response to cocaine in the presence of combined β- and cholinergic blockade (Figure 5).

The temporal relation of the cholinergic modulation of cocaine's coronary vascular effects in the presence of β-blockade is depicted in Figure 5. Despite similar responses in mean arterial pressure over time, the coronary vasoconstrictor response was significantly (p<0.05) more intense in the presence of β-blockade alone than with β- plus cholinergic blockades. At the common point where mean arterial pressure was increased by 38% (β-blockade, 10 minutes; β- plus cholinergic blockade, 5 minutes), coronary vascular resistance was significantly (p<0.05) greater in the presence of β-blockade (+51±8%) than the response in the presence of combined β- and cholinergic blockades (+24±8%) (Figure 3). This difference could not be attributed to differences in either the arterial oxygen content or the myocardial oxygen consumption response (Figure 4).

The mechanism whereby the cholinergic effects modulate the coronary vasoconstrictor response to cocaine was dependent on the adrenergic influences. When α- and β-adrenergic effects of cocaine were blocked, the modulating influence of cholinergic blockade on coronary vascular resistance (Figure 3) and arterial oxygen content and consumption (Figure 4) was abolished.

Comparison of Effects of Cocaine and Norepinephrine on Coronary Hemodynamics

Given that cocaine is believed to exert its cardiac effects via the adrenergic neurotransmitter norepinephrine, we compared the coronary hemodynamic effects of cocaine (1 mg/kg) with those of norepinephrine with heart rate held constant in the presence of β-blockade to maximize the comparison of α-adrenergic vasoconstrictor effects and to minimize differences in the myocardial oxygen consumption response. In addition, norepinephrine was administered in doses (0.2–0.4 μg·kg⁻¹·min⁻¹) designed to elicit comparable systemic pressor effects (Table 3). Nonetheless, the α-adrenergically mediated coronary vasoconstrictor response to
cocaine was significantly more intense (cocaine, +44±6%; norepinephrine, +19±2%; p<0.01). The difference was due, in part, to greater metabolic vasodilation, since the myocardial oxygen response to norepinephrine tended to be greater. However, the coronary vasoconstrictor effects of cocaine were comparable to those of norepinephrine in the presence of combined β- plus cholinergic blockade (Table 3).

**Discussion**

In the present study, we observed that cocaine administered intravenously to conscious dogs caused a significant increase in coronary vascular resistance in the setting of significant increases in myocardial oxygen consumption. The magnitude of the coronary vasoconstrictor response to cocaine was modified significantly by cholinergic influences; i.e., withdrawal of parasympathetic tone augmented the vasoconstrictor response both in the intact state and in the presence of β-adrenergic blockade. The vasoconstrictor effects were attenuated when cholinergic influences were abolished by pretreatment with muscarinic blockade. In addition, cocaine appears to be a more potent coronary vasoconstrictor than equipressor doses of norepinephrine, but these differences were attributable to differences in myocardial oxygen consumption and to differing effects of these two infusions on cholinergic responses. Finally, cocaine causes significant increases in arterial oxygen content that minimize the need to extract more oxygen from the coronary circulation, except under circumstances in which the α-adrenergically mediated vasoconstriction was enhanced in the presence of β-blockade.

Two important methodological considerations distinguish these findings from the conflicting previously published results in animals, particularly canine models,11–14,17–21 in which the cardiovascular effects of cocaine have been studied. First, all experiments were conducted in the fully conscious, unrestrained state in dogs who were trained to lie quietly on the examining table. This allows for the full manifestations of the effects of cocaine on coronary hemodynamics unaffected by the influences of sedation, anesthesia, or acute instrumentation, which have been shown to alter cocaine's cardiovascular profile.13,21 Furthermore, the effects of cocaine on coronary hemodynamics were interpreted in association with direct measures of myocardial oxygen content and consumption, which allow for a complete profile of the competing influences of autonomic mediated coronary vasoconstriction and met-

**Figure 4.** Bar graphs showing effects of cholinergic modulation on the arterial oxygen content and myocardial oxygen consumption responses to cocaine taken at the same time points as the hemodynamic responses in Figure 3. There were no differences in these metabolic responses to explain the difference in coronary vasoconstrictor potency depicted in Figure 3.

**Figure 5.** Graphs showing time course of the mean arterial pressure and coronary vascular resistance (CVR) responses to intravenous cocaine (1 mg/kg) with heart rate held constant after β-blockade (Beta) and β- plus cholinergic blockades (Beta + Chol). The CVR response after β- plus cholinergic blockades was significantly less (p<0.05) than after β-blockade alone.
Table 3. Comparison of the Effects of Cocaine and Norepinephrine on Coronary Hemodynamics

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<th></th>
<th>Baseline</th>
<th>% Change</th>
<th>Baseline</th>
<th>% Change</th>
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<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Cocaine</td>
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<td>Arterial \text{O}_2 content (vol%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>15.3±0.4</td>
<td>14±2</td>
<td>14.3±0.7</td>
<td>15±1</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>15.0±0.6</td>
<td>5±1*</td>
<td>13.9±0.7</td>
<td>13±3</td>
</tr>
<tr>
<td>Coronary sinus \text{O}_2 content (vol%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>3.8±0.3</td>
<td>1±5</td>
<td>3.5±0.2</td>
<td>13±4</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>3.7±0.3</td>
<td>−15±6*</td>
<td>3.5±0.3</td>
<td>9±7</td>
</tr>
</tbody>
</table>

Chol, cholinergic block; LV, left ventricular; bpm, beats per minute.
*\(p<0.05\) compared with cocaine.

abolorically mediated coronary vasodilation. Such competing influences have been noted previously in response to norepinephrine infusion,\(^{31,33,34}\) sympathetic stimulation,\(^{35,35}\) and exercise.\(^{36}\)

Previous studies that have investigated the influences of cocaine on the coronary circulation in dogs have yielded conflicting results, including observations that cocaine induced increases in coronary blood flow,\(^{12,13}\) decreases in coronary blood flow,\(^{11,18,19}\) or no effect.\(^{14,17,20}\) Similarly, cocaine-induced coronary vasoconstriction has been noted in some\(^{11,13,18,19}\) but not all reports.\(^{14,17,20}\) These discrepancies probably relate to studies conducted under anesthesia or sedation, different methods for measuring coronary blood flow, and use of a wide range of cocaine doses (0.5–10 mg/kg). Furthermore, these studies have failed to consider whether cocaine affects myocardial oxygen content under circumstances in which myocardial metabolic demands were increased significantly and have generally assumed that coronary vasoconstriction implies an inability to meet oxygen demands. Most studies have relied on indirect measures of oxygen consumption that underestimate the influences on myocardial metabolic demand. In this regard, Fraker et al\(^{13}\) found that 4 mg/kg of intravenous cocaine administered to conscious dogs caused increases in coronary blood flow (38%) and coronary resistance (18%) comparable to those observed in the present study, but they used considerably higher doses to achieve these results. However, these authors, without measuring oxygen consumption, suggested that the negative inotropic effects of cocaine offset the associated increases in heart rate and blood pressure, such that oxygen consumption was not altered. In contrast, we observed a 59±5% increase in calculated myocardial oxygen consumption using direct measures of oxygen content across the coronary circulation under circumstances in which heart rate was allowed to vary and a 41±9% increase when heart rate was held constant.

Of note, the findings of cocaine-induced coronary vasoconstriction in the present study are in keeping with recent observations in humans,\(^{15,16}\) although the proposed mechanisms and interpretations of the findings differ significantly. This discrepancy may relate to limitations in the thermodilution technique to accurately assess relatively small changes in coronary blood flow under non–steady-state conditions,\(^{37}\) to different doses and routes of administration, or to potential species differences in the coronary hemodynamic response to cocaine.

In addition, whereas previous studies have demonstrated that the coronary vasoconstrictor effects of cocaine are enhanced in the presence of \(\beta\)-blockade,\(^{16}\) much like the effects reported here, the present study is the first to demonstrate the significant influence of cholinergic mechanisms modulating the vasoconstrictor effects of cocaine. Although most previous studies did not examine the role of parasympathetic mechanisms in mediating cocaine's coronary effects, one study suggested that pretreatment with atropine alone had no
effect on the coronary vascular response to cocaine.\textsuperscript{12} It is important to note that pentobarbital anesthesia was used, which would have obscured cholinergic mechanisms. It is well recognized that pentobarbital anesthesia possesses an important parasympatholytic effect.\textsuperscript{38} In contrast, in the present study, the coronary vasoconstrictor responses to cocaine were greater in the presence of $\beta$-blockade than after combined $\alpha$- and cholinergic blockade (Table 2), and these differences were not attributable to significant differences in myocardial oxygen consumption. Furthermore, an examination of the time course of the response to cocaine in the intact state and after cholinergic blockade alone revealed that the vasoconstrictor response to cocaine was attenuated by cholinergic blockade (Figure 5).

There are several possible mechanisms whereby cocaine may influence parasympathetic activity. These include evidence that cocaine is a competitive antagonist of muscarinic cardiac receptors in rats\textsuperscript{39} and the fact that cocaine may indirectly induce parasympatholytic effects by inhibiting arterial baroreflexes.\textsuperscript{40} In support of this is the finding that heart rate increased despite increases in mean arterial pressure in response to cocaine and that previous studies demonstrated that $\beta$-blockade alone did not abolish the chronotropic response to cocaine.\textsuperscript{22} This raises the interesting possibility that cocaine induces withdrawal of parasympathetic coronary vasodilator tone,\textsuperscript{23,24} resulting in coronary vasoconstriction. Equally plausible is the consideration that the parasympatholytic effects of cocaine are mediated via modulation of sympathetic neurotransmission.\textsuperscript{25,26,41-44} Figure 3 compares the effects of cocaine in the presence of $\alpha$- and $\beta$-adrenergic blockades with the same response in the presence of combined $\alpha$, $\beta$, and cholinergic blockade. If cholinergic influences were exerting a direct effect on coronary vascular tone, then cocaine-related cholinergic effects should result in residual vasoconstrictor responses in the presence of $\alpha$- and $\beta$-adrenergic blockade. However, cocaine caused no significant change in coronary vascular resistance in the presence of $\alpha$- and $\beta$-blockade (Figure 3), suggesting that adrenergic influences were essential to the coronary vasoconstrictor effects of cocaine and that the anticholinergic effects were probably modulating these adrenergic influences rather than exerting direct effects on coronary vascular tone.

In further support of the importance of parasympathetic modulation of sympathetic tone were the comparative vasoconstrictor effects of cocaine relative to equipressor doses of intravenous norepinephrine. It should be pointed out that although the primary mode of cocaine’s cardiovascular effects is thought to be mediated via the sympathetic nervous system and its neurotransmitter, norepinephrine, the effects of infusions of norepinephrine differ in two important ways from those of cocaine. First, norepinephrine possesses potent positive inotropic effects in the doses required to achieve comparable systemic pressor responses, whereas intravenous cocaine depresses myocardial contractility acutely (first 2.5 minutes), reflecting its properties as a local anesthetic.\textsuperscript{15,22} However, the myocardial oxygen consumption response to norepinephrine tended to be greater even in the presence of $\beta$-blockade. Second, intravenous infusion of norepinephrine causes increases in mean arterial pressure and resultant baroreflex activation with its attendant increases in parasympathetic tone, e.g., bradycardia, if heart rate is allowed to vary. This is in contrast to the prominent anticholinergic effects evident in response to cocaine and the resultant tachycardia, which was mitigated but not abolished by $\beta$-blockade alone.\textsuperscript{22} These two important differences in response to intravenous administration of these agents explain the apparently greater potency of cocaine as a coronary vasoconstrictor. Of note, in the presence of $\beta$-adrenergic blockade, the increase in coronary vascular resistance was greater in response to cocaine, but, importantly, the increase in myocardial oxygen consumption was less. However, the differences were no longer apparent under circumstances in which the cholinergic effects were eliminated and myocardial oxygen consumption was controlled, i.e., $\beta$- plus cholinergic blockades. It should be noted that there are important differences in the potency of the cardiac response to intravenous norepinephrine infusion compared with sympathetic stimulation mediated by endogenous norepinephrine release.\textsuperscript{45} It is conceivable that, despite comparable mean arterial pressure responses, the actual neurohormonal activation in the coronary circulation varied considerably between cocaine administration and norepinephrine. However, given that coronary and systemic responses were similar in the presence of $\beta$- plus cholinergic blockades, the degree of $\alpha$-adrenergic stimulation was seemingly comparable with the two infusions. Therefore, the comparison serves to highlight the importance of considerations with regard to both myocardial oxygen consumption and modulating effects of cholinergic influences in interpreting the mechanisms of the vasoconstrictor responses to cocaine.

Finally, an important component of the present investigation was to assess the effects of intravenous cocaine on myocardial oxygen content. Of particular note was the fact that increases in arterial oxygen content were seen after cocaine administration. The mechanism whereby cocaine produces an increase in arterial oxygen content is unknown but may involve an increase in oxygen saturation due to pulmonary effects on ventilation and perfusion or to an increase in hemoglobin concentration and oxygen-carrying capacity. In this regard, it is interesting to note that cocaine caused an increase in arterial oxygen content in all circumstances except in the presence of pretreatment with $\alpha$-adrenergic blockade (Table 2), supporting the notion that the effects of cocaine to increase arterial oxygen content were dependent either on hemodynamic alterations or on $\alpha$-receptor stimulation. These findings are consistent with previous studies that have demonstrated potent influences of $\alpha$-adrenergic stimulation on $V/Q$ match.\textsuperscript{46,47} However, a further definition of the precise mechanism of this observation remains to be elucidated.

The increase in arterial oxygen content after cocaine administration obviated the need to extract additional oxygen from the coronary circulation; therefore, coronary sinus oxygen content did not fall despite significant coronary vasoconstriction in the intact state. Furthermore, in the presence of cholinergic blockade when the coronary vasoconstrictor effects of cocaine were attenuated, coronary sinus oxygen content actually increased. In contrast, in the presence of $\beta$-blockade, the coronary vasoconstrictor effects of cocaine were inten-
sified, resulting in a significant reduction in coronary sinus oxygen content, which was not observed when the coronary vasconstrictor response was reduced in the presence of combined β- and cholinergic blockade. The relation between the intensity of coronary vasoconstriction and the coronary sinus oxygen content is in keeping with the competing influences of adrenergically mediated increases in coronary resistance and metabolic vasodilation that have been reported previously in response to norepinephrine33,34 or left stellate ganglion stimulation.35 However, these previous studies have failed to observe the contribution of increases in arterial oxygen content to the observed findings. This is attributable to the fact that previous studies reported only the partial pressure of oxygen in the arterial samples or used sympathetic stimulation selective to the heart35 or intracoronary administration of norepinephrine,33 which did not elicit the pulmonary and systemic effects observed in the present study.

It is important to consider several differences in our experimental studies that may serve to reconcile these findings with previous reports in both canine models and human studies. First, we administered cocaine acutely via an intravenous route and in moderate doses over 1 minute, which is similar to doses used in acute cardiovascular studies in human subjects15,16 and chronic cocaine users.27,28 Acute doses >2 mg/kg produced unpredictable agitation and dystonia in our conscious, unrestrained dogs. In anesthetized dogs, however, larger doses (5–15 mg/kg) were required to elicit comparable hemodynamic effects, given the dramati-
cally altered cardiovascular profile of cocaine in the presence of anesthesia.12,22 Finally, although the cumulative doses of cocaine used by patients who incurred cardiovascular toxicity are higher than the doses reported here,1,48 it is important to note that the drug is generally consumed over several hours by users and not as a single acute dose. Thus, the use of anesthesia, route and time course of administration, and the chronicity of use may all be factors contributing to these apparent differences. In addition, species differences may influence the contribution of parasympathetic effects to cocaine. However, in most large mammalian and nonhuman primate models, as well as in humans, parasympathetic control of heart rate49 and coronary vascular tone50 has been demonstrated, although the magnitude of these effects may be smaller in humans. Given the important modulating influence of cholinergic mechanisms on the coronary vasoconstrictor effects of cocaine demonstrated here, it will be important to consider these influences both in acute human studies and after chronic exposure to cocaine.

In summary, these studies in conscious, chronically instrumented dogs illustrate the importance of cholinergic modulation of the coronary vasoconstrictor effects of cocaine, which has heretofore gone unrecognized. Furthermore, cocaine causes significant increases in arterial oxygen content without lowering coronary sinus oxygen content further in the presence of significant coronary vasoconstriction. These findings provide important new mechanisms for understanding the acute effects of cocaine on the coronary circulation.

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