Intracoronary Versus Intravenous Effects of Cocaine on Coronary Flow and Ventricular Function

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**Background**  Cocaine use has been associated with cardiomyopathy and ischemic coronary syndromes. However, the pathophysiological mechanisms responsible for these syndromes are not clear and have been suggested to involve direct effects of cocaine on myocyte contractility and coronary resistance as well as indirect effects via altered autonomic tone, secondary mediators, and myocardial metabolism. We sought to distinguish direct from indirect effects of cocaine on ventricular function and coronary resistance by comparison of the administration of intracoronary cocaine (0.12 to 0.36 mg/min constant infusion) with intravenous cocaine (5 mg/kg bolus infusion) in an in vivo anesthetized pig preparation.

**Methods and Results**  To control for changes in coronary resistance secondary to autoregulation and myocardial metabolism, the left anterior descending coronary artery was perfused at constant coronary pressure and the interventricular vein was cannulated for coronary venous oxygen saturation measurement. Coronary blood flow, regional percent segment shortening, myocardial oxygen consumption, and serum cocaine concentrations were measured. Intracoronary cocaine produced a dose-dependent decrease in percent segment shortening in the absence of significant changes in coronary flow or systemic hemodynamics. In contrast, intravenous cocaine had mild biphasic effects on coronary resistance with an initial brief vasodilation (30.0±5% increase in flow from control) followed by more prolonged vasoconstriction (17.0±3.3% decrease in flow from control), which were independent of autoregulation or myocardial metabolism. In addition, intravenous cocaine caused an early 48% decrease in percent segment shortening, at which time the measured cocaine concentration was 20.1 µg/mL blood. This was comparable to the intracoronary cocaine concentration of 17.1 µg/mL blood, which produced a similar 48% decrease in percent segment shortening.

**Conclusions**  We conclude that the effects of acute cocaine exposure on ventricular function are predominantly direct but of brief duration and therefore probably not clinically relevant. The effects of cocaine on coronary tone are predominantly indirect and biphasic, with early vasodilation followed by mild and more prolonged vasoconstriction. In the absence of coronary stenosis or ventricular hypertrophy, this small amount of vasoconstriction is unlikely to cause ischemia. (Circulation. 1994;89:1819-1828.)

**Key Words**  • inotropic agents • microcirculation • perfusion • vasoconstriction • pressure

Increased cocaine use in the United States has resulted in continued reports of cocaine-related cardiomyopathy and ischemic coronary syndromes.1,2 Cocaine cardiomyopathy has been described in many case reports, yet the pathogenesis of this syndrome is largely unexplained.3,4 Cocaine use has been associated with premature coronary stenosis and ventricular hypertrophy, but these have not been prerequisite for myocardial infarction.5-7 In more than 100 reported cases of cocaine-related myocardial infarction, only 2 cases of focal coronary spasm have been observed at coronary catheterization.5,8 Cocaine-related myocardial infarction without fixed coronary artery disease has also been reported in the setting of rhinolaryngolic surgery.9 Controlled conscious human studies demonstrate only modest epicardial coronary constriction without evidence of ischemia.10 Thus, the clinical evidence for a relation between the ischemic syndromes of cocaine and coronary constriction is weak, and the pathophysiology of the inotropic and coronary effects of cocaine remains controversial. It has long been known that cocaine has systemic sympathomimetic effects caused by blocked reuptake of norepinephrine at postsynaptic sympathetic nerve terminals.2 However, in addition to these indirect adrenergic effects, contradictory evidence exists as to whether cocaine also affects the coronary microcirculation and myocardium directly.

Cocaine's direct negative inotropic effect on ventricular function independent of coronary blood flow (CBF) is well established and has been demonstrated in in vitro and in vivo preparations.11-14 Fraker et al11 first described impaired ventricular function secondary to cocaine at a time when CBF was increased in an in vivo preparation. Subsequently, more accurate measurement of left ventricular (LV) contractility independent of loading conditions during cocaine exposure in in vivo conscious dog preparations have confirmed Fraker's findings.15,16 Thus, the existence of a direct negative inotropic effect of cocaine independent of CBF and hemodynamic loading conditions is clear. However, the time course, magnitude, and clinical significance of this direct negative inotropic effect remain incompletely described and controversial.
The direct and indirect effects of cocaine on the coronary circulation are not as well established. In vitro studies show the effect of cocaine on coronary tone to be both concentration- and species-dependent. Coronary constriction with low concentrations (<10^-4 mol/L) and coronary dilation with high concentrations (>10^-4 mol/L) of cocaine have been shown in ferret and pig coronary ring preparations.13,17 Other in vitro pig and human coronary tissue preparations have shown predominantly vasodilation at all concentrations.18 In any case, these studies used large conduit arteries and cannot be easily extrapolated to the coronary microcirculation and blood flow regulation.

In vivo anesthetized and intact preparations that have measured CBF in the microcirculation of dog and pig species show both increased and decreased CBF and resistance responses to cocaine.11,12,16,19 Rarely have these studies controlled for the metabolic and autoregulatory effects of cocaine. Recently, Shannon et al15 controlled for myocardial oxygen consumption in a conscious dog preparation and reported a modest increase in coronary resistance but no change in myocardial oxygen extraction in the presence of increased CBF and perfusion pressure. Several studies have indirectly controlled for coronary perfusion pressure changes without control for oxygen consumption and reported both coronary vasodilation and vasoconstriction in response to intravenous cocaine.20,21 Thus, cocaine-related changes in coronary tone are controversial, and vasoconstriction independent of both myocardial oxygen consumption and autoregulatory effects remains unproven.

The objective of the present study was to distinguish the time course and magnitude of the direct and indirect effects of cocaine on coronary vascular resistance and LV function in a controlled setting. Our approach was to compare the effects of cocaine administered via the intracoronary (IC) route with those of cocaine administered intravenously (IV). Coronary perfusion pressure was held constant and regional myocardial oxygen consumption was determined, enabling us to define the magnitude and time course of the direct and indirect effects of cocaine on coronary tone and LV function independent of autoregulation and metabolic mechanisms.

Methods

Surgical Preparation and Instrumentation

Fifteen domestic swine of either sex weighing 18 to 23 kg were initially sedated with ketamine hydrochloride (25 mg/kg IM) and anesthetized 10 to 15 minutes later, first with sodium thiopental (10 to 15 mg/kg IV), followed by α-chloralose (100 mg/kg IV) and morphine sulfate (30 mg/h SC). Animals were intubated and then ventilated with a positive-pressure respirator (Harvard Apparatus, South Natick, Mass). The level of anesthesia was maintained with bolus doses of α-chloralose (250 to 300 mg IV).

Aortic blood pressure was measured with a strain-gauge manometer through a catheter placed in the aorta via the right femoral artery. LV pressure and dp/dt were obtained by use of a catheter-tip manometer (model 7F, Millar, Houston, Tex) inserted into the LV via the right carotid artery.

The heart was exposed through a midline sternotomy and left thoracotomy in the fourth intercostal space and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected in its proximal portion and then perfused with arterial blood via a Silastic extracorporeal circuit after anticoagulation with sodium heparin (500 U/kg IV). Coronary perfusion pressure was measured continuously and held constant during each experimental run at an initial level approximating mean aortic pressure (70 to 90 mm Hg) by use of a low-pulsation servo-controlled roller pump. CBF was measured with a transit-time flow transducer (Transonics Inc) in the perfusion circuit that was calibrated with blood at the end of each experiment. To allow for coronary venous blood sampling for oxygen saturation, oxygen content, and hemoglobin (OSM 3-Radiometer, Copenhagen, Denmark), the interventricular vein adjacent to the LAD was cannulated with a 20-gauge Teflon and Silastic catheter. Simultaneous coronary artery oxygen saturation, oxygen content, and hemoglobin were obtained from blood in the perfusion line. Oxygen consumption (ml O2 · min^-1 · 100 g ^-1) was calculated by the formula (A − V O2 diff) × CBF/g per fused mass of myocardium, where A is arterial, V is venous, and diff is difference. Oxygen supply (ml O2 · min^-1 · 100 g ^-1) was calculated by the formula (A O2 content) × CBF/g. Regional segment shortening was measured by use of pairs of lensed ultrasonic dimension crystals (2 mm in diameter) placed in both the cannulated LAD (treatment) region and the left circumflex artery (LCX) (control) region at a depth of 6 to 8 mm. Percent segment shortening (%SS) was calculated with the formula (EDL − ESL) × 100/EDL, where EDL is end-diastolic length and ESL is end-systolic length. Samples for plasma cocaine concentration determination were obtained from the perfusion circuit at appropriate times into tubes containing sodium fluoride (7.5 mg). These samples were centrifuged to separate out plasma and frozen at <−10°C until assayed by gas chromatography/mass spectrometry (GC/MS) (see below). At the termination of each experiment, 2 mL monastral blue dye (Sigma Chemical Co, St Louis, Mo) was rapidly injected into the perfusion line. The weight of the dyed portion was used to estimate the mass of the LAD-perfused myocardium for normalization of measured CBF per gram of myocardium.

Cocaine Preparation

Cocaine HCl (Sigma) was dissolved at room temperature to desired concentrations (IV experiments, 5 mg · kg^-1 · 5 mL^-1 and IC experiments, 0.12 to 0.36 mg/mL). Cocaine administered via the IC route was further filtered (0.4 μm) before infusion. Cocaine solutions were prepared just before use and shielded from light to prevent decay.

Cocaine Measurement

Cocaine concentrations were measured by GC/MS. The three-step liquid/liquid extraction of plasma samples used provided a clean extract for analysis by MS.22 After the deuterated internal standard (cocaine-d15, Sigma) was added, the pH of a 1-ML plasma sample was adjusted to approximately 9 by addition of 1 mL of saturated sodium borate. Samples were extracted with 3 mL of organic solvent (toluene/hexane/isooctamyl alcohol 78/20/2 vol/vol/vol) by gentle shaking for 5 minutes. After centrifugation, the organic layer was pipetted off into a clean test tube and back-extracted into 0.5N sulfuric acid by vigorous vortexing. The organic layer was discarded, and the acid layer was made basic by the addition of sodium bicarbonate/potassium carbonate (3/2 wt/wt) and extracted with 150 μL of the organic solvent.

One microliter of the plasma extract was injected into the GC/MS by use of a splitless injection. The mass spectrometer is operated in the electron impact ionization mode. Molecular ion quantification was based on area ratios of the cocaine relative to that of the internal standard. The linear range of this method is 0.200 to 6.00 μg/mL. After preliminary experiments demonstrated that the first time points would contain concentrations of cocaine greater than the linear range, these samples were diluted with water before extraction. The precision of the assay was determined by injecting a control plasma sample on five different days for an N=12. The mean concentration was
8.83±0.38 μg/mL, showing that the day-to-day precision had a coefficient of variation of <5%. The percent error of the method from the range of 6.0 to 0.2 μg/mL was <6% (N=6 at each concentration).

Cocaine serum-to-blood conversion factor was obtained by spiking pig whole blood with cocaine, separating out the plasma, and assaying the plasma by GC/MS. Three different concentrations (5 to 15 μg/mL) were analyzed in duplicate, and the ratio of cocaine in plasma to whole blood was 0.80±0.06.

**Statistical Analysis**

A paired t test with Bonferroni’s correction was used to test for statistical significance between the control value and the response after each intervention in all experimental groups and is indicated in the figures. All confidence intervals represent SEM.

**Experimental Design**

Two groups of experiments were performed. The goal of the first group was to distinguish direct from indirect effects of cocaine by comparison of IC and IV cocaine administration. Five animals were instrumented as above, and each was treated with three or four consecutive doses of IC cocaine followed by one dose of IV cocaine. Thus, group 1 had two subgroups, which will be referred to as “Group 1: IC Cocaine” and “Group 1: IV Cocaine” in the remainder of this article. The goal of the second group was to determine the relation between cocaine-induced changes in myocardial metabolism and changes in CBF. Ten animals were instrumented as above and treated with only IV cocaine. This second group will be referred to as “Group 2: Myocardial Metabolism.”

**Group 1: IC Cocaine**

After control data were collected, IC cocaine was administered through the LAD (treatment) perfusion circuit at doses of 0.12 to 0.36 mg/mL with a Harvard infusion pump at rates of 0.5 to 1.6 mL/min for 6 minutes, which yielded cocaine blood concentrations of 2 to 20 μg/mL in the various animals based on CBF. This dose range was based on pilot studies (n=2) demonstrating no significant response to concentrations <2 μg/mL and the upper values of blood cocaine concentrations (>25 μg/mL) associated with cocaine-related death in humans.30 Variables recorded were heart rate, LV end-systolic and end-diastolic (LVEDP) pressures, dP/dt, coronary pressure, mean and raw CBF, and segment shortening in the LAD (treatment) and LCx (control) coronary beds. The variables were recorded and analyzed with analog records at 0-, 3-, 6-, 10-, 16-, and 24-minute time points. Baseline steady-state flow and function were achieved before repeat IC or IV cocaine was administered. After completion of the highest dose of IC cocaine, coronary artery serum cocaine concentration was measured to assess for the extent of recirculation of drug and was found to be <0.250 μg/mL.

Control IC infusions of vehicle (normal saline) performed at 2 mL/min excluded a possible effect of the infusion rate on CBF measurements. Tachyphylactic and additive effects were excluded by three consecutive 10-minute infusions of IC cocaine (0.36 mg/min) in a pilot study in which no additional effects were observed. Six-minute infusions were sufficient for steady state.

**Group 1: IV Cocaine**

After the last dose of IC cocaine, the animal was allowed to return to baseline steady state for at least 30 minutes. A bolus injection of IV cocaine (5 mg/kg) was then given via the femoral vein. Variables were recorded as above and coronary artery serum cocaine levels determined at 0-, 2-, 4-, 6-, 10-, 16-, and 30-minute time points.

**Group 2: Myocardial Metabolism**

After instrumentation and baseline data were recorded, a bolus injection of IV cocaine (5 mg/kg) via the femoral vein was given. Segment shortening in the LCx coronary bed was not measured. Measurements of serum cocaine levels were performed in five of the animals from group 2, with additional samples taken at 30, 60, and 90 minutes to determine the elimination rate of cocaine during this period. All other variables were recorded as above at 0-, 2-, 4-, 6-, 10-, 16-, and 30-minute time points with the additional simultaneous collection of coronary venous and coronary arterial blood for myocardial oxygen consumption analysis at all time points.

Since the IV experimental runs from group 1 (n=5) and group 2 (n=10) were identical with regard to dose, the data on CBF, %SS, and hemodynamics were combined and presented as a single data set (n=15).

**Results**

**IC Cocaine**

Average values for measured variables in five pigs that were given IC cocaine for 6 minutes at varying concentrations are presented in Table 1 and Figs 1 and 2. Three whole-blood IC cocaine concentrations were calculated on the basis of the infusion concentrations and CBF of the individual animals: low, 4.6±0.4 μg/mL; mid, 9.8±0.4 μg/mL; and high, 15.1±0.8 μg/mL (Fig 1B). IC cocaine administration was associated with minor (<10% baseline) changes in both heart rate and systolic blood pressure at all doses (Table 1).

**IC cocaine caused a significant decrease in LAD %SS at 6 minutes, which was dose dependent in the five animals (Figs 1 and 2B). All %SS LAD decreases were significantly different from %SS LCx (control) at the 6-minute equilibrium time point (Fig 2A). The onset to peak effect on decreased %SS LAD occurred within 6 minutes at all three cocaine concentrations. The recovery from maximum decrease %SS LAD occurred within 10 minutes of stopping the cocaine infusion at all concentrations (Fig 2A). These changes occurred in the absence of decreases in CBF at constant perfusion pressure (Fig 1) or changes in LCx %SS (Fig 2A) during the cocaine infusion. In contrast, CBF at the steady-state 6-minute time was not significantly different from baseline at all IC cocaine concentrations tested (Fig 1A). The only statistically significant change in CBF occurred as a late response 4 minutes after the IC cocaine infusion was completed during the mid and high IC cocaine concentrations (Fig 2B). The decreases in CBF were 9.2±2.4% and 14.4±3.2%, respectively, for mid and high concentrations and returned to baseline control CBF within the subsequent 6 minutes.

**IV Cocaine**

Mean values for 15 pigs (5 from group 1, 10 from group 2) given IV cocaine 5 mg/kg are presented in Figs 3 through 6. Measured cocaine concentrations during the IV cocaine administration are presented in Fig 3. IV cocaine produced a peak increase to 16.1±2.4 μg/mL plasma (20.1 μg/mL whole blood) at 2 minutes, followed by a rapid decrease due to distribution within 6 minutes to 2.9 μg/mL plasma (3.6 μg/mL whole blood). Between 30 and 90 minutes, cocaine was being eliminated from the plasma with a half-life of 50.0±1.3 minutes (n=5).
TABLE 1. Raw Time Course Responses to Intracoronary Cocaine

<table>
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<tr>
<th>Time, min</th>
<th>0</th>
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<tr>
<td>Heart rate, bpm</td>
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<td>89±4</td>
<td>89±4</td>
<td>90±4</td>
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<td>92±5</td>
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<td>LVSBP, mm Hg</td>
<td>92±6</td>
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<td>90±5</td>
<td>90±5</td>
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<td>90±5</td>
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<tr>
<td>LVEDP, mm Hg</td>
<td>6±0.2</td>
<td>6±0.4</td>
<td>6±0.2</td>
<td>6±0.5</td>
<td>6±0.4</td>
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<td>CBF, mL·min⁻¹·g⁻¹</td>
<td>0.79±0.10</td>
<td>0.79±0.08</td>
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<td>31±2</td>
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<td>LVEDP, mm Hg</td>
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<td>CBF, mL·min⁻¹·g⁻¹</td>
<td>0.74±0.07</td>
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<td>LAD %SS</td>
<td>29±3</td>
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<td>Heart rate, bpm</td>
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<td>CBF, mL·min⁻¹·g⁻¹</td>
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<tr>
<td>LAD %SS</td>
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<td>20±3</td>
<td>15±3</td>
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bpm indicates beats per minute; LVSBP, left ventricular systolic blood pressure; LVEDP, left ventricular end-diastolic pressure; CBF, coronary blood flow; and LAD%SS, left anterior descending coronary artery percent segment shortening. Responses to three doses of intracoronary cocaine given during the first 6 minutes: low, 4.6±0.4 µg/mL; mid, 9.8±0.4 µg/mL; and high, 15.1±0.8 µg/mL. There were no significant changes from baseline in heart rate, LVSBP, and LVEDP. *Statistically significant difference from baseline (P<.05).

IV cocaine produced changes in systemic hemodynamics compared with IC cocaine (Tables 1 and 2, Fig 4), resulting in an initial significant decrease in rate-pressure product from control (Fig 4). The CBF response to IV cocaine was biphasic, with an initial brief significant 30.0±5.3% increase followed by a significant 17.0±3.3% maximum decrease, which was more sustained (Fig 5) and still significant at 30 minutes after injection. The %SS LAD was observed to decrease significantly (48%) from control by 4 minutes and return to control by 30 minutes (Fig 5). This was comparable to the IC cocaine concentration of 17.1 µg/mL blood, which produced a similar 48% decrease in %SS (Fig 1A). Regarding ventricular diastolic function, the LVEDP was observed to increase significantly by 4 minutes (Table 2) and return to control by 30 minutes. In comparison, LVEDP did not change with IC cocaine administration (Table 1).

**IV Cocaine: Myocardial Metabolism**

Oxygen content, extraction, and consumption data in 10 pigs given only IV cocaine 5 mg/kg are shown in Figs 5 through 8. An early significant increase in coronary venous oxygen content was observed, followed by a later significant decrease in coronary venous oxygen content at 10 minutes (Fig 6A). In contrast, the coronary artery oxygen contents did not change significantly from control. The coronary artery to coronary vein oxygen content difference was significantly decreased at 2 minutes and significantly increased at 10 minutes (Fig 6B). Analysis of oxygen consumption and supply relative to their control values demonstrated changes from control at the 2-, 4-, 6-, and 10-minute time points, all of which were significant (P<.05, Fig 7).

A "supply/demand" plot of coronary vasomotion was performed to analyze the effects of cocaine on CBF. In this plot, which is a modification of the plot of CBF versus myocardial oxygen consumption of Ekhenhoff et al, oxygen supply is plotted against oxygen consumption, resulting in a series of "isoeXtraction" lines representing changes in oxygen supply and myocardial oxygen consumption. This allowed us to interpret changes in CBF relative to the myocardial metabolism at various times. Vectors to the left of an initial isoeXtraction line represent relative coronary vasodilation, and vectors to the right indicate relative coronary vasoconstriction. The early vasodilatory and later vasoconstrictive effects of cocaine are demonstrated in Fig 8A. IV cocaine 5 mg/kg caused vasodilation at the early 2-minute time, as depicted by the upward vector perpendicular to the isoeXtraction line. This represented an increase in CBF despite a concurrent decreased oxygen consumption stimulus for decreased CBF. The 4-minute vector is nearly parallel to the original isoeXtraction line and therefore represents a transition between vasodilation and vasoconstriction in which the change in CBF can be accounted for by changes in myocardial oxygen consumption. At 6 minutes, the vertical down vector represents pure coronary vasoconstriction independent of metabolic effects. The 10-minute vector is perpendicular to the isoeXtraction line and thus represents vasoconstriction. Here CBF decreased de-
Fig 1. Graphs showing the effects of 6 minutes of intracoronary (IC) cocaine at various concentrations on percent segment shortening (%SS) and coronary blood flow (CBF) as depicted by linear regression analysis (top) and grouped analysis (bottom) in 5 animals from group 1. Coronary flow was independent of cocaine concentration. Segment shortening decreased proportionately to cocaine concentration (*P<.007 compared with baseline response at the depicted concentration point). LAD indicates left anterior descending coronary artery.

Fig 2. Graphs showing effect on percent segment shortening (%SS, top) and coronary blood flow (CBF, bottom) at three concentrations of intracoronary (IC) cocaine (lo, 4.6±0.4 μg/mL; mid, 9.8±0.4 μg/mL; hi, 15.1±0.8 μg/mL) over time in five animals from group 1. CBF was significantly decreased from baseline in the mid and hi concentration groups at the 10-minute point (*P<.02). %SS was significantly decreased from both baseline and left circumflex coronary artery (CX) control at all concentrations at 6 minutes (*P<.007). LAD indicates left anterior descending coronary artery.

Despite an increased oxygen consumption stimulus for increased CBF, the 16-minute vector is nonsignificant and smaller than the 6-minute vector but is once again in the vertical down position, suggesting pure vasoconstriction independent of metabolic effects. At 30 minutes, mild nonsignificant metabolically induced vasodilation is evident because of a relatively greater decrease in oxygen consumption than oxygen supply. In summary, over times of 2 to 30 minutes, the vectors rotated between vasodilation and vasoconstriction. There was evidence for early significant vasodilation at 2 minutes and later significant vasoconstriction at 6 to 10 minutes independent of and at times despite the effect of cocaine on oxygen consumption.

Discussion
There are several significant findings from the current study: (1) Cocaine had no detectable direct effect on CBF during cocaine administration. (2) There was a modest biphasic indirect effect on CBF independent of coronary perfusion pressure or myocardial oxygen consumption assessed over a 30-minute time course. (3) Cocaine had a brief direct depressive effect on LV function.

LV Function
In agreement with prior studies, our results clearly show that decreased LV function associated with both IC and IV cocaine occurs independent of changes in CBF. \cite{11,13,26} In the IC cocaine group, %SS decreased in a dose-dependent linear fashion, whereas CBF was unchanged (Fig 1A and 1B). Likewise, in the IV cocaine group, CBF was increasing simultaneously with the significant decrease in %SS (Fig 5). The majority of the effect on function appeared not to be secondary to indirect hemodynamic effects. Evidence for this was...
seen during IC cocaine administration, when decreases in %SS occurred in the absence of significant hemodynamic changes (Table 1). Furthermore, similar decreases of %SS were found at comparable cocaine levels with either IC or IV administration (Figs 1, 3, and 5). However, the hemodynamic changes associated with IV cocaine were possibly responsible for the more prolonged decrease in %SS seen in the IV group (Fig 5). These findings agree with prior work by Pagel et al,15 who used adrenergic and cholinergic blocking agents to show that cocaine had a brief negative inotropic effect independent of hemodynamic loading conditions. Our study extends these findings by establishing that the negative direct effect of cocaine on LV function is linear over a large range of tested concentrations and is independent of coronary perfusion pressure and CBF changes.

The mechanism responsible for the negative inotropic effect of cocaine is unclear from the present study but has been postulated to be secondary to membrane anesthetic effects.2 Whatever the cause, it remains unclear whether the negative inotropic effect is clinically significant. The rapid recovery response after IC cocaine (Fig 2B) observed in our study would support the view, suggested by a recent study by Shannon et al,16 that the negative inotropic effect of cocaine is not clinically significant. Under usual circumstances present in the conscious state, augmentation of sympathetic tone or changes in loading conditions may overcome the direct depressant effect of cocaine. It remains possible, however, that with repetitive or chronic cocaine use, decreased contractility would be sustained and contribute to cardiomyopathy.

Coronary Flow

In contrast to the effects of cocaine on LV function, there was no observed direct effect of IC cocaine on CBF at constant coronary perfusion pressure during any of the tested infusion concentrations. A mild late decrease in CBF of 15.4±3.2% occurred well after the IC cocaine infusion was stopped. The mechanism of this response is not clear. It is possible that this represented a delayed response to cocaine not apparent in the 6-minute infusion period. However, in our pilot studies, 6 minutes was sufficient for steady state, and an increase to 10 minutes was without additional effect. It is also conceivable that the decrease in CBF was a response to very low levels of cocaine due to recirculation in the IC experiments and redistribution in the IV experiments. This dose-dependent effect has been reported to be a characteristic of some local anesthetics.22 Evidence arguing against this possibility is shown in Fig 1A, which shows that IC cocaine concentrations <5 μg/mL were
not measured in this experimental group. Arguing against this possible explanation is the observation that %SS had nearly returned to baseline control levels by the time of late decreased CBF. One last possibility would be the presence of cocaine metabolites. Benzoylcegonine and ethyl methyl ecgonine have been shown to appear 30 to 60 minutes after IV cocaine infusion.28 However, because of the low dose of IC cocaine and time course of late decreased CBF, this seems unlikely. We are thus unsure as to the explanation for the observed late decreased CBF at the present time; however, its magnitude was small, and it was unlikely to represent the mechanism of clinical cocaine-related ischemia.

The observation of a mild late coronary constriction observed during IV cocaine is in accord with several prior studies. Hayes et al 19 measured CBF with microspheres 30 minutes after 1 to 9 mg/kg IV cocaine exposure in an angiographic study on anesthetized dogs. They reported a decrease in CBF at this latter time point of 23% after IV cocaine 10 mg/kg. A recent perfused septum preparation by Morcos et al 21 performed at constant coronary pressure conditions described mild coronary vasoconstriction after 30 minutes

Table 2. Raw Time Course Responses to Intravenous Cocaine

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<tr>
<th>Time, min</th>
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<th>2</th>
<th>4</th>
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<td>Heart rate, bpm</td>
<td>95±4</td>
<td>84±5</td>
<td>83±4*</td>
<td>89±4</td>
<td>92±4</td>
<td>95±4</td>
<td>93±5</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>83±5</td>
<td>69±4*</td>
<td>76±7</td>
<td>85±7</td>
<td>97±6</td>
<td>90±5</td>
<td>76±4</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>5±3</td>
<td>8±7</td>
<td>9±8*</td>
<td>8±8</td>
<td>6±5</td>
<td>6±5</td>
<td>5±3</td>
</tr>
<tr>
<td>CBF, mL·min⁻¹·g⁻¹</td>
<td>.77±.05</td>
<td>.95±.05*</td>
<td>.64±.04*</td>
<td>.68±.04</td>
<td>.69±.05</td>
<td>.70±.05</td>
<td>.69±.05</td>
</tr>
<tr>
<td>LAD %SS</td>
<td>26±1</td>
<td>18±2</td>
<td>15±2*</td>
<td>17±2</td>
<td>22±2</td>
<td>23±2</td>
<td>24±1</td>
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</tbody>
</table>

bpm indicates beats per minute; LVSP, left ventricular systolic blood pressure; LVEDP, left ventricular end-diastolic pressure; CBF, coronary blood flow; and LAD%SS, left anterior descending coronary artery percent segment shortening. Responses to intravenous cocaine 5 mg/kg in 15 animals (except LAD%SS, which was 10 animals because of technical problems). *Statistically significant difference from baseline (P<.05).
of perfusion with as high as $10^{-3}$ mol/L cocaine solution. It is possible that this mild coronary constriction corresponds to the later decreased CBF observed between 6 and 16 minutes in our in vivo preparation. Studies performed on humans using intranasal cocaine 2 mg/kg have consistently shown mild decreases in CBF of 16% baseline as measured by coronary sinus thermodilution techniques. In agreement with our findings of late increased coronary resistance, the peak decrease in flow occurred 15 minutes after intranasal cocaine exposure. An early increase in flow was not reported in these studies, perhaps secondary to the low dose of cocaine used.

The observation of a late IV cocaine-induced decreased CBF despite a metabolic stimulus for increased flow can be explained by several possible mechanisms. First, this may reflect two competing influences on coronary tone with indirect cocaine-related vasoconstriction competing with metabolic-induced vasodilation. Alternatively, this observation may be due to a dissociation of the normal link between myocardial oxygen consumption and coronary tone. Cocaine may impair either the signal or reception of the signal for myocardial oxygen consumption-induced vasodilation and thereby result in a “coronary paralysis.” Evidence for this has been seen previously by Fraker et al, who observed an unexplained dissociation in rate-pressure product and CBF in a dog preparation given IV cocaine. Our data support this concept at both the early vasodilation and later vasoconstriction time periods, when flow changed despite metabolic stimuli. This later vasoconstriction could therefore represent a period of myocardial vulnerability to ischemia caused by an inability of the coronary microvasculature to react to increased myocardial consumption. Further experimentation will be necessary to distinguish these possible mechanisms.

Our findings of an early coronary vasodilation response to IV cocaine are in agreement with a prior in vivo study by Friedrichs et al that also controlled for coronary perfusion pressure. This study exposed anesthetized beagles to IV cocaine (0.4 to 10 mg/kg) while maintaining constant CBF. Measured coronary pressure was found to decrease 65% from control after the high dose of IV cocaine. When CBF was allowed to vary, it increased 175% from control 60 seconds after administration. It was concluded that cocaine caused dose-dependent coronary vasodilation. Consideration of later time course effects was not performed in their study. As an anecdote, it was mentioned that a single dog was given an unspecified dose of IC cocaine, with equivalent coronary dilation observed.

The early vasodilation we observed is in disagreement with conclusions from a recent study by Shannon et al. They measured changes in myocardial oxygen consumption and CBF in a conscious dog preparation subjected to 1 mg/kg IV cocaine. They observed an early increase in CBF at 2 minutes, but they concluded that coronary constriction was present because of an increased difference in measured coronary sinus and arterial oxygen contents due entirely to an unexplained increase in arterial oxygen content. Given the concomitant increased systolic blood pressure response to cocaine, it was concluded that the early increase in CBF represented coronary vasoconstriction independent of myocardial oxygen consumption. However, when these data are analyzed by the technique of Mohrmon et al described above, the vector describing the effects of cocaine on supply versus demand is nearly parallel to the initial isoeastension line (Fig 8B). This suggests that the observed changes in CBF at the time oxygen saturation was measured were largely explained by an increase in myocardial oxygen consumption. Interestingly, only with norepinephrine given IV alone (Fig 8B) did a vector significantly cross an isoeastension line, indicating a partial primary coronary constrictive effect. Thus, a primary change in coronary tone independent of myocardial oxygen consumption was not apparent at this time of early increased CBF when analyzed in this fashion. A similar analysis of the data from our preparation over a 30-minute time course (Fig 8A) demonstrates that the early (2-minute) increase in CBF corresponding to the time assessed by Shannon et al was secondary to pure coronary vasodilation despite a decreased oxygen consumption. Only at later times (6 to

Fig 8. Supply/demand diagrams showing oxygen (O2) consumption-supply vectors at various times after intravenous cocaine 5 mg/kg in 10 animals from group 2 (top) and oxygen consumption-supply vectors determined from data presented by Shannon et al (bottom) obtained within 2 minutes of (1) intravenous cocaine 1 mg/kg, (2) cocaine 1 mg/kg plus β-blocker, (3) cocaine 1 mg/kg plus cholinergic blocker, (4) cocaine 1 mg/kg plus α-blockade plus cholinergic (chol) blockade, and (5) norepinephrine alone.
10 minutes) was a true vasoconstriction independent of metabolism apparent (Fig 8A).

Previously reported variability in the coronary vascular resistance effects of IV cocaine has been ascribed to differences in preparations with regard to conscious versus anesthetized, type of anesthetic, and species studied. An additional source of variability suggested by our results is failure to consider effects of metabolic regulation on CBF. The biphasic nature of this response adds yet another element of variability to coronary resistance measurement. Thus, both metabolic influences and the timing of sample measurement during the first 4 minutes after cocaine administration are critical to interpretation of the effects of cocaine on coronary tone.

There are several possible explanations for the biphasic CBF response observed with IV but not IC cocaine. First, in vitro studies have reported that adrenergic blockade can influence the effects of cocaine on coronary vascular tone. Increased adrenergic activity has therefore been proposed as an explanation for the effect of cocaine on coronary tone. Also, in vitro evidence suggests that a direct vasodilatory effect of cocaine is apparent at 10^{-4} M (30 μg/mL) concentrations. It is therefore possible that the biphasic coronary resistance response to IV cocaine can be explained by competing influences of high-dose direct membrane anesthetic (vasodilation) and low-dose indirect sympathomimetic (vasoconstriction) effects of cocaine. Absence of effect with high doses of IC cocaine (20 μg/mL) in our study argues against this theory; however, it is feasible that cocaine levels during the initial distributive phase of our intravenous bolus injection were >20 μg/mL. It is thus conceivable that IC cocaine at concentrations greater than 30 μg/mL (not tested in our IC preparation) would have produced vasodilation.

Alternatively, the biphasic CBF response observed with IV but not IC cocaine could be due to the presence of one or more vasoactive blood-borne substances. It is possible that serotonin, because of its dual vasoconstrictive and vasodilatory properties (HT₁, versus HT₂, receptor effects) and release from platelets that aggregate in response to cocaine and norepinephrine, may be involved. However, other vasoactive mediators capable of this degree of coronary constriction, such as thromboxane and norepinephrine, are known to be present after cocaine administration. If in future work vasoactive substances are found to be involved in the CBF response described above, a primary prothrombotic state with secondary release of vasoactive substances might better account for the clinical ischemic syndromes associated with cocaine abuse.

Whatever the mechanism for the vasoconstriction in this animal preparation, the observed magnitude of the change in coronary resistance is not likely to completely account for the observed clinical ischemic syndromes associated with cocaine abuse. The use of general anesthesia in this preparation had the potential to blunt some of the indirect effects of cocaine on coronary resistance. Thus, in conscious preparations, one might expect coronary vasoconstriction to have been greater. However, in conscious preparations that measure oxygen consumption, the magnitude of coronary vasoconstriction independent of metabolism appears to be quite small early after IV cocaine (Fig 8B). Thus, both conscious and anesthetized studies indicate that coronary vascular resistance changes secondary to cocaine appear to be too mild to cause ischemia. It is possible that in the presence of minimal coronary atherosclerosis, which has been shown to alter coronary vasoconstrictive responses, the response to cocaine could be potentiated. Both myocardial hypertrophy and premature coronary atherosclerosis have been associated with chronic cocaine use and could, in addition to acute mild vasoconstriction, contribute to clinical ischemia.

**Limitations**

This preparation had both advantages and disadvantages. Its primary advantage was that it provided a highly controlled means of assessing the complex coronary vascular, inotropic, metabolic, and hemodynamic effects of acute cocaine administration. Also, use of the pig has the advantage of its having essentially no collateral coronary circulation, which may confound studies in dogs. The primary disadvantage of our preparation is that anesthesia was used, which probably blunted part of the indirect hemodynamic effect of IV cocaine. This may have resulted in higher doses of cocaine being required to produce the measured effects as previously described by Fraker et al. To minimize the effects of anesthetic on the sympathetic nervous system, α-chloralose anesthesia was used. Although the doses of cocaine were higher than those in conscious studies, they appeared to be clinically relevant on the basis of our measured cocaine levels, which correlate with cocaine serum concentrations measured in autopsy studies taken well after the victim was exposed to cocaine. Also, cocaine is commonly used as a topical agent during human rhinolaryngologic surgery under anesthetized conditions at doses exceeding 400 mg. Last, the surgery that was required to instrument the animal required dissection of the proximal LAD, which could have impaired its sympathetic innervation. However, it is unlikely that this could have accounted for our results of a clear vasoconstriction when cocaine was given IV but not IC.

**Summary**

The above results demonstrate that cocaine causes direct decreases in contractile function that are sustained for the duration of exposure but rapidly recover after cocaine is removed. This argues against the clinical significance of the observed negative inotropic effect. Conversely, over a wide range of doses, cocaine has minor direct effects on coronary vascular resistance. When it is given IV, the effects of cocaine on coronary tone are predominantly indirect and biphasic in nature, with early brief vasodilation followed by more sustained vasoconstriction independent of metabolic changes. The magnitude of this later effect is small and thus unlikely to be clinically significant in individuals without coronary disease or myocardial hypertrophy.

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References

Intracoronary versus intravenous effects of cocaine on coronary flow and ventricular function.

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