Effects of the Intracoronary Infusion of Cocaine on Left Ventricular Systolic and Diastolic Function in Humans

William R. Pitts, MD; Wanpen Vongpatanasin, MD; Joaquin E. Cigarroa, MD; L. David Hillis, MD; Richard A. Lange, MD

**Background**—In dogs, a large amount of intravenous cocaine causes a profound deterioration of left ventricular (LV) systolic function and an increase in LV end-diastolic pressure. This study was done to assess the influence of a high intracoronary cocaine concentration on LV systolic and diastolic function in humans.

**Methods and Results**—In 20 patients (14 men and 6 women aged 39 to 72 years) referred for cardiac catheterization for the evaluation of chest pain, we measured heart rate, systemic arterial pressure, LV pressure and its first derivative (dP/dt), and LV volumes and ejection fraction before and during the final 2 to 3 minutes of a 15-minute intracoronary infusion of saline (n = 10, control subjects) or cocaine hydrochloride 1 mg/min (n = 10). No variable changed with saline. With cocaine, the drug concentration in blood obtained from the coronary sinus was 3.0 ± 0.4 (mean ± SD) mg/L, similar in magnitude to the blood cocaine concentration reported in abusers dying of cocaine intoxication. Cocaine induced no significant change in heart rate, LV dP/dt (positive or negative), or LV end-diastolic volume, but it caused an increase in systolic and mean arterial pressures, LV end-diastolic pressure, and LV end-systolic volume, as well as a decrease in LV ejection fraction.

**Conclusions**—In humans, the intracoronary infusion of cocaine sufficient in amount to achieve a high drug concentration in coronary sinus blood causes a deterioration of LV systolic and diastolic performance. *(Circulation. 1998;97:1270-1273.)*

**Key Words:** cocaine ■ ventricles ■ systole ■ diastole

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In dogs, a large amount of intravenous cocaine (4 to 10 mg/kg) causes a worsening of left ventricular (LV) systolic function (decline in LV dP/dt<sup>1,2</sup> and ejection fraction<sup>1,4,5</sup>) and a rise in LV end-diastolic pressure.<sup>2,3</sup> In contrast, in humans, a small amount of intranasal cocaine (2 mg/kg) induces a modest increase in LV contractility, as reflected by the first derivative of LV pressure (dP/dt),<sup>5</sup> and LV end-diastolic pressure is unchanged. The influence of a large amount of cocaine on LV systolic and diastolic performance in humans is unknown.

In previously published studies,<sup>6</sup> we showed that the intracoronary infusion of cocaine in humans (1) was safe, (2) caused no change in coronary arterial blood flow, and (3) allowed us to achieve a large “local” (intracoronary) cocaine concentration, similar in magnitude to that reported in cocaine abusers dying of intoxication, with minimal systemic effects. With this in mind, we designed the present study to assess the effects of a direct intracoronary infusion of cocaine on LV systolic and diastolic performance in humans. On the basis of previously published data from anesthetized and conscious dogs,<sup>1,4-6</sup> we hypothesized that the attainment of a high intracoronary cocaine concentration would cause a substantial deterioration of LV systolic function (dP/dt and ejection fraction) as well as an increase in LV end-diastolic pressure.

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**Patient Population**

We studied 20 patients (14 men and 6 women aged 39 to 72 years) undergoing cardiac catheterization for the evaluation of chest pain. None had an unstable cardiac condition or other acute medical illness, active congestive heart failure, or valvular heart disease, and none admitted to previous cocaine use. Patients with ≥50% luminal diameter narrowing of the left main coronary artery were not enrolled in the study. The protocol was approved by the Human Subjects Review Committee of the University of Texas Southwestern Medical Center, and all subjects gave written informed consent. Medications that could influence LV function (β-adrenergic blockers, calcium antagonists, and long-acting nitrates) were discontinued ≥12 hours before study. All subjects were studied in the fasting state after premedication with oral diazepam 5 to 10 mg.

**Experimental Protocol**

Under local anesthesia with marcaine, an 8F sheath was inserted percutaneously in the right femoral artery, through which a Judkins catheter was advanced to the ostium of the left coronary artery. A single angiogram was performed with nonionic contrast material to exclude left main coronary artery disease, after which the catheter was removed. After infiltration with marcaine, a 6F sheath was inserted percutaneously in the left femoral artery, and a cutdown was performed in the right antecubital fossa for isolation of a basilic vein. An 8F Goode-Lubin catheter was advanced to the coronary sinus via the right basilic vein; its position was confirmed fluoroscopically and oximetrically, and it was secured in place for the duration of the study. A 7F micromanometer-
A tipped pigtail catheter (Millar Instruments) was advanced to the left ventricle via the right femoral artery, and a 6F Judkins catheter was advanced to the ostium of the left coronary artery via the left femoral artery. Systemic arterial pressure was measured through the side-port extension of the right femoral arterial sheath, and heart rate was determined electrocardiographically.

Once all catheters were positioned appropriately, heart rate, systemic arterial pressure (phasic and mean), and LV pressure and its first derivative (dP/dt) were recorded, and single-plane left ventriculography was performed in the 30° right anterior oblique projection with 50 to 55 mL of nonionic contrast material. Then, 15 minutes was allowed to elapse so that all variables returned to baseline. Each patient was then randomly assigned to receive a 15-minute intracoronary infusion of saline (group 1, control subjects, n = 10) or cocaine hydrochloride (10% solution at 1 mg/min; total dose, 15 mg) (group 2, n = 10). During the final 2 to 3 minutes of the 15-minute intracoronary infusion, hemodynamic measurements and left ventriculography were repeated, and blood was procured from the femoral artery and coronary sinus for measurement of cocaine concentration. Subsequently, each subject received nitroglycerin 0.4 mg sublingually, and selective coronary angiography was completed.

Statistical Methodology
All results are reported as mean ± SD. The two groups were compared with Student’s t test. Within each group, the changes induced by saline or cocaine were assessed with a repeated measures ANOVA. For all analyses, a value of P < .05 was considered significant.

Results
The two groups were similar in age, sex, extent of coronary artery disease, and LV ejection fraction (Table). Among the hemodynamic variables at baseline, only LV -dP/dt differed between the groups.

Intracoronary saline (n = 10) induced no change in any variable (Table). Intracoronary cocaine (n = 10) resulted in an average cocaine concentration in coronary sinus blood of 3.0 ± 0.4 mg/L and in systemic (femoral arterial) blood of 0.17 ± 0.06 mg/L. Of the hemodynamic and ventriculographic variables measured, heart rate, LV dP/dt (positive and negative), and LV end-diastolic volume did not change with cocaine. Systolic and mean arterial pressures, LV end-diastolic pressure (Fig 1), and LV end-systolic volume all increased, and LV ejection fraction fell (Fig 2).

Discussion
In the present study, a high intracoronary cocaine concentration in humans, achieved via a direct infusion into the left coronary artery, exerted a deleterious effect on LV systolic and diastolic performance. Intracoronary cocaine induced no significant change in heart rate, LV dP/dt (positive or negative), or LV end-diastolic volume (Table). At the same time, it caused systolic and mean arterial pressures, LV end-diastolic pressure, and LV end-systolic volume to rise (Table, Fig 1) and LV ejection fraction to fall (Fig 2).

In previously published studies in dogs, a large dose of intravenous cocaine (4 to 10 mg/kg) caused an immediate and profound decrease in LV contractile performance2,3 and ejection fraction3,4 as well as an increase in LV end-diastolic pressure.2,3 In anesthetized dogs, the intravenous infusion of cocaine (0.5 mg · kg⁻¹ · min⁻¹) increased systemic arterial pressure and LV end-diastolic pressure and decreased LV ejection fraction3,4; heart rate, LV dP/dt, and coronary arterial dimensions were unchanged. In a similar experimental preparation (anesthetized dogs) in which heart rate and systemic arterial pressure were held constant, cocaine 0.25 mg · kg⁻¹ · min⁻¹ IV caused a fall in positive and negative LV dP/dt and a rise in LV end-diastolic pressure,1 suggesting that the drug had direct cardiotoxic effects. Also in anesthetized dogs, Hale
Cocaine and LV Function in Humans

Hemodynamic Variables at Baseline and 15 Minutes After Administration of Saline or Cocaine

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Mean ± SD 52 ± 6 | 77 ± 18 | 77 ± 19 | 132 ± 16 | 131 ± 19 | 93 ± 13 | 92 ± 14 | 22 ± 8 | 23 ± 8 | 1329 ± 276 | 1358 ± 264 | −1417 ± 306 | −1417 ± 288

Cocaine

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Mean ± SD 53 ± 10 | 77 ± 15 | 81 ± 17 | 138 ± 21 | 148 ± 20* | 100 ± 15 | 108 ± 14* | 15 ± 7 | 22 ± 9 | 1568 ± 359 | 1578 ± 453 | −1822 ± 274 | −1807 ± 262

CAD indicates coronary artery disease (≥70% luminal diameter narrowing); HR, heart rate; BL, baseline; SAP, systolic arterial pressure; MAP, mean arterial pressure; LV, left ventricular; EDP, end-diastolic pressure; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction.

*P < .03 compared with baseline; †P > .001 compared with baseline; ‡P > .003 compared with cocaine group.

et al compared the effects of an intravenous bolus of cocaine (10 mg/kg) with those of a 10-minute intravenous cocaine infusion (10 mg/kg). Both preparations induced a decrease in LV dP/dt, an increase in echocardiographically determined LV diastolic and systolic dimensions, and an increase in LV end-diastolic pressure. More recently, Fraker et al gave intravenous cocaine (4 mg/kg) to conscious and sedated dogs. In conscious dogs, heart rate and systemic arterial pressure rose, and echocardiographically determined regional LV ejection fraction fell precipitously. In sedated dogs, heart rate and systemic arterial pressure did not change; nonetheless, LV ejection fraction fell dramatically. In short, large amounts of intravenous cocaine in anesthetized and conscious dogs, resulting in peak blood concentrations of 3.5, 4.1, and 7.5 mg/L, caused a substantial deterioration of LV systolic performance as well as a rise in LV end-diastolic pressure.

In humans, long-term cocaine use has been reported to cause LV systolic dysfunction. Wiener et al described dilated cardiomyopathy in two long-term cocaine abusers, after which others reported an association of cocaine use and LV systolic dysfunction. Chokshi et al described a young woman with reversible, profound myocardial depression after binge cocaine use. They hypothesized that the observed LV dysfunction was due to a direct cardiotoxic effect of the drug rather than drug-induced catecholamine excess or metabolic derangements (eg, hypoxia or acidosis). Bertolet et al found evidence of LV systolic dysfunction (by radionuclide ventriculography) in 7% of asymptomatic long-term cocaine users. These and other reports provide evidence that repetitive cocaine exposure may depress LV systolic function. However, the effects of short-term cocaine administration on LV performance in vivo have not been well characterized in that no study has examined the immediate effects of a large dose of cocaine on LV systolic and diastolic function in humans.

In our study, we infused cocaine directly into the left coronary artery in humans to achieve a relatively high “local” (intracoronary) drug concentration. The cocaine concentration in coronary sinus blood in our 10 group 2 subjects averaged 3.0 mg/L, similar in magnitude to the peak blood concentration in dogs reported by Bedotto et al and Fraker et al and in drug abusers dying of cocaine intoxication; the corresponding systemic concentration averaged 0.17 ± 0.06 mg/L. Similar to the results obtained in dogs, high-dose intracoronary cocaine in humans exerted a deleterious effect on LV systolic performance, as reflected by a rise in LV end-systolic volume and a fall in ejection fraction (Table, Fig 2). Additionally, it caused an increase in LV end-diastolic pressure without a concomitant change in LV end-diastolic volume (Table, Fig 1). Thus, dogs and humans appear similar in the manner in which their LV systolic performance responds to a high intracoronary concentration of cocaine; moreover, LV diastolic function in both species is impaired after drug administration. Myocardial relaxation occurs when calcium ions dissociate from contractile...
Our study has limitations. First, we did not assess the effects of a high systemic cocaine concentration on LV function. The systemic infusion of cocaine in doses of sufficient size to achieve a drug concentration comparable to those reported in experimental animals is not feasible in human volunteers. However, we achieved a high cocaine concentration in the coronary circulation via direct intracoronary infusion. It is possible that high systemic concentrations of the drug, with associated secondary effects (ie, elevated catecholamines or systemic arterial pressure), may cause a change in myocardial calcium ion sensitivity, resulting in impaired LV systolic or diastolic performance.

In conclusion, in humans, the intracoronary infusion of cocaine sufficient in amount to achieve a high concentration of cocaine on myocardial function in human subjects.

Acknowledgment

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References


Proteins and are sequestered by the sarcoplasmic reticulum. In isolated myocardial tissue, cocaine-induced alterations in calcium ion handling result in an increase in the intracytosolic calcium concentration, causing prolongation of the calcium transient and a negative lusitropic effect. Alternatively, cocaine may cause a change in myofilament calcium ion sensitivity, resulting in impaired LV systolic or diastolic performance.

In the future, the measurement of diastolic function, increased LV end-diastolic pressure without altering LV end-diastolic volume, may provide a more sophisticated analysis of the effects of cocaine on diastolic function. Third, we cannot exclude the possibility that the modest increase in systemic arterial pressure after intracoronary cocaine administration contributed to the observed decline in LV systolic function. Previous studies have demonstrated that serum cocaine concentrations similar to those obtained in the present study cause a modest increase in systemic arterial pressure, resulting from inhibition of presynaptic reuptake of epinephrine and norepinephrine by peripheral neurons. However, we showed previously that LV performance increases after intranasal cocaine despite an increase in systemic arterial pressure similar in magnitude to that observed in the present study. Thus, the small increase in afterload probably does not explain the decrease in LV systolic function. Our study also has certain strengths in that it is the first to assess the direct effects of large amounts of cocaine on myocardial function in human subjects.
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