Acute Effects of Intravenous Cocaine on Pulmonary Artery Pressure and Cardiac Index in Habitual Crack Smokers*

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**Background:** Some habitual crack cocaine smokers who deny IV drug abuse show decreased pulmonary transfer of carbon monoxide (Dco). We speculated that repeated elevations in pulmonary artery pressure (PAP) might cause pulmonary capillary damage and result in a lowered Dco, or that the reduction could be due to anoxic lung injury secondary to repeated episodes of cocaine-induced pulmonary vascular constriction.

**Study Objective:** Compare the acute effects of IV cocaine HCl and placebo on PAP, cardiac stroke volume, and cardiac output estimated indirectly by continuous Doppler echocardiography.

**Design:** A single-blind crossover study in which placebo always preceded the active drug.

**Subjects:** Ten current crack-smoking subjects, 32 to 47 years of age, with a history of limited previous IV cocaine use.

**Methods:** PAP, cardiac stroke volume, heart rate, and BP were measured continuously after injection of placebo followed by cocaine HCl (0.5 mg/kg).

**Results:** IV cocaine resulted in no significant change in PAP (-0.14±3.3[SD] mm Hg, 95% confidence interval [CI] for difference -2.48, +2.21). Stroke volume index showed no significant change after cocaine (-0.1±2.0 mL; 95% CI, -1.5, +1.3). Heart rate showed a significant increase (10.0±7.2 min⁻¹; p=0.0017, 95% CI, +4.9, +15.1). Cardiac index showed a significant increase (0.48±0.32 L/min; p=0.0012, 95% CI, +0.25, +0.71). Pulmonary vascular resistance showed no significant change (-44±101 dyne · s · cm⁻⁵/m², 95% CI, -116, +29).

**Conclusions:** IV cocaine HCl does not cause short-term increases in PAP or stroke volume index, but causes an increase in cardiac index due to its chronotropic effect.  

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**Key words:** cardiac output; cocaine HCl; pulmonary artery pressure

**Abbreviations:** AT/ET=acceleration time/ejection time; CI=cardiac index; CI=confidence interval; Dco=diffusing capacity of the lung for carbon monoxide; HR=heart rate; mPAP=mean pulmonary artery pressure; NIDA=National Institute on Drug Abuse; PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; SVI=stroke volume index; VTI=velocity time integral

We have previously shown that heavy, habitual cocaine smoking is associated with a significant abnormality in gas transfer (diffusion) in the lung,¹ consistent with findings of other investigators.²,³ The presence of an abnormality in diffusion capacity suggests structural lung damage. Clinical reports of acute noncardiogenic (“increased permeability”) pulmonary edema⁴ and diffuse alveolar hemorrhage in temporal association with cocaine use,⁵,⁶ as well as autopsy evidence of frequent, clinically occult pulmonary hemorrhage⁶-⁸ and interstitial pneumonitis and/or fibrosis⁹ in lung specimens from cocaine users who die suddenly, provide support for the concept of cocaine-induced damage to the alveolar-capillary membrane. It has been suggested⁹ that this damage could result from either (1) a direct toxic effect of the inhaled cocaine on the alveolar epithelium and/or capillary endothelium and/or (2) an intense vasoconstrictor effect of cocaine on the pulmonary circulation, causing a marked reduction in pulmonary cap-

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illary perfusion that leads to anoxic cellular damage. However, a vasoconstrictor effect of cocaine on the intact pulmonary circulation has not yet been demonstrated experimentally in man. The possibility of cocaine-induced pulmonary vasoconstriction is suggested by the following: (1) an autopsy report revealing medial hypertrophy and hyperplasia involving small or medium-sized pulmonary arteries in 20% of young cocaine users (without evidence of foreign-body microembolization) who died suddenly from acute cocaine intoxication;10 (2) a report of biopsy specimen-proved symptomatic pulmonary vascular disease (intimal and medial hypertrophy of muscular pulmonary arteries) in a small group of crack-smoking women with borderline to severe pulmonary hypertension;11 (3) in vitro studies of rabbit pulmonary artery segments with either intact or denuded endothelium;12 (4) studies in animal models in which cocaine has been reported to accentuate pulmonary arterial pressor responses;13 and (5) a recent clinical report of pulmonary arterial hypertension in asymptomatic IV cocaine users.14 This latter finding, however, could be secondary to microembolization of particulate material injected IV, rather than to a toxic effect of cocaine itself on the pulmonary circulation.

In the absence of any reports of direct evidence of cocaine effects on pulmonary hemodynamics in man, we estimated pulmonary vascular pressures and resistance noninvasively by Doppler echocardiography in ten habitual crack users and examined the short-term effect of experimental administration of cocaine in the same subjects. We hypothesized that IV cocaine HCl would acutely produce pulmonary arterial/arteriolar vasoconstriction, as manifested by an increase in pulmonary artery pressure (PAP) out of proportion to the increase in cardiac output estimated by Doppler echocardiography.

**Materials and Methods**

**Subjects**

Ten healthy current crack-smoking subjects, nine men and one woman, were recruited for experimental cocaine administration studies from chemical dependency treatment programs in the local community (after relapse) and from a cohort of crack smokers participating in ongoing studies of the pulmonary effects of habitual use of cocaine. Inclusionary criteria included age 25 to 50 years, current smoking of alkaloidal (crack) cocaine on a regular basis, and previous occasional use of IV cocaine (from 1 to 12 times per lifetime). Exclusionary criteria included the following: IV drug abuse more than 12 times per lifetime or within the previous year; history of smoking (>20 times/lifetime) other illicit substances (eg, phencyclidine, heroin, opium, methamphetamine) except for cannabis; a history of chronic lung disease (eg, asthma, interstitial lung disease); history or clinical evidence of systemic or pulmonary hypertension; history of coronary artery disease, angina, arrhythmia, or congenital heart disease; abnormal 12-lead ECG; history or clinical evidence of hyperthyroidism or peripheral vascular disease; history of stroke, seizure disorder, or other neurologic abnormality; history of significant psychiatric disorder; or pseudocholinesterase deficiency. Women of child-bearing potential were not studied if they were pregnant, lactating, or not using a medically acceptable method of contraception. A urine pregnancy test was performed on all female subjects at the beginning of each study day to detect unsuspected pregnancy. Subjects without measurable tricuspid regurgitation by Doppler echocardiography (see below) were excluded from analysis. Eligible volunteers were studied after signing informed consent forms approved by the UCLA School of Medicine Human Subject Protection Committee and the West Los Angeles VA Medical Center Human Studies Committee.

**Procedures**

Preliminary examination procedures included the following: a detailed respiratory and drug use questionnaire modified from the American Thoracic Society/National Heart, Lung and Blood Institute respiratory questionnaire15 and National Institute on Drug Abuse (NIDA) National Survey on Drug Abuse16; medical history and physical examination; serum pseudocholinesterase determination; urine drug screen; 12-lead ECG; spirometry and single-breath diffusing capacity for carbon monoxide (Dco) measurement (adjusted for hemoglobin17 and carboxyhemoglobin18); and a urine pregnancy test in female subjects. Eligible volunteers were advised to refrain from smoking cocaine or marijuana, taking any prescription or over-the-counter medication, or consuming any caffeine-containing beverage for at least 8 h prior to visiting the laboratory. They were also admonished not to smoke tobacco for at least 2 h before testing or to use any antihistamine preparation for at least 48 h. Studies were performed with a physician in attendance and emergency resuscitation equipment nearby.

At the beginning of each study, the amount of daily drug use (crack cocaine, marijuana, tobacco, and other drugs) during the preceding week and the time of last use were ascertained by questionnaire (self-report), and a urine sample was obtained for determination of cocaine metabolite (benzoylcegonine). A 12-lead ECG was performed. A catheter was inserted in an arm vein for injection of saline solution or cocaine HCl. A standard two-dimensional echocardiogram (Acuson 128XP; Mountain View, Calif.) was performed to rule out structural malformations and to assess right ventricular outflow diameter. Finger arterial blood pressure was monitored continuously and noninvasively on the second or third finger of the left hand (Finapres 2300E; Ohmeda; Boulder, Colo). The sum of chest and abdominal wall excursions (proportional to tidal volume) measured by inductive plethysmography (Respirtrace Plus; Non-Invasive Monitoring Systems; Miami Beach, Fla) was recorded directly on the echocardiographic recording tape. Doppler echocardiographic assessment of the right ventricular outflow tract was performed continuously from before administration of placebo until after return to baseline following cocaine administration.

The cocaine HCl was obtained from the NIDA in crystalline form. The dose of IV cocaine HCl (0.35 to 0.5 mg/kg) used was selected since it has been shown to yield euphoric effects comparable to those achieved during recreational use of cocaine19 and to be below the dose levels associated with significant cocaine toxicity, according to unpublished NIDA guidelines for experimental cocaine administration. The subject was blinded to the administration of drug vs placebo. For each subject, the first injection consisted of a volume of 0.9% NaCl identical to that of the cocaine administered later, injected over 30 s, and followed by 6 mL 0.9% NaCl flush over 60 s. The second injection consisted of (1) cocaine HCl (7.67 mg/mL in 0.9% NaCl) at a
Table 1—Demographic, Smoking, and Physiologic Characteristics (n=10; 9 Men, 1 Woman)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>38.7±4.9</td>
<td>32-47</td>
</tr>
<tr>
<td>Cocaine, g/wk</td>
<td>0.93±0.58</td>
<td>0.25-2.2</td>
</tr>
<tr>
<td>Tobacco, cigarettes per day (n=7*)</td>
<td>13.6±12.9</td>
<td>3-40</td>
</tr>
<tr>
<td>Marijuana, joints per week (n=6*)</td>
<td>7.5±9.9</td>
<td>0.2-21</td>
</tr>
<tr>
<td>DCO, % predicted</td>
<td>75.1±4.9</td>
<td>67-80</td>
</tr>
<tr>
<td>DCO/VA, % predicted</td>
<td>85.4±9.1</td>
<td>66-100</td>
</tr>
</tbody>
</table>

*Current smokers of tobacco and/or marijuana.


dose of 23 mg (2 subjects, average dose 0.35 mg/kg lean body weight [body mass index of 22.0]) or (2) cocaine HCl (5 mg/mL in 0.9% NaCl) at a dose of 0.5 mg/kg lean body weight (8 subjects, average dose 36.5±4.6 [SD] mg). This also was injected over 30 s and followed by a 6-mL flush of 0.9% NaCl over 60 s. The change in dose from 0.35 to 0.5 mg/kg was made after the first 2 subjects had been studied to assure a consistent chronotropic response based on the results of concurrent studies.

Individual beats from the Doppler spectral recordings obtained at end-expiration at approximately 1-min intervals were analyzed for acceleration time/ejection time (AT/ET), velocity time integral (VTI), and instantaneous heart rate (HR). Ectopic and postectopic beats were excluded from analysis. Mean pulmonary arterial pressure (mPAP) was estimated from AT/ET.20 Stroke volume was calculated from the product of right ventricular outflow tract cross-sectional area and VTI.21 Cardiac output was calculated as the product of HR and stroke volume. Right atrial pressure was estimated at 5 mm Hg (no subject had evidence of jugular venous distention). Pulmonary vascular resistance was calculated from the Doppler-estimated mPAP divided by the cardiac index (Ci). Stroke volume, cardiac output, and pulmonary vascular resistance (PVR) were indexed to body surface area for intersubject comparisons. A physician was present at all times during the cocaine infusion experiments. Following cocaine administration, subjects were carefully monitored for evidence of acute cocaine toxicity such as systemic hypertension, tachycardia, clinically significant arrhythmia, chest pain, or headache.

Data Analysis

Paired t tests were used to compare measurements obtained following placebo with (1) those obtained in the first 5 min following cocaine, and (2) all measurements following cocaine until returned to baseline. A Hotelling T², a multivariate analogue of the t-statistic, was used to assess differences in mPAP, HR, stroke volume index (SVI), Ci, and PVR index given their correlation structure.22 A repeated-measures model using the variance of each subject during the measurement period was used to derive 95% confidence intervals (CIs) for the difference between cocaine and placebo values.23

RESULTS

Mean age, smoking history, and diffusing capacity of the study participants are shown in Table 1. Subjects were young to middle-aged adults who, on the average, were heavy smokers of cocaine base (mean of 0.93 g/wk). Most were also current smokers of tobacco and marijuana. DCO was mildly reduced (<75% predicted) in 4 of the 10 subjects.

Valid echocardiographic observations at end-expiration were obtained (mean±SD) 10.0±3.3 times (range, 5 to 16 times) following placebo infusion, 7.0±3.0 (3 to 10) times in the first 5 min following cocaine infusion, and 15.8±6.0 (7 to 24) times over the full observation period of 16.0±6.5 (10.0 to 31.9) min following cocaine infusion. Mean results are shown in Table 2 and Figure 1.

Table 2—Hemodynamic Changes Following Cocaine Administration*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean</th>
<th>First 5 min After Cocaine</th>
<th>All Measurements After Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP, mm Hg</td>
<td>18.0±5.7</td>
<td>17.8±6.6</td>
<td>18.0±5.9</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>44.5±9.0</td>
<td>44.4±8.5</td>
<td>46.1±8.5</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>62.4±7.9</td>
<td>72.4±10.7</td>
<td>75.4±10.8</td>
</tr>
<tr>
<td>Ci, L/min/m²</td>
<td>2.72±0.57</td>
<td>3.20±0.69</td>
<td>3.45±0.72</td>
</tr>
<tr>
<td>PVR index, dyne·s·cm⁻⁵/m²</td>
<td>300±177</td>
<td>256±181</td>
<td>232±161</td>
</tr>
</tbody>
</table>

*For each subject, a mean of the placebo, first 5 min after cocaine, and all values after cocaine is calculated as well as the change (mean difference [after cocaine-mean placebo]). The table displays group (10 subjects) values as mean±SD (low, high), p value (repeated measures model), 95% CI (low, high).

Clinical Investigations
Mean PAP following placebo was slightly elevated (18.0±5.7 mm Hg, mean±SD; 7 of 10 subjects >16), compared with normal (9 to 16 mm Hg²⁴), (Fig 1, left). Mean PAP did not change significantly comparing placebo to either the first 5 min following cocaine infusion or all measurements obtained following cocaine infusion (Fig 1, right, and Table 2). The 95% CI for the difference in mPAP between placebo and cocaine was −2.5 to +2.2 mm Hg for the first 5 min. This was determined from a repeated-measures model using the variance of each subject during the measurement period. Each point in Figure 1 represents a mean of between 3 and 24 individual measurements. The 95% CI was derived from 100, 65, and 158 individual measurements for placebo, first 5 min following cocaine administration, and all measurements following cocaine administration, respectively. The maximum mean increase was 6.0 mm Hg and the maximum mean decrease was −4.7 mm Hg for any individual in the first 5 min following cocaine administration. The subject with the highest mPAP during placebo (32.9 mm Hg) did not respond differently from the others (change in mPAP, 0.1 mm Hg in the first 5 min).

Mean SVi following placebo (44.5±9.0 mL/m², mean±SD) was within the normal range (30 to 65 mL/m²).²⁴ SVi did not change significantly comparing placebo to the first 5 min following cocaine infusion. The 95% CI for the difference in SVi between placebo and cocaine was −1.5 to +1.3 mL/m² for the first 5 min.

Mean HR following placebo (62.4±7.9 min⁻¹, mean±SD) was within the normal range (60 to 90 min⁻¹),²⁵ although 3 subjects had mild bradycardia. Mean HR significantly increased (p=0.0017) comparing placebo to the first 5 min following cocaine infusion (72.4±10.7 min⁻¹, an increase of 10.2±7.0 min⁻¹). The 95% CI for the difference in HR between placebo and cocaine was +4.8 to +15.1 min⁻¹ for the first 5 min.

With the SVi remaining the same and the HR increasing, the calculated product, CI, increased. Mean Ci following placebo (2.72±0.57 L/m², mean±SD, 6 of 10 less than 2.8) was slightly below normal range (2.8 to 4.2 L/m²).²⁴ Mean Ci significantly increased (p=0.0012) comparing placebo to the first 5 min following cocaine infusion (3.20±0.69 L/m², an increase of 0.48±0.32 L/m²). The 95% CI for the difference in Ci between placebo and cocaine was +0.25 to +0.71 L/m² for the first 5 min. A significant correlation was found between change in HR and change in Ci (r²=0.91), but not between change in SVi and change in Ci (r²=−0.24) (Fig 2).

PVR index was highly variable. Mean PVR index following placebo infusion (300±177 dyne·s·cm⁻⁵/m², 2 subjects above 430 dyne·s·cm⁻⁵/m², 5 below 250 dyne·s·cm⁻⁵/m²) was within the normal range (250 to 430 dyne·s·cm⁻⁵/m²).²⁴ Mean change in PVR index (−44±101 dyne·s·cm⁻⁵/m²) from placebo to the first 5 min after cocaine administration was also highly variable and not statistically significant (95% CI −116 to +29 dyne·s·cm⁻⁵/m²).

Systemic BP increased following cocaine administration. Maximal systemic systolic BP increased from 138±19 mm Hg following placebo to 166±22 mm Hg following cocaine. Maximal systemic diastolic BP also increased from 77±12 mm Hg after placebo to 94±14 mm Hg after cocaine. The median time to the maximal systemic systolic BP following cocaine administration was 2.8 min and to maximal diastolic BP, 2.0 min.
DISCUSSION

Cocaine blocks the reuptake of catecholamines at adrenergic nerve endings, causing a local increase in norepinephrine and dopamine levels and sensitization to systemic catecholamines (epinephrine).\textsuperscript{26,27} As a consequence, cocaine produces systemic vasocostriction that is blocked by \( \alpha \)-adrenergic blocking agents (phentolamine) and potentiated by \( \beta \)-adrenergic blockade.\textsuperscript{28-30} In addition to pulmonary toxicity,\textsuperscript{31,32} cocaine may also have direct toxic effects on end organs such as the myocardium, independent of neurogenic effects.\textsuperscript{33-35}

Dogs receiving a continuous infusion of cocaine at 0.5 mg/kg/min show a decrease in stroke volume and cardiac output, but no change in mPAP or HR.\textsuperscript{36} In rabbit pulmonary artery segments, norepinephrine contracted the larger intrapulmonary vessels, but this vasoconstrictor effect was not potentiated by cocaine.\textsuperscript{37} The latter results are contrary to a later report in abstract form demonstrating cocaine-induced vasoconstriction of rabbit pulmonary artery segments.\textsuperscript{12}

Previous reports of echocardiographic measurements in asymptomatic IV cocaine users have shown elevations in estimated PAP (systolic PAP >30 in 8 of 13 subjects).\textsuperscript{14} The pulmonary hypertension has been hypothesized to be due to granulomatous inflammation from injected insoluble agents (talc, corn starch, microcrystalline cellulose). However, an autopsy study demonstrated pulmonary artery medial hypertrophy in the absence of foreign particle microembolization in 4 of 20 deaths from cocaine overdose,\textsuperscript{10} raising the possibility that repeated episodes of cocaine-induced acute pulmonary vasoconstriction might eventually produce pulmonary hypertension and medial hypertrophy. However, acute administration of intranasal cocaine, 2 mg/kg, results in an increase in HR and CI, but no change in mPAP or SVi assessed at 15, 30, or 45 min by pulmonary artery catheterization.\textsuperscript{38}

Since cocaine-induced subjective effects and tachycardia are of short duration, we postulated that any change in mPAP might be transient. Nominvasive measurement of mPAP using the AT/ET at the right ventricular outflow tract has a good correspondence to pressures measured by pulmonary artery catheterization (\( r=0.94 \))\textsuperscript{39} and also allows almost continuous measurements that can be gated to end-expiration. Using a moderate dose of cocaine, this study shows no change in mPAP compared with placebo. We also establish a 95% CI for the group mean that narrowly defines the change in mPAP and makes it unlikely that a clinically significant change in mPAP occurred in this group. This lack of change is present in the first 5 min after infusion of cocaine and for all measurements following cocaine.

It is possible that higher doses of cocaine or a different route of administration might provoke a significant increase or decrease in mPAP. However, higher doses also would make acute untoward side effects more likely in this volunteer subject population. Although it is possible that some subjects are responders and some are nonresponders to pulmonary vasomotor effects of cocaine, the outlying subjects with either high or low initial mPAP did not respond differently from the remainder of the group in our study. In dogs, tachyphylaxis to the hypertensive and myocardial oxygen consumption effects occurs at higher doses of cocaine (0.8 mg/kg) administered at 1-h intervals, but lower doses result only in an elevation of the baseline hemodynamic variables.\textsuperscript{40} Although our subjects stated that they had refrained from smoking cocaine in the 8 h prior to the study day, it is possible they did not abstain or that the duration of abstinence was insufficient. However, we did observe the expected chronotropy and systemic BP increases after cocaine, so that it is less likely that our failure to demonstrate acute pulmonary vasoconstriction following cocaine was due to the development of tolerance as a result of recent cocaine use.

The marked difference in response to cocaine between the systemic and pulmonary vasculature may be due to several factors. First, the greater compliance of the pulmonary vasculature may prevent rises in PAP through the recruitment of additional, previously collapsed vessels, even though all the vessels might be constricted secondary to cocaine administration (excess capacitance). Second, the pulmonary vascular system may be unable to respond to a given constrictor stimulus to the same degree as the systemic vasculature due to decreased or absent smooth muscle in the pulmonary arteries and arterioles (decreased responsivity). Finally, the pulmonary vascular smooth muscle may have a lower density of adrenergic receptors for stimulation by catecholamines causing less constriction in response to local increases in norepinephrine and dopamine than in the systemic circulation (decreased sensitivity).

In the absence of apparent change in the mPAP during acute administration of cocaine, it is difficult to postulate microvascular damage due to repeated vasoconstriction as an explanation for low DCO observed in some crack cocaine users. Moreover, the lack of a marked elevation in mPAP either acutely following experimental cocaine administration or chronically in habitual crack cocaine smokers argues against redistribution of blood flow to upper lung zones resulting from pulmonary hypertension with
compensatory recruitment of capillaries from upper lung zones as an explanation for pseudonormalization of DCO in crack smokers with cocaine-related lung injury.

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REFERENCES