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# Intravenous Cocaine Infusions in Humans: Dose Responsivity and Correlations of Cardiovascular vs. Subjective Effects

CARLES MUNTANER, KAREN M. KUMOR, CRAIG NAGOSHI AND JEROME H. JAFFE

*NIDA, Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224*

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MUNTANER, C., K. M. KUMOR, C. NAGOSHI AND J. H. JAFFE. *Intravenous cocaine infusions in humans: Dose responsivity and correlations of cardiovascular vs. subjective effects.* PHARMACOL BIOCHEM BEHAV **34**(4) 697–703, 1989.—Eight experienced IV cocaine users were intravenously administered 0, 10, 20, and 40 mg of cocaine hydrochloride on separate days in a pseudo-randomized ascending dose series, such that the 20 mg dose always preceded the 40 mg dose. They were subsequently administered 0, 20, and 40 mg of cocaine in a fully randomized presentation order. Cardiovascular effects of cocaine were significantly different from placebo for the 20 mg, but not the 10 mg dose, in contrast to subjective responses which differed from placebo for the 10 mg dose. Cardiovascular and subjective effects of cocaine did not differ between the 20 and 40 mg dose conditions for the pseudo-randomized trials, but did differ in the fully randomized trials. This lack of difference in responsivity between the 20 and 40 mg dose in the earlier trials may possibly have been due to contrast effects. Cardiovascular responses were not consistently correlated with subjective responses, either within a cocaine dose condition or across doses.

Cocaine Dose response Cardiovascular effects Subjective effects Human

COCAINE produces dose-dependent increases in cardiovascular function and subjective effects (10,28). The study of cardiovascular function is particularly relevant to cocaine, since clinical (4) and experimental (26) literature provide evidence of its cardiac toxicity. Further, the study of subjective effects is central to cocaine investigations, as subjective effects are often predictors of the abuse liability of drugs (32) and the ability of drugs to act as reinforcers (31).

Few cocaine studies have included both cardiovascular and subjective effects measures (6, 8–10, 18, 28), and none has addressed the question of quantifying the correlation between cardiovascular and subjective effects. Since cocaine produces simultaneous dose-dependent increases in both cardiovascular function and subjective effects, a positive correlation between the two has been suggested or assumed (7, 10, 18, 28). Such a correlation might be expected if the acute subjective effects of cocaine were due in part to the peripheral actions of cocaine (6, 21, 32).

On the other hand, a direct relationship between the cardiovascular and subjective responses may not exist. There are high-affinity binding sites for cocaine in peripheral tissues, which may act independently from the central nervous system cocaine receptors (2).

The primary goal of the present study was to assess the relationship between acute subjective and cardiovascular effects of intravenously administered cocaine in human volunteers. This relationship may be of importance in the behavioral patterns related to cocaine cardiac toxicity. If the cardiovascular and subjective responses to cocaine are not proportionate to one another, it is possible that under certain circumstances a cocaine user may administer cardiotoxic amounts with little subjective response being present, continuing self-administration to achieve "euphoria," while endangering his/her health (22).

A related purpose of the study was to compare the threshold doses for cardiovascular and subjective cocaine effects. We used low doses of cocaine similar to the studies of Fischman *et al.* (10) and Resnick *et al.* (28) in order to ascertain if these doses could produce cardiovascular effects without producing subjective effects or the converse. Recent studies with squirrel monkeys (30) have shown that doses of cocaine having minimal effects on cardiovascular function maintain self-administration.

## METHOD

### *Subject Population*

Eleven male volunteers (mean age = 35 years, range = 27–42 years) participated in the protocol, which had been approved by the Institutional Review Board at the Francis Scott Key Medical Center. All subjects provided written informed consent. Criteria for subject selection required a history of intravenous cocaine use during the three weeks prior to admission to the study, being HIV antibody negative, and a minimum mental age score of 12.3 on the vocabulary part of the Shipley-Hartford Retreat Scale (36). In addition, during a three-day observation period, subjects were required to pass physical and laboratory screening tests, manifest no symptoms of drug withdrawal and illicit drug use, have a normal EKG, and not fulfill criteria for current DSM III Axis I disorders other than substance abuse disorders. Subjects were

housed on a closed research ward, where random urine screens were performed throughout the study.

Subjects' psychiatric status was assessed with the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS) (29) adapted for computer administration. Two subjects had a past history of major depressive disorder. Within the substance abuse disorders, six subjects had a past history of alcohol dependence, six of tobacco dependence, two of barbiturate dependence, and five of opioid dependence. In addition, four subjects had a history of cannabis abuse and four of cocaine abuse. Two subjects had a history of antisocial personality disorder, and four had features of this diagnosis, while one subject had a history of pathological gambling. No diagnosis of current Axis I disorder other than substance abuse disorders was met by any subject.

Besides cocaine use, within the two weeks prior to admission all subjects reported smoking cigarettes, four reported drinking alcoholic beverages, three reported smoking marijuana, one had used barbiturates, and one had used benzodiazepines at least once during that period. All subjects had used alcohol, tobacco, opioids and cannabis at least once in their lifetime. Six subjects used cocaine exclusively by the intravenous route. Reported frequency of cocaine averaged 7 days per month, and reported quantity of use per day averaged 0.84 grams, with little intersubject variability.

*Procedure*

After medical assessment, subjects were administered cocaine using a series (described below) of single IV infusions of cocaine to screen subjects for unusually sensitive responses to the 40 mg dose of cocaine. On the basis of this procedure three research volunteers were rejected for further study, one because of elevated blood pressure and pulse after the 20 mg dose of cocaine, another because of premature nodal contractions following the 40 mg dose of cocaine. One additional subject withdrew for personal reasons.

The pseudo-randomized cocaine dosing procedures used to screen subjects for unusual sensitivity to cocaine were part of a broader protocol on the interactions of cocaine with potential blocking agents (21,25). For these safety-screening purposes, subjects participating in the study received four different experimental drug conditions presented in a pseudo-randomized order, such that the 20 mg dose was always scheduled before the 40 mg dose. These conditions were: 1) placebo IV administration, 2) 10 mg IV cocaine administration, 3) 20 mg IV cocaine administration, and 4) 40 mg IV cocaine administration. Experimental sessions were conducted no more frequently than every 24 hours.

Data from a second block of randomized cocaine doses will also be presented from the 1) placebo, 2) 20 mg IV cocaine, and 3) 40 mg IV cocaine conditions that were part of the six fully randomized conditions these subjects subsequently received in the main study testing the effects of nifedipine, a dihydropyridine calcium channel modulator, on the actions of cocaine (25). The other three conditions consisted of the same cocaine doses preceded by a 10 mg oral nifedipine pretreatment. After a minimum of 48 hr following the pseudo-randomized block had elapsed, these trials were scheduled no more frequently than every 48 hours. The short half-life of nifedipine makes it unlikely that there were carry-over effects of this drug across the different conditions. Differences in dose response between the earlier and later sets of trials may reflect order effects, i.e., sequentially increasing cocaine doses versus random ordering of the doses. Another possibly confounding factor, however, is the order effect associated with the pseudo-randomized trials always preceding the fully randomized trials.

Each trial was conducted under double-blind conditions in the same noise-insulated room. Three staff members were present, including for the first half hour after injection at least one physician fully trained in cardiac support. The staff refrained from talking or initiating conversations with the subjects and provided a supportive nondirective milieu. Cardiac function was periodically monitored prior to the IV infusion, continuously monitored for the first 30 min after the IV infusion, and periodically monitored thereafter. Intervention protocols were in place to respond in the event of cardiac arrhythmias.

On each study day, following an overnight fast, an indwelling IV heparin-lock catheter was inserted into a forearm vein and flushed with heparinized saline 60 min before the infusion. Subjects reclined in bed during the sessions. Subjects were informed that they could receive up to a 40 mg dose of cocaine or a placebo dose. Cocaine or placebo (saline) infusions were administered using a pressure pump (Sage Instruments Syringe Pump model 341) which infused 0.5 ml of drug solution over a period of 12 seconds into the indwelling catheter via a needle inserted into the heparin lock. The start of the infusion was determined by a computer which was programmed to activate the pump randomly during a 5-min interval after the attending physician pressed a start key. No visual or auditory cues indicated the moment in which the infusion started. A "beep" sounded 2 min after the end of the infusion. The injections were given at approximately 9 a.m. Subjects remained at bedrest during the 30 min following the infusion. Limited ambulation was allowed thereafter, but subjects were not permitted to exercise.

*Measures*

Blood pressure and heart rate were measured at 60 and 10 min before the infusion and 2, 10, 15, 30, 55, 85, and 115 min after the infusion. Systolic and diastolic blood pressure and heart rate were sampled via a BARD Biomedical Sentron automated blood pressure monitor. Cardiac monitors could not be seen by the subjects.

We used a computer-administered 30-item rating scale, the Cocaine Sensitive Scale (38), as a measure of the subjective effects produced by IV cocaine administration. The majority of items on this scale had been used in previous IV cocaine studies (24, 33, 35) in which they showed adequate validity when assessed against the Addiction Research Center Inventory (15) and sensitivity to cocaine effects. The items were rated on a five point scale (1 = not at all, 2 = a little bit, 3 = average, 4 = quite a lot, 5 = extremely).

Principal components analysis of the 30-item scale produced three major subscales with high face validity. These Scales were labeled General Drug Effect (8 items: "How confused does the drug make you feel?," "How much rush do you feel?," "How confused do you feel?," "How anxious do you feel?," "How weird do you feel?," "How much do you feel the drug?," "How high do you feel?," "How anxious does the drug make you feel?"), Feel Good (5 items: "How good do you feel?," "How clear is your thinking?," "How good does the drug make you feel?," "How pleasant do you feel?," "How pleasant does the drug make you feel?"), Suspiciousness (3 items: "How suspicious do you feel?," "Can the staff tell what you are thinking?," "How uncomfortable do you feel?"). A single item scale was also included for "crash," a dysphoria sometimes reported within hours after cocaine administration ("How much crash do you feel?"). Reported scores are means across the relevant items on a scale and thus reflect the original 5-point responses. In previous analyses (25), responses on this brief measure have been found to be highly correlated with some scales from the Profile of Mood States (24).

Subjects made their ratings by using an arrow key controlling a cursor. The scale was administered at 60 and 10 min before the beginning of the infusion and 2, 10, 15, 30, 55, 85, 115 min after the infusion. The scale was administered to seven subjects out of

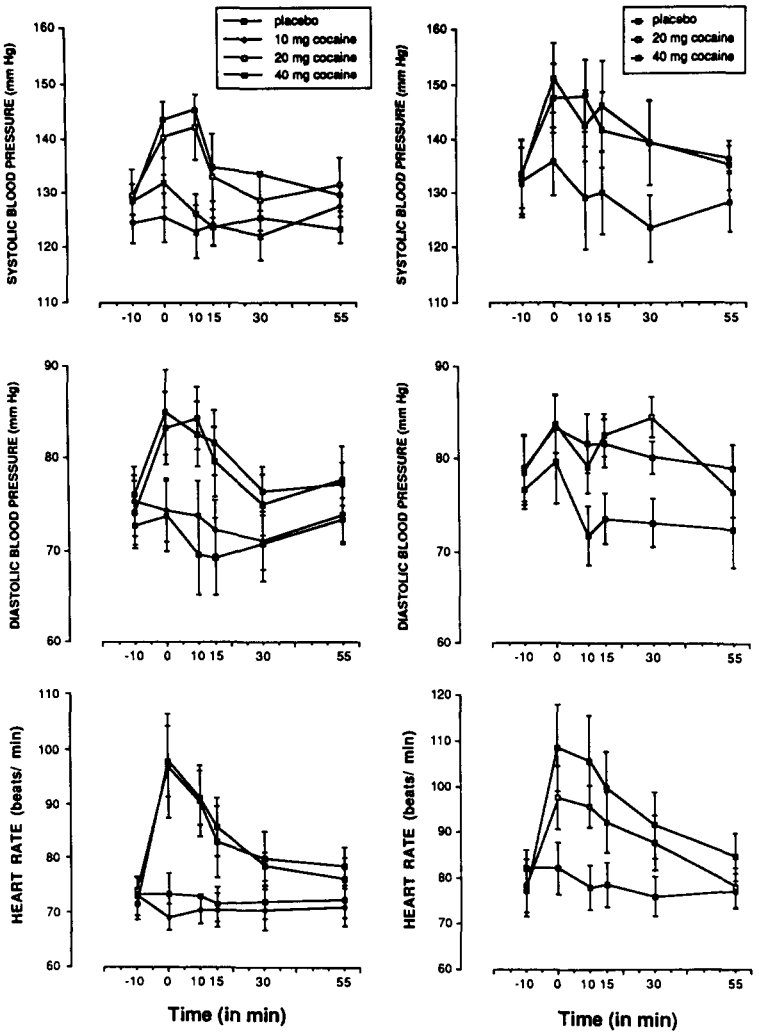


FIG. 1. Effects of pseudo-randomized order placebo, 10, 20, and 40 mg and fully randomized order placebo, 20, and 40 mg cocaine injections on systolic and diastolic blood pressure (mmHg) and heart rate (beats/minute) as a function of time. Each point in the pseudo-randomized trials represents the mean of 8 subjects; each point in the randomized trials represents the mean of 7 subjects.

the eight being assessed on their cardiovascular responses.

Data from the pseudo-randomized trials were analyzed by two-way repeated measures analyses of variance (ANOVA) followed by planned orthogonal paired *t*-tests. The main factors in the analysis were the cocaine intravenous dose (placebo, 10, 20, or 40 mg cocaine) and the time points. In order to protect the experiment-wise error rate, only five times were chosen for these ANOVA's (−10, and +2, +15, +30 and +55 minutes with respect to the injection). More time points would increase the likelihood of Type 1 errors (19).

Three-way repeated measures ANOVAs for pseudo-randomized trials vs. randomized trials, dose (placebo, 20, or 40 cocaine), and time (5 timepoints as above) were performed to test for differences in responses across different doses between the earlier and later sets of trials. These analyses would also reveal any significant dose response effects in the later set of trials.

We assessed the relation of cocaine dose-related effects between cardiovascular and subjective effects by first calculating difference scores (scores for +2 min postinjection minus scores at −10 min preinjection) for a variable for each dose (0, 10, 20, and 40 mg cocaine for the pseudo-randomized and 0, 20, and 40 mg cocaine for the randomized trials). Linear regression slopes across doses were then calculated for each individual subject for these difference scores on selected cardiovascular and subjective effects variables, with separate slopes calculated for the pseudo-randomized vs. the randomized trials. The regression slopes, based on subjects' responses across all doses, were expected to be more stable than scores on the dependent variables during any particular dose. We calculated the intercorrelations among selected dependent variables on these dose-response slopes.

## RESULTS

Cocaine produced dose-dependent increases in systolic and diastolic blood pressure and heart rate. In all three measures for the pseudo-randomized trials the 10 mg cocaine dose did not differ from placebo and the 40 mg cocaine dose showed only insignificant increases relative to the 20 mg cocaine dose (see Fig. 1). For

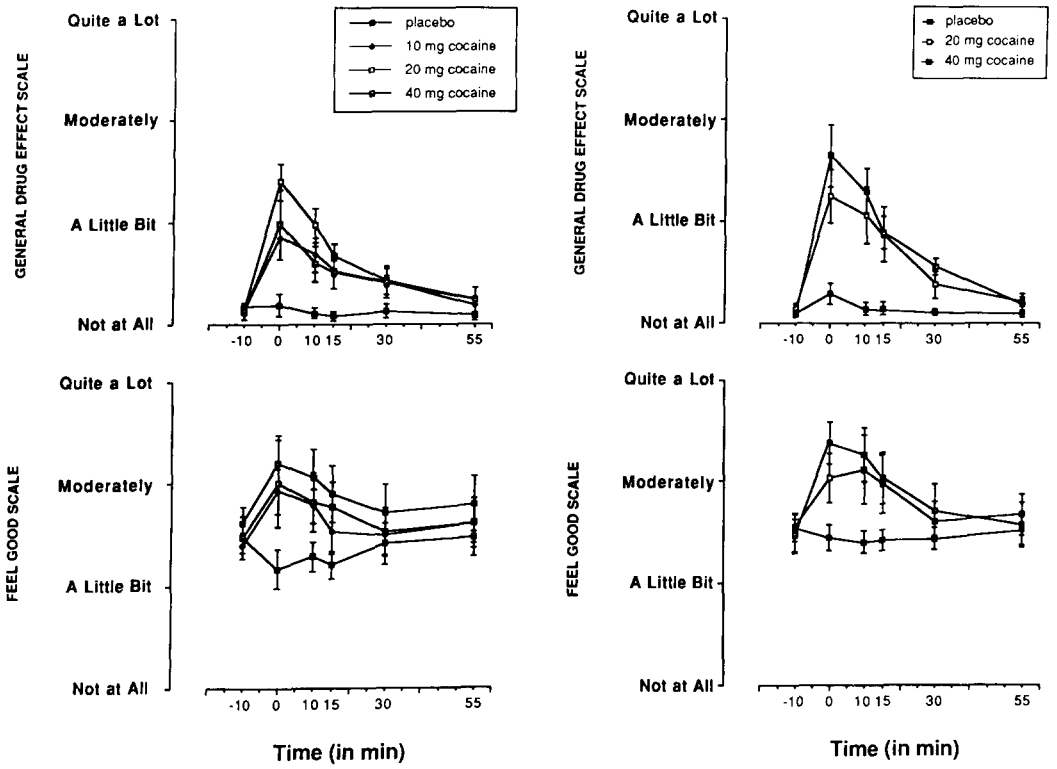


FIG. 2. Effects of pseudo-randomized order placebo, 10, 20, and 40 mg and fully randomized order placebo, 20, and 40 mg cocaine injections on the General Drug Effect, Feel Good, Suspiciousness, Craving, Sexual Arousal, and Crash self-reported subjective scales as a function of time. Each point represents the mean of 7 subjects.

the randomized trials, the 40 mg dose produced greater increases in systolic blood pressure and heart rate than the 20 mg cocaine dose. Peak effects of cocaine on blood pressure and heart rate were observed at the 2 min observation after cocaine injections. Heart rate returned close to baseline values about 2 hours after the injections. Systolic blood pressure returned close to baseline levels at about 1 hour and diastolic blood pressure at about 30 min after the injection. These results are consistent with earlier studies using similar cocaine doses (10,11).

The main effect of cocaine dose for the pseudo-randomized trials (placebo, 10, 20 and 40 mg) approached significance on systolic blood pressure, $F(3,21)=2.27$, $p<0.110$, and diastolic blood pressure, $F(3,21)=2.87$, $p<0.061$, and was significant for heart rate, $F(3,21)=6.68$, $p<0.002$. Significant main effects of time were found for systolic blood pressure, $F(4,28)=3.44$, $p<0.021$, diastolic blood pressure, $F(4,28)=3.37$, $p<0.023$, and pulse rate, $F(4,28)=11.32$, $p<0.001$. ANOVA results for the interaction of cocaine dose and time approached significance for systolic blood pressure, $F(12,84)=1.81$, $p<0.059$, and were significant for heart rate, $F(12,84)=5.61$, $p<0.001$. We used paired $t$-tests to compare the change scores from baseline, 10 min before the injection, to the 2 min postinjection values between the dose conditions. Paired $t$-tests between the 10 mg dose of cocaine and the 20 mg dose of cocaine revealed near-significant differences for systolic blood pressure (paired $t=2.13$, $p<0.070$) and significant differences for heart rate (paired $t=3.94$, $p<0.006$), with no other differences between adjacent cocaine doses approaching significance.

The three-way ANOVAs with the pseudo-randomized vs. randomized trials as an additional factor produced similar dose and time effects on the cardiovascular measures. There were significant main effects for pseudo-randomized vs. randomized trials on systolic blood pressure, $F(1,6)=12.68$, $p<0.012$, diastolic blood pressure, $F(1,6)=8.22$, $p<0.029$, and heart rate, $F(1,6)=20.00$, $p<0.004$, reflecting the higher baseline scores in the randomized trials. One likely explanation for these baseline differences is that, as has been previously found (3), there was conditioning of cocaine-induced cardiovascular responses to the test environment. Although there was a trend for the increase in systolic blood pressure and heart rate after 40 mg cocaine to be higher than that after 20 mg in the randomized trials, but not during the pseudo-randomized trials, the interactions of type of trial by dose by time did not reach significance.

In the analyses of data from the pseudo-randomized trials, cocaine produced dose-dependent increases on the General Drug Effect and the Feel Good scale scores (see Fig. 2). As opposed to cardiovascular measures, responses to the 10 mg cocaine dose were clearly above placebo on both measures during the pseudo-randomized trials. However, for both scales, the 20 mg dose of cocaine produced greater increases than the 40 mg dose of cocaine, whereas during the randomized trials the 40 mg dose produced a greater increase than the 20 mg dose. Scores for both scales in both sets of trials peaked at 2 min after cocaine injections. Scores for General Drug Effect returned to baseline, but scores on the Feel Good scale remained slightly above baseline at 2 hours after the injection.

The main effect of cocaine dose in the pseudo-randomized trials (placebo, 10, 20, 40 mg) was significant for the General Drug Effect, $F(3,21)=5.70$, $p<0.006$, and was almost significant for the Feel Good scale scores, $F(3,21)=3.01$, $p<0.057$. Significant main effects of time were found for the General Drug Effect scale, $F(4,28)=27.11$, $p<0.001$. Interaction of cocaine dose and

TABLE 1

INTERCORRELATIONS OF INDIVIDUAL BASELINE-COCAINE DIFFERENCE SCORES FOR CARDIOVASCULAR RESPONSES AND THE DRUG EFFECT AND FEEL GOOD SCALES AT THE 40 mg COCAINE DOSE

| | Systolic b.p. | Diastolic b.p. | Pulse | Drug Effect |
|---|---|---|---|---|
| Sequential Trials: | | | | |
| Diastolic blood pressure | .50 | | | |
| Pulse | .38 | .70 | | |
| Drug Effect scale | .50 | .73 | .79* | |
| Feel Good scale | .60 | .39 | .48 | .86* |
| Randomized Trials: | | | | |
| Diastolic blood pressure | .27 | | | |
| Pulse | .63 | .84* | | |
| Drug Effect scale | .34 | −.53 | −.17 | |
| Feel Good scale | −.06 | −.69 | −.45 | .91† |

N = 8 for pseudo-randomized trials cardiovascular responses; N = 7 for pseudo-randomized trials subjective scales and all randomized trials measures.

*$p<0.05$, †$p<0.01$.

TABLE 2

INTERCORRELATIONS OF INDIVIDUAL DOSE-RESPONSE SLOPES FOR CARDIOVASCULAR RESPONSES AND THE DRUG EFFECT AND FEEL GOOD SCALES

| | Systolic b.p. | Diastolic b.p. | Pulse | Drug Effect |
|---|---|---|---|---|
| Sequential Trials: | | | | |
| Diastolic blood pressure | .16 | | | |
| Pulse | .16 | .62 | | |
| Drug Effect scale | .29 | .91† | .84* | |
| Feel Good scale | .46 | .78* | .71 | .95† |
| Randomized Trials: | | | | |
| Diastolic blood pressure | .49 | | | |
| Pulse | .64 | .89† | | |
| Drug Effect scale | .24 | −.16 | .00 | |
| Feel Good scale | .27 | −.49 | −.28 | .84* |

N = 8 for pseudo-randomized trials cardiovascular responses; N = 7 for pseudo-randomized trials subjective scales and all randomized trials measures.

*$p<0.05$, †$p<0.01$.

time (changes observed on the different doses of cocaine over time) were significant for the General Drug Effect, $F(12,84) = 3.32$, $p<0.001$, and the Feel Good, $F(12,84) = 2.30$, $p<0.015$, scale scores. Post hoc paired $t$-tests conducted on the change scores from 10 min before the injection to 2 min after the injection revealed significant differences between the placebo and the 10 mg dose of cocaine condition on the General Drug Effect (paired $t = -3.21$, $p<0.018$) and Feel Good scales (paired $t = -3.03$, $p<0.023$) and a near-significant difference between the 10 and 20 mg doses on the General Drug Effect scale (paired $t = -2.05$, $p<0.087$). No other comparisons between adjacent cocaine doses approached significance.

The three-way ANOVAs with pseudo-randomized vs. randomized trials as an additional factor produced similar dose and time effects on the Feel Good and General Drug Effect scale scores. Unlike the cardiovascular results, there were no significant main effects for type of trial on these subjective scales, i.e., no significant elevation of baseline scores in the randomized trials compared to the pseudo-randomized trials. The interaction of pseudo-randomized vs. randomized trials by dose by time was significant for the General Drug Effect scale, $F(8,48) = 2.64$, $p<0.018$, reflecting the greater increase in responding to the 40 mg dose compared to the 20 mg dose in the latter randomized but not the pseudo-randomized trials.

With respect to the other subjective effects scale scores, the Suspiciousness scale scores showed changes over time, $F(4,28) = 6.69$, $p<0.001$, indicating that subjects became more suspicious after injection regardless of the cocaine dose, and the Crash item showed main effects of cocaine dose, $F(3,21) = 3.65$, $p<0.032$, with greater crash occurring after larger doses. These scales did not produce significant interactions with pseudo-randomized vs. randomized trials.

In contrast to a previous report (17), we did not find significant cocaine dose-dependent increases in craving for cocaine. Measurement procedures differed between the two studies, with subjects in the earlier study being asked by a nurse/observer about their craving for cocaine. Similarly, the inability to replicate an earlier report of increased suspicion following continuous infusion of cocaine (34), was probably due to the different dosing and measurement procedures used in the earlier study. In this earlier study, self-reported suspiciousness did not increase in the course of the cocaine infusion, but observers did note increases in suspiciousness.

As an initial assessment of the relationship between cardiovascular and subjective responses to cocaine, difference scores between the −10 min baseline and +2 min postinjection scores were intercorrelated separately (mean correlations) for each dose condition and for the pseudo-randomized vs. randomized trials. The small difference scores for the placebo and 10 mg dose resulted in small, erratic correlations. Table 1 presents the intercorrelations among systolic and diastolic blood pressure, heart rate, and the General Drug Effect and Feel Good scale scores for the 40 mg dose during the pseudo-randomized and the randomized trials. For both sets of trials, cardiovascular responses to cocaine are positively correlated with each other, and responses on the Drug Effect scale are correlated with the Feel Good scale. The correlations between cardiovascular and subjective responses to cocaine, however, are equivocal. For the pseudo-randomized trials, cardiovascular responses are positively correlated with the subjective responses, while smaller negative correlations are found for the randomized trials.

To stabilize these correlations and to assess individual differences in responses across doses, individual regression slopes were calculated by regressing difference scores for each variable on the cocaine doses (0, 10, 20, and 40 mg for the pseudo-randomized trials and 0, 20, and 40 mg for the randomized trials), i.e., each subject was characterized by a dose response slope for each dependent variable. Table 2 presents the intercorrelations of these dose response slopes for systolic and diastolic blood pressure, heart rate, and the Drug Effect and Feel Good scales. The results in Table 2 parallel those in Table 1, indicating that cocaine dose-related cardiovascular responses are positively correlated with each other, the Drug Effect and Feel Good responses are highly correlated, but the correlation between cardiovascular and subjective responses is not consistent between the two types of trials.

## DISCUSSION

Cardiovascular measurements, systolic blood pressure and heart rate in particular, were sensitive to the manipulation of cocaine dose. The 20 mg dose produced significant increases in cardiovascular measurements over the placebo condition, but the 10 mg dose did not. This result parallels Fischman *et al.*'s (10) finding that an 8 mg dose of cocaine did not produce an increase in absolute heart rate, whereas a 16 mg dose produced a substantial increase. On the other hand, using measures such as median percent change from baseline (7,10) or mean peak change from baseline (28), doses of 8 or 10 mg have been observed to produce increases in heart rate.

Peak effects on heart rate were observed at the 2-min timepoint after the injection. Other studies using longer infusion periods, such as 60 sec (7, 10, 18) or 90 sec (28) found peak effects of cocaine on heart rate at 8–12 min and 5–10 min after the injection, respectively. Speed of infusion, as well as the timing of measurements, may affect when the time of "peak" cocaine effects in heart rate are observed.

For blood pressure, the 10 mg dose of cocaine was again not different from placebo and was significantly below the 20 mg cocaine dose. Fischman *et al.* (10) also found no difference between an 8 mg dose of cocaine and placebo in systolic blood pressure, in contrast to Resnick *et al.* (28), who found significant increases in blood pressure after administration of a 10 mg dose of cocaine. The difference found between the 10 and 20 mg doses of cocaine in the present study parallels previous reports with 8 and 16 mg (10) and 10 and 25 mg (28) of cocaine.

As with the similar doses used in the Fischman *et al.* (10) study, significant changes in heart rate and blood pressure were not found between the 20 and 40 mg doses in the present study. Greater increases in cardiovascular measures have been found using higher doses (28), suggesting a flattening of the dose response curve on these responses at lower doses.

All subjects discriminated subjective effects from placebo at low doses of cocaine, replicating previous studies with similar doses (10,28). Subjective effects peaked at the 2-min postinjection measurement timepoint, which is consistent with previous studies (6) and user's reports of an intense "rush" within the first minutes after self-injection of cocaine (6,22). In the present study, a short infusion period was used (12 sec). Further studies could investigate if the intensity of the acute effects of cocaine (the "rush") is directly related to the speed of the infusion.

As we predicted, the 10 mg dose of cocaine, even in the absence of significant cardiovascular changes, produced subjective effects discriminable from placebo, i.e., there are discriminative stimulus properties of cocaine which do not involve cardiovascular changes in humans. It is also possible that the 10 mg dose could serve as a reinforcer in humans, since subjective effects of abused drugs usually can predict the ability of a drug to serve as a reinforcer (31).

In the pseudo-randomized trials, in contrast to the fully randomized trials, the 20 mg dose produced more intense subjective effects than the subsequently given 40 mg dose of cocaine. Previous studies of ascending dose series (10,28) also yielded several inversions with doses of 16, 24, and 32 mg of cocaine. The phenomena could not be explained in terms of acute tolerance to subjective effects, since acute tolerance disappears within 24 hours (9). Habituation, through diminution of the unconditioned response by a conditioned stimulus or by the repeated presentation of the unconditioned stimulus (1), could be an alternative explanation of the lessened response to the 40 mg dose of cocaine. However, data provided by randomized trials in another study (3) showed a strong trend towards conditioned responses isodirectional to cocaine effects, i.e., sensitization.

An alternate explanation of our results on subjective responses would be in terms of the sequential effects during the pseudo-randomized trials. It has been found in psychophysical scaling experiments, that when a high stimulus is preceded by a stimulus of lower intensity, assimilation (bias towards the responses to the previous stimuli) tends to diminish the response to the high stimulus (5,37). Since subjects in the pseudo-randomized trials always received the 20 mg cocaine dose before the 40 mg dose, assimilation would tend to diminish their subjective responses to the 40 mg dose. This suggests that infusion studies of cocaine subjective effects should use randomized trials and not only ascending dose series, or the interpretation of subjective effects may be jeopardized by assimilation. However, we believe that ascending doses are necessary for safety screening purposes before the actual studies of cocaine doses in the 20 to 60 mg range.

The randomized administration of placebo, 20 and 40 mg doses of cocaine only partially replicated the results obtained with the first administration. The General Drug Effect scale scores showed an increase in responding in the 40 mg condition (also observed on the difference scores from baseline to 2 min postinjection) relative to the same dose condition in the pseudo-randomized trials. This could be interpreted as a trend towards sensitization to cocaine (27) or a contrast with the assimilation effect in the earlier trials. A similar trend was observed for systolic blood pressure and pulse.

Clear baseline increases during the later randomized trials suggest the conditioning of cocaine-induced cardiovascular responses (3). Therefore, it is possible that either conditioned cardiovascular responses to cocaine and conditioned sensitization (16,27) or both are present in our experiment.

The General Drug Effect dose-response slope was correlated with the Feel Drug scale slope on both occasions. It was correlated with diastolic blood pressure and heart rate during the pseudo-randomized, but not the randomized trials. Similarly, the Feel Good scale dose-response slope correlated with the diastolic blood pressure slope during the earlier, but not the later trials. This pattern suggests that the often assumed correlation between cardiovascular and subjective measures is not consistent and may be subject to relevant intra- as well as intersubject variability. The correlation found during the pseudo-randomized trials could be accounted for by the subjects' use of cardiovascular reactivity as a cue for rating the magnitude of the drug effect (20), particularly during the transition between placebo or 10 and 20 mg. These cues might not have been used to rate subjective effects during the randomized trials, since subjects had already experienced each dose and may have had less concern about their intensity. The small sample size makes us cautious in interpreting these correlations.

We conclude that human IV cocaine users may self-administer small euphorigenic doses which do not necessarily produce cardiovascular effects. Further, subjective effects of IV cocaine may be influenced in part by psychophysical mechanisms, such as assimilation effects, which could have implications in the understanding of factors leading to the administration of repeated or high doses with cardiovascular toxicity.

The present study also suggests that the conditioning of cardiovascular and subjective effects to cocaine may be an important variable in the drug response. Finally, different subjective effects produced by IV cocaine are consistently correlated, different cardiovascular effects are consistently correlated, but the correlation between cardiovascular and subjective effects is not consistent across study designs in humans. The overriding implication is that procedural factors can have a major influence on subjects' responses to cocaine.

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