Persistent Left Ventricular Dysfunction after Cocaine Treatment in Rabbits (43579)

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Abstract. **The present study was undertaken to determine whether the diminished cardiac performance associated with cocaine administration persists after the drug has been eliminated from the body. Cocaine (5 or 10 mg/kg iv) was administered to conscious ($n = 7$) or pentobarbital-anesthetized ($n = 7$) rabbits, respectively. Seven conscious and seven anesthetized control rabbits received the saline vehicle. Two and one-half hours later, the hearts were removed from the animals and perfused under cocaine-free conditions. Left ventricular (LV) contractility was evaluated by plotting steady-state LV systolic and diastolic pressures as a function of LV end-diastolic volume (preload). LV systolic performance was diminished in a dose-related manner in hearts isolated from cocaine-treated rabbits, but was statistically different from control only at the higher cocaine dose ($P < 0.05$). In a second set of experiments, hearts ($n = 6$) were isolated, and their LV function was evaluated before, during, and after cocaine exposure. In these experiments, cocaine was added to the perfusate in increments to produce concentrations of 5, 10, and 15 mg/liter. After LV function was evaluated at the highest cocaine dose, cocaine-free perfusion conditions were restored, and LV function was reevaluated. In these experiments, cocaine produced a dose-dependent decrease in LV function that readily reversed when cocaine-free perfusion was reinstated. We conclude that cocaine diminishes LV contractility, and that the diminished cardiac performance may not readily reverse after *in vivo* exposure. Moreover, the rapid restoration of cardiac performance after exposure to cocaine *in vitro* suggests that the mechanism operating *in vivo* involves more than a simple direct action on the myocyte. Catecholamine cardiotoxicity does not appear to be a primary factor.** [P.S.E.B.M. 1993, Vol 203]

The results from several studies using both conscious and anesthetized animal preparations show that acute administration of cocaine decreases myocardial performance (1–4). In these studies, cardiac performance was evaluated soon after cocaine administration while the drug was active in the animal. Thus, the depressed cardiac performance may have been a manifestation of cocaine's anesthetic properties and, if so, should have readily reversed after the drug was metabolized. This hypothesis is consistent with the data of Stewart *et al.* (5), which show that cocaine-induced decreases in intracellular Ca^{2+} transients of isolated rat ventricular myocytes are quickly restored when the drug is removed from the superfusate bathing the cells. Although no indices of function were measured in this study, diminished cardiomyocyte performance would be expected to accompany the smaller Ca^{2+} transients. In this regard, Perreault *et al.* (6) found that both the intracellular Ca^{2+} transient and contractile function were diminished in ferret papillary muscle exposed to cocaine concentrations greater than 10^{-5} *M*. Both investigative groups concluded that cocaine's anesthetic action on the Na^+ channel was the most likely reason for the decreased Ca^{2+} transients.

Although the study of Stewart *et al.* suggests that the cocaine-induced depression of cardiac function *in vitro* can be rapidly reversed, the actions of cocaine *in vivo* may be more complex, and left ventricular (LV) function might remain depressed after cocaine has been degraded in the body. One such complexity may involve cocaine's well known ability to potentiate the actions of the sympathetic nervous system (SNS). We previously reported that plasma norepinephrine concentrations are markedly elevated, and LV function is diminished after massive SNS activation in the anes-

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thetized rabbit (7, 8). The deterioration of LV performance could be prevented by administering catecholamine antagonists before activating the SNS (8), which indicates that the functional impairment is caused by excessive concentrations of catecholamines. Cocaine administration also increases plasma catecholamine concentrations (9–11) by inhibiting neuronal uptake of norepinephrine (12) and causing a centrally mediated increase in sympathetic activity to the adrenal medulla (9). Chiueh and Kopin (9) administered cocaine (10 mg/kg intra-arterially) to conscious rats and reported plasma catecholamine concentrations that were similar to those we observed in rabbits after massively activating the SNS. Thus, cocaine, at least at higher doses, may lead to a depression of LV function by causing an excessive release of catecholamines. Unlike the depressed contractility that results from the anesthetic properties of cocaine, this functional impairment would not immediately reverse after the removal of cocaine.

Accordingly, the goal of this study was to determine whether the depressed LV function associated with acute cocaine administration in intact rabbits persists beyond the time that the heart is exposed to cocaine. To make this determination, hearts were isolated from animals 150 min after the administration of cocaine, and LV function was evaluated *in vitro* under cocaine-free perfusion conditions. For comparison, LV function was also evaluated in hearts that were first isolated and then exposed to cocaine.

Materials and Methods

***In Vivo* Cocaine Administration.** In every experiment, both a control and an experimental New Zealand White rabbit (~3.5 kg) of either sex were studied at the same time. Except for receiving cocaine, the control rabbits were subjected to the same surgical and experimental manipulations as the cocaine-treated rabbits. Cocaine doses of 5 and 10 mg/kg were used in this study, because these doses are considered to produce blood concentrations that approximate those produced in humans after a large intravenous injection or after inhaling "crack" smoke. Moreover, similar doses have been commonly employed by others to study the acute effects of cocaine on the cardiovascular system (1–4, 9). Each of the two studies described below consisted of seven control and seven experimental animals.

Cocaine, 5 mg/kg. Two conscious animals, a control and an experimental, were placed in standard rabbit-restraining devices. Under local anesthesia (2% lidocaine), the central ear artery and vein were dissected from the surrounding tissue and cannulated with 22-gauge intravenous placement units (Angiocath; Deseret, Sandy, UT) to measure arterial pressure, to collect arterial blood samples for plasma catecholamine determinations, and for intravenous administration of cocaine (Sigma Chemical Co., St. Louis, MO). Baseline arterial pressure and heart rate measurements were taken 15–30 min after the surgical procedures were completed, and then 5 ml of saline containing cocaine were infused intravenously over 14 min to a cumulative dose of 5 mg/kg free base (5.6 mg/kg cocaine hydrochloride). The control animal received a comparable volume of saline without cocaine during this time. Arterial blood samples were taken immediately before and at the end of the cocaine infusion to determine norepinephrine and epinephrine concentrations with high performance liquid chromatography, as described previously (7). Two and one-half hours after cocaine administration, both animals were anesthetized with sodium pentobarbital (30 mg/kg), and their hearts were removed to evaluate LV function (described below).

Cocaine, 10 mg/kg. In this study, the animals were anesthetized before receiving cocaine to avoid the extreme agitation, convulsions, and death that often occur in conscious animals exposed to higher concentrations of the drug (13, 14). The animals were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with room air at a frequency of 20 breaths/min and with end-inspiratory pressure set at 15 cm H_2O. The right or left femoral artery was cannulated with polyethylene tubing (PE 90) to monitor arterial pressure and withdraw blood for catecholamine determinations. The corresponding femoral vein was cannulated with a 22-gauge intravenous placement unit so that cocaine (10 mg/kg administered over 14 min) or supplemental doses of anesthetic could be administered. Except for these differences, all other experimental procedures were performed as described for the 5 mg/kg cocaine dose in conscious rabbits.

LV function was evaluated *in vitro* 2.5 hr after the onset of cocaine treatment. This time was selected because it corresponds to the time we evaluted LV function after massive SNS activation (7, 8). Additional details concerning this 2.5-hr period were provided previously (8).

***In Vitro* Cocaine Administration.** These experiments were conducted so that the effect of cocaine on the *in vitro* heart could be compared to its effect on the heart of the intact animal. Hearts were isolated from six pentobarbital-anesthetized rabbits and perfused as described above. After evaluating LV function under control conditions, cocaine was added to the perfusate in 5 mg/liter increments to a final concentration of 15 mg/liter. LV function was reevaluated under steady-state conditions 5–10 min after each increase in cocaine concentration. After the highest cocaine dose was studied, control perfusion conditions (cocaine-free) were reestablished, and LV function was evaluated a final time. Coronary perfusate flow was measured with LV end-diastolic volume set at 1.6 ml under the two control conditions (before and after cocaine treatment) and at each concentration of cocaine.

To determine whether the duration of cocaine exposure could explain any differences in LV function between the *in vivo* and *in vitro* experiments, two additional hearts were isolated, and their LV functions were evaluated under control conditions. Cocaine (15 mg/liter) was then added to the perfusate, and LV function was evaluated during a 2.5-hr period, comparable in duration to that of our *in vivo* experiments. After the 2.5-hr treatment period, the cocaine-containing perfusate was replaced with normal perfusate, and a final evaluation of LV function was made.

Isolated Heart Preparation and Assessment of LV Function. Heparin (1000 units/kg iv) was administered to rabbits under pentobarbital anesthesia, and midline thoracotomies were performed. The hearts were quickly removed from the thoracic cavity, immediately arrested in chilled (0°C) physiologic saline, and prepared for coronary arterial perfusion. The perfusion system consisted of a reservoir, placed above the heart at a hydrostatic level that provided a driving pressure of 80 mm Hg, and an in-line heat exchanger that warmed the perfusate to 32°C. A T-connector was placed in the tubing leading from the heat exchanger so that the experimental and the control hearts could be mounted on the perfusion system simultaneously. This ensured that they were both perfused under identical conditions with the same solution. The hearts were mounted on the perfusion system by cannulating the aortas in a retrograde manner. Coronary perfusion was accomplished by directing the bicarbonate-buffered perfusate from the reservoir toward the closed aortic valve, thus driving the fluid through the coronary circulation. Coronary flow was determined from a timed measurement of the perfusate as it discharged from the pulmonary artery. The venous effluent was collected in a container and pumped back to the reservoir. The perfusion pressure was kept constant with an overflow system between the reservoir and the collecting container. The perfusate was gassed with 95% O_2-5% CO_2 and had the following composition (millimoles per liter): NaCl, 89.0; KCl, 5.0; $CaCl_2$, 2.0; $MgSO_4$, 1.0; $NaHCO_3$, 24.0; Na_2HPO_4, 1.0; CH_3COONa, 20.0; and dextrose, 10.0. The pH and PO_2 of this solution were 7.4 and approximately 550 mm Hg, respectively.

After the hearts were attached to the perfusion system, the atrioventricular node was crushed with forceps. Electrodes were then placed against the basal epicardial surface of each LV, and the LVs were paced at 90 beats/min (Grass SD9 stimulator). LV systolic and diastolic pressures of each isovolumically contracting heart were measured by placing a saline-filled balloon, connected to a pressure transducer, into the left ventricle through a small incision in the left atrium. LV preload could be changed by varying the volume of fluid in the balloon. Initially, 1.6 ml of fluid were added to each balloon. When steady-state LV systolic and diastolic pressures were attained for both hearts, balloon volume was decreased to 0.1 ml, and the systolic and diastolic pressures were recorded. Then the LV end-diastolic volume was increased in 0.3-ml increments every 3 min until balloon volume was 1.6 ml. This provided LV systolic and diastolic pressures at six different preloads along the ascending limb of Starling's curve. This procedure was performed in duplicate, and the peak systolic and end-diastolic pressures for each preload were averaged over the two runs. The mean pressures were then plotted as a function of LV end-diastolic volume to generate Starling curves that were used to evaluate LV performance. The pressure-volume relationship of each balloon was evaluated and judged to be acceptable if no detectable pressures were generated by the balloon over the range of volumes used to assess LV function. At the end of the experiment, the atria and right ventricular free wall were removed, and the LV weighed.

Statistical Analysis. Analysis of variance for two-factor experiments with repeated measures was used to determine whether heart rate, mean arterial pressure, and LV function were significantly different among control and experimental groups. The statistical significance of mean differences in plasma catecholamine concentration, LV weight, and coronary perfusate flow of the hearts while they were studied *in vitro* was tested with a one-factor analysis of variance. When the analyses of variance indicated significance, Neuman-Keuls post-hoc testing was performed to determine which individual mean values were statistically different ($P < 0.05$). A linear trend test with equally spaced coefficients was performed to determine whether there was a significant relationship between cocaine concentration and the degree of LV dysfunction. All values reported in the text, tables, and figure legends are the mean ± SE.

Results

***In Vivo* Studies.** The effect of cocaine on mean arterial pressure is shown in Figure 1. When the 5 mg/kg dose of cocaine was administered to conscious rabbits (Fig. 1, upper panel), mean arterial pressure increased from 86 ± 4 to 120 ± 6 mm Hg ($P < 0.01$) during the cocaine infusion period. Arterial pressure increased rapidly during the first 1–2 min of cocaine treatment and then continued to increase slowly during the remainder of the infusion period. The hypertension quickly subsided after the completion of the infusion period. A statistically significant increase in arterial pressure also occurred in the control animals during the cocaine infusion period that was probably a response to the restlessness exhibited by the cocaine-treated animals, because both rabbits were side by side in their respective restrainers. Baseline heart rates of 216 ± 10 and 207 ± 8 beats/min in cocaine-treated

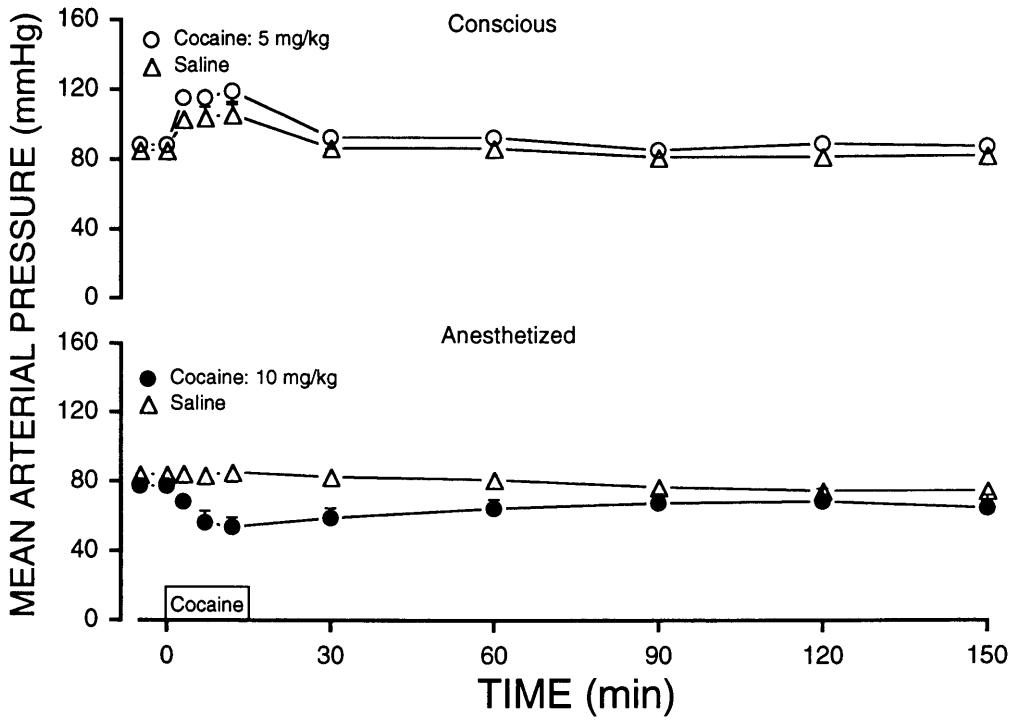

Figure 1. Differential hemodynamic responses to cocaine. The lower cocaine dose caused mean arterial pressure to increase in conscious rabbits (upper panel), whereas the higher dose produced hypotension in anesthetized animals (lower panel).

and control animals, respectively, did not change significantly.

The arterial pressure response of anesthetized rabbits to the 10 mg/kg cocaine dose (Fig. 1, lower panel) was different from that of conscious animals. In this group, mean arterial pressure decreased from 77 ± 5 to a minimum of 52 ± 5 mm Hg ($P < 0.03$) after 12 min of cocaine treatment and partially recovered to 84% of precocaine pressure by the end of the observation period. Heart rate also decreased from 236 ± 9 to 213 ± 6 beats/min ($P < 0.02$) during cocaine infusion, but returned to baseline by 30 min. Mean arterial pressure of control animals remained constant over the first 90 min and then decreased by about 10 mm Hg over the final hour of the experiment. Heart rate remained constant throughout the experiment in these animals.

Figure 2 shows the plasma norepinephrine and epinephrine concentrations immediately before and after 14 min of cocaine treatment. In the conscious animals treated with the lower dose of cocaine, the norepinephrine concentration increased from a mean baseline value of 409 ± 54 to 2,088 ± 694 pg/ml at the end of the 14-min cocaine infusion period ($P < 0.05$). The mean plasma epinephrine concentration increased from 179 ± 41 to 2,547 ± 1,604 pg/ml during this time. However, this increase was not statistically significant, since most of it was due to an increase of about ~12,000 pg/ml observed in one animal. Modest increases in epinephrine concentration of less than 300 pg/ml generally occurred in the other experiments. In contrast to those in conscious animals, the mean plasma concentrations of norepinephrine and epinephrine did not increase in the anesthetized rabbits treated with the 10 mg/kg dose.

Left ventricular systolic function was significantly diminished in the hearts taken from rabbits treated with the 10 mg/kg dose of cocaine ($P < 0.05$). As shown in Figure 3, the ability of these hearts to generate isovolumic pressure was less at all six preloads studied, which resulted in a downward displacement of the LV systolic function curve compared with the curve representing control hearts. Although the downward shift in the mean Starling curve displayed by the hearts of the 5 mg/kg cocaine-treated group was not statistically significant, there was a significant relationship ($P < 0.01$) between cocaine dose and the degree of LV dysfunction. Diastolic function was not affected by cocaine at any dose studied. LV mass and coronary perfusate flow (Table I) were the same in all three groups of hearts.

***In Vitro* Studies.** The effects of stepwise increases in cocaine concentration on the *in vitro* heart are shown in the upper panel of Figure 4. Cocaine concentrations from 5 to 15 mg/liter produced dose-dependent decreases in LV pressure development. However, the decrease in LV performance was rather modest. At an end-diastolic volume of 1.6 ml, the 5, 10, and 15 mg/liter doses of cocaine decreased LV pressure development by only 3.7%, 11.7%, and 16.9%, respectively.

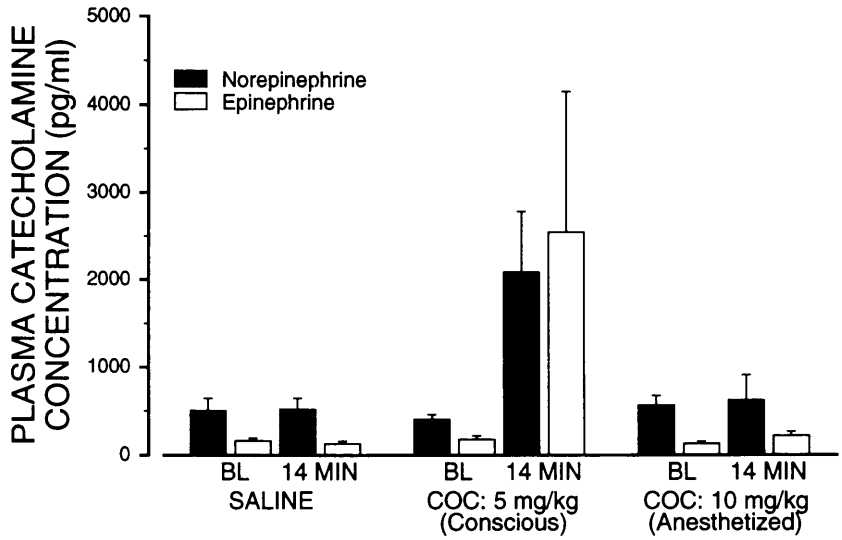

Figure 2. The effect of cocaine on plasma norepinephrine and epinephrine concentrations. Baseline catecholamine concentrations were not affected by the higher dose of cocaine in anesthetized rabbits. COC, Cocaine; BL, baseline.

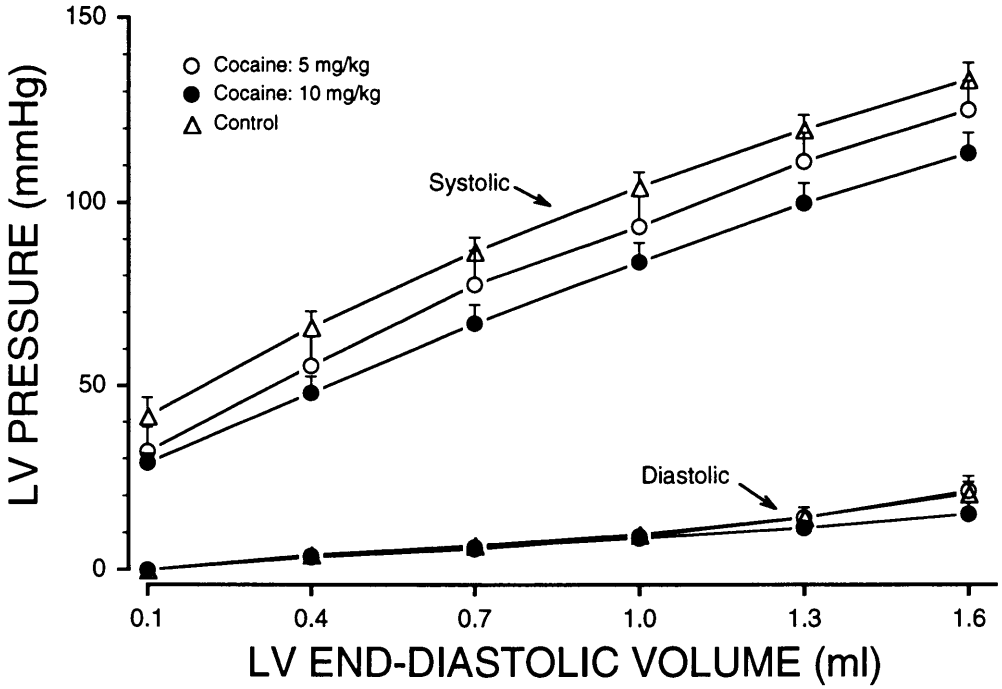

Figure 3. LV function of hearts removed from rabbits 2.5 hr after cocaine administration. A dose-dependent decrease in LV systolic function is apparent. LV diastolic function did not appear to be affected by cocaine. LV function was evaluated under cocaine-free conditions.

Table I. LV Mass and Coronary Perfusate Flow During *In Vitro* Perfusion of Hearts from Animals Treated with Cocaine

Cocaine (mg/kg)	LV mass (g)	Coronary perfusate flow (ml/min)
0	5.1 ± 0.4	25.2 ± 1.8
5	5.5 ± 0.5	26.8 ± 3.2
10	4.5 ± 0.4	26.9 ± 1.9

The slight decrease in LV function at the 5 mg/liter dose was not statistically significant. When cocaine-free perfusion conditions were reestablished after exposure to the highest cocaine dose, the LV systolic dysfunction completely reversed within 10 min. Mean coronary perfusate flow before cocaine treatment of 28.3 ± 3.2 ml/min did not change with any of the doses of cocaine. These experiments were completed in approximately 45 min.

Two additional experiments were conducted to determine if LV function recovers after hearts are ex-

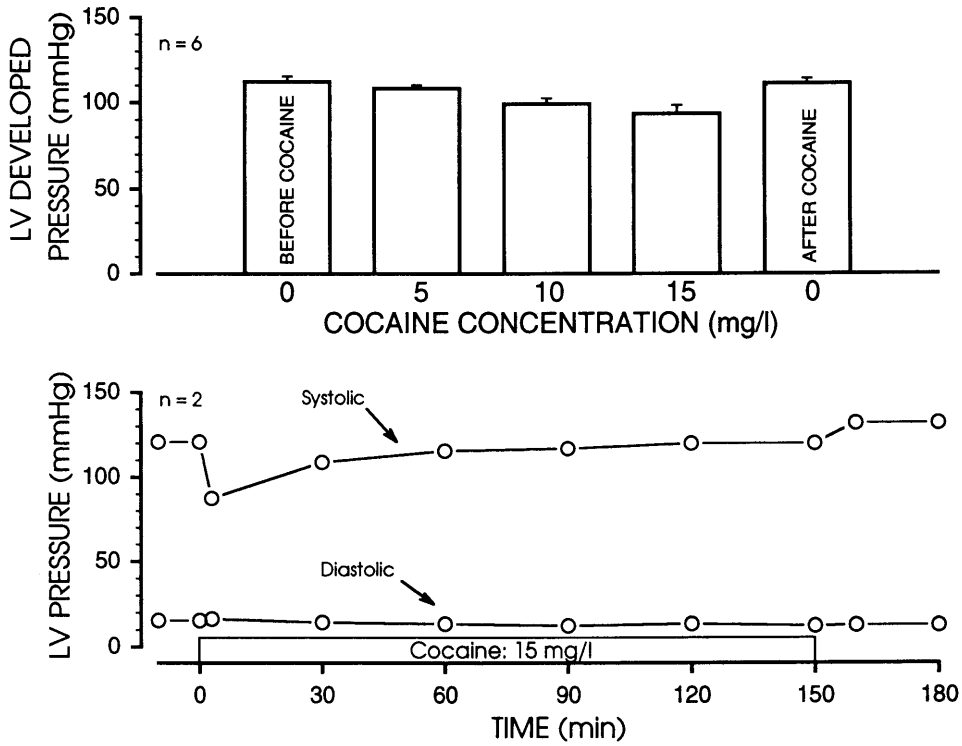

Figure 4. The effect of cocaine on the isolated heart. *In vitro* cocaine treatment produced a dose-dependent decrease in LV pressure-generating ability that quickly reversed when cocaine-free conditions were reestablished (upper panel). Even in the presence of cocaine, the initial depression in LV function reversed in about 2 hr (lower panel).

posed to cocaine (15 mg/liter) for the same duration (2.5 hr) as hearts in the *in vivo* study. As shown in Figure 4 (lower panel), LV systolic pressure decreased (28%) immediately after the addition of cocaine to the perfusate. However, LV function continued to improve with time and was not different from baseline by 2 hr even though cocaine was still present. When the cocaine-containing perfusate was replaced with normal perfusate after 2.5 hr, LV systolic pressure increased to 110% of precocaine levels.

Discussion

The results of our *in vitro* experiments show that cocaine produces a dose-dependent decrease in contractile function that quickly reverses upon removal of the drug. This was not surprising, but it was somewhat surprising that the degree of dysfunction was rather modest even at the highest cocaine dose (15 mg/liter). More surprising was our observation that at this dose of cocaine, the depressed LV function completely reversed in about 2 hr even though cocaine was still present in the perfusate. These curious findings may be the end result of a complex interplay between cocaine's opposing actions on the myocardium. Its ability to inhibit norepinephrine uptake would tend to enhance mechanical performance, whereas its anesthetic action diminishes Ca^{2+} transients and contractile function (5, 6). The predominant effect may be a function of both time and cocaine dose and may explain why lower concentrations seem to augment (6, 15), whereas higher concentrations consistently depress, LV contractility (1–4, 6).

In contrast to our findings regarding *in vitro* cocaine exposure, we found that the LV function of hearts removed from animals after *in vivo* cocaine treatment remains depressed despite perfusion with cocaine-free perfusate. The reasons for the persistent LV dysfunction are not clear. One possibility is that cocaine may have remained in the myocardial tissue and continued to exert its negative inotropic effect despite perfusion with cocaine-free perfusate. However, this explanation is unlikely, because there was no evidence that this occurred after *in vitro* cocaine exposure. In these experiments, the diminished LV function reversed immediately after replacing the cocaine-containing perfusate with normal perfusate. Furthermore, LV function completely recovered in the two isolated hearts exposed to the 15 mg/liter cocaine dose within 2 hr even though the hearts were still exposed to cocaine. Thus, it seems improbable that the diminished LV function after *in vivo* cocaine could have resulted from a failure to wash cocaine from binding sites within the tissue.

Since cocaine potentiates the actions of the sympathetic nervous system (12) and may result in relatively large increases in plasma catecholamine concentrations (9–11), we had hypothesized that cocaine could produce a persistent LV dysfunction through a mechanism similar to the one that impairs LV function after

massive SNS activation. We have recently shown that SNS-induced LV dysfunction is due to toxic concentrations of catecholamines (8). However, in the present study, the plasma catecholamine concentration was not elevated in the rabbits treated with the 10 mg/kg cocaine dose. This may have been due to the anesthetic. Nevertheless, hearts from these animals demonstrated a significant reduction in LV function. In contrast, the conscious rabbits that received the lower dose of cocaine had a substantial increase in plasma norepinephrine concentration, yet LV function was diminished to a lesser extent. Thus, if the plasma catecholamine concentration is at least a qualitative indicator of tissue levels, catecholamine cardiotoxicity does not appear to be the primary factor that produced the persistent LV dysfunction after *in vivo* cocaine administration in these experiments. Furthermore, since LV functions of anesthetized and conscious control rabbits were identical, anesthesia does not seem to explain the greater LV dysfunction observed in the rabbits exposed to the higher cocaine dose.

The impaired cardiac performance observed after *in vivo* cocaine exposure may have resulted from myocardial ischemia. Although Friedrichs *et al.* (16) observed coronary vasodilation during cocaine administration, several investigators have reported decreases in either coronary blood flow or coronary arterial diameter (3, 4, 17–21) as well as contraction of isolated coronary and aortic smooth muscles (22, 23) in a variety of species, including humans. The data from recent studies indicate that the vasoconstrictor actions of cocaine involve both adrenergic (17, 22) and nonadrenergic (21, 23) mechanisms. The fact that myocardial infarction has been associated with cocaine use in humans with normal coronary arteries (24, 25) suggests that the drug can cause substantial reductions in coronary blood flow. Moreover, a relatively brief period of ischemia is all that is needed to produce myocardial stunning (26). Although ischemia is a plausible explanation for the diminished LV performance after exposure to cocaine, additional studies are needed to confirm (or refute) its role in this disorder.

The apparent anomaly between cocaine dose and plasma norepinephrine concentration that we report in this study may reflect differential responses to cocaine between conscious and anesthetized rabbits. In conscious animals, an increase in arterial pressure typically follows cocaine administration (2, 10, 14, 15, 17, 27), whereas a period of hypotension may be observed when comparable doses of cocaine are given to anesthetized animals (3, 16, 19, 28). Our observations of increased arterial pressure and increased plasma norepinephrine concentrations in conscious rabbits suggest that the two could be causally related. The fact that catecholamine concentration (and very likely sympathetic activity) did not increase in the anesthetized rabbits with the higher dose of cocaine could explain why we and others have not observed systemic hypertension under these conditions.

The results of this study indicate that there are at least two independent actions of cocaine that can diminish myocardial performance. Cocaine produces a readily reversible myocardial dysfunction that probably stems from its anesthetic properties. In addition, our results also show that cocaine may produce a longer term LV dysfunction that continues to be evident after the drug has been eliminated from the body. Although the mechanism for this persistent LV dysfunction is uncertain, catecholamine cardiotoxicity does not appear to be a primary factor.

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