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Chronic Exposure to Cocaine Binging Predisposes to an Accelerated Course of Dilated Cardiomyopathy in Conscious Dogs Following Rapid Ventricular Pacing

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Chronic Cocaine predisposes to DCM

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ABSTRACT

Background: Despite extensive study, the extent to which cocaine use predisposes to cardiac injury remains unknown. We hypothesized that chronic cocaine binging would increase susceptibility to a subsequent cardiac insult, even in the absence of demonstrable effects on baseline hemodynamics. **Methods:** We studied progression of dilated cardiomyopathy (DCM) induced by rapid ventricular pacing (240 bpm) in 5 conscious, chronically instrumented dogs, after exposure to repetitive cocaine binging (COC) in the form of 4 consecutive 1 mg/kg iv boluses daily for 8 days, to simulate human cocaine abuse. We compared the results to 9 control dogs (CON) undergoing the exact pacing protocol, without prior cocaine exposure. **Results:** Baseline hemodynamics were not significantly altered by chronic cocaine exposure. Following 2 weeks of pacing, COC dogs exhibited accelerated progression to DCM, depressed plasma nitric oxide (NO) levels (CON: 17± 2, COC: 10± 2 μM, $p < 0.05$) and a significantly greater increase in plasma epinephrine (CON: 33±6, COC: 104±24 pg/ml). After only 2 weeks of pacing, COC dogs demonstrated progressive DCM of a magnitude comparable to end stage pacing induced DCM. **Conclusions:** Chronic cocaine binging increases susceptibility to a subsequent myocardial insult and accelerates progression of DCM in conscious dogs following rapid pacing. These data suggest that while chronic cocaine use alone may not affect myocardial function, it predisposes to greater susceptibility to a superimposed insult.

INTRODUCTION

Cocaine is responsible for the greatest number of hospitalizations in US attributable to illicit drug use (DAWN report, NIDA 2001). According to a survey, it was reported that more than 25 million people had used cocaine at some time in their life and 1.5 million were chronic users (Substance Abuse and Mental Health Services Administration, 2000). The effects of cocaine on the cardiovascular system are multifaceted and remain incompletely understood. Cardiovascular manifestations of cocaine abuse include chest pain, myocardial ischemia and infarction, arrhythmias, infective endocarditis, aortic dissection and development of dilated cardiomyopathy and heart failure (Kloner et al., 1992; Mouhaffel et al., 1995; Weiner et al., 1986). There have been increasing numbers of reports of dilated cardiomyopathy in cocaine abusers. Weiner et al. (1986) were the first to describe the occurrence of DCM in the absence of atherosclerotic CAD in two patients who were cocaine abusers.

Chronic cocaine use in young men who were normotensive and had no symptoms or signs of heart diseases had electrocardiographic and echocardiographic abnormalities including LV hypertrophy (54%), LVEF <0.45(4%), increased QRS voltage (23%) and episodes of ST-segment elevation on ambulatory monitoring (33%)(Chakko et al., 1995). However, the mechanism where by chronic cocaine use predisposes to myocardial injury remains incompletely understood.

There has been both confusion and controversy as to whether cocaine use predisposes to decreased myocardial contractility. Much of the evidence of cocaine induced myocardial depression comes from studies in anaesthetized animals. Prior studies from our laboratory (Shannon et al., 1996; Stambler et al., 1993) have failed to demonstrate adverse effects of acute cocaine administration (1mg/kg) in conscious dogs. The major effects of cocaine under the

circumstances are mediated by increased sympathetic nervous system activation. More over, we and others have demonstrated that tolerance develops to the LV and systemic hemodynamic effects of cocaine when administered in a binge fashion (Shannon et al., 1996; Fischman and Schuster, 1982; Fischman et al., 1985; Foltin and Fischman, 1991; Ambre et al., 1991; Tella et al., 1999). Similarly, we have shown that cocaine produces rapid and exaggerated chronotropic, inotropic, and coronary vasoconstrictor responses in conscious dogs with established dilated cardiomyopathy induced by rapid pacing (Mathier et al., 2002). However, relatively few studies have examined the effects of repetitive cocaine exposure over time as consumed by human cocaine users.

Thus, the purpose of the present study was to determine the cardiovascular consequences of chronic cocaine binging in conscious dogs using dose and frequency of administration that mimic human use. A second goal was to determine if chronic cocaine binging predisposes to or accentuates the cardiovascular effects of a superimposed insult and by what mechanisms.

Methods

Instrumentation

Fourteen mongrel dogs of either sex weighing 14-19 kg were instrumented as described below. Dogs were pre-medicated with a combination of intramuscular injection of Atropine (0.05 mg/kg) and Acepromezine (0.1-0.5 mg/kg). After approximately 20 minutes, Pentothal (5% of 1 gm) was administered intravenously for induction and intubation. Inhalational anesthesia was maintained by isoflurane (1.0-1.5%) with 2 liters 100% oxygen.

Using sterile technique through a left atrial thoracotomy, Tygon catheters were implanted in the descending thoracic aorta, right and left atrium. A Silastic catheter was implanted in the coronary sinus. A solid-state miniature pressure transducer (Konigsberg Instrument) was

implanted in the apex to measure LV pressures. A suture less pacing lead was attached to the right ventricular free wall and stainless steel pacing leads was attached to the left atrial appendage. The left circumflex coronary artery was dissected free for a distance of ~ 3 cm, taking care not to damage the vessel adventitia and surrounding nerves. Transonics transit time flow probes were implanted around the circumflex coronary artery for measuring coronary blood flow and around the proximal aorta to measure aortic flow. Ultrasonic dimension crystals were placed in the long and short axis across the endocardial surface on the left ventricle. Following completion of the instrumentation, catheters and wires were tunneled subcutaneously and externalized intracapsularly. The thoracotomy was closed in layers.

The dogs were allowed to recover from the surgical procedure for two weeks, during which time they were trained to lie quietly on the experimental table in a conscious, unrestrained state. Hemodynamic measurements were made with the dogs fully awake, lying quietly on their right side. Animals were maintained in accordance with the "Guide for the Care and Use of Laboratory Animal Resources" [DHHS Publication NO (NIH) 86-23, Revised 1996] and the guidelines of the Institutional Animal Care and Use Committee at Allegheny General Hospital.

Experimental measurement

Aortic and left atrial pressures were recorded from the implanted catheters using Triton System 6-Model 200, (San Diego, CA) calibrated on the day of each experiment using a mercury manometer. Left ventricular pressure was measured using the implanted solid-state micromanometer. The micromanometer was calibrated in vitro using a mercury manometer and in vivo using the aortic and left atrial catheters. Coronary and aortic blood flows were measured using a Transonics flowmeter (T206 Series) Ithaca, NY. Measurements of plasma norepinephrine and epinephrine concentration were made using a commercially available high-

pressure liquid chromatography kit (Chromosystems Instruments and Chemicals, Munich, Germany). Plasma NO levels were carried out using a kit purchased from R&D Systems, Inc. (Minneapolis, MN).

Two weeks after surgery, five of dogs (n=5, COC) were administered cocaine hydrochloride (1 mg/kg over 1 minute) dissolved in normal saline, for four doses in a day with 20 minutes in between the doses. Drug was administered via the right atrial catheter. The individual dose was chosen as the maximally tolerated dose in a conscious dog that did not result in uncontrollable agitation based on our prior studies (Stambler et al., 1993, Shannon et al., 1993 and Shannon et al., 1995). This protocol was repeated for total of eight days (four days a week for 2 weeks in continuation). Nine dogs served as a control. Hemodynamic data were recorded daily during the binge administration and compared prior to and following the chronic cocaine exposure.

Three days after completion of the binging protocol, rapid ventricular pacing was instituted at 240 beats/min in both the group of dogs (CON and COC) using a programmable pacemaker (Pace Medical, Waltham, MA) worn externally in a protective vest. Pacing was continued until the dogs developed signs and symptoms of severe heart failure. Hemodynamic measurements were made during sinus rhythm after the pacer had been discontinued for at least 30 minutes.

Data Analysis

Digital Instrumentation Cassette Recorder (PC216Ax, Sony Magnescale Inc.) was used to record hemodynamic data. The first derivative of left ventricular pressure (dP/dt) was derived continuously from the LV pressure signal using an online differentiator calibrated against a

triangular wave signal of known slope. Mean arterial pressure was derived continuously from the phasic aortic pressure signal using as online electric filter. Stroke Volume ((i) SV=1000*CO/HR), Left Ventricular Ejection Fraction ((ii) LVEF=100* (SV/LVEDV)), Left Ventricular End-Diastolic Volume ((iii) LVEDV=($LVEDD^3$)/1000) and Systemic Vascular Resistance ((iv) SVR=80*(MAP-RAP/CO)) were derived using shown equations.

Statistical analysis

All data are expressed as mean ± standard error of the mean. Comparisons of measured parameters between groups were made using repeated measures analysis of variance on a SPSS software program.

RESULTS

The Effects of Chronic Cocaine Binging on LV and Systemic Hemodynamic

Figure 1 summaries the effects of repetitive cocaine binging on left ventricular systolic (LVP), LV end diastolic (LVEDP), and mean arterial pressures (MAP) as well as LV dP/dt. The data are summarized based on response to the cocaine binging on day 1, day 4, and day 8 of the protocol. The first dose of cocaine caused a marked increase in LVP, LVEDP, and MAP that was transient, returning towards but not back to baseline within 20 minutes. Subsequent doses of cocaine demonstrated an attenuated response, such that, by the fourth dose, there was little hemodynamic response. A similar pattern was observed on day 4 and day 8. Notably, the chronic exposure to the binging protocol did not alter the baseline measures (Table 1). A similar pattern was observed with LV dP/dt, where the first dose of cocaine was associated with a marked positive inotropic effect while tolerance developed to the subsequent doses. The pattern was identical on day 4 and day 8 of the protocol. Notably, there was no evidence that chronic cocaine

exposure over 8 days leads to depressed myocardial contractility or altered systemic or ventricular hemodynamics (Table 1).

Table 2 revels that there was no statistically significant change in baseline resting hemodynamics including LV systolic and diastolic function in the dogs exposed to chronic cocaine binging when compared to same dogs before cocaine administration.

The Hemodynamic Effects of Rapid Ventricular Pacing (RVP) following Chronic Cocaine Binging

Figure 2 illustrates the effects of rapid ventricular pacing on LVP, LVEDP, LV dP/dt and MAP in control and dogs exposed to chronic cocaine binging. The decrease in the LVP after initiation of pacing was more rapid and of a greater magnitude in cocaine exposed dogs compared to control dogs. Similar observations were also evident for LV dP/dt and MAP. An increase in LVEDP was of a greater magnitude at the 2-weeks in the dogs exposed to chronic cocaine binging. Figure 3 shows the effects of rapid pacing on heart rate, stroke volume and posterior wall thickness. The compensatory tachycardia occurred more rapidly and was of a greater magnitude in dogs exposed to chronic cocaine binging compared to control dogs.

While the decline in CO was not statistically different in the two groups at 2 weeks of RVP (CON: 2.2±0.3 to 1.9±0.2 vs. COC: 2.6±0.3 to 2.2±0.3, $p=0.43$), stroke volume fell to a significantly greater extent in dogs exposed to chronic cocaine binging compared to control (CON: 27±4 to 20±3 vs. COC 29±3 to 17±2, $p<0.05$). The failure to observe a difference in the CO responses was attributed to greater compensatory tachycardia in dogs exposed to chronic cocaine binging compared to control (CON: 85±4 to 99±6 vs. COC 91±6 to 131±6, $p<0.05$).

Regional Posterior wall thickness decrease to a much greater extent during 2 weeks of pacing in the cocaine treated animals (Table 3). With respect to global ventricular function,

LVEF (CON: 44±7 to 26±3 vs. COC 50±3 to 22±3) declined significantly in both groups and to a greater extent in the cocaine treated dogs, but the difference was p=0.056.

Although the decrease in the coronary blood flow was not statistically significant at the end of 2 weeks of pacing, coronary blood flow/beat and coronary perfusion pressure were decreased to a significantly greater extent in dogs exposed to chronic cocaine binging compared to control.

The Neurohormonal Effects of Rapid Ventricular Pacing (RVP) following Chronic Cocaine Binging

Table 3 illustrates that there was no difference in baseline catecholamines and nitric oxide (NO) between control dogs and dogs exposed to chronic cocaine binging prior to pacing. Figure 4 illustrates the alterations in plasma catecholamines and NO during sustained rapid pacing. Norepinephrine levels increased modestly in both groups following 2 weeks of RV pacing. Notably, the relative increase in plasma norepinephrine was comparable between groups. However, cocaine-treated animals demonstrated a very significant increase in plasma epinephrine levels. RVP was associated with greater decrease in NO (CON: 17± 2, COC: 10± 2 μM, $p < 0.05$) at 2 weeks.

DISCUSSION

In the present study, we examined whether chronic cocaine binging was associated with the development of LV and systemic hemodynamic abnormalities in conscious dogs. We observed no significant abnormalities in baseline hemodynamics despite repetitive administrative of cocaine over a two week period. However, chronic cocaine binging predisposed to an accelerated course of dilated cardiomyopathy following rapid pacing in these dogs. These data

demonstrate for the first time that while cocaine binging may itself not cause hemodynamic perturbations, it may predispose to accelerated courses following superimposed cardiac insults.

Prior studies have demonstrated conflicting results with respect to whether continuous cocaine administration leads to altered cardiac contractility as the signature feature of dilated cardiomyopathy (Moritz et al., 2003(a); Sutliff et al., 1996). Many of these differences can be reconciled based upon different experimental models used. Under circumstances in which anesthetized animal models have been studied, acute cocaine administration has been shown to be a myocardial depressant (Fraker et al., 1990; Hale et al., 1991; Hale et al., 1989; Bedotto et al., 1988; Hayes et al., 1991). In contrast, several laboratories, including our own, have demonstrated that in conscious, chronically instrumented dogs, cocaine has a sympatho-stimulatory effect in increasing myocardial contractility and heart rate (Stambler et al., 1993; Shannon et al., 2000; Shannon et al., 1993; Shannon et al., 1995; Shannon et al., 1996; Kiritsy-Roy et al. 1990, Knuepfer and Branch, 1992; Wilkerson et al., 1988). The critical dependence of cocaine on the integrity of sympathetic nervous system likely reconciles these differences. In contrast, under anesthetized conditions when sympathetic tone is altered, the effects are predominantly those of its local anesthetic properties leading to depressed contractility (Wilkerson et al., 1991; Crumb and Clarkson, 1990; Przywara and Dambach; 1989).

Most prior studies have also examined the acute effects of cocaine or have administered cocaine in a continuous fashion, intraperitoneally (Mortiz et al., 2003(a)), subcutaneously, or intravenously (Nunez et al., 1997; Tella et al., 1999). However, these protocols do not closely recapitulate the habitual use of cocaine by humans. The study attempted to recapitulate recreational binging by giving multiple, repetitive doses of cocaine over a two hour period and then repeating this every day for a total of eight days. On any specific day, we observed that

cocaine was associated with an initial stimulatory effect (hypertension, tachycardia, and positive inotropy) followed by the development of tolerance. Prior studies have suggested that cocaine self-administration occurs every 20-30 minutes to recapitulate the "high"(Fischman et al., 1982). Our goal was to mimic this administration. Our laboratory has previously described the mechanism of this tolerance as involving depressed central sympathetic stimulation (Shannon et al., 1996). Notably, this is the first report of tolerance occurring on multiple days following the repetitive administrative of cocaine. Importantly, there is no sensitization that occurs following chronic cocaine binging and no effect on resting hemodynamics. We did not attempted to overcome hemodynamic tolerance by increasing the dose, as 1mg/kg is the near maximal dose of cocaine tolerated by a conscious dog without agitation and seizures (Shannon et al., 1993; Stambler et al., 1993).

In addition, this is the first report that demonstrates that chronic cocaine binging appears to predispose to accelerated course of dilated cardiomyopathy following the imposition of a subsequent cardiovascular insult. In this particular series of studies, we use a well-described reproducible model of rapid ventricular pacing, which has been used extensively in our laboratory (Nikolaidis et al., 2004; Mathier et al., 2002; Nikolaidis et al., 2001). Prior studies from our laboratory have demonstrated that dogs undergoing rapid ventricular pacing developed progressive dilated cardiomyopathy over a 4-week period (Nikolaidis et al., 2001). When acute cocaine was administered to conscious dogs with established DCM, they develop more marked hemodynamic abnormalities than when acute cocaine was administered to a normal dog (Mathier et al., 2002). In this study, we conducted experiments in which the chronic cocaine binging predisposed to an accelerated course of cardiomyopathy. We observed that conscious, chronically instrumented dogs develop severe end stage cardiomyopathy within two weeks of

rapid ventricular pacing when the usual course takes four weeks (Nikolaidis et al., 2001). Furthermore, the development of dilated cardiomyopathy in dogs exposed to chronic cocaine binging was associated with increase in epinephrine at an earlier time point. Notably, plasma norepinephrine levels increased similarly in both groups as reported previously (Nikolaidis et al., 2001). Taken together, these data suggest that dilated cardiomyopathy in chronic cocaine users may represent the cumulative effects of chronic cocaine predisposing to an accelerated course following the superimposition of a cardiovascular insult such as rapid pacing.

We used the highly reproducible model of pacing induced dilated cardiomyopathy because of the consistent and time dependent course of cardiac decompensation. While not a common cause of human cardiomyopathy, tachycardia induced DCM is a recognized cause of demand related LV dysfunction (Gillette et al., 1985; Grogan et al., 1992)

The mechanism by which chronic cocaine binging predisposes to an accelerated course remains unknown. We have shown previously (Nikolaidis et al., 2001) that dilated cardiomyopathy may be accelerated by inhibition of nitric oxide synthesis and lower plasma NO levels. While basal nitric oxide levels were not different, it is conceivable that nitric oxide production (Roig et al., 2000) or metabolism may be altered by chronic cocaine binging. Alternatively, chronic cocaine binging might alter signaling pathways down stream of NO production such as cyclic GMP. Finally, cocaine binging may alter nitroso-redox balance (Kovacic et al., 2005; Moritz et al., 2004; Moritz et al., 2003 (b); Pacifici et al., 2003; Fineschi et al., 2001; Devi and Chan, 1996) by increasing oxidative stress.

Determining the cellular mechanisms associated with the chronic cocaine induced predisposition to development of DCM is the subject of ongoing investigation. Nonetheless, this study is the

first to document a relationship between chronic cocaine use and the development of an accelerated course of DCM following superimposed insult in a conscious large animal model.

Limitations:

We did not measure plasma cocaine levels during the acute binging protocols and we acknowledge this limitation. We have however in previous studies published from our laboratory following similar protocol did prove that there was a progressive increase in both baseline plasma cocaine levels and plasma cocaine responses during the binge protocol (Shannon et al., 1996).

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FOOTNOTES

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Figure Legends

Figure 1

Effects of chronic cocaine binging on left ventricular pressure (LVP), left ventricular end diastolic pressure (LVEDP), LV dP/dt and mean arterial pressure (MAP) on day 1, day 4, and day 8.

Figure 2

Effects of Rapid Ventricular Pacing on left ventricular pressure (LVP), left ventricular end diastolic pressure (LVEDP), LV dP/dt and heart rate in control dogs compared to dogs exposed to chronic cocaine binging.

Figure 3

Effects of Rapid Ventricular Pacing on Mean arterial pressure (MAP), LV ejection fraction (LVEF), Stroke Volume (SV) and Posterior wall thickness in control dogs compared to dogs exposed to chronic cocaine binging.

Figure 4

Effects of Rapid Ventricular Pacing on Epinephrine, Nor-epinephrine and Nitric Oxide (NO) in control dogs compared to dogs exposed to chronic cocaine binging.

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Table 1: Baseline Hemodynamic During Cocaine Binging:

	Exposure to Cocaine Binging		
	Day 1	**Day 4**	**Day 8**
LVP *(mmHg)*	133±4	126±4	140±7
LVEDP *(mmHg)*	13±1	15±3	11±1
LV dP/dt *(mmHg/s)*	2731±137	2618±136	3229±190
MAP *(mmHg)*	102±3	98±3	104±4
CO *(L/min)*	2.7±0.3	2.3±0.1	2.7±0.3
CBF *(ml)*	25±2	26±2	31±3

LVP: left ventricular pressure, LVEDP: left ventricular end-diastolic pressure, LV dP/dt: first derivative of LVP with respect to time, MAP: mean arterial pressure, CO: cardiac output, and CBF: coronary blood flow

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Table 2: Resting Hemodynamic Before and 72 Hours After Chronic Cocaine Binging:

	Cocaine (n=5)	
	Before Cocaine Binging	***After Cocaine Binging***
LVP (mmHg)	133±5	131±6
LVEDP (mmHg)	13±1	13±2
LV dP/dt (mmHg/s)	2731±168	2922±73
MAP (mmHg)	102±3	98±5
LAP (mmHg)	7±1	8±1
HR (bpm)	89±6	91±6
CO (L/min)	2.7±0.3	2.6±0.3
SV (ml)	31±4	29±3
WTH (mm)	2.8±0.3	2.7±0.3
CBF (ml)	25±2	29±3
CBF/beat (μl)	290±30	318±30
LVEDD (mm)	38±1	38±1
LVESD (mm)	33±1	33±1
LVEF (%)	57±5	50±3
SVR (dyne·cm^{-5}·s^{-1})	3234±397	3170±334

CO: cardiac output, SV: stroke volume, WTH: posterior wall thickness, CBF: coronary blood flow, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVEF: left ventricular ejection fraction and SVR: systemic vascular resistance.

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Table 3: The Effects of Rapid Ventricular Pacing on Hemodynamics:

	CONTROLS (n=9)			**COCAINE (n=5)**		
	BASELINE	**2 weeks RVP**	**% Change from Baseline**	**BASELINE**	**2 weeks RVP**	**% Change from Baseline**
LVP (mmHg)	117±4	110±5	-5±3 %	131±6	100±3‡	-23±3 %**
LVEDP (mmHg)	14±1	26±2‡	+77±2 %	13±2	37±3‡	+206±4 %**
LV dP/dt (mmHg/s)	2583±123	1544±74‡	-40±3 %	2922±73	1147±98‡	-61±5 %**
MAP (mmHg)	89±4	89±5	-2±5 %	98±5	80±3†	-20±4 %*
HR (bpm)	85±4	99±6	+16±8 %	91±6	131±6‡	+46±12 %*
CO (L/min)	2.2±0.3	1.9±0.2	-6±9 %	2.6±0.3	2.2±0.3	-15±9 %
SV (ml)	27±4	20±3‡	-20±3 %	29±3	17±2†	-40±8 %*
WTH (mm)	2.7±0.3	2.1±0.3†	-21±7 %	2.7±0.3	1.1±0.4‡	-67±12 %**
CBF (ml)	26±2	28±2	11±10 %	29±3	30±3	12±13 %
CBF/beat (μl)	311±26	296±32	-5±5 %	318±30	226±24	-25±6 %*
LVEF (%)	44±7	26±3	-32±5%	50±3	22±3	-54±6%*
LVEDD (mm)	39.2±1.3	41.2±1.4†	+5.8±1.7%	38.5±1	42.1±0.9‡	9.6±1.8%
NOREPI (pg/ml)	150±33	195±41	65±35 %	98±29	154±45	65±36 %
EPI (pg/ml)	43±7	35±5	-7±18 %	43±19	156±17†	185±22 %**
NO (μM)	14±2	15±2	21±13 %	16±2	10±2‡	-43±10 %*

**=p<0.05, **=p<0.01, comparing % changes from baseline between control and cocaine dogs and †=p<0.05, ‡=p<0.01, when comparing baseline values with 2 week pacing within the individual group.*

CO: cardiac output, SV: stroke volume, WTH: posterior wall thickness, and CBF: coronary blood flow, LVEDD: Left Ventricular End Diastolic Diameter, LVEF: Left Ventricular Ejection Fraction.

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Figure 1

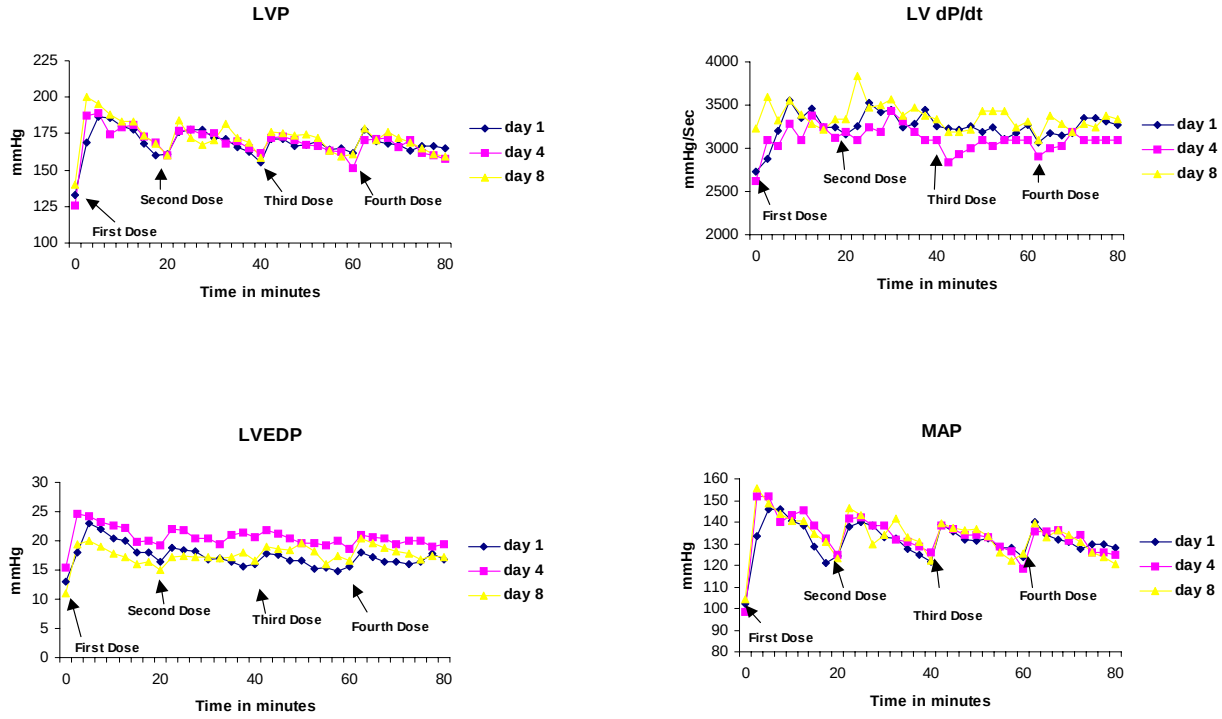

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Figure 2

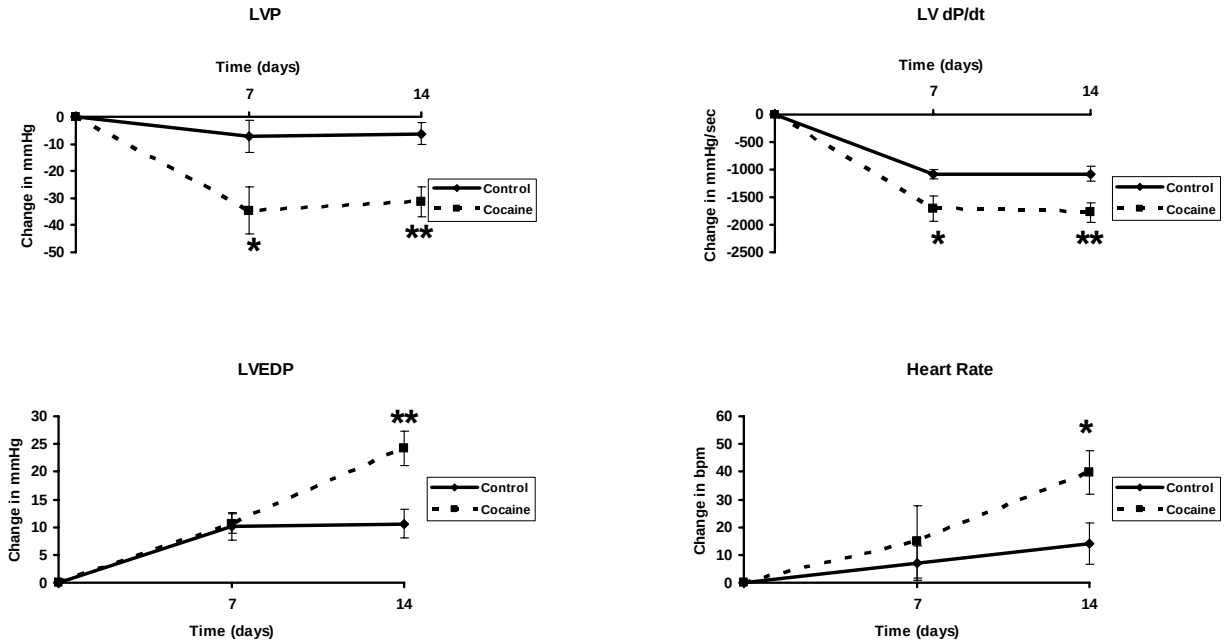

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Figure 3

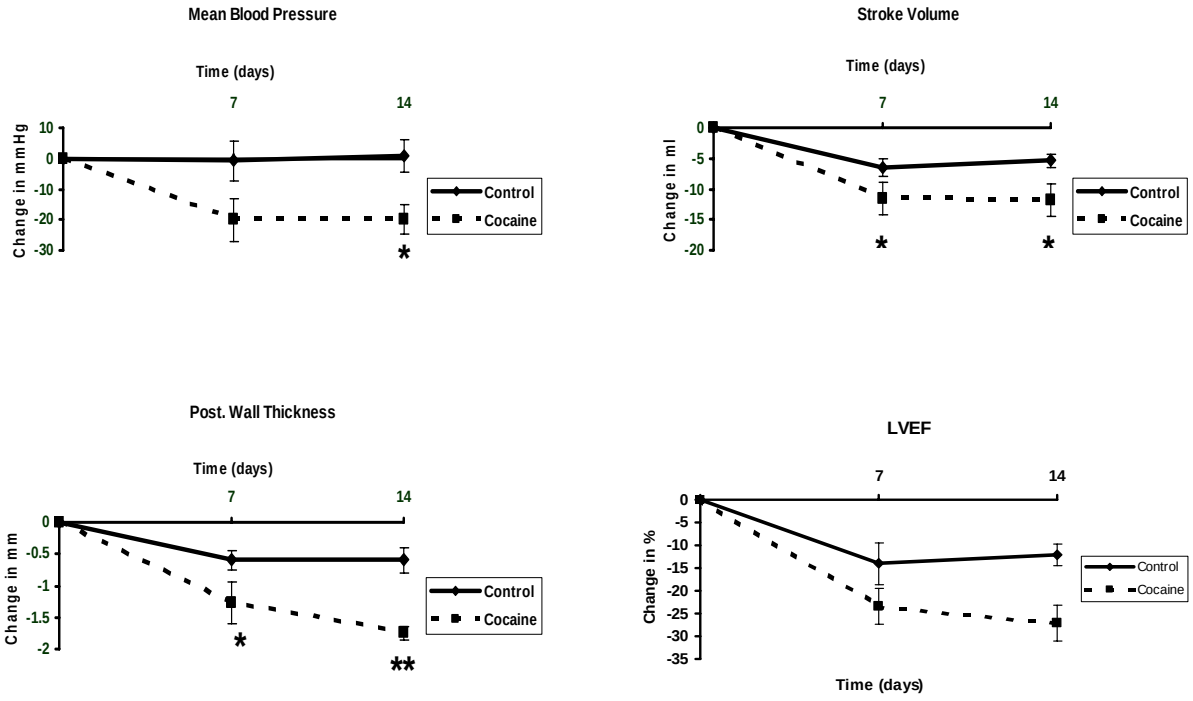

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Figure 4