Characterization of the In Vivo Cardiac Electrophysiologic Effects of High-Dose Cocaine in Closed-Chest, Anesthetized Dogs with Normal Hearts

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Objective - *To characterize the cardiac electrophysiologic effects of cocaine.*

Methods - *In 8 dogs (9-13 kg), electrophysiologic parameters and programmed stimulation were undertaken using transvenous catheters at baseline, and after cocaine intravenous infusion (12 mg/kg bolus followed by 0.22 mg/kg/min for 25 minutes).*

Results - *Cocaine plasma levels (n=5) rose to 6.73± 0.56 µg/mL. Cocaine did not affect sinus cycle length and arterial pressure. Cocaine prolonged P wave duration (54±6 vs 73±4 ms, P<0.001), PR interval (115±17 vs 164±15 ms, P<0.001), QRS duration (62±10 vs 88±14 ms, P<0.001), and QTc interval (344±28 vs 403±62 ms, P=0.03) but not JT interval (193±35 vs 226±53 ms, NS). Cocaine prolonged PA (9±6 vs 23±8 ms, P<0.001), AH (73±16 vs 92±15 ms; P=0.03), and HV (35±5 vs 45±3ms; P<0.001) intervals and Wenckebach point (247±26 vs 280±28 ms, P=0.04). An increase occurred in atrial (138±8 vs 184± 20 ms; P<0.001) and ventricular (160±15 vs 187±25 ms; P=0.03) refractoriness at a cycle length of 300 ms. Atrial arrhythmias were not induced in any dog. Ventricular fibrillation (VF) was induced in 2/8 dogs at baseline and 4/8 dogs after cocaine.*

Conclusion - *High doses of cocaine exert significant class I effects and seem to enhance inducibility of VF but not of atrial arrhythmias.*

Keywords: cocaine, electrophysiology, ventricular fibrillation

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Cocaine abuse has markedly increased over the past decade having reached epidemic levels in Western countries [1-4]. Cocaine intoxication is associated with a significant morbidity and mortality and is a frequent cause of drug-related sudden death [2,3]. Most evidence suggests that cocaine-induced sudden death results from its cardiovascular consequences, particularly ventricular arrhythmias [1]. However, the mechanisms involved in the genesis of these arrhythmias remain incompletely understood. Although cocaine-induced arrhythmias may be associated with myocardial ischemia or infarction [3,5], cocaine may be arrhythmogenic in the absence of an ischemic event [1]. In addition to its powerful indirect sympathomimetic actions [1-4] (promoted by blockade of presynaptic reuptake of norepinephrine and dopamine), high doses of cocaine exert significant local anesthetic effects that could promote conduction disturbances and reentrant arrhythmias [1,3,6,7]. Nevertheless, experimental studies evaluating cocaine's effects on programmed electrical stimulation-induced arrhythmias have had conflicting results, with cocaine either increasing or having a neutral effect on inducibility of ventricular arrhythmias [6,8-11]. Further, although supraventricular tachyarrhythmias, including atrial tachycardia, atrial flutter, and atrial fibrillation, can also occur in the setting of cocaine abuse [1,3,12-14], limited data are is available assessing the impact of the drug on inducibility of atrial arrhythmias.

Therefore, we sought to characterize the actions of high plasma concentrations of cocaine on atrial and ventricular electrophysiology and arrhythmia inducibility in a canine preparation with normal hearts.

Methods

Beagle dogs (n=12; weight, 9-13 kg) were divided into 2 groups: cocaine (n=8) and sham control (n=4). The study protocol was approved by the research committee of the

Federal University of São Paulo and was conducted according to guidelines of the American Society of Physiology.

Animals were premedicated with morphine (2 mg/kg IM). After 15 minutes, dogs were anesthetized (propofol, 6-8 mg/kg IV), intubated, placed on a fluoroscopy table and mechanically ventilated with room air and supplemental oxygen. Anesthesia was maintained by an intravenous infusion of propofol (100 μg/k/min) administered with an infusion pump. Body temperature was maintained at 37°C with a heating blanket. Continuous electrocardiogram (ECG) and pulse oximetry monitoring were performed. The right external jugular and both femoral veins were cannulated for fluids and drug administration, whereas the right femoral artery was cannulated for arterial blood sampling and invasive pressure monitoring. Blood gases and pH were monitored and maintained within physiological ranges.

Standard 6F quadripolar mapping catheters were introduced via the jugular and femoral veins and placed in the right atrial appendage, right ventricular apex and His bundle position under fluoroscopy guidance. Surface ECG and bipolar intracardiac electrograms filtered at 30-500 Hz were displayed on a monitor and stored on optical disk by a standard computerized recording system (Tecnologia Eletrônica Brasileira, São Paulo, Brazil) that also features a programmable electrical stimulator.

The sinus cycle length, surface electrocardiographic (P, PR, QRS, QT, corrected QT, JT) and intracardiac conduction (PA, AH, HV) intervals were measured during sinus rhythm as previously reported. The antegrade Wenckebach point was determined with usual techniques [15]. The effective refractory period (ERP) of the atrium and ventricle were measured during continuous pacing at 300 ms cycle lengths at 4 times the threshold and a pulse width of 2.0 ms with the decremental stimulus technique. After 2 minutes of continuous pacing, a premature stimulus (S2) was introduced after every 8 basic (S1) stimuli, with the S1S2 interval decreased by 10 ms decrements until failure to capture occurred. ERP was defined as the longest extrastimulus coupling interval (S1S2) that failed to produce a propagated response 3 consecutive times. Inducibility of atrial and ventricular arrhythmias was assessed at a cycle length of 300 ms with up to 3 extrastimuli. Rapid burst pacing for 15 seconds at a 200 ms cycle length was undertaken during atrial stimulation only. Atrial and ventricular tachyarrhythmias longer than 30 seconds in duration or resulting in hemodynamic collapse were considered sustained. Atrial electrophysiologic measurements were made prior to initiating ventricular stimulation. Arterial pressures were determined at least 5 minutes after any pacing maneuvers during sinus rhythm.

In 8 dogs, cocaine hydrochloride (from the Federal University of São Paulo) was freshly dissolved in isotonic saline and administered (12 mg/kg bolus for 5 minutes followed by 0.22 mg/kg/min for 25 min) via the femoral venous access with an infusion pump. Surface ECG, electrophysiologic and hemodynamic parameters and arrhythmia inducibility were assessed at baseline and 30 minutes after initiation of cocaine infusion. Sham control dogs (n=4) underwent the same protocol, but a benign vehicle (0.9% saline) was given instead of cocaine.

Arterial blood samples were obtained just prior to electrophysiologic measurements. Blood was collected into heparinized tubes containing sodium fluoride, immediately placed on ice, and centrifuged at 4°C. Plasma was separated and stored at -20°C until the assay. Plasma cocaine levels were determined by gas chromatography mass spectrometry as previously described [16].

Results are reported as mean±1SD. The Student *t* test and the Fisher's test were used as appropriate. A P value <0.05 was considered significant.

Results

The electrophysiologic effects of cocaine were evaluated in 8 dogs. Cocaine plasma levels were available in 5 dogs and increased to 6.73±0.56 μg/mL (range 5.90-7.20). These levels correspond to those reported in the setting of cocaine abuse [1,6].

Hemodynamic, electrocardiographic, and electrophysiologic effects (tab. I) - Infusion of cocaine did not significantly affect systolic (116±39 vs 141±33 mmHg, NS) and diastolic (63±19 vs 85±26, P=0.07) arterial pressure. In addition, no changes in sinus cycle length (539±83 vs 626± 126 ms, NS) were noted. However, as illustrated in figure 1, cocaine prolonged P wave duration (54±6 vs 73±4 ms, P<0.001) and QRS duration (62±10 vs 88±14 ms, P<0.001). Of note, the percent increase in P wave duration was similar to the increase in QRS duration (respectively, 37%, 19±5 ms vs 51%, 30±22 ms; NS). The PR interval (115±17 vs 164±15, P<0.001), QT interval (252±34 vs 317±73 ms, P=0.04) and QTc interval (344±28 vs 403±62 ms, P=0.03) were prolonged as well but the JT interval (193±35 vs 226±53 ms, NS) did not change. Cocaine also prolonged PA (9±6 vs 23±8 ms, P<0.001), AH (73±16 vs 92±15 ms; P=0.03), and HV (35±5 vs 45±3ms; P<0.001) intervals as well as the Wenckebach point (247±26 vs 280±28 ms, P=0.04). Cocaine-induced prolongation of electrocardiographic and intracardiac intervals appeared to be rate-dependent. That is, the increase in these intervals became progressively larger as the pacing cycle length was decreased (fig. 2). However, because of drug-induced increases in atrioventricular node refractoriness, this phenomenon could be demonstrated in 3 dogs only. Further, cocaine induced a marked increase in atrial (138±8 vs 184±20 ms; P<0.001) and ventricular (160±15 vs 187±25 ms; P=0.03) ERP at a paced cycle length of 300 ms. Cocaine produced a greater increase in atrial ERP than in ventricular ERP (32%, 45±20 ms vs 18%, 27±20 ms; P=0.08). No changes in hemodynamic and electrophysiologic parameters occurred in sham controls (tab. II).

Spontaneous atrial and ventricular arrhythmias did not occur after cocaine administration. Notably, despite aggressive stimulation protocols, atrial arrhythmias were not induced in any dog, either at baseline or after cocaine infusion. Ventricular fibrillation (VF) could be induced in 2/8 (25%) dogs at baseline and 4/8 (50%) dogs after cocaine, but this

Table I - Hemodynamic, electrocardiographic, and electrophysiologic effects of cocaine in 8 dogs

	Baseline	Cocaine	P value
SAP (mmHg)	116±39 (75-198)	141±33 (87-180)	NS
DAP (mmHg)	63±19 (45-100)	85±26 (49-117)	0.07
Heart rate (ms)	539±83 (375-638)	626±126 (400-767)	NS
P wave duration (ms)	54±6 (40-60)	73±4 (70-80)	<0.001
PR interval (ms)	115±17 (86-140)	164±15 (134-185)	<0.001
QRS duration (ms)	62±10 (50-70)	88±14 (70-150)	<0.001
QTc interval (ms)	344±28 (311-400)	403±62 (350-540)	0.03
JT interval (ms)	193±35 (144-250)	226±53 (150-320)	NS
Wenckebach point (ms)	247±26 (200-285)	280±28 (250-340)	0.04
PA interval (ms)	9±6 (0-20)	23±8 (10-35)	<0.001
AH interval (ms)	73±16 (40-90)	92±15 (60-110)	0.03
HV interval (ms)	35±5 (30-40)	45±3 (40-65)	<0.001
Atrial ERP (ms)	138±8 (130-150)	184±20 (150-210)	<0.001
Ventricular ERP (ms)	160±15 (130-180)	187±25 (150-220)	0.03

Data expressed as mean ± standard deviation and range. DAP- indicates diastolic arterial pressure; ERP- effective refractory period; NS- nonsignificant; QTc, corrected QT; SAP, systolic arterial pressure. See text for details.

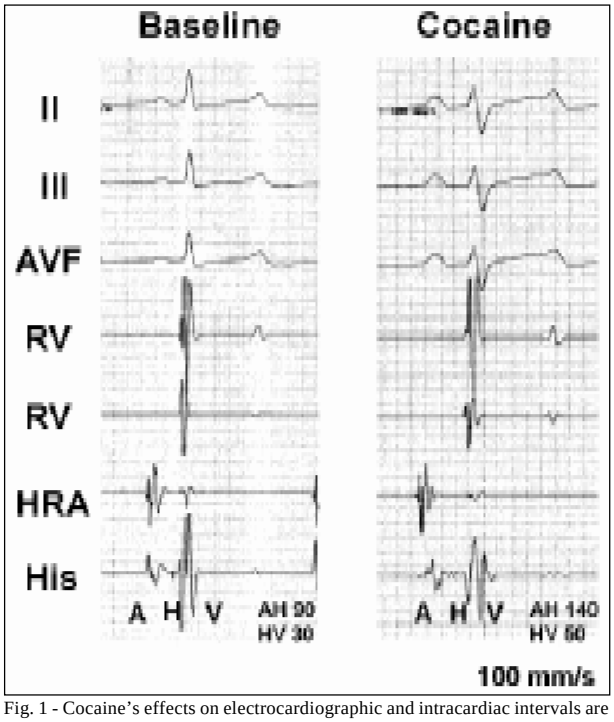

Fig. 1 - Cocaine's effects on electrocardiographic and intracardiac intervals are exemplified. From top to bottom: ECG leads II, III, and AVF, and bipolar electrograms recorded from the right ventricular apex (RV), high right atrium (HRA), and His bundle (His). The atrial (A), ventricular (V) and His bundle (H) electrograms are indicated. Tracings during sinus rhythm before (baseline) and after cocaine administration (cocaine). Note the marked drug-induced prolongation of electrocardiographic and intracardiac intervals. Paper speed at 100 mm/s.

difference was not statistically significant. Both animals that had VF induced at baseline also had the arrhythmia following cocaine injection. In a single dog, monomorphic ventricular tachycardia was induced after cocaine injection and was interrupted by rapid ventricular pacing. Ventricular fibrillation could also be induced in this dog (fig. 3). In all these animals, induction of sustained ventricular arrhythmias required the application of triple extrastimuli. Spontaneous or induced arrhythmias did not occur in any sham control animal.

Discussion

The present study has demonstrated in dogs with normal hearts and intact autonomic nervous system that intravenous cocaine, at doses resulting in plasma levels comparable to those reported in the setting of cocaine intoxication [1,6], has remarkable atrial and ventricular electrophysiologic effects. Cocaine has been found to significantly slow conduction in the atrium, AV node, His-Purkinje system, and ventricles. In addition, cocaine induced a marked increase in atrial and ventricular refractoriness. Nevertheless, cocaine did not produce spontaneous arrhythmias and had no effect on electrical induction of atrial arrhythmias, but appeared to modestly increase inducibility of ventricular arrhythmias. These results cannot be attributed to the animal preparation, because changes in hemodynamic and electrophysiologic parameters did not occur in sham controls.

A consistent finding in all dogs was that high-doses of cocaine produced significant conduction-slowing effects on cardiac tissues (fig. 1). Cocaine slowed conduction in the atrium (P wave duration and PA interval), AV node (AH interval), His-Purkinje system (HV interval), and ventricle (QRS duration). Further, these actions seemed to be use- and rate-dependent, or in other words, they became progressively larger as the heart rate was increased (fig. 2). Our results are in agreement with previous reports [1,3,6] that have shown in canine models that cocaine has conduction-slowing characteristics similar to class IB antiarrhythmic agents (lidocaine and mexiletine). Notably, these effects are modulated by the autonomic nervous system and are exacerbated following combined muscarinic and β1 adrenergic blockade [6]. Further supporting these findings, it has been demonstrated in isolated ventricular myocytes that cocaine depresses the cardiac sodium current in both a use- and rate-dependent manner, with kinetics of interaction with sodium channels that approximates that reported for lidocaine [17].

In accordance with previous investigations [6,18], the present study has clearly shown that high-dose cocaine markedly increases atrial and ventricular refractoriness.

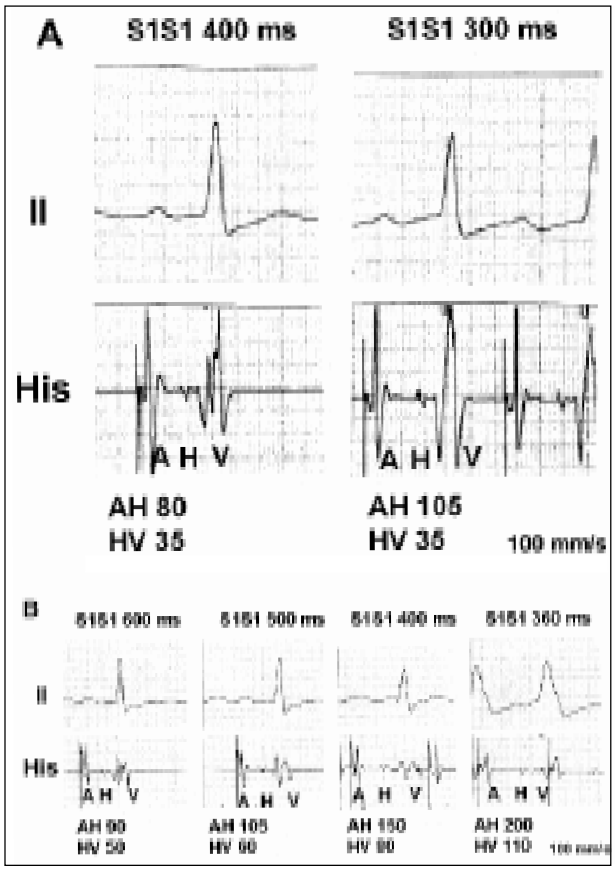

Fig. 2 - Cocaine's marked rate-dependent effects on conduction are depicted. The ECG lead II and bipolar electrograms recorded from the His bundle (His) during continuous right atrial pacing at progressively shorter cycle lengths (S1S1) are shown. The atrial (A), ventricular (V), and His bundle (H) electrograms are indicated. At baseline (panel A), shortening of S1S1 from 400 to 300 ms results in physiological prolongation of the AH interval without changes in QRS duration and HV interval. Note that after cocaine (panel B), drug-induced prolongation of electrocardiographic and intracardiac intervals are already apparent at a pacing cycle length of 600 ms, becoming progressively larger as the pacing cycle length was decreased to 360 ms. Paper speed at 100 mm/s.

Interestingly, as reported by Clarkson et al [6], this effect seems to be more pronounced in the atrium as compared to the ventricle, although this difference did not reach significance (P=0.081) in our study. Although cocaine has been shown to depress both calcium and potassium currents[18,19], most of cocaine-induced ERP prolongation may be attributed to its potent class I effects [18]. In addition to slowing action potential upstroke velocity, sodium channel blocking drugs delay the time-dependent recovery of excitability, thus prolonging refractoriness beyond repolarization, a phenomenon called postrepolarization refractoriness [20]. In support of this hypothesis, the present study and another [6] have demonstrated that cocaine increases the QT interval without affecting the JT interval. This evidence indicates that cocaine-induced QT lengthening results from QRS prolongation and suggests that the drug does not primarily affect ventricular repolarization. Noteworthy, cocaine's class I effects appear to be dose-dependent: at low doses (2.1 mg/k, IV), cocaine decreased ventricular ERP and did not affect right intra-atrial conduction, QRS or QTc [9].

In our investigation, the electrophysiological effects of cocaine were not accompanied by significant changes in arterial blood pressure and sinus cycle length. However, Clarkson et al [6] have shown that cocaine, at doses resulting in plasma levels similar to those achieved in the present study, does not affect arterial pressures either but increases heart rate. On the other hand, in dogs undergoing combined (muscarinic and β1 adrenergic) autonomic blockade, cocaine decreased arterial pressures and heart rate suggesting that the depressant effects of cocaine on blood pressure and sinus node automaticity are offset by the autonomic nervous system. Further, it has been reported that the hemodynamic response to cocaine correlates strongly with plasma adrenaline levels but not with plasma cocaine levels [8]. Accordingly, in vitro studies have indicated that cocaine has direct depressant effects on tissues isolated from the sinus node [18,21]. Therefore, the discrepancy in heart rate response to cocaine between the 2 studies may be accounted for by variations in autonomic tone secondary to different animal preparations.

In our study, in spite of aggressive stimulation protocols, cocaine did not increase inducibility of atrial arrhythmias but seemed to modestly enhance electrical induction of sustained ventricular arrhythmias (50% vs 25% in controls). Clarkson et al [6] obtained similar figures. They reported that in the presence of cocaine, at doses comparable to those used in the present study, sustained VT/VF could be induced in 2/10 (20%) dogs as compared to 0/13 (0%) controls. In dogs undergoing autonomic blockade, sustained VT/VF was induced in 2/6 (33%) dogs vs 0/12 (0%) controls. However these numbers did not reach statistical significance. In addition, the incidence of inducible sustained ventricular arrhythmias was further increased (33% without autonomic blockade) at higher cocaine plasma levels. In contrast, Tisdale et al [10] have reported that cocaine did not significantly decrease VF threshold. Further, Schwartz et al [8] have shown in conscious dogs that low-dose cocaine (2.8 mg/kg, IV) does not result in induced ventricular arrhythmias but increases susceptibility to atrial fibrillation (3/14 dogs). Except for the latter, inducibility of atrial arrhythmias was not assessed in these studies. As opposed to the findings of Schwartz et al [8], inducible atrial arrhythmias did not occur in the present study. The reasons for that are unclear but could be connected to the higher cocaine doses used in our investigation. The wavelength (ie, product of refractory period and conduction velocity) is a critical determinant of inducibility of reentrant arrhythmias [22]. Shorter wavelengths are more likely to set up reentrant circuits than longer wavelengths. In agreement with our findings, in vitro studies have shown that right atrial cells exhibit a greater increase in action potential duration and ERP than right ventricular cells, at each cocaine concentration [18]. Furthermore, cocaine has been found to equally slow conduction in the atrium and ventricle [6]. Theoretically, in a reentrant circuit with a fixed path length, this situation would result in relatively longer wavelengths in the atrium as compared to the ventricle. Therefore, although the wavelength of excitation was

Table II - Hemodynamic, electrocardiographic, and electrophysiologic parameters in 4 sham control dogs

	Baseline	Saline	P value
SAP (mmHg)	143±38 (105-194)	146±26 (114-180)	NS
DAP (mmHg)	94±15 (78-112)	93±13 (75-105)	NS
Heart rate (ms)	476±109 (343-571)	511±64 (472-571)	NS
P wave duration (ms)	55±6 (50-60)	56±5 (50-60)	NS
PR interval (ms)	107±28 (70-133)	105±26 (70-133)	NS
QRS duration (ms)	66±5 (60-70)	67±5 (60-70)	NS
QTc interval (ms)	390±54 (353-470)	378±61 (333-470)	NS
JT interval (ms)	170±21 (150-200)	170±20 (153-200)	NS
Wenckebach point (ms)	220±28 (200-260)	217±12 (200-230)	NS
PA interval (ms)	5±5 (0-10)	3±5 (0-10)	NS
AH interval (ms)	66±20 (40-85)	65±19 (40-80)	NS
HV interval (ms)	36±5 (30-40)	34±4 (30-40)	NS
Atrial ERP (ms)	147±17 (130-170)	145±17 (130-170)	NS
Ventricular ERP (ms)	157±5 (150-160)	155±5 (150-160)	NS

Data expressed as mean ± standard deviation and range. DAP- indicates diastolic arterial pressure; ERP- effective refractory period; NS- nonsignificant; QTc, corrected QT; SAP, systolic arterial pressure. See text for details.

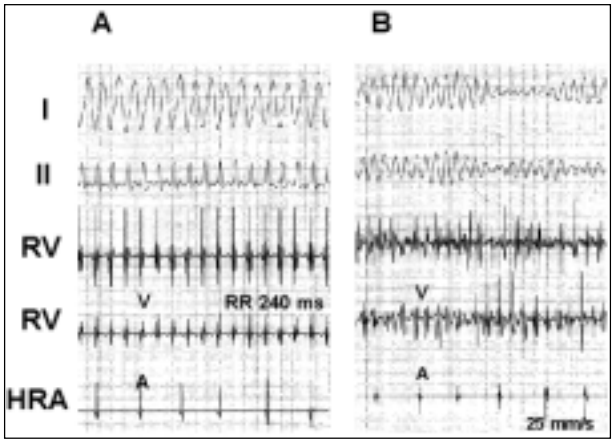

Fig. 3 - Sustained ventricular arrhythmias induced with triple extrastimuli during cocaine intoxication in the same dog. From top to bottom: ECG leads I and II, and bipolar electrograms recorded from the right ventricular apex (RV) and high right atrium (HRA). The atrial (A) and ventricular (V) electrograms are indicated. In panel A, a monomorphic ventricular tachycardia with a cycle length of 240 ms is shown, whereas ventricular fibrillation is depicted in panel B. Paper speed at 25 mm/s.

not directly measured in this study, it is tempting to speculate that cocaine's differential effects on inducibility of atrial and ventricular arrhythmias may be related in part to different drug-induced changes in wavelength mediated by alterations in action potential duration and conduction. However, it is important to remark that small (9-13 kg) dogs were used in our study, which takes on much greater importance because reentrant arrhythmias are less likely to occur in small-sized atria [22]. Hence, further studies are needed to confirm our observation that high plasma levels of cocaine do not render the atrium susceptible to inducible arrhythmias.

The modest effects of cocaine on inducibility of atrial and ventricular arrhythmias and also on production of spontaneous arrhythmias are consistent with the hypothesis that the development of malignant arrhythmias in the setting of cocaine intoxication may require additional pathological conditions, such as metabolic disturbances or myocardial ischemia [1,3]. Accordingly, it has been shown that cocaine increases the frequency of spontaneous and induced ventricular arrhythmias in the presence of myocardial infarction or a hyperadrenergic state [8,11,23]. Interestingly, in one of these series [23], spontaneous supraventricular arrhythmias and sustained atrial fibrillation were noted in dogs receiving low-dose cocaine (0.5 mg/kg, IV) plus norepinephrine, whereas dogs receiving cocaine alone had no arrhythmias. Notwithstanding these observations, it is important to point out that cocaine per se may promote or exacerbate cardiac arrhythmias. The sympathomimetic actions of cocaine could lead to automatic or triggered arrhythmias [19]. Further, because of its prominent conduction-slowing effects (class I effects), cocaine may shorten the excitation wavelength or create areas of unidirectional block, thus providing the conditions for reentry [1,3,6,7]. Notably, these class I effects are markedly modulated by the autonomic nervous system and heart rate [6]. As evidenced by this and other studies [6], sustained monomorphic VT and VF may be induced in the setting of cocaine abuse (fig. 3). In addition, several clinical reports [1-4,12-14,24] have documented that cocaine may lead to conduction disturbances, supraventricular and ventricular arrhythmias, and sudden death in the absence of myocardial ischemia or heart disease. Further supporting this premise, the proarrhythmic effects of sodium channel blocking drugs are well recognized, particularly in the presence of structural heart disease [25].

The present study evaluated the acute electrophysiologic effects of cocaine in a dog model with normal hearts. In addition, concomitant ethanol ingestion and cigarette smoking exacerbate the deleterious effects of cocaine on the heart [3,26]. Thus, our findings may not apply directly to humans with structural heart diseases, long-term cocaine users, or those using additional drugs. The effects of cocaine on coronary circulation were not assessed. However, electrocardiographic manifestations of acute myocardial ischemia or infarction were not noted in any dog.

In conclusion, in this dog model, high-doses of cocaine exert significant class I effects on the atrium, AV node,

His-Purkinje system, and ventricles. In addition, cocaine seems to modestly enhance inducibility of ventricular fibrillation but not of supraventricular arrhythmias. These findings further suggest that cocaine has direct myocardial actions that may create a substrate for the development of proarrhythmias.

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