Electrophysiological Effects of High Cocaine Concentrations on Intact Canine Heart
Evidence for Modulation by Both Heart Rate and Autonomic Nervous System

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Background. Previous clinical reports have suggested that cocaine intoxication may produce severe ventricular arrhythmias due to a direct effect on the heart. However, the effects of high plasma levels of cocaine on the electrophysiology of the heart have not been well characterized and remain poorly understood.

Methods and Results. The purpose of this study was to characterize the electrophysiological effects of high doses of cocaine on the in situ dog heart. In dogs anesthetized with morphine and α-chloralose, cocaine (2–11 μg/mL) increased both atrial and ventricular refractory periods and produced rate-dependent increases in atrial, atrioventricular, His-Purkinje, and ventricular conduction intervals. The time constant for the onset of cocaine’s conduction slowing effect following a reduction in pacing cycle length from 400 to 260 msec was approximately two beats, and the time constant for diastolic recovery from conduction slowing was ~200 msec, which are similar to values reported for several class Ib antiarrhythmic drugs. Cocaine produced a rate-dependent increase in QT interval that was greatest at high heart rates yet produced no change in the ST (QT-QRS) interval. This suggests that high plasma levels of cocaine delay repolarization primarily via slowing of conduction. Cocaine’s effects on both atrioventricular and intraventricular conduction were significantly larger in autonomically intact animals.

Conclusions. We conclude that high plasma levels of cocaine, similar to those reported in autopsy reports following fatal cocaine overdose in humans, produce significant rate-dependent conduction slowing effects on atrial, atrioventricular, and ventricular conduction in the in situ heart. These rate-dependent effects are intensified following autonomic blockade. (*Circulation* 1993;87:950–962)

KEY WORDS • use dependence • arrhythmias • drug abuse • cocaine

Within the past decade, there has been a large increase in the incidence of emergency department episodes and deaths involving cocaine overdose.1 Associated with the rise in cocaine abuse has been an increasing frequency of clinical reports documenting incidences of cocaine-induced cardiac arrhythmias, myocardial infarctions, and sudden death.2–4 However, despite the rise in concern over cocaine’s possible cardiotoxic effects, the evidence linking cocaine abuse to specific cardiac disorders has remained circumstantial because the effects of high or potentially lethal plasma concentrations of cocaine on the in situ heart have not been thoroughly defined.

Although cocaine may produce its cardiotoxic effects by multiple mechanisms, one mechanism that has been postulated is that cocaine may produce conduction disturbances and reentrant arrhythmias due to its sodium channel-blocking properties.5–7,11–12 There are a number of case reports indicating that high doses of cocaine may induce potentially lethal disturbances in cardiac conduction and cardiac arrhythmias.2,8,9 The average concentration of cocaine found in the blood of patients who died from a cocaine overdose has been reported to be approximately 6 μg/mL (20 μM), although the range of postmortem plasma concentrations of cocaine is fairly wide (e.g., 0.1–21 μg/mL).10 Previous in vitro studies have documented that within this concentration range, cocaine produces a significant depressant effect on both the cardiac sodium current11,12 and action potential upstroke velocity.13,14 Recent reports have also shown that administration of intravenous boluses of cocaine that produce peak plasma concentrations of cocaine within this concentration range can result in disturbances in intraventricular conduction.6,7,15

The primary goal of this study was to define the effects of high plasma concentrations of cocaine on the electrophysiological properties of the in situ canine...
heart. Cocaine dosage regimens were used to achieve stable plasma levels of cocaine similar to those reported to be present after fatal overdose in humans (e.g., 2–11 μg/mL). Because high doses of cocaine are also known to produce profound increases in both sympathetic tone and heart rate, factors known to modulate antiarrhythmic drug effects,16–21 we also investigated how changes in autonomic tone and heart rate modulate the electrophysiological effects of cocaine in this animal model.

Methods

Twenty-five mongrel dogs (weight, 9–15 kg) of either sex were studied. The procedures used in all experiments conformed with the guiding principles of the American Physiological Society. Dogs were premedicated with morphine sulfate (1 mg/kg s.c.), and general anesthesia was induced with α-chloralose (150 mg/kg) administered via a superficial lig. Additional α-chloralose was administered periodically as required to maintain an even plane of general anesthesia. Dogs were intubated with a cuffed endotracheal tube and placed on a mechanical ventilator (Model 613, Harvard Apparatus, South Natick, Mass.). Dogs were ventilated at a rate of 15 min−1 using room air supplemented with oxygen. Arterial blood gases were determined before electrophysiological parameters were recorded and were monitored every 30 minutes to ensure that arterial pH remained at 7.35–7.45, PO₂ was >100 mm Hg, and both Pco₂ and bicarbonate levels remained within their normal physiological range. Changes in ventilation rate or administration of sodium bicarbonate were used to adjust these parameters when necessary. Body temperature was monitored with a rectal thermometer and maintained constant at 38–39°C with a homeothermic heating blanket system (Harvard Apparatus).

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Three polyethylene catheters were inserted intravenously into the left femoral vein—one for infusion of cocaine, one for infusion of isoproterenol, and one for bolus administration of α-chloralose, cocaine, saline, or sodium bicarbonate. A single polyethylene catheter was placed into the left femoral artery and advanced into the descending aorta for monitoring arterial blood pressure and obtaining arterial blood samples for drug analysis and blood gas determinations. Arterial blood pressure was measured using a Statham P23-ID transducer. Three electrical catheters were positioned in the heart under fluoroscopic guidance by transvascular approaches: a quadripolar (5F) catheter in the right high right atrium via the right femoral vein; a quadripolar (5F) catheter in the apex of the right ventricle, also via the right femoral vein; and a triopolar (4F or 5F) catheter in the noncoronary cusp of the aorta via the left carotid artery for recording and pacing of the His bundle. Intracardiac electrogams were amplified at filter settings of 100–1,000 Hz. Two surface ECGs (leads II and V₁) were monitored and filtered at 0.05–100 Hz. Arterial blood pressure and surface and intracardiac electrograms were recorded on a Gould TA-2000 recorder. Most recordings were made at a paper speed of 200 mm/sec. However, determinations of effective refractory periods (ERPs) and arrhythmia inductions were recorded at 100 mm/sec. Programmed stimulation of the heart was performed using a Bloom DTA-210 programmable stimulator. Stimuli were delivered at twice threshold with a pulse duration of 2 msec.

Animal Subgroups

Dogs were arbitrarily divided into one of two groups. In the autonomic nervous system–blocked (ANS-blocked) group (n=12), the modulatory effects of the autonomic nervous system on the heart were blocked to allow a more accurate assessment of the direct effects of cocaine on the heart. The regimen for producing autonomic blockade consisted of cutting both right and left vagosympathetic trunks between ligatures, followed by administration of 1 mg atropine sulfate i.v. and 0.5 mg/kg atenolol hydrochloride i.v. to block responses produced by muscarinic and β₁-adrenergic receptors. Because of their hypotensive effects, no attempt was made to use α-adrenergic blockers to reduce any cardiac responses mediated by a-receptors in this animal group. The adequacy of muscarinic and β₁-adrenergic blockade was assessed hourly using test doses of atropine and isoproterenol. Adequate muscarinic blockade was defined as an absence of sinus slowing when using a test bolus of atropine that produced a >2-second sinus pause before administration of atropine in the same animal. Adequate β₁-adrenergic blockade was defined as a <5 beat-per-minute rise in heart rate after isoproterenol challenge when using the test dose of isoproterenol that produced an increase in heart rate of ≥35 beats per minute before atenolol administration in the same animal. These criteria are similar to those used previously by other investigators.22 Additional supplemental doses of 0.25 mg/kg atenolol or 1 mg atropine were administered as needed to maintain autonomic blockade. In a second group (ANS-intact) of dogs (n=13), autonomic reflexes were left intact: that is, autonomic blocking drugs were not administered, and the vagosympathetic nerves were left intact.

Pacing Protocols

Studies were performed to assess the influence of cocaine on the electrophysiological characteristics of the right atrium, atrioventricular (AV) node, His-Purkinje conduction system, and right ventricle. Determinations of atrial and ventricular ERPs were performed by introducing a premature beat (S₀) after every eighth beat of a basic (S₁S₉) train at a cycle length of 300 msec. The S₁S₀ interval was initially set to 220 msec and then decreased in 10-msec decrements until the ERP was reached. The ERP was defined as the longest S₁S₀ interval that failed to result in an atrial or a ventricular depolarization.

Drug effects on conduction through the AV node were assessed during 30-second bursts of rapid atrial pacing starting at a cycle length slightly shorter (<50 msec) than the sinus rate and decreasing in 50-msec decrements until a pacing cycle length of 300 msec was achieved, followed by 20-msec decrements in pacing cycle length until a cycle length was achieved at which conduction through the AV node became less than 1:1 (Wenckebach cycle length). Intracardiac conduction intervals (SA interval: intra-atrial conduction time; AH interval: AV nodal conduction time; HV interval: His-Purkinje conduction time) were measured according to previously defined methods.23,24
Direct His bundle pacing was performed at cycle lengths similar to those used for atrial pacing to define the rate dependence of drug effects on conduction time through the His-Purkinje system (SV interval) and QRS and QT intervals and at cycle lengths shorter than those that could be conducted 1:1 through the AV node during atrial pacing. Criteria for adequate evidence for His bundle pacing included the same QRS and T wave morphology as observed during sinus rhythm or atrial pacing at a similar cycle length, a time interval between the onset of the stimulus and first evidence for ventricular depolarization (SV interval) that was within 5 msec of the HV interval obtained during atrial pacing at the same cycle length, and evidence for either AV dissociation or retrograde ventriculatrial conduction (most typically). The His bundle was paced for approximately 30 seconds at each cycle length to ensure that steady-state changes were achieved. SV intervals were measured from the onset of the pacing artifact to the first evidence for ventricular depolarization seen in either surface or intracardiac recordings. QRS duration was measured by drawing vertical lines at the first and last evidence of QRS inscription in surface leads II and V1. All measurements for a given dog were performed by the same investigator. The time course of diastolic recovery from conduction slowing was evaluated by measuring the SV interval of single extrastimuli evoked after different S1S2 intervals following a basic (S1S1) train consisting of 40 beats at a cycle length of 250 msec.

Pacing of the right ventricular apex was performed to evaluate both drug effects on intraventricular conduction and cocaine's ability to cause inducible ventricular tachycardia or fibrillation. Both burst ventricular pacing and extrastimulus protocols were used for arrhythmia induction. Ventricular burst pacing consisted of pacing the right ventricular apex for 30-second intervals beginning at a cycle length slightly shorter than the sinusal cycle length, followed by repetition at progressively shorter cycle lengths until either a minimum cycle length of 180 msec was achieved or a sustained ventricular tachycardia or ventricular fibrillation was induced. Ventricular tachycardia was defined as a run of three or more consecutive beats of ventricular origin shorter than the sinus cycle length. Ventricular tachycardias were considered to be nonsustained (from a minimum of three beats to a maximum of 30 seconds' duration) or sustained (more than 30 seconds in duration and/or more than 10 seconds and accompanied by severe hypotension). Ventricular fibrillation was defined as an extremely rapid, disorganized ventricular arrhythmia characterized by an undulating baseline on the surface ECG. The extrastimulus protocols consisted of a constant basic train of eight beats at a cycle length of 300 msec, followed by either one or two extrastimuli. When using a single extrastimulus for ventricular stimulation, the S1S2 interval was initially set at 220 msec and decreased in 10-msec decrements until the ERP was achieved. When using two extrastimuli, the S1S2 interval was initially set at 50 msec beyond the ERP, and the S1S3 interval was set at 220 msec. The S1S2 interval was then decreased in 10-msec decrements until the ERP was achieved. The S1S3 interval was then decreased by 10 msec, and the S1S3 scan was repeated. This protocol was repeated until the S1 became refractory or a sustained ventricular tachycardia or ventricular fibrillation was induced.

**Drug Administration, Sampling, and Analysis**

Cocaine hydrochloride (from the National Institute on Drug Abuse) was freshly dissolved in isotonic saline immediately before the start of the cocaine infusion (following the collection of control data). Several cocaine dose regimens were studied (Table 1) consisting of a loading dose infused intravenously over 5 minutes followed by an intravenous maintenance infusion of cocaine designed to maintain plasma cocaine concentration within a narrow range of 2–3 μg/mL (7–10 μM) for the dose 1 regimen, 6–7 μg/mL (20–23 μM) for the dose 2 regimen, and 9–11 μg/mL (30–37 μM) for the dose 3 regimen (Table 1). Plasma samples were taken at 30-, 60-, and 90-minute intervals following the onset of a cocaine dose regimen. Pacing protocols were not performed during the initial 30-minute time interval after the onset of a dosage regimen to allow for drug distribution. In most experiments, dose 1 was adminis-
**TABLE 2. Hemodynamic and Electrophysiological Effects of Cocaine in the Nonpaced Dog**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
<th>HR (bpm)</th>
<th>PR interval (msec)</th>
<th>AH interval (msec)</th>
<th>HV interval (msec)</th>
<th>QRS interval (msec)</th>
<th>QT interval (msec)</th>
<th>QTc (msec)</th>
<th>No. of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANS-intact dogs</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>131±8</td>
<td>75±5</td>
<td>94±6</td>
<td>107±3</td>
<td>80±4</td>
<td>26±1</td>
<td>44±1</td>
<td>228±8</td>
<td>279±7</td>
<td>13</td>
</tr>
<tr>
<td>Dose 1</td>
<td>129±10</td>
<td>81±6</td>
<td>128±11*</td>
<td>108±6</td>
<td>80±7</td>
<td>25±1</td>
<td>47±3</td>
<td>211±14</td>
<td>306±22</td>
<td>6</td>
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<tr>
<td>Dose 2</td>
<td>113±7</td>
<td>78±6</td>
<td>150±2*</td>
<td>101±3</td>
<td>79±3</td>
<td>37±2*</td>
<td>54±3*</td>
<td>206±5</td>
<td>326±8*</td>
<td>10</td>
</tr>
<tr>
<td>Dose 3</td>
<td>88±9*</td>
<td>57±7</td>
<td>142±8*</td>
<td>119±4</td>
<td>81±5</td>
<td>40±4*</td>
<td>59±4*</td>
<td>193±28</td>
<td>324±13*</td>
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<tr>
<td>ANS-blocked dogs</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
<td>129±6</td>
<td>92±4</td>
<td>126±6</td>
<td>102±4</td>
<td>69±4</td>
<td>25±1</td>
<td>44±2</td>
<td>209±5</td>
<td>301±5</td>
<td>12</td>
</tr>
<tr>
<td>Dose 1</td>
<td>115±3</td>
<td>73±3*</td>
<td>107±5†</td>
<td>113±4</td>
<td>76±4</td>
<td>29±1</td>
<td>50±3</td>
<td>226±5†</td>
<td>299±6</td>
<td>10</td>
</tr>
<tr>
<td>Dose 2</td>
<td>100±9*</td>
<td>61±8*</td>
<td>100±6*</td>
<td>130±3*</td>
<td>121±36†</td>
<td>35±1*</td>
<td>50±5*</td>
<td>236±8†</td>
<td>304±6</td>
<td>6</td>
</tr>
</tbody>
</table>

BP, blood pressure; HR, heart rate; bpm, beats per minute; QTc, corrected QT interval; ANS, autonomic nervous system.
*p<0.005 vs. control (one-way ANOVA).
*tp<0.05 vs. control (one-way ANOVA).
*tp<0.01 vs. control (one-way ANOVA).
Values are mean±SEM.

Cocaine achieved using each dose regimen (dose 1, dose 2, or dose 3) did not vary significantly as a function of time during the 60-minute time period within which the hemodynamic and electrophysiological effects of cocaine were defined (Table 1).

**Hemodynamic and Electrophysiological Effects in Nonpaced Dogs**

Under control conditions, ANS-intact animals had a significantly lower heart rate and diastolic blood pressure compared with ANS-blocked dogs (p<0.05, Table 2). Administration of dose 1 or 2 of cocaine produced no significant effect on blood pressure in ANS-intact dogs, whereas dose 3 of cocaine produced a significant decrease in systolic blood pressure (Table 2). In contrast, cocaine produced a significant decrease in systolic and diastolic blood pressures over the same dosage range in ANS-blocked dogs (Table 2). ANS-blocked dogs became severely hypotensive and unstable during the administration of dose 3 cocaine. Therefore, only the effects of dose 1 and dose 2 cocaine could be defined in ANS-blocked animals.

In ANS-intact dogs, cocaine produced a dose-dependent increase in heart rate from 94±6 beats per minute to an apparent maximum of 150±2 beats per minute in the presence of dose 2 cocaine (Table 2). In contrast, cocaine produced a dose-dependent decrease in heart rate in ANS-blocked dogs from a control value of 129±6 to 100±6 beats per minute in the presence of dose 2 cocaine (Table 2). In ANS-blocked dogs, the negative chronotropic effects of cocaine resulted in the loss of sinus rhythm with the subsequent development of a junctional rhythm in five of nine (56%) dogs during exposure to dose 2 cocaine. Development of a junctional rhythm was also observed in two of six (30%) ANS-intact dogs exposed to dose 3 cocaine. Animals developing a junctional rhythm also displayed a marked increase in the threshold for pacing the right atrium and/or atrial inexcitability. Development of a junctional rhythm was not observed during the administration of dose 1 cocaine to ANS-blocked dogs (none of 10) or during administration of either dose 1 cocaine (none of six) or dose 2 cocaine (none of 10) to ANS-intact dogs.
In addition to effects on automaticity and blood pressure, cocaine produced a dose-dependent increase in HV, QRS, and corrected QT intervals in ANS-intact dogs (Table 2). Although cocaine produced qualitatively similar dose-dependent effects on QRS and HV intervals in ANS-blocked dogs, significant increases in PR, AH, and QT intervals were also seen in ANS-blocked dogs (Table 2).

**Atrial and Ventricular ERPs**

In the absence of cocaine, the ERP of the atrium was significantly shorter in ANS-intact dogs than in ANS-blocked dogs (Figure 1A) \( p<0.02 \). In contrast, the difference in the ventricular ERP for ANS-intact versus ANS-blocked dogs was small and not significant (Figure 1B). These differences are consistent with the relief of sympathetic and vagal tone produced by ANS blockade. Exposure to cocaine produced a significant and dose-dependent increase in atrial and ventricular ERPs in both ANS-intact and ANS-blocked dogs (Figures 1A and 1B), and the percent increase in atrial ERP was significantly greater than the increase in ventricular ERP in both groups of dogs (Figure 1C). Dose 2 cocaine also produced a significantly greater increase in the ventricular ERP in ANS-blocked dogs than in ANS-intact dogs (Figure 1C). These results indicate that cocaine produces a significantly greater effect on the atrial ERP than on the ventricular ERP and that autonomic tone can modify the effects of cocaine on ventricular refractoriness.

**Rapid Atrial Pacing**

The effects of cocaine on conduction through the atrial myocardium (SA interval), AV node (AH interval), and His-Purkinje fiber system (HV interval) were characterized during rapid atrial pacing over a range of cycle lengths (Figure 2). In the absence of cocaine, AH conduction times gradually increased as the pacing cycle length was shortened until AV nodal block (Wenkebach type) was achieved. In ANS-blocked dogs, exposure to dose 1 or 2 cocaine produced a significant rate-dependent increase in AH conduction time, with the effect of cocaine on AH being largest at short cycle lengths (Figure 2). In ANS-blocked dogs, both the intra-atrial conduction time (SA interval) (Figure 2) and the His-Purkinje conduction time (HV interval) (Figure 2) were significantly increased at cycle lengths and doses that produced a significant increase in the
AH interval. Thus, cocaine does not show a clear selectivity in its depressant effects on conduction in the atrium, AV node, and His-Purkinje conduction system. In contrast, in ANS-intact dogs, cocaine did not produce a significant effect on the AH interval at any cycle length between the normal sinus cycle length and that which induced a Wenckebach-type conduction block in the AV node (Figure 2). However, significant increases in SA and HV intervals were observed in the presence of dose 2 cocaine in ANS-intact dogs (Figure 2). This suggests that changes in autonomic tone in animals with intact reflexes can mask cocaine’s depressant effects on conduction through the AV node. Consistent with its effects on AV nodal conduction, cocaine was found to produce a dose-dependent increase in the Wenckebach cycle length in ANS-blocked dogs while producing no significant effect on the Wenckebach cycle length in ANS-intact dogs (Table 3).

His and Ventricular Pacing

Figure 3 shows the dependence of the SV and QRS intervals as a function of cycle length during direct pacing of the His bundle in the presence and absence of cocaine. In both ANS-intact and ANS-blocked groups, cocaine resulted in a dose-dependent increase in SV intervals that was small and insignificant at long cycle lengths but became progressively larger and significant ($p<0.05$) when the pacing cycle length was decreased to ≤500 msec (one-way ANOVA). In addition, dose 2 cocaine produced a significantly larger effect on QRS intervals in ANS-blocked dogs than in ANS-intact dogs at short cycle lengths (Figure 3). A qualitatively similar rate-dependent effect of cocaine on QRS was also observed during direct pacing of the right ventricular apex (Figure 4A). Similar to during His pacing, there was a significantly greater amplitude of QRS widening during ventricular pacing observed in ANS-blocked dogs compared with ANS-intact dogs (Figure 4A). These results suggest that cocaine’s effect on conduction through the His-Purkinje system and ventricular myocardium is in-

**TABLE 3. Effects of Cocaine on Atroventricular Node Wenckebach Cycle Length**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Wenckebach cycle length (msec)</th>
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<tbody>
<tr>
<td></td>
<td>ANS-blocked dogs</td>
</tr>
<tr>
<td>Control</td>
<td>198±8 (n=12)</td>
</tr>
<tr>
<td>Dose 1</td>
<td>250±5 (n=10)*</td>
</tr>
<tr>
<td>Dose 2</td>
<td>358±32 (n=5)†‡</td>
</tr>
<tr>
<td>Dose 3</td>
<td>...</td>
</tr>
</tbody>
</table>

ANS, autonomic nervous system.

* $p<0.005$ vs. control ANS-blocked (one-way ANOVA).

† $p<0.001$ vs. control ANS-blocked (one-way ANOVA).

‡ $p<0.0005$ vs. ANS-intact in dose 2 cocaine (one-way ANOVA).

All differences among mean values in the ANS-intact group are NS. Values are mean±SEM.
tensified after ANS blockade. Mean plasma levels of cocaine obtained during administration of dose 2 cocaine in ANS-blocked (6.96±0.70 μg/mL, n=7) and ANS-intact dogs (6.59±0.75 μg/mL, n=4) were not significantly different, indicating that the difference in cocaine's effect in the two groups cannot be explained by differences in plasma cocaine concentrations.

During pacing of the right ventricle, we also observed a small (~6–8 msec) but significant difference in control QRS intervals between the two animal groups, with control QRS intervals in ANS-intact dogs being significantly shorter than control values in ANS-blocked dogs (Figure 4A). This contrasts with a lack of difference observed in either SV or QRS intervals during pacing of the His bundle (Figure 3) and suggests that autonomic (sympathetic) tone may affect intramyocardial and His-Purkinje conduction unequally.

Because the modulation of ventricular function by the autonomic nervous system is believed to be primarily
due to activation of β-adrenergic receptors by catecholamines, we investigated the effect of an infusion of the β-agonist isoproterenol in eight ANS-intact dogs in both the presence and the absence of cocaine. The infusion rate for isoproterenol was adjusted to maintain the sinus cycle length between 310 and 330 msec. In the absence of cocaine, infusion of isoproterenol had no effect on QRS during ventricular pacing at cycle lengths between 160 and 300 msec (Figure 4B). In contrast, in the presence of dose 2 cocaine, infusion of isoproterenol produced a consistent reduction in QRS duration of

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**FIGURE 3.** Plots of changes in the SV interval and QRS duration during direct His bundle pacing as a function of paced cycle length (PCL). Open symbols, autonomic nervous system (ANS)-intact dogs; filled symbols, ANS-blocked dogs. Significant rate-dependent increases in SV and QRS were observed during exposure to cocaine. The increase in QRS duration was also significantly larger in ANS-blocked than in ANS-intact dogs at cycle lengths of 260–400 msec in the presence of dose 2 cocaine. His bundle pacing could not be reliably achieved at cycle lengths >400 msec in ANS-intact dogs exposed to dose 2 cocaine due to sinus competition. Mean values of SV intervals for dose 1 cocaine in the ANS-intact group (PCL, 220, 260, and 300 msec) are superimposed under mean values for dose 1 cocaine in the ANS-blocked group. Blk, blocked.

**FIGURE 4.** Plots of changes in the QRS duration during right ventricular pacing as a function of paced cycle length (PCL). Panel A: QRS during ventricular pacing in the presence and absence of cocaine. Open symbols, autonomic nervous system (ANS)-intact dogs; filled symbols, ANS-blocked dogs. Blk, blocked. Significant rate-dependent increases in QRS were observed during exposure to cocaine. The increase in QRS duration was also significantly larger in ANS-blocked than in ANS-intact dogs over a wide range of cycle lengths in the presence of dose 1 or 2 cocaine. The QRS intervals for control ANS-blocked dogs were also significantly larger than the control QRS intervals for ANS-intact dogs. Panel B: Effect of isoproterenol (130) infusion on QRS during ventricular pacing. The isoproterenol infusion rate was adjusted to maintain the sinus cycle length between 310 to 330 msec. Isoproterenol produced a consistent but nonsignificant reduction in QRS duration of 5–20 msec in the presence of dose 2 cocaine. Data represent mean values for six to eight dogs at each cycle length in the presence of isoproterenol and four to 13 dogs in the absence of isoproterenol. Isoproterenol did not produce a definable effect on QRS in the absence of cocaine.
10–20-msec duration. Although this effect was qualitatively similar to the effects produced by changes in autonomic tone, the magnitude of this effect was not large enough to reach statistical significance ($n=8$). Isoproterenol also produced a significant antagonism of cocaine’s effect on ventricular refractoriness. In the absence of cocaine, isoproterenol produced a significant (~15 msec) shortening of the ventricular ERP (Table 4). Administration of dose 2 cocaine alone prolonged the ventricular ERP by approximately 17 msec, and infusion of isoproterenol during exposure to dose 2 cocaine antagonized cocaine’s effect (Table 4). These results support the hypothesis that β-adrenergic stimulation can antagonize the effects of cocaine on both intraventricular conduction and refractoriness.

One possible mechanism by which changes in autonomic tone could modulate the use-dependent effect of cocaine on cardiac tissue is by altering the duration of the cardiac action potential.28,29 To evaluate this hypothesis, we defined the effects of both autonomic blockade and cocaine exposure on QT and ST (QT-QRS) intervals. Under control conditions, the QT interval was a function of paced cycle length in both ANS-blocked and ANS-intact dogs (Figure 5). However, there was no significant difference in control QT intervals when comparing mean values obtained from ANS-intact and ANS-blocked dogs at paced cycle lengths ranging from 180 to 500 msec (one-way ANOVA). Exposure of both ANS-intact and ANS-blocked dogs to dose 1 or dose 2 cocaine resulted in a significant rate-dependent increase in QT interval (compared with controls) that was greatest at short cycle lengths (Figure 5). Because cocaine was observed to produce a rate-dependent increase in QRS interval over the same range of cycle lengths, we also calculated the ST interval (QT-QRS) and found no significant effect of cocaine exposure on the ST interval over the range of cycle lengths that it could be resolved (160–550 msec) (Figure 5). These results indicate that cocaine’s effect on QT interval, at least over the range of cycle lengths defined, results primarily from its effect on QRS.

**Kinetics of Onset and Recovery From Use-Dependent Conduction Slowing by Cocaine**

To further define cocaine’s use- and time-dependent effects on cardiac conduction, we defined the kinetics of the onset of its conduction-slowing effects as well as the kinetics of recovery from its conduction-slowing effects during pacing of the His bundle. Figure 6A shows the mean change in the SV interval during the first 30 beats after an abrupt shortening of the paced cycle length from 400 to 260 msec in the presence ($n=6$) and absence ($n=8$) of dose 2 cocaine in ANS-intact dogs.

### Table 4. Effects of ANS Blockade and Isoproterenol Infusion on Ventricular Effective Refractory Period

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ventricular effective refractory period (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANS-blocked dogs</td>
</tr>
<tr>
<td>Control</td>
<td>141±5 ($n=12$)</td>
</tr>
<tr>
<td>Dose 2 cocaine</td>
<td>174±12 ($n=5$)</td>
</tr>
</tbody>
</table>

ANS, autonomic nervous system. Cycle length of S1S1 train was 300 msec. *p<0.05 vs. ANS-blocked dose 2 cocaine (unpaired t test). †p<0.01 vs. ANS-intact without isoproterenol (paired t test). ‡p<0.05 vs. dose 2 cocaine ANS-intact without isoproterenol (paired t test).

Values are mean±SEM.

**Figure 5.** Plots of changes in the QT and ST intervals during direct His bundle pacing as a function of paced cycle length (PCL). Cocaine produced a rate- and dose-dependent increase in QT interval compared with control that was largest at short cycle lengths. The effect of cocaine on QT was larger in autonomic nervous system (ANS)-blocked dogs (top left) than in ANS-intact dogs (top right). Cocaine did not produce a significant effect on the ST (QT-QRS) interval, suggesting that cocaine’s rate-dependent effect on QT results primarily from its rate-dependent effect on the QRS duration. Data indicate mean±SEM values. The SEM bars are not visible when smaller than the symbol.
A

![Plot showing steady-state level of SV in the presence of cocaine in autonomic nervous system (ANS)-intact dogs. Panel A: Changes in the SV interval as a function of beat number during direct His bundle pacing following a sudden change in paced cycle length (PCL) from 400 to 260 msec. SS, steady-state level of SV at PCL=400 msec immediately before reduction in PCL to 260 msec. Open symbols, control; filled symbols, dose 2 cocaine. The solid curve is a least-squares best fit to an exponential equation: S1V1=49.7 msec × exp(−n/1.215 beats), where n is number of beats. Note that cocaine’s conduction-slowing effect approaches steady state within five to 10 beats. Panel B: Kinetics of diastolic recovery from conduction slowing following a conditioning train of 30 His-paced beats at a cycle length (S1S1) of 250 msec. Recovery from conduction slowing produced by the conditioning train was defined using a single His-paced extrastimulus (S2) after a variable S1S2 coupling interval. Under control conditions, there was no significant change in the conduction time (S1S2 interval) of the extrastimulus beat as the S1S2 interval was varied over the range of 200–500 msec. In contrast, during exposure to dose 2 cocaine, there was a use-dependent slowing of the S1S2 interval that recovered toward control with a time course that could be well fit by the exponential equation: S1V1=115.1 msec × exp(−S1S2/119.6 msec)+32.2 msec. Data values indicate mean±SEM values for ANS-intact dogs (n=4–8). (See text for further discussion.)](http://circ.ahajournals.org/content/full/87/3/958/F6.large.jpg)

B

![Plot showing SV intervals for dose 2 and control conditions](http://circ.ahajournals.org/content/full/87/3/958/F6.large.jpg)

**FIGURE 6.** Plots of kinetics of onset and recovery from use-dependent conduction slowing in the presence of dose 2 cocaine in autonomic nervous system (ANS)-intact dogs. Panel A: Changes in the SV interval as a function of beat number during direct His bundle pacing following a sudden change in paced cycle length (PCL) from 400 to 260 msec. SS, steady-state level of SV at PCL=400 msec immediately before reduction in PCL to 260 msec. Open symbols, control; filled symbols, dose 2 cocaine. The solid curve is a least-squares best fit to an exponential equation: S1V1=49.7 msec × exp(−n/1.215 beats), where n is number of beats. Note that cocaine’s conduction-slowing effect approaches steady state within five to 10 beats. Panel B: Kinetics of diastolic recovery from conduction slowing following a conditioning train of 30 His-paced beats at a cycle length (S1S1) of 250 msec. Recovery from conduction slowing produced by the conditioning train was defined using a single His-paced extrastimulus (S2) after a variable S1S2 coupling interval. Under control conditions, there was no significant change in the conduction time (S1S2 interval) of the extrastimulus beat as the S1S2 interval was varied over the range of 200–500 msec. In contrast, during exposure to dose 2 cocaine, there was a use-dependent slowing of the S1S2 interval that recovered toward control with a time course that could be well fit by the exponential equation: S1V1=115.1 msec × exp(−S1S2/119.6 msec)+32.2 msec. Data values indicate mean±SEM values for ANS-intact dogs (n=4–8). (See text for further discussion.)

Before cocaine administration, no significant change was observed. In the presence of dose 2 cocaine, the increase in SV interval was significant and increased with a time course that could be well approximated by an exponential function with a mean onset time constant (τonset) of 2.2±0.8 beats (n=6). Qualitatively similar observations were also made in four ANS-blocked dogs (τonset, 1.6±0.7 beats).

The kinetics of diastolic recovery from cocaine’s conduction-slowing effects were also defined using critically timed His bundle extrastimuli (S2) coupled to the end of a 30-beat conditioning train of His-paced beats at a cycle length (S1S1) of 250 msec. Under control conditions, the conduction time of extrastimyos (S2V2) did not change significantly for S1S2 intervals >200 msec (Figure 6B). A large and sudden increase in S2V2 conduction time was commonly observed at S1S2 intervals <200 msec as the S1S2 interval approached within 20 msec of the ERP of the His-Purkinje system (data not shown). After administration of cocaine, there was a clear time-dependent recovery of conduction time following a conditioning train that could be defined over S1S2 intervals between 200 and 700 msec (Figure 6B). The kinetics of diastolic recovery from conduction slowing could be well approximated by a single exponential function (A × exp[−t/τrec]+B) with a characteristic recovery time constant (τrec). Although the mean time constant obtained for ANS-intact dogs (τrec, 147±28 msec; n=5) was smaller than that observed in ANS-blocked dogs (τrec, 225±27 msec; n=12), the difference was not statistically significant (Student’s t test). The average time constant for all ANS-intact and ANS-blocked dogs grouped together was 202±22 msec (n=17). Qualitatively identical observations were also made using measurements of the QRS interval evoked by His-paced extrastimyos (data not shown), suggesting that slowing of intraventricular conduction also recovers during diastole with a similar time course.

**Arrhythmia Induction**

Ventricular tachyarrhythmias did not occur spontaneously during the infusion of cocaine in either ANS-intact (n=13) or ANS-blocked (n=12) dogs but could be induced in some animals during programmes electrical stimulation of the right ventricle. In the absence of cocaine, either 30-second burst pacing or application of double extrastimyos to the right ventricular apex induced a nonsustained ventricular tachycardia of less than five beats in two of 13 dogs (15%) in the ANS-intact group (Table 5). Although the overall cumulative incidence of inducible nonsustained or sustained ventricular tachycardia was greater in the presence of dose 1, dose 2, or dose 3 cocaine, the increase did not achieve statistical significance by χ² analysis. In contrast, a significant (p<0.03) increase in the incidence of electrically inducible ventricular arrhythmias was observed in the presence of dose 2 cocaine in ANS-blocked dogs (Table 5). Although we observed a lower incidence of inducible ventricular arrhythmias during the control period in ANS-blocked versus ANS-intact dogs and a higher incidence of sustained ventricular tachycardia in ANS-blocked versus ANS-intact dogs in the presence of dose 2 cocaine, the differences between control groups and cocaine groups did not achieve statistical significance. In animals in which ventricular tachycardia could be induced in the presence of cocaine, the majority were induced using double extrastimyos (80%) compared with rapid ventricular pacing (20%).

**Discussion**

Within the past decade, cocaine abuse has become a major medical problem in the United States. Clinical reports have indicated that cocaine may produce ventricular arrhythmias and sudden death in patients who have no evidence of underlying heart disease or isch-
This suggests that cocaine may produce a direct arrhythmogenic effect on the myocardium in addition to its effects on the coronary circulation. Our data support this hypothesis in that plasma levels of cocaine similar to those achieved after a fatal overdose in man were found to produce significant and relatively nonselective conduction-slowing effects in different regions of the heart, including the atrium, AV node, His-Purkinje system, and ventricular myocardium. These conduction-slowing effects were found to be strongly dependent on both heart rate and autonomic tone.

**Cocaine Has Class Ib–Like Sodium Channel–Blocking Characteristics**

The effects of cocaine on conduction in vivo were found to be both use and rate dependent. For example, after a sudden shortening in the paced cycle length cocaine produced a beat-by-beat (use-dependent) increase in SV conduction delay that approached a steady state within only a few beats (τbeat, approximately two beats) (Figure 6A). Recovery from cocaine-induced conduction-slowing during diastole also occurred with fairly rapid kinetics (τrec, ≈200 msec) (Figure 6B). Such rapid diastolic recovery kinetics can account for cocaine having a rate-dependent effect that becomes large only at relatively short cycle lengths (e.g., <600 msec) (Figures 3 and 4) where the diastolic interval is too short for complete recovery to occur. Cocaine’s conduction-slowing characteristics appear to be very similar to those previously reported for class Ib antiarrhythmic agents such as lidocaine and mexiletine and the antiarrhythmic drug amiodarone. These all share the common characteristic of having relatively fast (fast-in–fast-out) kinetics of interaction with cardiac sodium channels.

These characteristics differ from those shared by class Ia drugs such as quinidine and procainamide and class Ic drugs such as flecainide and propafenone, which have much longer time constants for onset and recovery from use-dependent conduction slowing and produce significant rate-dependent effects on QRS at cycle lengths >600 msec (heart rates, <100 min⁻¹). These in vivo observations are also qualitatively consistent with our previous in vitro results defining cocaine’s effect on the cardiac sodium current in isolated ventricular myocytes. In cooled (16°C) guinea pig myocytes, 10–50 μM cocaine depresses the cardiac sodium current in both a use- and rate-dependent manner, with a time constant of recovery (~8 seconds) at hyperpolarized potentials that is intermediate between that reported for lidocaine (~1 second) and quinidine (~30 seconds) under similar experimental conditions.

Cocaine was not found to be highly selective in its ability to slow conduction in the atrium (SV interval), AV node (AH interval), His-Purkinje system (HV and SV intervals), or ventricle (QRS duration) in ANS-blocked dogs (Figures 2 and 3). However, cocaine did produce a significantly greater effect on the atrial versus ventricular ERP (Figure 1). A similar tissue-specific difference in the potency of cocaine effect on the ERP has also been observed in isolated rabbit tissue.

**Autonomic Tone Modulates Cocaine’s Electrophysiological Effects**

Cocaine’s electrophysiological effects in an autonomically intact group were compared with one in which both muscarinic and β₁-adrenergic effects on the heart were blocked. Significant differences were found in cocaine’s effect on heart rate, PR and AH intervals, Wenckebach cycle length, atrial ERP, and ventricular ERP in these two animal groups. In ANS-blocked dogs, cocaine produced marked increases in atrial and ventricular refractoriness, depressed sinus node automaticity, increased the Wenckebach cycle length, and increased conduction times through the atrium, AV node, His-Purkinje system, and ventricle. These effects are consistent with previous in vitro reports of direct depressant effects of cocaine on tissue isolated from the SA node, atrium, Purkinje fiber system, and ventricle and may be attributed to cocaine’s effect on cardiac sodium, calcium, and potassium channels.

In contrast to its effects in ANS-blocked dogs, cocaine in ANS-intact dogs produced an increase in heart rate and no significant effect on the Wenckebach cycle length or PR or AH intervals. In effect, these differ-

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**Table 5. Incidence of Arrhythmias Induced by Programmed Electrical Stimulation of the Right Ventricular Apex**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nonsustained VT</th>
<th>Sustained VT</th>
<th>Nonsustained or sustained VT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANS-intact dogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2/13 (15%)</td>
<td>0/13 (0%)</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>Control+isoproterenol</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>Dose 1 cocaine</td>
<td>1/6 (17%)</td>
<td>1/6 (17%)</td>
<td>2/6 (33%)</td>
</tr>
<tr>
<td>Dose 2 cocaine</td>
<td>2/10 (20%)</td>
<td>2/10 (20%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Dose 2 cocaine+isoproterenol</td>
<td>1/8 (13%)</td>
<td>0/8 (0%)</td>
<td>1/8 (13%)</td>
</tr>
<tr>
<td>Dose 3 cocaine</td>
<td>1/6 (17%)</td>
<td>2/6 (33%)</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td><strong>ANS-blocked dogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Dose 1 cocaine</td>
<td>0/10 (0%)</td>
<td>0/10 (0%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Dose 2 cocaine</td>
<td>2/6 (33%)</td>
<td>2/6 (33%)</td>
<td>3/6 (50%)</td>
</tr>
</tbody>
</table>

ANS, autonomic nervous system; VT, ventricular tachycardia. Ratios indicate number of animals in which arrhythmia induction was successful divided by the total number of animals for which the protocol was attempted. Percent of successful induction is shown in parentheses.

* *p<0.03 vs. control in ANS-blocked dogs (χ²).
ences suggest that the autonomic nervous system can strongly mask the expression of cocaine's depressant effects on both the atrium and AV node. Cocaine-induced changes in both sympathetic and parasympathetic tone are likely to have contributed to this masking effect since cocaine is known to act both as an indirect sympathomimetic agent, and as an antimuscarinic agent (K, 19 μM) at high concentrations similar to those used in this study.

Interestingly, we also found that changes in autonomic tone could significantly modulate the effects of cocaine on conduction parameters within the ventricle (e.g., QRS duration). During direct pacing of the His bundle or ventricle, we found that the conduction-slowing effects of cocaine were significantly larger in ANS-blocked dogs than in ANS-intact dogs (Figures 3 and 4). A qualitatively similar modulation of the conduction-slowing effects of lidocaine, mexiletine, quinidine, cibenzoline, and amiodarone by changes in sympathetic tone has also been reported recently. Iso-proterenol has also been reported to partially reverse lidocaine's inhibitory effect on the cardiac sodium current in vitro. This effect appears to be due to an effect of β-adrenergic agonists to increase the sodium current amplitude without changing the kinetics of lidocaine unblocking at diastolic potentials.45,46 Our observations of a tone-dependent change in the magnitude of cocaine's effects on intraventricular conduction without a major change in cocaine's rate-dependent properties or in its kinetics of conduction-slowing onset or recovery seems consistent with these in vitro findings. Additional mechanisms, however, also could contribute to the effects of sympathetic tone on conduction. For example, β-adrenergic agonists have been shown to increase gap junctional conductance by a cyclic AMP-dependent mechanism, an effect that could contribute to an effect of autonomic tone on conduction velocity. Consistent with this hypothesis, we observed a significantly (p<0.05) shorter QRS duration in ANS-intact than in ANS-blocked dogs during ventricular pacing in the absence of cocaine. However, the effect on QRS duration was smaller in dogs under control conditions as compared with the differences observed in the presence of cocaine (Table 5). This suggests that, like lidocaine, cocaine may have an effect on conduction that is enhanced under conditions of autonomic tone.

We also considered the possibility that autonomic tone might modulate cocaine's effect on intraventricular conduction by altering the duration of the ventricular action potential, thereby leading to a change in the extent of use-dependent block.11 β-Adrenergic stimulation of the ventricular muscle is known to influence action potential duration, and changes in action potential duration have been shown to modulate the effects of the sodium channel–blocker lidocaine in vitro and in vivo. However, we found no significant difference in QT intervals between ANS-blocked and ANS-intact dogs under control conditions. This suggests that the change in the duration of the ventricular action potential following autonomic blockade is relatively small, which is consistent with the results of previous studies defining the effects of sympathetic tone on the canine ventricle and His-Purkinje fiber system.50

It appears that changes in action potential duration cannot adequately account for how autonomic tone modulates cocaine's effect on intraventricular conduction.

Cocaine's Effect on QT Results From Its Effect on QRS

Previous reports have indicated that high levels of cocaine produce an increase in both QT and QRS intervals. The results of the current study confirm this conclusion and provide new evidence that cocaine's effect on the QT interval is highly rate dependent. Cocaine's rate-dependent effect on the QT interval was found to parallel its effect on the QRS interval (compared to Figure 5 with Figure 3), suggesting that cocaine's effect on the QT interval is primarily due to its effect on conduction. This hypothesis was supported by the finding that cocaine had no significant effect on the ST interval (where ST=QT−QRS) in either ANS-intact or ANS-blocked dogs (Figure 5). These results indicate that cocaine plasma levels of 2−11 μg/mL do not produce a significant effect on ventricular repolarization in the in situ canine heart.

Clinical Relevance

In our animal model, clinically significant ventricular arrhythmias in the presence of 2−11 μg/mL cocaine were observed only after direct programmed stimulation of the ventricle (p<0.03 in ANS-blocked dogs) (Table 5). The effects produced by higher plasma levels of cocaine were not defined due to cocaine's hypotensive effects at high doses in this animal model. The observation that cocaine does not produce a high frequency of spontaneous ventricular arrhythmias in dogs with normal cardiovascular parameters under these conditions suggests that either additional physiological derangements or much more massive doses of cocaine may be necessary for cocaine to produce spontaneous ventricular arrhythmias and sudden death. Nevertheless, the observation of a proarrhythmic effect during programmed stimulation suggests that cocaine's effects on intraventricular conduction may contribute to the development of an "arrhythmic substrate" in which reentrant excitation may occur. This substrate may then be further enhanced by other arrhythmogenic influences that may occur during a cocaine overdose, such as seizure-induced acidosis and hypoxia, hyperthermia, coronary vasoconstriction, and changes in autonomic tone. Our observation of a strong rate-dependent action of cocaine on different cardiac conduction parameters suggests that heart rate may also be an important variable modulating cocaine's proarrhythmic effects on the in situ heart. Patients suffering from a cocaine overdose have been documented to have heart rates in the range of 150−180 min−1 (cycle length, 333−400 msec), at which high plasma levels of cocaine begin to produce a significant conduction-slowing effect in the ventricle and His-Purkinje fiber system (Figures 2−4). In addition to heart rate, we observed that autonomic blockade can significantly intensify cocaine's conduction-slowing effects. This suggests that caution may be warranted in administering β-blockers to control heart rate in patients suffering from a cocaine overdose. Although reduction in heart rate may be beneficial in reducing the magnitude of cocaine's rate-dependent effect on conduction, a reduct-
tion in sympathetic tone can also paradoxically intensify cocaine's conduction-slowing properties in the ventricle. Thus, the ability of a β-blocker to reduce cocaine's effect by slowing the heart rate may be offset, or potentially overwhelmed, by the blockade of a second independent action of sympathetic tone to reduce cocaine's effect on conduction and refractoriness.

Summary

We have demonstrated that in an animal model, high plasma levels of cocaine similar to those reported to be achieved after a fatal overdose in man produce significant electrophysiological effects on the in situ heart, including rate-dependent slowing of conduction through the atrium, AV node, His-Purkinje conduction system, and ventricular myocardium, as well as prolongation of atrial and ventricular refractoriness and increases in AV nodal Wenckebach cycle length. In addition, we have provided the first data to show that cocaine's conduction-slowing effects in the His-Purkinje conduction system and ventricular myocardium are markedly dependent on autonomic tone.

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