Coronary Vascular Responses to Short-term Cocaine Administration in Conscious Baboons Compared With Dogs

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OBJECTIVES Cardiovascular complications of cocaine use represent an important clinical problem, yet the mechanisms by which cocaine predisposes to myocardial ischemia are poorly understood.

BACKGROUND The effects of cocaine on the coronary circulation have been studied extensively in experimental animal models, but have failed to recapitulate the clinical findings reported in humans who use cocaine.

METHODS We studied 12 conscious, chronically instrumented dogs and 5 conscious, chronically instrumented baboons to determine whether there were important species differences in the response to cocaine.

RESULTS Comparable doses of intravenous cocaine caused similar increases in left ventricular systolic, diastolic and mean arterial pressure in the two species. However, the peak coronary blood flow response in baboons (186 ± 6 from 47 ± 6 ml/min) was less compared with dogs (115 ± 6 from 41 ± 4 ml/min), while the coronary vascular resistance response was greater in baboons (0.60 ± 0.09 from 1.94 ± 0.09 mm Hg/ml/mm) compared with dogs (0.35 ± 0.09 from 2.24 ± 0.10 mm Hg/ml/min). Although myocardial oxygen consumption responses were similar between species, there was a significant difference (p < 0.05) in oxygen delivery between baboons (164 ± 47 from 705 ± 59 ml of oxygen per minute) and dogs (397 ± 51 from 656 ± 33 ml of oxygen per minute) that was attributable to a significant (p < 0.05) increase in hemoglobin concentration in dogs (+2.1 ± 0.5 g/dl) that was not observed in baboons. Consequently, cocaine caused a significant increase in myocardial oxygen extraction and decreased coronary sinus pH in baboons, but not dogs.

CONCLUSIONS Cocaine caused greater coronary vasoconstriction and greater requirements for oxygen extraction in baboons compared with dogs. (J Am Coll Cardiol 2000;35:1347–54) © 2000 by the American College of Cardiology
METHODS

Surgical instrumentation. Twelve mongrel dogs of either gender (23 to 29 kg) were sedated with xylazine (10 mg/kg) and anesthetized with halothane (1 to 1.5 vol%). Through an incision in the fifth intercostal space, Tygon catheters were placed in the descending thoracic aorta and left atrium, and a Silastic catheter was placed in the coronary sinus. A solid-state miniature pressure transducer (Konigsberg Instruments) was placed in the LV through an apical approach for the high-fidelity recording of LV pressure. Either Transonics (n = 6) or Doppler (n = 6) flow probes were placed on the proximal portion of the left circumflex coronary artery for continuous measurement of coronary blood flow (CBF). All catheters were tunneled subcutaneously and externalized infrascapularly, after which the thoracotomy was closed in layers and the thoracic cavity was evacuated of air. All animals received analgesics as needed for the first 72 h and cephalothin (1 g V) was administered daily for seven days. Dogs were allowed to recover from the surgical procedure for 10 to 12 days during which time the catheters were flushed every other day with a 50% heparin solution (750 U; 1.5 ml per catheter) to ensure patency. The heparin solution was withdrawn prior to study and normal saline solution was used to flush the catheters during the protocol. Animals used in this study were maintained in accordance with the Guidelines of the Committee on Animals of Harvard Medical School and the NIH Guide for the Care and Use of Laboratory Animals (Department of Health and Human Services publication No. NIH 85-23, revised 1985).

Experimental protocols. All dogs studied were in the fully conscious state while resting quietly on the experimental table. Following a 30-min stabilization period, baseline hemodynamic recordings and blood samples were obtained. Nine dogs received a peripheral IV infusion of cocaine hydrochloride (1 mg/kg over 1 min) dissolved in normal saline solution. Baboons were sedated initially with ketamine (4 mg/kg intramuscularly) to facilitate transfer from their cage to the laboratory and removal of catheters from the subcutaneous space. The animals were positioned, lightly restrained, in an experimental chair. Following a 60-min period of stabilization, baseline hemodynamic recordings and blood samples were obtained with the baboons fully awake (29,30) and cocaine hydrochloride (1 mg/kg over 1 min) was administered into the left atrial catheter. To control for potential effects of different routes of administration, three dogs received cocaine hydrochloride (1 mg/kg over 1 min) via the left atrial catheter. An additional three dogs received the IV cocaine protocol after which they underwent surgical splenectomy. Briefly, the dogs were fasted, induced and underwent general inhalational anesthesia as described above. Splenectomy was performed through a midline laparotomy incision after which the animals received three days of cephalothin therapy as described above. The IV cocaine protocol was repeated seven to 10 days following splenectomy, when the dogs had recovered fully.

In all animals, hemodynamic recordings were made at baseline and continuously throughout the 60-min period of observation following cocaine administration. Simultaneous samples of arterial and coronary sinus blood for measurement of oxygen content were drawn into heparin-coated 3-ml syringes at baseline and at 2.5, 10, 20 and 30 min following cocaine administration. Arterial blood samples for determination of plasma catecholamine levels were drawn at baseline and 5 min following cocaine administration. In the three dogs studied before and after splenectomy, plasma lactate samples were drawn from the coronary sinus at baseline and at 10 min following short-term cocaine administration.
Table 1. The Peak LV Systemic and Coronary Hemodynamic Responses to Intravenous Cocaine in Conscious Dogs and Baboons

<table>
<thead>
<tr>
<th></th>
<th>Canine</th>
<th>Change</th>
<th>Baboon</th>
<th>Change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline Peak</td>
<td>Baseline Peak</td>
<td>Baseline Peak</td>
<td>Baseline Peak</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>123 ± 5</td>
<td>164 ± 6</td>
<td>41 ± 4*</td>
<td>127 ± 11</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10 ± 1</td>
<td>17 ± 2</td>
<td>7 ± 1*</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/s)</td>
<td>3,225 ± 108</td>
<td>3,675 ± 147</td>
<td>450 ± 119*</td>
<td>3,284 ± 267</td>
</tr>
<tr>
<td>Ao mean (mm Hg)</td>
<td>92 ± 3</td>
<td>133 ± 5</td>
<td>41 ± 4*</td>
<td>91 ± 7</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>82 ± 6</td>
<td>122 ± 7</td>
<td>40 ± 7*</td>
<td>99 ± 8</td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>41 ± 4</td>
<td>56 ± 7</td>
<td>15 ± 4*</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>CVR (mm Hg/ml/min)</td>
<td>2.24 ± 0.10</td>
<td>2.59 ± 0.07</td>
<td>0.35 ± 0.09*</td>
<td>1.94 ± 0.09</td>
</tr>
<tr>
<td>MVO₂ (ml O₂/min)</td>
<td>451 ± 29</td>
<td>640 ± 54</td>
<td>189 ± 36*</td>
<td>470 ± 47</td>
</tr>
<tr>
<td>O₂ delivery (ml O₂/min)</td>
<td>656 ± 33</td>
<td>1,053 ± 48</td>
<td>397 ± 51*</td>
<td>705 ± 59</td>
</tr>
<tr>
<td>O₂ extraction (%)</td>
<td>69 ± 1</td>
<td>65 ± 1</td>
<td>−4 ± 2</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>CS [H⁺] (nM/l)</td>
<td>41 ± 3</td>
<td>42 ± 3</td>
<td>1 ± 3</td>
<td>41 ± 2</td>
</tr>
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</table>

*p < 0.05 compared with baseline. †p < 0.05 compared with peak response in canine.

Ao mean = mean aortic pressure; CBF = coronary blood flow; CS = coronary sinus; CVR = coronary vascular resistance; LVP = left ventricular pressure; LV dP/dt = derivative of LV systolic pressure with respect to time; LVEDP = left ventricular end-diastolic pressure; MVO₂ = myocardial oxygen consumption.

Data Analysis. Hemodynamics were recorded simultaneously on a multichannel tape recorder (Honeywell 101) and played back on a strip chart recorder. Aortic and left atrial pressures were measured with the use of the chronically implanted catheters and a strain gauge (Statham) calibrated with a mercury manometer. Left ventricular pressure was measured using the solid-state miniature pressure transducer calibrated in vitro with a mercury manometer and in vivo using the aortic and left atrial pressures. Continuous recordings of LV derivative of LV systolic pressure with respect to time (dP/dt) were derived from the LV pressure signals with operational amplifiers connected as differentiators with a frequency response of 700 Hz. The differentiator was calibrated directly as described previously (16,27). A cardiotachometer triggered by the LV pressure wave form was used to record heart rate. Mean arterial pressure was derived through the use of an electronic filter applied to the phasic arterial pressure signal. Mean left circumflex CBF was measured directly (Transonics) using a similar electronic filter applied to the phasic CBF or calculated (Doppler) as the product of the measured mean velocity (cm/s) and the internal cross-sectional area of the artery at the site of implantation obtained at the time of euthanasia. The mean CVR was calculated as the quotient of mean arterial pressure and mean CBF. Measurements of arterial and coronary sinus oxygen content, hemoglobin concentration and pH were made with an IL-483 Co-Oximeter System (Instrumentation Laboratories; Lexington, Massachusetts). An index of MVO₂ was calculated as the product of CBF and the arterial-coronary sinus oxygen content difference. An index of myocardial oxygen delivery was calculated as the product of CBF and arterial oxygen content. Myocardial oxygen extraction was calculated as the quotient of the arterial-coronary sinus oxygen content difference and the arterial oxygen content, and expressed as a percentage. Measurements of plasma catecholamine levels (epinephrine [EPI] and norepinephrine [NE]) were made using the radioimmunoassay as described previously (15,16,27). Coronary sinus lactate concentrations were measured in the three dogs studied before and after splenectomy using 2 ml of coronary sinus blood in a gray top tube and the colorimetric assay (Johnson and Johnson Clinical Diagnostics).

Statistical analysis. All statistical analyses were performed using software (Excel and SuperAnova). Differences between the baseline and the peak hemodynamic responses, oxygen content measurements and plasma catecholamine levels were analyzed using Student t test. The differences in the time course of the hemodynamic responses between baboons and dogs were compared using a repeated measures analysis of variance. All data are reported as mean ± standard error of the mean, and p < 0.05 was considered statistically significant. Data from dogs receiving cocaine via the left atrial catheter did not differ from those receiving cocaine via a peripheral vein. These two groups were therefore combined for the statistical analyses.

RESULTS

Effects of cocaine on LV and systemic hemodynamics. Table 1 reveals the baseline and peak LV and systemic hemodynamic responses to short-term cocaine administration in conscious dogs and baboons. The peak LV systolic and end-diastolic pressure responses were comparable in dogs and baboons, although the peak LV systolic pressure response occurred later in baboons (10 to 15 min) as compared with dogs (2.5 to 5 min) (Fig. 1). The LV dP/dt response was similar and modest in both dogs and baboons. The increases in mean arterial pressure and heart rate were similar between the two groups.

Effects of cocaine on coronary hemodynamics. The baseline and peak effects of short-term IV cocaine on coronary hemodynamics in the two groups are depicted in Table 1.
There were no significant differences in the LV/body weight ratio between the two species (dog: 4.15 ± 0.23 g/kg; baboon: 3.94 ± 0.34 g/kg). The increase in CBF was greater in dogs compared with baboons while the increase in coronary vasoconstriction was greater in baboons. These differences, however, were only evident during the first 5 min following cocaine administration. Thereafter, there were no significant differences between the two species (Fig.

Figure 1. Time course of the left ventricular systolic (LVP), end-diastolic (LVEDP) pressure, heart rate and LV dP/dt responses in dogs and baboons. There were no differences in either the peak responses or the time course of the response to IV cocaine.

Figure 2. The time course of the coronary flow (CBF), vasoconstrictor (CVR), myocardial oxygen consumption (MVO₂) and myocardial oxygen delivery (O₂ delivery) responses to IV cocaine in dogs and baboons. The CBF and the CVR responses over time were similar. While the MVO₂ responses were comparable, the O₂ delivery was significantly greater in dogs than baboons (p < 0.05).
2). To determine how the coronary vasoconstrictor responses to cocaine affected oxygen delivery in the two species, we measured MVO₂ and oxygen delivery responses in nine dogs and four of five baboons. This measurement could not be made in one baboon due to failure of the coronary sinus catheter. Although both the peak and the time course of the MVO₂ responses were comparable, the myocardial oxygen delivery response to short-term IV cocaine was markedly attenuated in baboons compared with dogs (Table 1 and Fig. 2). The consequence was an increase in myocardial oxygen extraction (Table 1) and a decrease in coronary sinus PO₂ and an increase in coronary sinus hydrogen ion concentration (Fig. 3) in baboons compared with dogs. There were no differences in the arterial or coronary sinus PCO₂ responses between the groups. These differences were evident not only early following cocaine administration when the coronary vasoconstrictor responses were greater in baboons compared with dogs, but also later, when the vasoconstrictor responses were comparable. Therefore, the early and brief limitations in the CBF and the exaggerated vasoconstrictor responses to short-term IV cocaine administration in the baboons were insufficient to explain the attenuation of oxygen delivery observed throughout and the associated increased oxygen extraction required in baboons compared with dogs.

Analysis of the arterial blood samples revealed the arterial oxygen content to be elevated in a significant and sustained fashion following cocaine administration in conscious dogs but not in baboons (Fig. 3). The increase in arterial oxygen content was a result of significant and sustained increases in hemoglobin concentrations in dogs compared with baboons (dogs: +2.1 ± 0.5 g/dl from 12.6 ± 0.3 g/dl; baboons: +0.4 ± 0.2 g/dl from 11.4 ± 0.7 g/dl, p < 0.05).

**Effects of cocaine on plasma catecholamine levels.**

Plasma catecholamine levels at baseline did not differ between the two species (dogs: NE 235 ± 63 pg/ml, Epi 104 ± 36 pg/ml; baboons: NE 274 ± 114 pg/ml, Epi 212 ± 98 pg/ml; p = NS). Following the administration of cocaine, plasma catecholamine levels rose significantly and comparably at 5 min in the two species (dogs: NE +1418 ± 127 pg/ml, Epi +463 ± 167 pg/ml; baboons: NE +347 ± 123 pg/ml, Epi +310 ± 96 pg/ml; p < 0.05 vs. baseline for both, p = NS dog vs. baboon).

**Effects of cocaine in dogs before and after splenectomy.**

To determine the role of splenic contraction and the resultant increase in circulating hemoglobin concentrations on myocardial oxygen delivery following short-term cocaine administration, we studied the systemic and coronary response to cocaine in three additional dogs before and after splenectomy. There was no significant difference in the peak systemic hemodynamic responses to cocaine before and after splenectomy (Table 2). Similarly, there was no significant difference in the peak coronary flow or the CVR responses to cocaine before and after splenectomy (Table 2). However, despite a comparable MVO₂ response to cocaine, there was
a significant reduction in the myocardial oxygen delivery response to cocaine in splenectomized dogs compared with normal dogs. This significant difference was attributable to a lack of an increase in arterial oxygen content which was, in turn, due to a lack of an increase in circulating hemoglobin concentration in the splenectomized dogs (Fig. 4). This response in the splenectomized dogs resembled closely the response observed in the baboons. As a consequence, there was a greater decrease in coronary sinus PO2 and increase in coronary sinus (H⁺) concentration (Table 2) and a significant increase in coronary sinus lactate concentration in splenectomized dogs compared with normal dogs.

**DISCUSSION**

In the present study, we observed that the coronary vasoconstrictor effects of cocaine were more intense in nonhuman primates than in canines, although this effect was limited to the first 2 to 5 min following IV cocaine administration. However, the limitations in myocardial

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**Table 2.** The Peak LV Systemic and Coronary Hemodynamic Responses to Intravenous Cocaine in Conscious Dogs Before and After Splenectomy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Peak Change</th>
<th>Baseline</th>
<th>Peak Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVP (mm Hg)</strong></td>
<td>113 ± 5</td>
<td>37 ± 5</td>
<td>120 ± 11</td>
<td>24 ± 7</td>
</tr>
<tr>
<td><strong>LVEDP (mm Hg)</strong></td>
<td>7 ± 1</td>
<td>6 ± 2</td>
<td>8 ± 3</td>
<td>8 ± 3</td>
</tr>
<tr>
<td><strong>LV dP/dt (mm Hg/s)</strong></td>
<td>2,775 ± 226</td>
<td>3,171 ± 347</td>
<td>3,96 ± 211</td>
<td>422 ± 111</td>
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<tr>
<td><strong>Ao mean (mm Hg)</strong></td>
<td>82 ± 13</td>
<td>41 ± 8</td>
<td>90 ± 7</td>
<td>38 ± 6</td>
</tr>
<tr>
<td><strong>Heart rate (min⁻¹)</strong></td>
<td>96 ± 9</td>
<td>27 ± 5</td>
<td>99 ± 11</td>
<td>32 ± 7</td>
</tr>
<tr>
<td><strong>CBF (ml/min)</strong></td>
<td>46 ± 6</td>
<td>11 ± 4</td>
<td>47 ± 6</td>
<td>10 ± 4</td>
</tr>
<tr>
<td><strong>CVR (mm Hg/ml/min)</strong></td>
<td>1.79 ± 0.10</td>
<td>2.16 ± 0.1</td>
<td>0.37 ± 0.08</td>
<td>0.33 ± 0.09</td>
</tr>
<tr>
<td><strong>MVO₂ (ml O₂/min)</strong></td>
<td>441 ± 69</td>
<td>208 ± 34</td>
<td>495 ± 57</td>
<td>203 ± 67</td>
</tr>
<tr>
<td><strong>O₂ delivery (ml O₂/min)</strong></td>
<td>639 ± 33</td>
<td>279 ± 34</td>
<td>687 ± 59</td>
<td>151 ± 37</td>
</tr>
<tr>
<td><strong>CS PO₂ (mm Hg)</strong></td>
<td>28 ± 6</td>
<td>-5 ± 4</td>
<td>25 ± 7</td>
<td>-8 ± 6</td>
</tr>
<tr>
<td><strong>CS [H⁺] (nM/l)</strong></td>
<td>44 ± 4</td>
<td>1 ± 5</td>
<td>42 ± 3</td>
<td>10 ± 2</td>
</tr>
<tr>
<td><strong>CS lactate (mg/dl)</strong></td>
<td>6.4 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>9.8 ± 2.9</td>
<td>9.1 ± 2.0</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with baseline. †p < 0.05 compared with before splenectomy.

Abbreviations are listed in Table 1.

Figure 4. The MVO₂, O₂ delivery, arterial oxygen content and hemoglobin responses to IV cocaine in conscious dogs before and after splenectomy. The O₂ delivery response was attenuated and the arterial O₂ content and hemoglobin responses were abolished (p < 0.05) after splenectomy.
oxygen delivery were greater in baboons. This resulted in a requirement for increased myocardial oxygen extraction and the development of myocardial acidemia. The increased oxygen extraction was not related to differences in MVO₂ but rather to differences in arterial oxygen content responses. Specifically, there was a significant increase in circulating hemoglobin and consequently, oxygen-carrying capacity in dogs but not in baboons. Finally, this increase in circulating hemoglobin concentration in response to cocaine was abolished in splenectomized dogs, resulting in a greater decrease in coronary sinus PO₂ and increase in coronary sinus (H⁺) concentration, recapitulating the response to cocaine observed in baboons.

Previous experimental studies of cocaine-induced myocardial ischemia. There have been numerous reports in the literature of myocardial ischemia and infarction (1–5) and malignant arrhythmias (31) following recreational cocaine use, and a number of prior studies have examined the effects of cocaine on the coronary vasculature (7,20–23,26,27). These studies have been limited by the relatively low doses of cocaine used and by a failure to measure directly myocardial oxygen delivery and consumption, given the transient nature of cardiovascular effects of cocaine. As such, the experimental studies in humans have failed to elucidate fully the mechanisms whereby cocaine exerts adverse cardiovascular effects.

Experimental animal studies have demonstrated adverse coronary vascular and myocardial effects of cocaine (10–13,22), but most have been conducted in anesthetized preparations. Anesthesia-related perturbations in autonomic responses require higher doses and alter the hemodynamic responses to cocaine (10,14). Prior work from this laboratory (27) and others (11,13,18) has emphasized the importance of the intact autonomic nervous system in both the contractile and the coronary effects of cocaine.

The importance of direct measurements of the myocardial oxygen supply-demand relationship in determining the coronary vascular effects of cocaine was demonstrated by recent data from our laboratory (15). We have shown that short-term cocaine administration is associated with a "blood doping" effect (i.e., an acute increase in blood hemoglobin concentration) in conscious dogs that mitigated against the effects of coronary vasoconstriction to limit oxygen supply. In the present study, we have confirmed the physiological significance of this phenomenon, by demonstrating that the blood doping effects of cocaine and the resultant enhancement in myocardial oxygen delivery were abolished by splenectomy in the dog. The consequence was that the myocardial response to cocaine was similar between splenectomized dogs and baboons. More importantly, in the absence of augmented oxygen-carrying capacity, cocaine-induced coronary vasoconstriction may limit oxygen delivery, resulting in transient declines in coronary sinus PO₂ and lactate production.

The role of splenic contraction. Previous studies have documented splenic contraction during exercise in numerous species whose spleens contain capsular smooth muscle, including dogs (32,33). The human spleen does not contain significant amounts of smooth muscle (34), and the existence of active splenic contraction in humans has been controversial (35). Furthermore, the effect of splenic shrinkage during exercise on arterial oxygen-carrying capacity may be less marked (36). It is not known if the spleen of baboons exhibits active contraction during sympathetic stimulation, but the phylogenetic similarity to humans would suggest less profound splenic responses to these stimuli than are seen in dogs. Importantly, Shen et al. (29) have shown that there is no difference in the cardiovascular response to alpha-adrenergic stimulation or in the density of alpha-adrenergic receptors in the myocardium of dogs compared with baboons. This observation, together with the plasma catecholamine responses measured herein and previously (15), makes potential species differences in adrenergic responsiveness an unlikely explanation for the observed results.

Significance of the current findings. To our knowledge, there are no previous studies of the effects of cocaine on the coronary circulation in nonhuman primates. Accordingly, the baboon represents an ideal model to study the coronary vascular and myocardial effects (29,37) of cocaine similar to those employed by human users. The results of the current study reconcile several controversies. First, studies reporting only peak responses as opposed to the time course of the hemodynamic response to cocaine tend to exaggerate transient effects. Second, when metabolically mediated vasodilation is offset by direct cocaine-induced coronary vasoconstriction, the inability to augment myocardial oxygen delivery in nonhuman primates was associated with greater myocardial oxygen extraction and myocardial acidemia, suggestive of transient myocardial ischemia. This difference in physiological response between dogs and nonhuman primates may explain a greater predisposition to ischemic complications in humans following cocaine use.

Study limitations. In this study, we did not measure plasma cocaine levels, but we did measure early plasma catecholamine responses to cocaine. There were no significant differences in plasma catecholamine responses between dogs and baboons, which argues against the possibility that the sympathetic stimulation associated with cocaine administration was greater in baboons and contributed to the greater limitation in oxygen delivery. Rather, the major difference appears to be the absence of blood doping effect in baboons compared with dogs. We cannot exclude the possibility that the small dose of ketamine used to sedate the baboons during the experimental preparation may have had an effect on hemodynamic responses to cocaine. Previous studies from our laboratory in baboons found no significant effect on baseline hemodynamics (29,30). Finally, we made our hemodynamic observations during a 45-min period following cocaine administration and did not examine
whether further differences were evident again at a later time point as reported by Brogan et al. (20).

Taken together, these data suggest that the coronary vasoconstrictor response to cocaine caused greater supply-demand imbalance in nonhuman primates compared with dogs. The greater supply-demand imbalance in the baboon would be expected in the splenectomized dog. These data suggest that humans may be at greater risk of ischemic consequences from typically employed doses of cocaine than would be expected from studies of the coronary responses in other species.

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REFERENCES


