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Cocaine-induced microvascular vasoconstriction but differential systemic haemodynamic responses in Yucatan versus Yorkshire varieties of swine

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1 Systemic and coronary haemodynamics were measured in 6 Yorkshire swine and 6 Yucatan miniature swine under isoflurane anaesthesia to investigate the influence of cocaine following its intravenous administration at 1, 3 and 7 mg kg^{-1}.

2 Cocaine in Yorkshire swine *decreased* mean arterial pressure and rate pressure product (systolic pressure × heart rate), suggesting a cardiac depressant effect, whereas cocaine in Yucatan miniature swine *increased* these parameters, consistent with a hyperadrenergic state.

3 Cocaine in both Yorkshire swine and Yucatan miniature swine decreased coronary blood flow and coronary flow reserve, and increased coronary vascular resistance.

4 A modest generalized epicardial coronary artery constriction was observed by angiography, without evidence of focal spasm.

5 Our results confirm a marked vasoconstrictor effect of cocaine on the coronary arterial circulation, predominantly distal to the epicardial coronary arteries, but also indicate important differences in the systemic cardiovascular responses to the drug between two closely related strains of animals within the same species. Due to the similarities between the swine and human coronary arterial vasculature, we suggest that vasoconstriction in the coronary microcirculation may produce cardiac toxicity in man.

Keywords: Cocaine; coronary blood flow; coronary flow reserve; microcirculation; microvascular spasm

Introduction

Cocaine toxicity has been associated with cardiovascular complications and death (Isner *et al.*, 1986; Nanji & Filipenko, 1984; Wetli & Wright, 1979), although the mechanism for cardiac toxicity has not yet been fully delineated. Epicardial vasospasm, coronary thrombosis and direct myocardial toxicity have been proposed as precipitating events in cocaine-mediated death (Isner & Chokshi, 1991; Rezkalla *et al.*, 1990; Zimmerman *et al.*, 1987). However, in experimental animals cocaine administration has been associated with a wide spectrum of systemic responses. Cocaine has been reported to produce a variety of effects among animal species under different experimental conditions ranging from severe systemic hypertension with seizure activity to severe hypotension, myocardial depression and shock (see Table 1). Available data in experimental animals suggest that cocaine administration may precipitate myocardial ischaemia either by increasing myocardial oxygen demand, decreasing coronary blood flow, or through a combination of both effects (Hollander & Carter, 1992; Kuhn *et al.*, 1989; Lange *et al.*, 1989).

Egashira *et al.* (1991) have shown that cocaine produces a dose-related increase in mean artery pressure (MAP) and heart rate (HR) in miniature swine, whereas we found that cocaine (1, 3 and 10 mg kg^{-1}, i.v.) decreases MAP and HR in Yorkshire swine (Núñez *et al.*, 1993). Because our previous work indicated that cocaine could cause cardiac ischaemia and infarction in both varieties of swine (Núñez *et al.*, 1994a,b,c), the purpose of this study was to test the hypothesis that the drug can produce constriction of the large epicardial coronary arteries and/or the small microvascular coronary vessels regardless of its systemic cardiovascular effects. Our results confirm a marked vasoconstrictor effect of cocaine on the coronary arterial circulation, particularly at the level of the microvasculature, but also indicate important differences in the systemic cardiovascular responses to the drug between two closely related strains of animals within the same species.

Methods

Six Yorkshire swine (YS) and six Yucatan miniature swine (MS) (Charles River Breeding Laboratories, Inc., Wilmington, MA, U.S.A.), 3–4 months old, of either sex and weighing 30–40 kg (weight, age and sex matched), were sedated with intramuscular ketamine hydrochloride (12.5 mg kg^{-1}, Quad Pharmaceutical, Inc., Indianapolis, IN, U.S.A.) and diazepam (10 mg, Roche Laboratories, Inc., Nutley, NJ, U.S.A.). The animals were intubated and mechanically ventilated (Harvard Respirator, Harvard Apparatus, South Natick, MA, U.S.A.). Anaesthesia was maintained with a mixture of 1.5–2% isoflurane and oxygen. Arterial pH, partial pressure of oxygen (P_{O_2}) and partial pressure of carbon dioxide (P_{CO_2}) were maintained within normal limits. Normal saline solution (50 ml h^{-1}) and heparin (5000 units bolus injection followed by 1000 units h^{-1}) were continuously infused through a cannula inserted into an ear vein during the experiment. The femoral artery and vein were exposed through a right femoral cutdown and cannulated with a 9 French sheath. A thermo-

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Table 1 Spectrum of cardiovascular effects of cocaine

HP and BP increase	*HR and BP no change*	*HR and BP decrease*
Monkeys	*Dogs*	*Dogs*
Gonzalez & Byrd (1977)	Hayes *et al.* (1991)	Fraker *et al.* (1990)
	Koerker & Moran (1971)	Hale *et al.* (1991)
Dogs	Graham *et al.* (1965)	Abel *et al.* (1989)
Stambler *et al.* (1993)	Schwartz *et al.* (1989)	Pierre *et al.* (1985)
Wilkerson (1988)	Kuroda (1915)	Morcos *et al.* (1988)
Catravas & Waters (1981)	Wilkerson (1988)	Johnson *et al.* (1989)
Mosso, (1887)		Herman & Vick (1987)
Kuhn *et al.* (1989)		Roth (1971)
		Prus (1913)
Swine		Bayer (1938)
Egashira *et al.* (1991)		
		Turtles
		Kochmann & Dales (1908)
		Bush (1920)

dilution Swan-Ganz catheter (Baxter Healthcare Corp., Irvine, CA) was advanced to the pulmonary artery for cardiac output determinations. An 8 French, left Judkins 1.5 catheter (Medtronic Interventional Vascular, Inc; Danvers, MA, U.S.A.) was advanced from the right femoral artery and selectively engaged in the orifice of the left coronary artery.

Systemic haemodynamics and coronary angiography

Systemic and pulmonary pressures were constantly monitored and recorded by the use of a multichannel pen recorder (Hewlett-Packard Co., Andover, MA, U.S.A.). A bipolar chest lead was attached to provide ECG and arrhythmia monitoring. Cardiac output (CO) was measured by thermodilution in triplicate at each time period. Calculations included:

$$\text{Systemic vascular resistance (SVR)} = (\text{MAP} - \text{RA})/\text{CO}(\text{dynes s}^{-1}\ \text{cm}^{-5})$$

$$\text{Rate pressure product (RPP)} = \text{Systolic blood pressure} \times \text{HR (mmHg beats min}^{-1})$$

Angiography of the left coronary artery was performed in a 44 degree right anterior oblique projection and recorded on 35 mm film at a speed of 50 frames/second, using non-ionic contrast medium (iopamidol 76%, Squibb Diagnostic, Princeton, NJ, U.S.A.). Coronary arteriography was performed under basal conditions, 5 min after each dose of cocaine. Epicardial coronary artery diameter was measured with digital calipers (Fowler-Ultra Cal II, Zurich, Switzerland). The proximal coronary artery segment in the left anterior descending artery (LAD) was measured 1 cm before the first septal branch. The proximal coronary artery segment was also measured in the left circumflex artery (LCX) 1 cm before the first obtuse marginal branch. The contrast-filled coronary guiding catheter was used as a known reference for standard measurements. The intraobserver variability for 175 consecutive measurements was $r=0.88$ with slope $=0.85$ for one observer and $r=0.84$ with slope $=0.88$ for another observer. The interobserver variability for 100 consecutive measurements was $r=0.82$ with slope $=0.81$.

Coronary flow measurement

A 0.018-inch Doppler flow wire (Cardiometrics, Inc., Mountain View, CA, U.S.A.) was positioned in the proximal segment of the LAD to measure coronary flow velocity. The system coupled to the flow wire consisted of a Doppler instrument, a real time spectrum analyzer, a videocassette recorder and a video printer (Cardiometrics Flowmap, Model 5500, Mountain View, CA, U.S.A.). This Doppler system included simultaneous ECG recording and a software package to provide on-line computation and characterization of diastolic and systolic flow velocity patterns. This allowed calculation of coronary blood flow (CBF) and coronary vascular resistance (CVR).

$$\text{CBF (ml min}^{-1}) = \pi\ \text{D}^2/4 \times \text{APV} \times 60$$

where D = diastolic diameter of the coronary artery in cm; APV = average peak velocity in cm s^{-1}.

$$\text{CVR (mmHg ml}^{-1}\ \text{min}^{-1}) = \text{mean arterial pressure/CBF}$$

The APV measured 5 s after a 10 cc contrast injection was considered the hyperaemic response.

Drugs and chemicals

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse, Rockville, MD, U.S.A; isoflurane from Anaquest, Madison, WI, U.S.A.

Experimental protocol

First, a baseline angiogram was performed and the Doppler flow wire was positioned in the proximal segment of the LAD to measure coronary flow velocity. Flow velocity was measured at baseline and after cocaine doses (1, 3 and 7 mg kg^{-1} i.v.). Cocaine was given over 2 min as a bolus with successive incremental doses separated by 10 min intervals. Systemic haemodynamic and coronary flow measurements were obtained and analyzed 3 min after each cocaine dose and coronary angiography was performed immediately thereafter. Injection of contrast medium produced an increase in coronary flow velocity and the peak of this is referred to below as the hypertensive response to injection of contrast medium, indicating the status of constriction of the microvascular bed. At the end of the procedure the animals were killed with a lethal injection of KCl.

Statistical analysis

All data are expressed as mean ± s.e.mean. Dose-response relations were compared by analysis of variance for repeated measurements (ANOVA). A probability of $P<0.05$ was considered statistically significant.

Results

Systemic haemodynamics

The baseline systemic haemodynamics and cocaine dose-response measurements are shown in Table 2. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO) and

pulmonary artery diastolic pressure (PADP) were similar between YS and MS. However, systemic vascular resistance (SVR) was significantly higher in YS. MAP decreased significantly with 1, 3 and 7 mg kg^{-1} cocaine doses in YS. In

Table 2 Systemic haemodynamics

	Yorkshire swine ($n=6$)	*Miniature swine* ($n=6$)	*YS vs MS* (P value)
Mean arterial pressure (mmHg)			
Baseline	92±10	85±7	NS
1.0 mg kg^{-1}	63±8*	104±6*	<0.05
3.0 mg kg^{-1}	55±10*	105±7*	<0.05
7.0 mg kg^{-1}	38±7	116±9	<0.05
Heart rate (beats min^{-1})			
Baseline	108±14	93±2	NS
1.0 mg kg^{-1}	106±10	109±2	NS
3.0 mg kg^{-1}	112±6	112±4*	NS
7.0 mg kg^{-1}	110±6	116±4*	NS
Cardiac output (1 min^{-1})			
Baseline	4.2±0.5	3.3±0.8	NS
1.0 mg kg^{-1}	3.2±1.1	3.7±0.8	NS
3.0 mg kg^{-1}	2.5±0.4*	3.0±0.7	NS
7.0 mg kg^{-1}	1.4±0.4*	2.9±0.8	<0.05
Pulmonary artery diastolic pressure (mmHg)			
Baseline	15±3	16±1	NS
1.0 mg kg^{-1}	20±4	19±1	NS
3.0 mg kg^{-1}	22±3*	21±3*	NS
7.0 mg kg^{-1}	24±2*	26±2*	NS
Systemic vascular resistance (dynes s^{-1} cm^{-5})			
Baseline	1602±325	1070±81	<0.05
1.0 mg kg^{-1}	1514±320	1540±98*	NS
3.0 mg kg^{-1}	1440±350	1905±92	<0.05
7.0 mg kg^{-1}	1323±40*	2230±108*	<0.05
Rate pressure product (mmHg × beats min^{-1})			
Baseline	11124±168	10416±14	NS
1.0 mg kg^{-1}	8268±100	13407±18	<0.05
3.0 mg kg^{-1}	7504±48*	13888±32*	<0.05
7.0 mg kg^{-1}	5170±30*	15776±40*	<0.05

Data expressed as mean ± s.e.mean
* Significant differences from baseline values by ANOVA repeated measurements ($P<0.05$).

Table 3 Coronay haemodynamics

	Yorksire swine ($n=6$)	*Miniature swine* ($n=6$)	*YS vs MS* (P value)
Average peak flow velocity (cms^{-1})	16±2	16±2	NS
Baseline	14±2*	14±1*	NS
1.0 mg kg^{-1}	12±2*	13±1*	NS
3.0 mg kg^{-1}	9±1*	8±1*	NS
7.0 mg kg^{-1}			
Hyperaemic response (cms^{-1})		30±2	NS
Baseline	29±2	26±3	NS
1.0 mg kg^{-1}	21±2*	22±3*	NS
3.0 mg kg^{-1}	16±2*	14±7*	NS
7.0 mg kg^{-1}	10±3*		
Coronary blood flow (ml^{-1} mg^{-1})			
Baseline	98±20	80±8	NS
1.0 mg kg^{-1}	70±14	60±8	NS
3.0 mg kg^{-1}	48±8*	38±8*	NS
7.0 mg kg^{-1}	30±6*	20±18*	NS
Coronary vascular resistance (mmHg ml^{-1} min^{-1})			
Baseline	1.0±0.2	1.1±0.1	NS
1.0 mg kg^{-1}	1.1±0.2	2.0±0.4*	<0.05
3.0 mg kg^{-1}	1.3±0.1*	2.9±0.3*	<0.05
7.0 mg kg^{-1}	1.5±0.2*	3.8±0.2*	<0.05

Data expressed as mean ± s.e.mean.
*2Significant differences from baseline values by ANOVA repeated measurements ($P<0.05$).

contrast, MAP increased significantly with 1, 3 and 7 mg kg^{-1} cocaine doses in MS (Table 2, Table 3). CO decreased significantly after 3 and 7 mg kg^{-1} cocaine doses in YS ($P<0.05$). However, CO did not change in MS. In contrast, PADP increased significantly with 3 and 7 mg kg^{-1} cocaine doses in both YS and MS. SVR progressively decreased with each cocaine dose and reached statistical significance ($P<0.05$) with the 7 mg kg^{-1} dose in YS. In contrast, SVR increased significantly with 1, 3 and 7 mg kg^{-1} cocaine in MS ($P<0.05$). Similarly, RPP significantly increased with 3 and 7 mg kg^{-1} cocaine in MS, whereas RPP significantly decreased with 3 and 7 mg kg^{-1} cocaine in YS.

Coronary blood flow haemodynamics

The baseline coronary blood flow haemodynamics and cocaine dose-response measurements are shown in Table 3. There were no differences at baseline in average peak velocity (APV), hyperaemic response to injection of contrast medium, coronary blood flow (CBF) or coronary vascular resistance (CVR) between YS and MS. APV, the hyperaemic response to contrast and CBF all gradually and progressively decreased with 1 and 3 mg kg^{-1} cocaine in both YS and MS. With 7 mg kg^{-1} cocaine, APV decreased by 44%, the hyperaemic response to contrast decreased by 65%, and CBF decreased by 65% in YS. Similarly, APV decreased by 50%, the hyperaemic response to contrast decreased by 53%, and CBF by 68% in MS. In contrast, coronary vascular resistance (CVR) increased significantly with 3 and 7 mg kg^{-1} cocaine in both YS and MS (Table 3, Figure 1).

Epicardial coronary artery luminal diameter

The baseline luminal diameters of the LAD and LCX were similar in YS and MS (Table 4). The luminal diameter of LAD and LCX decreased significantly by 27% and 22% respectively with 7 mg kg^{-1} cocaine in YS. Similarly, the luminal diameters of the LAD and LCX decreased significantly by 22% and 19% respectively with the 7 mg kg^{-1} cocaine dose in MS ($P<0.05$) (Table 4, Figure 2). Thus, a modest epicardial vasoconstriction was observed in both YS and MS. In addition, focal epicardial vasospasm was not observed in either group.

Discussion

The important findings in this study are as follows: (1) Intravenous cocaine produced two completely different haemodynamic profiles in Yorkshire swine and Yucatan miniature swine. (2) Intravenous cocaine in Yorkshire swine decreased mean arterial pressure and rate pressure product, suggesting a cardiac depressant effect, whereas intravenous cocaine in Yucatan miniature swine increased mean arterial pressure, heart rate and rate pressure product, consistent with a state of high adrenergic tone. (3) Intravenous cocaine in both Yorkshire swine and Yucatan miniature swine produced a dose-dependent decrease in coronary blood flow and increased coronary vascular resistance. (4) Pulmonary artery diastolic pressure increased both in Yorkshire swine and Yucatan miniature

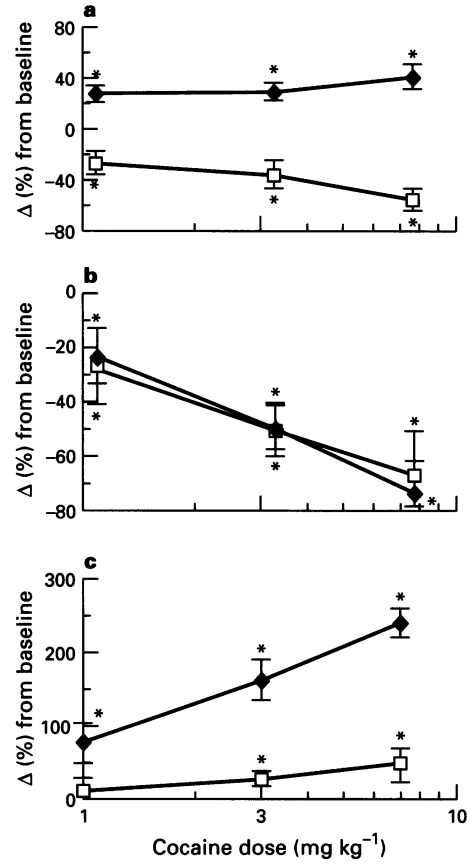

Figure 1 Percentage changes of mean arterial pressure (a) and coronary blood flow (b) are shown at baseline, after 1, 3 and 7 mg kg^{-1} cocaine doses. Mean arterial pressure increased significantly in Yucatan miniature swine (◆) but in contrast, decreased significantly in Yorkshire swine (□). Coronary blood flow (b), however, decreased significantly in both Yucatan miniature swine and Yorkshire swine with 1, 3 and 7 mg kg^{-1} cocaine. (c) Coronary vascular resistance increased significantly with 3 and 7 mg kg^{-1} cocaine in both Yucatan miniature swine and Yorkshire swine. *Significant differences from baseline value ($P<0.05$).

Table 4 Epicardial coronary artery lumen diameter

	Yorkshire swine ($n=6$)	*Miniature swine* ($n=6$)	*YS vs MS* (P value)
LAD diameter (mm)			
Baseline	3.4±0.1	3.2±0.1	NS
1.0 mg kg^{-1}	3.2±0.1	2.9±0.1	NS
3.0 mg kg^{-1}	3.2±0.1	2.7±0.2*	NS
7.0 mg kg^{-1}	2.7±0.4*	2.5±0.3*	NS
LCX diameter (mm)			
Baseline	3.2±0.3	2.7±0.3	NS
1.0 mg kg^{-1}	3.1±0.2	2.5±0.4	NS
3.0 mg kg^{-1}	2.8±0.1	2.3±0.4	NS
7.0 mg kg^{-1}	2.5±0.1*	2.2±0.4*	NS

Data expressed as mean±s.e.mean.
* Significant differences from baseline values by repeated measurements ($P<0.05$).

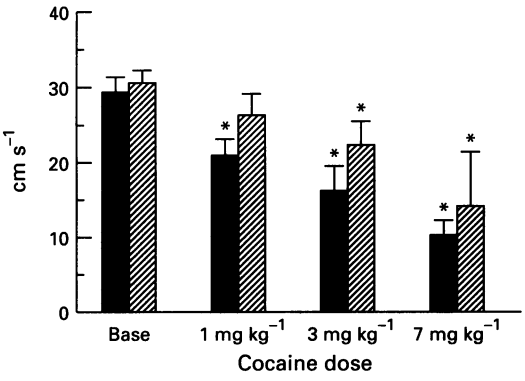

Figure 2 The luminal diameters of the LAD and LCX are shown at baseline and in response to 1, 3 and 7 mg kg^{-1} cocaine in Yucatan miniature swine (hatched columns) and Yorkshire swine (solid columns). *Significant differences from baseline value ($P<0.05$).

swine, suggesting myocardial ischaemia. (5) A modest generalized epicardial coronary artery constriction was observed in Yorkshire swine and Yucatan miniature swine, without evidence of focal vascular spasm.

Little is known about potential differences among Yucatan and Yorkshire swine with regard to anaesthetic distribution and pharmacokinetics. However, the ratios of lean to total body weight in these two species are probably different (Lan *et al.*, 1993), which could alter the volume of distribution of general anaesthetics used in these studies (isoflurane), influencing their effects on the central nervous system and thereby affecting the systemic response to cocaine. We cannot rule out such a mechanism for our results, although the depth of general anaesthesia in both species appeared similar, as judged by eye motor and jaw tone relaxation. Similarly, it is not known whether the volume of distribution and handling of cocaine are similar in the two varieties of swine.

The cardiovascular system of the pig has many similarities to that of man, including coronary anatomy and functional responsiveness. In particular, the relative density of α- and β-adrenoceptors and the general pharmacological profile of porcine epicardial coronary arteries are very similar to their human counterparts (Ginsburg *et al.*, 1980; Ginsburg, 1983; Moreland & Bohr, 1984; Bradley & Morgan, 1987). Therefore, it is probably not coincidental that the only animal model of coronary hyperreactivity and vasospasm has been developed in swine (Shimokawa *et al.*, 1983; Egashira *et al.*, 1986; Yamamoto *et al.*, 1987; Isner & Chokshi, 1991). The two different haemodynamic profiles seen in YS and MS in response to the administration of cocaine may be observed in human beings who abuse cocaine and present in the emergency room. At one extreme of the spectrum, patients present with severe hypotension that rapidly progresses to cardiogenic shock, suggesting that cocaine produced a significant myocardial depression (Kossowskey & Lyon, 1984). An analogous state of depressed myocardial function was found in our study, especially in YS. At the other extreme of the spectrum, and probably more commonly, other patients present to the emergency room with severe hypertension and tachycardia, suggesting that cocaine in these patients has a marked sympathomimetic effect (Ritchie & Green, 1990); in our study we were able to reproduce a similar state in MS. Other animal species under different experimental conditions also show this wide spectrum of cardiovascular actions of cocaine (see Table 1).

Despite the very different systemic haemodynamic profiles induced in MS and YS by cocaine, coronary haemodynamics in both YS and MS demonstrated a reduction in coronary flow, a reduction in the vasodilator response with an increased coronary resistance to contrast, suggesting that cocaine induced microvascular spasm, and probably myocardial ischaemia, with each successive dose. Consistent with this hypothesis, pulmonary artery diastolic pressure was significantly increased in both YS and MS which, as an indirect index of left ventricular end-diastolic pressure, is consistent with the presence of myocardial ischaemia, as well as direct myocardial depression (Grossman & Baim, 1991).

Coronary flow reserve was assessed by the hyperaemic response to contrast injection. While contrast agents do induce a vasodilator effect, more potent vasodilators such as adenosine or papaverine would provide a more standard assessment of true microvascular or vasodilator reserve. However, while the use of contrast rather than adenosine or papaverine might result in a smaller calculated flow reserve, the overall dose-dependent effects should be maintained. Although the MS and YS swine are genetically closely related, the haemodynamic responses lie at two different extremes of the cardiovascular spectrum of cocaine. Systemic haemodynamics in YS revealed a significant reduction in mean arterial pressure, cardiac output, stroke volume and rate-pressure product with each cocaine dose and a rise in ventricular filling pressures. This haemodynamic profile suggests a progressive and severe reduction in ventricular performance after intravenous cocaine in these Yorkshire swine. Similarly, it has been reported that cocaine increased left ventricular end-diastolic pressure and significantly decreased LV dp/dt and caused significant reduction in left ventricular ejection fraction and stroke volume in dogs (Abel *et al.*, 1989). These results are consistent with additional reports in the worldwide literature demonstrating similar cardiodepressant effects (Mosso, 1887; Kochmann & Dales, 1908; Prus, 1913; Bush, 1920; Pierre *et al.*, 1985; Morcos *et al.*, 1988).

There are at least two possible mechanisms that might explain the severe myocardial depression seen after cocaine administration in YS. First, cocaine may have a direct myocardial depressant effect. Second, cocaine might induce severe myocardial ischaemia resulting in cardiogenic shock. Ischaemia may result from coronary thrombosis, epicardial vasospasm or microvascular vasoconstriction (Zimmerman *et al.*, 1987; Rezkalla *et al.*, 1990; Beckman *et al.*, 1991; Isner & Chokshi, 1991). Although a moderate generalized narrowing of epicardial vessels was seen, no focal epicardial vasospasm or coronary thrombosis was observed in the present study. CBF was reduced by 29% with the first dose, by 52% with the second dose and by 69% by the third dose of cocaine in YS, and CBF was reduced by 25% with the first dose, by 52% with the second dose and by 68% after the third dose of cocaine in MS. The fall in CBF might be an appropriate response to the fall in MVO_2 associated with cocaine-induced bradycardia and hypotension in YS, but in MS the reduction in CBF cannot be explained by a reduction in cardiac rate, since in this group BP, RPP and HR increased. Thus, the reduction in CBF in both YS and MS may be related to increased resistance at the level of the microcirculation. Coronary vascular resistance progressively increased and the hyperaemic response to contrast gradually decreased with each cocaine dose in both groups. Thus, this reduction in coronary flow reserve reflects (1) a modest epicardial coronary vasoconstriction and (2) a significant rise in coronary resistance probably in the microvasculature. Similarly, previous studies have demonstrated in intact dogs that cocaine in high doses reduces the coronary lumenal diameter and coronary blood flow (Pierre *et al.*, 1985; Abel *et al.*, 1989; Hale *et al.*, 1991; Hayes *et al.*, 1991). Conversely, in conscious dogs, low cocaine doses did not reduce but instead increased coronary blood flow (Wilkerson, 1988; Fraker *et al.*, 1990). These effects may be mediated through α-adrenoceptor stimulation, since cocaine blocks reuptake of noradrenaline. Unfortunately, we did not have available electrocardiograms from all of the animals of adequate quality to assess ischaemia. However, we have previously reported that similar doses of cocaine produce ST–T wave changes on the electrocardiograms consistent with ischaemia in Yucatan miniswine (Egashira *et al.*, 1991; Núñez *et al.*, 1994c) and Yorkshire swine (Núñez *et al.*, 1993; 1994a; 1994b).

The mechanism of a cocaine-induced elevation in sympa-

thetic tone is relatively well described and appears to be related to several different effects. First, it is known that cocaine can block the uptake of noradrenaline and dopamine by the sympathetic nerve endings. Second, cocaine may release noradrenaline from the sympathetic nerve terminals. Third, the drug may release catecholamines from the adrenal glands themselves (Gillis *et al.*, 1992). Any and all of these effects could have been induced in our anaesthetized pigs. In addition to catecholamine-mediated vasoconstriction, cocaine may have a direct vasoconstrictor effect on the coronary arteries which could explain the increased coronary resistance observed in the present studies (Wang *et al.*, 1994). Cocaine also has well known local anaesthetic effects that occur at higher dosage levels (Perreault *et al.*, 1990). It is unlikely, but possible, that this action of the drug could have produced myocardial depression in conjunction with the other anaesthetics utilized in the Yorkshire swine. However, such effects are usually expected in concentrations greater that 10^{-5} M, which would not have been exceeded except at the higher doses in our experiments (Perreault *et al.*, 1990).

Our results, in particular the systemic haemodynamic profile of acute cocaine administration in YS, are different from those of Catravas *et al.* (1978) who reported that the administration of large doses of cocaine (0.5 mg kg^{-1} min^{-1}, i.v.; until death) given to conscious dogs caused an increase in heart rate, mean arterial pressure and cardiac output. All animals convulsed and died approximately 42 min after the beginning of the cocaine infusion. In a subsequent study, Catravas *et al.* (1978) investigated the influence of several pharmacological and physiological interventions on the cocaine-induced responses in mean arterial pressure, cardiac output, heart rate, arterial pH and temperature (Catravas *et al.*, 1978; Catravas & Waters, 1981). The authors concluded that hyperthermia was the most important factor in cocaine lethality. We did not observe hyperthermia or any kind of seizure activity in either group of swine; the discrepancies between the results may reflect differences between the species. Our study differs from Catrava's experiment in the fact that we used swine under general anaesthesia whereas his study was on conscious dogs.

In summary, this study demonstrates that cocaine produces a moderate epicardial vasoconstriction and dose-dependent decreases in CBF and CFR that are independent of changes in mean arterial pressure. Despite the different systemic haemodynamic profiles in YS and MS, the coronary vascular resistance was increased in both varieties of swine, which given the modest decrease in epicardial coronary artery diameter suggests constriction at the level of the microvessels. Due to the similarities between swine and human coronary vascular structure and function, these results raise the possibility that microvascular vasoconstriction may be responsible for cocaine-induced ischaemic events in man. The distinction between epicardial and microvascular effects is potentially important from a therapeutic standpoint since vasodilator agents may differentially affect tone in these two different parts of the coronary arterial tree (Braunwald & Sobel, 1992).

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