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Endothelium-Dependent Vasorelaxation Is Impaired in Cocaine Arteriopathy

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Objectives. **This study sought to assess endothelium-dependent vasorelaxation in long-term users of cocaine.**

Background. **Cocaine use has been associated with myocardial infarction, stroke and intestinal infarction. Previously demonstrated effects of the drug, including increased heart rate and blood pressure and increased vascular tone, do not explain the sporadic nature of these vascular events or the occurrence of ischemia remote from acute administration. Abnormal endothelial function could contribute to focal vasospasm and thrombosis and predispose to premature atherosclerosis, all of which have been demonstrated in cocaine users with myocardial infarction.**

Methods. **Using plethysmography, we studied the change in forearm blood flow in response to intraarterial acetylcholine and nitroprusside in 10 long-term cocaine users and 13 control subjects of similar age who had not used cocaine; sample size was based on a 70% power to detect a 20% reduction in flow with acetylcholine between subjects and control subjects. Using graded doses of intracoronary acetylcholine (from 10^{-9} to 10^{-6} mol/liter), we studied a second group of 10 cocaine users with angiographically normal or near-normal arteries.**

Results. **Mean forearm blood flow during acetylcholine infusion was significantly lower in cocaine users than in control subjects ($p = 0.02$). During nitroprusside infusion, there was no difference ($p = 0.2$) between cocaine users and control subjects. Cigarette smoking did not explain the differences between cocaine users and control subjects. Acetylcholine elicited coronary vasoconstriction in 8 of 10 subjects.**

Conclusions. **We conclude that endothelium-dependent vasorelaxation is impaired in long-term users of cocaine.**

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Although the rate of increase in cocaine abuse in this country has slowed, medical problems associated with abuse of the drug continue to be a major problem, probably because education efforts have had little effect on a core group of long-term heavy users. For instance, emergency room visits for cocaine-associated chest pain continue to increase.

It is well established that cocaine can cause catastrophic vascular events, including myocardial infarction (1–7), stroke (8,9) and intestinal infarction (10). Cocaine causes an increase in heart rate and blood pressure at acute administration (11), resulting from systemic catecholamine release and increased alpha-adrenergic effects due to blockade of norepinephrine reuptake. However, these phenomena cannot explain all the observed vascular events. Other drugs that inhibit norepinephrine reuptake, such as tricyclic antidepressants, are not associated with vascular catastrophes. The vast majority of cocaine administrations do not result in a vascular event, and the majority of myocardial ischemic events associated with cocaine use occur long after acute administration (12). Cocaine increases vascular tone because of its enhancement of alpha-adrenergic effects (13) and calcium influx into vascular smooth muscle (14). However, a diffuse increase in vascular tone does not explain the focal vasospasm that causes infarction. Cocaine appears to cause premature atherosclerosis (15,16), but cocaine-related infarction can occur in the absence of atherosclerosis. Vascular endothelium exerts control over local blood flow in many ways, including inhibition of thrombosis and release of vasodilating and vasoconstricting substances (17). Nitric oxide is released from the endothelium in response to a multitude of stimuli, including exposure to acetylcholine, and causes relaxation of underlying smooth muscle and inhibition of platelet aggregation. Impairment of this release may contribute to vasospasm and thrombosis. Dysfunction of the endothelium, in addition, is thought to be an essential step for initiating the process of atherosclerosis (18). Damage to vascular endothelium in long-term cocaine users would impair nitric oxide release, which in turn might contribute to vasospasm and thrombosis and the initiation of atherosclerosis.

We hypothesized that endothelium-dependent vasorelax-

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ation is impaired in long-term cocaine users. Measures of endothelial function in humans exposed to long-term cocaine use have not been reported.

Methods

Study subjects. All subjects gave written informed consent. The protocol was approved by our institutional review boards.

Patients were included if they gave a history of having used cocaine for at least 6 months before enrollment and were excluded for a history of hypertension, hyperlipidemia (serum cholesterol >5.53 mmol/liter [220 mg/dl] or low density lipoprotein-cholesterol >4.53 mmol/liter [180 mg/dl]) or diabetes or current vasodilator use. Control subjects had no history of cocaine use within 1 year of the study and no history of hypertension, diabetes, hyperlipidemia or current vasodilator use.

We studied 10 cocaine users by forearm plethysmography. Seven of the 10 had urine test results positive for cocaine metabolites within 1 week of the study. Two had a previous myocardial infarction; coronary angiographic findings were normal in one and showed obstructive coronary disease in the other. Of the remaining eight patients, six had presented with chest pain. Coronary angiography was performed in five of these six patients; four had normal coronary arteries, and one had nonobstructive disease. One patient had a reduced left ventricular ejection fraction thought to be consistent with cocaine-related cardiomyopathy but did not have congestive heart failure. The control group consisted of 13 healthy volunteers.

We studied 10 cocaine users during coronary arteriography for evaluation of cocaine-related chest pain (n = 8), dyspnea (n = 1) or an atrial septal defect (n = 1). Nine of 10 patients had a history of cocaine use within 3 weeks of the study. Two had a previous myocardial infarction. Angiographic findings were normal in eight patients and showed nonobstructive disease in the infarct-related artery in two; their adjacent arteries were normal. Clinical characteristics of the study cohort are presented in Table 1.

Table 1. Demographics of Study Cohort

	Plethysmography		Angiography:
	Cocaine Users (n = 10)	Control Subjects (n = 13)	Cocaine Users (n = 10)
Age (yr)	38.6 ± 3.4	31.3 ± 6.6	36.5 ± 5.1
Male/female	8/2	7/6	10/0
Ethnicity (white/black/Hispanic)	6/3/1	11/1/1	0/9/1
Current smoking	10/10	7/13	9/10
Blood pressure (mm Hg)			
Systolic	126 ± 14	113 ± 9	123 ± 27
Diastolic	77 ± 9	73 ± 6	78 ± 17

Data presented are mean value ± SD or number of patients.

Protocol. *Forearm plethysmography.* The technique of forearm plethysmography has been previously described (19,20). A 20-gauge catheter was inserted into the brachial artery before each study. Subjects were allowed to relax in a supine position with the arm elevated above the level of the midatrium to facilitate venous return from the limb. Room temperature was controlled at 72°F. A blood pressure cuff was inflated at the wrist to suprasystolic pressures to exclude the highly variable flow to the hand, and another cuff was inflated over the arm with a rapid inflator to less than diastolic pressure (~40 mm Hg) to prevent venous return from the forearm. Blood flow is proportional to the change in diameter of the widest part of the forearm, as measured by a mercury-filled Silastic strain gauge attached to a plethysmograph (Hokanson ECR). Once stable baseline flow rates were established during dextrose infusion, acetylcholine (7.5, 15 and 30 μg/min) and nitroprusside (0.3, 3 and 10 μg/min) were infused through the arterial catheter for 3 min at each dose. The order of drug administration was varied randomly. The flow rate was held constant for baseline and drug infusions. At the conclusion of each 3-min infusion, five measurements were made; flow was considered to be the average of these measurements. Strip-chart records were interpreted without knowledge of the drug or dosage involved.

Coronary arteriography. A 6F bipolar pacing catheter was placed in the right ventricle for demand pacing. An 8F large-lumen angioplasty guide catheter was advanced to the ostium of the left coronary artery using the Judkins technique. A screening, selective coronary angiogram of the left main coronary artery was then obtained to exclude significant coronary artery disease. A 2.5F infusion catheter was advanced within the guide catheter to the ostium on the left main coronary artery. This position allowed continuous infusion of acetylcholine during coronary angiography. After each infusion (vehicle, graded doses of acetylcholine or nitroglycerin), biplane coronary angiography was performed.

Serial 3- to 4-min infusions of vehicle (5% dextrose in water plus 0.005% mannitol) and graded concentrations of acetylcholine (to achieve estimated final blood concentrations in the coronary bed of 10^{-9}, 10^{-8} and 10^{-7} mol/liter) were given, followed after the last infusion by a bolus of 150 to 200 μg of intracoronary nitroglycerin. The final coronary blood concentrations of acetylcholine were estimated with the assumption that blood flow in the left main coronary artery is ~120 ml/min.

Biplane images of the coronary arteries were obtained with a standard cineangiographic system (Philips Optimus M-200 Generator and Poly-C, Eindhoven, The Netherlands). Nonionic contrast (Iohexol, Winthrop-Breon Laboratories) was used for each injection. A standard injection profile (4 ml/s for 9 ml) was power injected (Medrad). Optimal visualization in the right anterior oblique projection with caudal angulation and the left lateral projection with no or minimal angulation was obtained to maximize vessel separation. These projections were maintained throughout the study for each patient with care to maintain image intensifier and table position constant.

Coronary arteriograms were analyzed using the cardiovascular angiographic analysis system and previously described

JACC Vol. 28, No. 5
November 1, 1996:1168–74

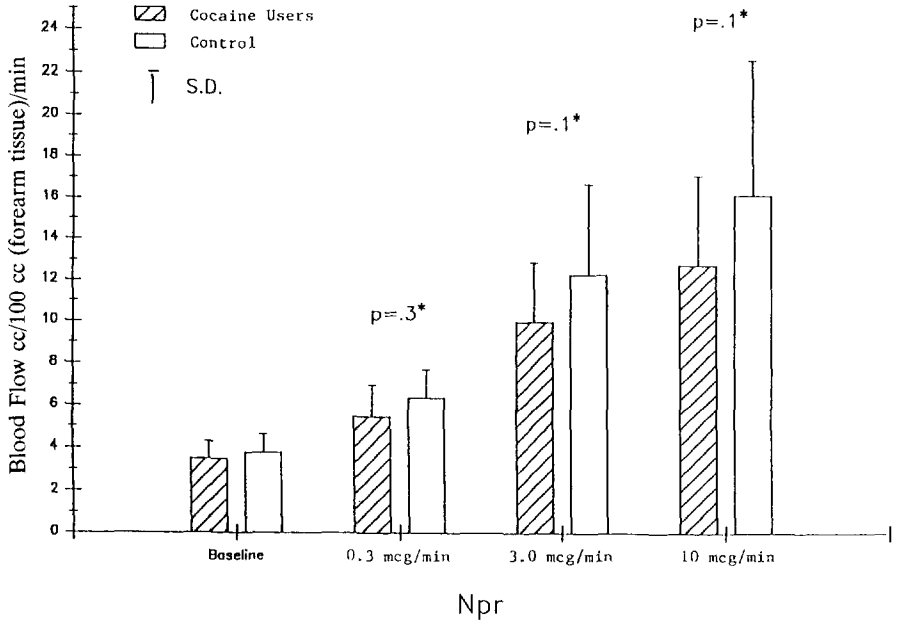


Figure 1. Forearm blood flow at increasing doses of nitroprusside (Npr) for cocaine users and control subjects. *Mann-Whitney rank-sum test. By analysis of variance for repeated measures, there is no difference in flow (p = 0.2).

methods (21). All angiograms were qualitatively interpreted by two unblinded independent observers (P.A.G., E.J.E.).

One proximal region of interest in the left anterior descending coronary artery was selected in each patient for analysis. A region was selected for ease of assessment and lack of overlapping branches. These same regions were analyzed after each intervention, using an end-diastolic frame.

The standard deviation for the difference between repeat measurements of the same lesion using the cardiovascular angiographic analysis system was 0.12 to 0.16 (21). Thus, we defined a significant change in vessel size as a >0.25-mm (>2 SD) change in diameter.

Statistical analysis. Comparisons of changes in forearm blood flow between cocaine users and normal control subjects were performed with the Mann-Whitney rank sum test. To confirm these results, and to study the dose effects of acetylcholine and nitroprusside on blood flow, a two-way repeated measures analysis of variance was performed. Because data did not conform to a normal distribution, log-transformed values were used. Sample size was based on a 70% power to detect a 20% reduction in flow with acetylcholine between cocaine users and control subjects. The coronary angiographic data were analyzed with a repeated measures analysis of variance. All results are expressed as mean value ± SD, unless otherwise stated. All analyses were computed using the BMDP statistical software. Significance was defined as $p \leq 0.05$.

Results

Forearm blood flow. In cocaine users, blood flow at baseline was 3.5 ± 0.8 ml/100 cm^3 forearm tissue per min, increased to a maximum of 12.8 ± 4.1 ml/100 cm^3 forearm tissue per min with nitroprusside and to a maximum of 6.1 ± 4.1 ml/100 cm^3 forearm tissue per min with acetylcholine. In control subjects, blood flow at baseline was 3.6 ± 0.9 ml/100 cm^3 forearm tissue per min, increased to a maximum of 18.4 ± 5.6 ml/100 cm^3 forearm tissue per min with nitroprusside and to a maximum of 10.3 ± 7.4 ml/100 cm^3 forearm tissue per min with acetylcholine.

Forearm blood flows at increasing nitroprusside doses are shown in Figure 1. By analysis of variance for repeated measures, there was no difference between cocaine users and control subjects (p = 0.2) with nitroprusside. The test for interaction effects was not significant (p = 0.20). By Mann-Whitney analysis, there were no significant differences in blood flow at any dose tested.

Forearm blood flows at increasing acetylcholine doses are shown in Figure 2. The difference in flow between cocaine users and control subjects was significant by analysis of variance for repeated measures, with control subjects having greater flow (p = 0.02). The test for interaction effects was not significant (p = 0.09). There were significant differences by Mann-Whitney testing at the first two but not the highest dose that was tested.

Because all 10 cocaine users and 7 of 13 control subjects were smokers, we used analysis of variance to test for the possibility that smoking alone was responsible for the differences in blood flow between users and control subjects. Results are shown in Table 2. There were no significant differences in blood flow between cocaine users and control subjects who did and did not smoke.

Coronary angiography. No patient developed severe bradycardia from the infusion of acetylcholine, although a prophylactic pacemaker was in place for each patient. Figure 3 is shows a representative example of vasoconstriction of the left anterior descending and left circumflex coronary arteries after intracoronary acetylcholine administration in a subject with angiographically normal coronary arteries. As is evident from

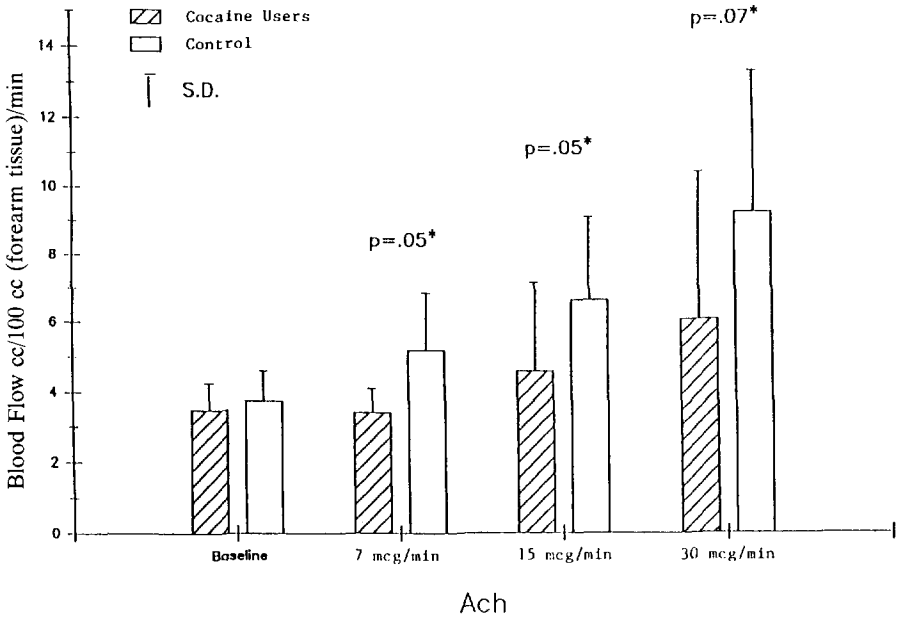


Figure 2. Forearm blood flow at increasing doses of acetylcholine (Ach) for cocaine users and control subjects. *Mann-Whitney rank-sum test. By analysis of variance for repeated measures, there is significant difference in flow (p = 0.02).

Figure 4, 2 of the 10 patients had normal vasodilator responses to acetylcholine, whereas 8 (80%) of these 10 demonstrated coronary artery vasoconstriction. This effect was subsequently abolished by the administration of intracoronary nitroglycerin. Seven of the 10 cocaine users demonstrated coronary artery vasodilation beyond baseline values with the administration of intracoronary nitroglycerin, thereby demonstrating the ability of the artery to vasodilate to endothelium-independent vasodilators.

Discussion

Previous studies of cocaine-induced ischemic heart disease in patients have focused on the pharmacologic properties of cocaine that promote vasoconstriction or thrombosis. Such studies have not explained why myocardial ischemic events are often seen days after cocaine ingestion (12). Our results show that long-term cocaine users have impaired endothelium-dependent vasorelaxation in both small-caliber forearm resistance vessels and large-caliber epicardial vessels.

Relation between endothelial dysfunction and ischemic events in cocaine users. These data provide a new and attractive hypothesis to explain the temporal disparity between cocaine use and ischemic events. Cocaine has three independent mechanisms of vasoconstrictive action: 1) There is direct vasoconstriction, which is calcium channel dependent (14) and endothelium independent (22). 2) There is indirect vasoconstriction, which is mediated through norepinephrine release by the sympathetic nervous system and alpha-receptors (13). 3) There is vasoconstriction as a consequence of platelet, white blood cell or endothelium-derived mediator release, alone or in combination, which promotes vasoconstriction (23). We propose that dysfunctional endothelium is an additional route that links cocaine to ischemic events.

Dysfunctional endothelium in cocaine users may participate in the genesis of ischemic vascular accidents in one of three ways: 1) Dysfunctional endothelium may contribute to a milieu conducive to thrombosis either at the time of cocaine use or at a time remote from use. Nitric oxide inhibits platelet aggregation (24,25); impairment of nitric oxide release from the endothelium would fail to counterbalance the effects of platelet aggregation. In addition, the ratio of thromboxane B_2 to 6-keto-prostaglandin F_1-alpha has been shown to be increased in a rabbit model of short-term cocaine administration (26). This finding suggests that cocaine produces changes in prostaglandin metabolism favoring vasoconstriction and thrombosis.

Table 2. Effect of Smoking on Blood Flow*

		Acetycholine (μg/min)			Nitroprusside (μg/min)		
	Baseline	7.5	15	30	0.3	3	10
Cocaine user	3.5 ± 0.8	3.4 ± 0.7	4.6 ± 2.6	6.1 ± 4.3	5.4 ± 1.5	10.0 ± 2.9	12.8 ± 4.4
Control subject							
Nonsmoker	4.0 ± 0.9	4.9 ± 1.4	6.1 ± 2.6	8.7 ± 3.9	5.9 ± 1.6	11.3 ± 4.3	15.3 ± 5.9
Smoker	3.2 ± 0.8	5.1 ± 1.1	6.5 ± 4.3	11.7 ± 10.3	6.2 ± 1.4	14.0 ± 4.5	20.7 ± 6.7
p value (within doses)			0.2			0.09	

*Values presented are mean forearm blood flow in ml/100 cm^3 tissue per min ± SD.

JACC Vol. 28, No. 5
November 1, 1996:1168–74

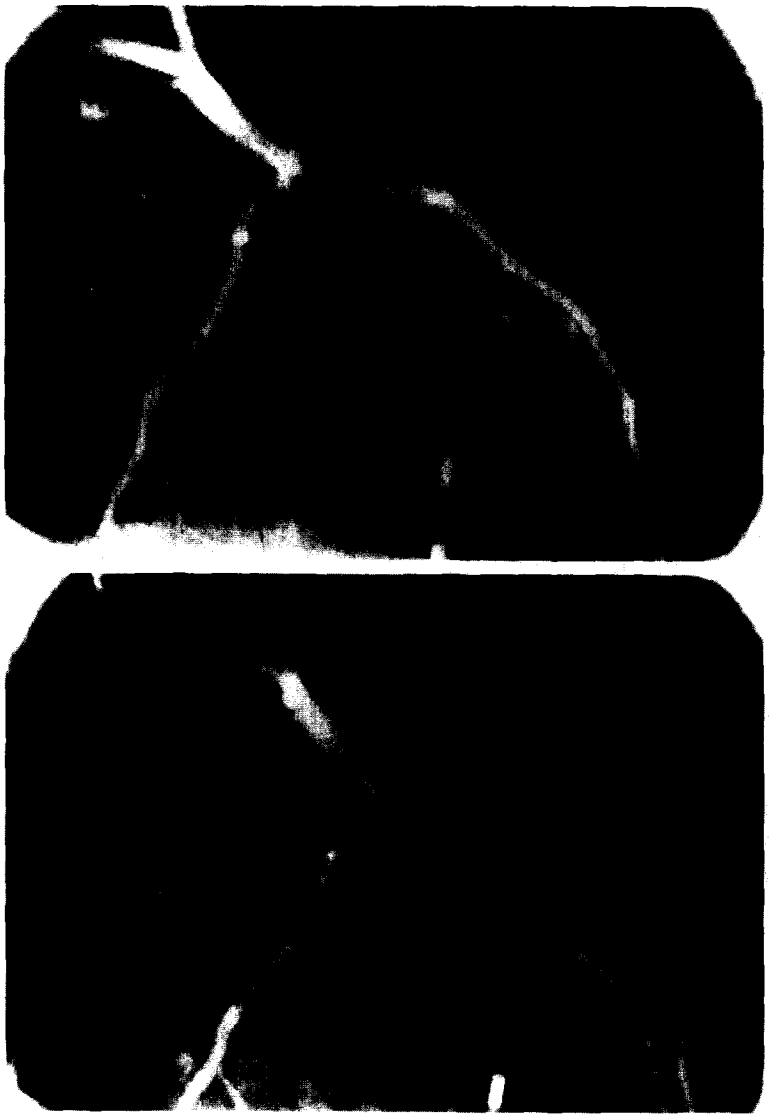
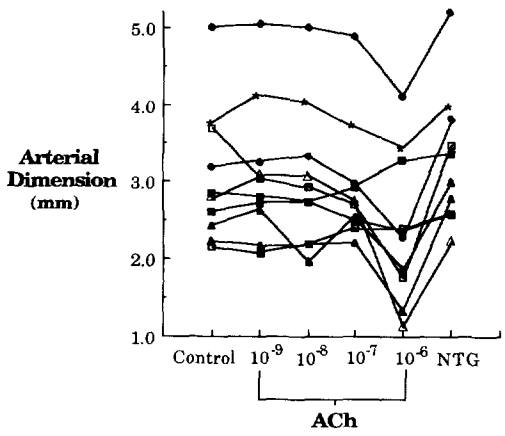


Figure 3. Representative angiograms showing vasoconstriction of the left anterior descending and left circumflex coronary arteries after intracoronary acetylcholine administration in a subject with angiographically normal coronary arteries. **Top,** Right anterior oblique view of the left coronary artery system before administration of acetylcholine (during administration of control vehicle). **Bottom,** Same projection of the left coronary artery system after administration of acetylcholine. Constriction was more pronounced in the left anterior descending than in the circumflex coronary artery in this case.

Figure 4. Individual responses of the left anterior descending coronary artery to acetylcholine (ACh). Note that two of the patients showed vasodilation, whereas eight demonstrated vasoconstriction. NTG = nitroglycerin.



2) Premature atherosclerosis is present in some long-term cocaine users. If impairment of endothelium-dependent relaxation in cocaine abusers is a marker for repetitive endothelial damage, the necessary first step in the atherosclerotic process (27) has been established. 3) A relative deficiency of vasodilating factors such nitric oxide and an increase in vasoconstricting factors such as thromboxane A_2, serotonin and endothelin may predispose to vasoconstriction and vasospasm. There is substantial evidence from published reports to support the latter mechanism (28).

Previous studies. Flores et al. (29) administered intranasal cocaine to 12 patients undergoing coronary angiography for evaluation of chest pain; apparently none had been exposed to long-term cocaine use. Quantitative analysis of coronary lumen diameter was performed before and after cocaine administration. Percent reduction in lumen diameter was greater in diseased than nondiseased segments. Flores et al. hypothesized

that this effect was the result of lack of nitric oxide as a counterbalance for cocaine-mediated alpha-adrenergic vasoconstriction.

Egashira et al. (30) provided support for this hypothesis in a study in a miniature swine model. Eight pigs underwent endothelial denudation in the left anterior descending coronary artery followed by 3 months of high cholesterol feeding. Intravenous cocaine was then administered in increasing doses, and the coronary lumen diameter was compared in previously denuded and nondenuded sites by means of angiography. No lumen narrowing was apparent at baseline in either site. After higher doses of cocaine, lumen diameter diminished more at previously denuded sites than at nondenuded sites. Furthermore, they observed vasospasm in all pigs after intracoronary histamine at the previously denuded sites.

Kuhn et al. (22) provide somewhat conflicting results. Using seven dogs, they administered cocaine immediately after endothelial denudation in the left anterior descending coronary artery. Angiographically, they were unable to show enhanced vasoconstriction at the denuded site. Explanations for the discrepancy include the lower dose of cocaine used by Kuhn et al. (2 vs. 10 mg/kg) and the difference in time between intervention and study. It may be that the myointimal proliferation observed by Egashira et al. (30) is crucial for potentiation of cocaine-induced vasoconstriction.

Our results differ somewhat from those of Halle et al. (31). These investigators studied seven subjects who had had cocaine-related chest pain using forearm plethysmography at baseline, after a cold pressor test, and after 10 min of forearm ischemia. They found no differences between cocaine users and control subjects in forearm blood flow for any of the conditions studied. If forearm flow after ischemia is taken as a measure of flow-mediated, endothelium-dependent vasorelaxation, the study of Halle et al. is evidence that cocaine use is not associated with impairment of endothelium-dependent vasorelaxation. It may be that the reactive hyperemia test was not sufficiently sensitive to detect endothelial dysfunction in their relatively small group of subjects. Another possible explanation is that the endothelial dysfunction induced by cocaine is not generalized but is limited to muscarinic-receptor and like pathways.

Effect of smoking. By forearm plethysmography, blood flow response was significantly less in cocaine users than in control subjects with acetylcholine. Smoking does not explain this impairment. If smoking were responsible for the impaired response to acetylcholine in cocaine users, we should have seen a difference within doses for acetylcholine, with nonsmoking control subjects having a greater response and cocaine users having essentially the same response as smoking control subjects. In the coronary arteries, 8 of 10 patients had coronary artery vasoconstriction in response to acetylcholine administration. Two of these eight had frank vasospasm and chest pain that reproduced previous symptoms. Because patients with normally functioning endothelium exhibit vasodilation in response to acetylcholine, this effect clearly represents an abnormal response (32).

It is not clear from previous studies whether smoking causes an abnormality in the phenomenon that we studied—differential change in blood flow in response to acetylcholine and nitroprusside or nitroglycerin. Two studies have investigated the effects of smoking on the response of coronary arteries to acetylcholine: One (32) found no difference in response between smokers and nonsmokers, and the other (33) showed diminished responsiveness in smokers. Using different methodology, Celermajer et al. (34,35) measured the diameter of the brachial artery in smokers and normal control subjects in response to ischemia and to nitroglycerin. These investigators found that the increase in diameter in response to ischemia was smaller in smokers than control subjects, but the response to nitroglycerin was no different. Estimated blood flow in response to ischemia was not different between smokers and control subjects. Similarly, our data are not consistent with differences in endothelium-mediated flow response between smokers and nonsmokers.

Possible mechanisms for cocaine-related endothelial dysfunction. The mechanism for the impairment of endothelium-dependent vasorelaxation is unclear. The most likely explanation is that of a direct toxic effect of cocaine on endothelial cells. In animals, repetitive exposure to cocaine has been reported (26) to cause endothelial proliferation, presumably an indicator of endothelial cell turnover. In porcine coronary arteries, regenerating endothelium shows a lack of responsiveness to some nitric oxide-releasing factors for up to 24 weeks after denudation (36). If cocaine is indeed toxic to vascular endothelium, repeated cycles of cell loss and regeneration may render the endothelium unable to respond to G protein-mediated releasing agents for nitric oxide, such as acetylcholine.

In a system as complex as that of control of vascular tone, there are many other ways in which cocaine might impair endothelium-dependent vasorelaxation. Several endothelium-derived contracting factors such as endothelin have been described; cocaine may enhance their activity. The physiologic importance of endothelium-derived contracting factors is as yet poorly established, although endothelin probably is responsible in part for maintaining basal arterial tone (37). Acetylcholine causes contraction of smooth muscle; long-term cocaine exposure might enhance the sensitivity of that tissue to muscarinic stimulation. In support of this notion, Shannon et al. (38) demonstrated that atropine attenuates the increase in coronary vascular resistance brought about by the acute administration of cocaine. This demonstration of an acute parasympatholytic effect of cocaine raises the possibility that long-term antagonist exposure may enhance sensitivity to muscarinic stimulation. Similarly, long-term stimulation of the sympathetic nervous system or long-term repeated agonistic catecholamine exposure caused by cocaine might downregulate the endothelium-dependent relaxation system; however, data on autonomic control of nitric oxide synthesis and release are conflicting (39,40).

Limitations of the study. There are several limitations to the present study: 1) The cocaine users studied were a selected

group, in that most of them had presented with chest pain. 2) Some may view the use of the forearm model as a limitation. However, because cocaine has produced vascular events in multiple organ systems, we postulated a generalized vascular disorder related to cocaine abuse and believed the forearm model to be relevant. 3) We did not include a group of healthy matched control subjects for comparison of coronary arteriographic data. We strongly believe that exposing a group of subjects without chest pain or suspicion of coronary disease to the risks of angiography is not justifiable, especially in light of the data acquired in the forearm portion of the study.

Conclusions. Endothelium-dependent vasorelaxation is impaired in long-term users of cocaine; this impairment may contribute to the genesis of vascular events in this patient group.

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