# Potentiation of Cocaine-Induced Coronary Vasoconstriction by Beta-Adrenergic Blockade

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*Study Objective:* To determine whether beta-adrenergic blockade augments cocaine-induced coronary artery vasoconstriction.

*Design:* Randomized, double-blind, placebo-controlled trial.

*Setting:* A cardiac catheterization laboratory in an urban teaching hospital.

*Patients:* Thirty clinically stable patient volunteers referred for catheterization for evaluation of chest pain.

*Interventions:* Heart rate, arterial pressure, coronary sinus blood flow (by thermodilution), and epicardial left coronary arterial dimensions were measured before and 15 minutes after intranasal saline or cocaine administration (2 mg/kg body weight) and again after intracoronary propranolol administration (2 mg in 5 minutes).

*Measurements and Main Results:* No variables changed after saline administration. After cocaine administration, arterial pressure and rate-pressure product increased; coronary sinus blood flow fell (139 ± 28 [mean ± SE] to 120 ± 20 mL/min); coronary vascular resistance (mean arterial pressure divided by coronary sinus blood flow) rose (0.87 ± 0.10 to 1.05 ± 0.10 mm Hg/mL · min); and coronary arterial diameters decreased by between 6% and 9% ($P < 0.05$ for all variables). Subsequently, intracoronary propranolol administration caused no change in arterial pressure or rate-pressure product but further decreased coronary sinus blood flow (to 100 ± 14 mL/min) and increased coronary vascular resistance (to 1.20 ± 0.12 mm Hg/mL · min) ($P < 0.05$ for both).

*Conclusions:* Cocaine-induced coronary vasoconstriction is potentiated by beta-adrenergic blockade. Beta-adrenergic blocking agents probably should be avoided in patients with cocaine-associated myocardial ischemia or infarction.

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As cocaine abuse has become commoner, the number of cocaine-associated deaths has increased dramatically (1, 2). Although many of these deaths are caused by cocaine's toxic effects on the central nervous system, many reports have linked cocaine use with angina pectoris and myocardial infarction (3-26). The sympathomimetic effects of cocaine, with resultant tachycardia and hypertension, increase myocardial oxygen demand and may induce ischemia in persons with severe coronary artery disease. In addition, cocaine reduces myocardial oxygen supply by diminishing coronary blood flow. This cocaine-induced vasoconstriction is due to alpha-adrenergic stimulation and is reversed by alpha-adrenergic blockade (27). Although use of beta-adrenergic blocking agents has been advocated for patients with cocaine-induced myocardial ischemia and other cardiovascular complications (28-37), the resultant unopposed alpha-adrenergic stimulation may be deleterious, leading to enhanced coronary vasoconstriction. Our study was done to assess the effects of beta-adrenergic blockade on cocaine-induced coronary vasoconstriction in humans.

## Materials and Methods

### Patients

Our studies were done in 30 patients (25 men and 5 women ranging from 38 to 68 years of age) having cardiac catheterization for evaluation of chest pain. Thirty-four consecutive patients with stable symptoms and without exclusion criteria (hypertension, recent myocardial infarction, or history of pseudocholinesterase deficiency) were eligible for study. Three patients declined to participate, and another was excluded when severe disease of the left main coronary artery was seen on initial angiography. The protocol was approved by the Human Subjects Review Committee of the University of Texas Southwestern Medical Center. All subjects gave written informed consent after being told of the possible adverse effects related to cocaine use (tachycardia, hypertension, arrhythmias, angina, and seizures). Anti-anginal medications (beta-adrenergic blocking agents, calcium antagonists, and long-acting nitrates) were discontinued more than 12 hours before the study. All subjects were studied in the fasting state after premedication with between 5 and 10 mg of oral diazepam.

### Experimental Protocol

A pacing thermodilution catheter (model CCS-7U-90B, Wilton Webster Laboratories, Altadena, California) was advanced to the coronary sinus via a basilic vein; its position was confirmed fluoroscopically and oximetrically, and it was secured in place for the duration of the protocol. Subsequent determinations of coronary sinus blood flow were done by the thermodilution technique (38), with which we have had extensive experience (27, 39-44). A 9 Fr arterial sheath was inserted percutaneously in the femoral artery, through which an 8 Fr Judkins catheter (Cordis Corporation, Miami, Florida) was ad-

 

**Table 1.** *Hemodynamic and Arteriographic Responses to Intranasal Saline or Cocaine Administration**

| Variable | Group 1, $n = 15$ | | | Group 2, $n = 15$ | | |
|---|---|---|---|---|---|---|
| | Baseline | Mean Change from Baseline | *P* Value | Baseline | Mean Change from Baseline | *P* Value |
| Heart rate, *beats/min* | 67 ± 3 | −1 (−2 to 1) | 0.46 | 77 ± 3 | 0 (−1 to 2) | 0.77 |
| Systolic arterial pressure, *mm Hg* | 133 ± 6 | 0 (−3 to 3) | 0.92 | 140 ± 6 | 11 (5 to 16) | <0.001 |
| Heart rate-systolic arterial pressure double product, $\times 10^3$ | 8.9 ± 0.6 | 0 (−0.3 to 0.3) | 0.87 | 10.8 ± 0.7 | 0.9 (0.4 to 1.4) | 0.002 |
| Mean arterial pressure, *mm Hg* | 95 ± 4 | −1 (−2 to 2) | 0.79 | 100 ± 4 | 9 (4 to 13) | <0.001 |
| Coronary sinus blood flow, *mL/min* | 137 ± 19 | 0 (−4 to 4) | 0.97 | 135 ± 20 | −17 (−29 to −5) | 0.01 |
| Coronary vascular resistance, *mm Hg/mL · min* | 0.81 ± 0.08 | 0 (−0.03 to 0.02) | 0.81 | 0.87 ± 0.07 | 0.18 (0.13 to 0.24) | <0.001 |
| Arterial-coronary sinus oxygen content difference, *mL/dL* | 10.1 ± 0.4 | −0.2 (−0.5 to 0.2) | 0.27 | 10.7 ± 0.5 | 0.6 (0.1 to 1.0) | 0.02 |
| Coronary arterial diameter, *mm* | | | | | | |
| Left anterior descending | | | | | | |
| Proximal | 2.62 ± 0.18 | −0.02 (−0.12 to 0.07) | 0.50 | 2.84 ± 0.21 | −0.16 (−0.30 to −0.02) | 0.026 |
| Mid | 1.83 ± 0.13 | −0.02 (−0.22 to 0.17) | 0.72 | 1.90 ± 0.12 | −0.17 (−0.24 to −0.09) | <0.001 |
| Distal | 1.39 ± 0.09 | −0.05 (−0.24 to 0.14) | 0.53 | 1.47 ± 0.12 | −0.15 (−0.23 to −0.08) | 0.001 |
| Left circumflex | | | | | | |
| Proximal | 2.77 ± 0.21 | −0.02 (−0.15 to 0.12) | 0.84 | 2.77 ± 0.22 | −0.25 (−0.44 to −0.07) | 0.012 |
| Mid | 2.20 ± 0.23 | −0.05 (−0.19 to 0.10) | 0.46 | 1.98 ± 0.15 | −0.14 (−0.32 to 0.05) | 0.13 |
| Distal | 1.61 ± 0.14 | 0.03 (−0.04 to 0.10) | 0.36 | 1.53 ± 0.10 | −0.10 (−0.22 to 0.02) | 0.087 |

*Baseline data are expressed as mean ± SE. For mean-change-from-baseline values, CIs are 95%.

vanced to the ostium of the left coronary artery. Systemic arterial pressure was measured through the sheath's side-port extension, and heart rate was determined by electrocardiographic monitoring.

Baseline heart rate, arterial pressure (phasic and mean), and coronary sinus blood flow were recorded; blood samples were obtained from the femoral artery and coronary sinus for measurement of oxygen content; and cineangiography of the left coronary artery was done in orthogonal views (right anterior oblique with caudal angulation and right anterior oblique with cranial angulation). Each subject was then randomly assigned to receive intranasal saline (group 1 [controls], $n = 15$) or a 10% cocaine hydrochloride solution (group 2, $n = 15$), 2 mg/kg body weight. Neither the investigator nor the subject knew which agent was administered. This dose of cocaine is one half to two thirds the amount routinely used for topical rhinolaryngologic anesthesia and was chosen because of its proven safety (28, 30). Fifteen minutes later, the hemodynamic, coronary sinus blood flow, and and oxygen content measurements were repeated; a blood sample was obtained for measurement of serum cocaine concentration (by gas chromatography); and cineangiography of the left coronary artery was done in identical obliquities.

Subsequently, 5 of the group 1 subjects and all 15 of the group 2 patients were randomly assigned to receive a 5-minute intracoronary infusion of saline (group 2A, $n = 5$) or propranolol (group 1A, $n = 5$; group 2B, $n = 10$), 0.4 mg/min (total, 2 mg) 15 minutes after cocaine administration (45). Pacing was done via the coronary sinus catheter to maintain heart rate, so that neither the investigator nor the subject knew which agent was infused. After this infusion, measurements of heart rate, arterial pressure, transcardiac oxygen content difference, and coronary sinus blood flow were made, and cineangiography of the left coronary artery was repeated.

The cineangiograms were obtained with a General Electric L-U System with an image resolution of 3.8 line pair/mm. Computer-assisted quantitative coronary analysis (Cardiovascular Angiography Analysis System, Rotterdam, the Netherlands) was done on orthogonal projections, according to methods previously described (46).

### Data Analysis

All results are reported as mean ± SE. All hemodynamic and arteriographic analyses were done without knowledge of which pharmacologic agents (intranasal saline or cocaine, intracoronary saline or propranolol) were administered. For each group, measurements at baseline, after intranasal saline or cocaine administration, and after intracoronary saline or propranolol administration were compared with a paired *t*-test (47). For all analyses, a *P* value of less than 0.05 was considered significant.

## Results

Of the 30 patients, 7 had angiographically normal coronary arteries (3 in group 2); 11 (6 in group 2) had one vessel coronary artery disease (defined as 70% or greater luminal diameter narrowing of a large epicardial coronary artery); 9 (5 in group 2) had two vessel disease; and 3 (all in group 2) had three vessel disease. No patient had a history of previous cocaine use.

### Control Group (Group 1)

In these 15 patients (11 men and 4 women ranging from 43 to 65 years of age), heart rate, arterial pressure, rate-pressure product, coronary sinus blood flow, coronary vascular resistance (mean arterial pressure divided by coronary sinus blood flow), transcardiac oxygen content difference, and epicardial coronary arterial diameters were similar before and 15 minutes after intranasal saline administration (Table 1). No variables were altered by the subsequent intracoronary administration of propranolol (group 1A, $n = 5$) (Table 2).

### Propranolol-Treated Group (Group 2)

These 15 subjects (14 men and 1 woman ranging from 38 to 68 years of age) received intranasal cocaine, 2 mg/kg (110 to 210 mg), achieving a serum concentration of 0.097 ± 0.051 mg/L (range, 0.02 to 0.22 mg/L). After cocaine administration, arterial pressure (systolic and mean), rate-pressure product, and transcardiac oxygen content difference increased (Table 1). Despite an increase in myocardial oxygen demand (as reflected by

rate-pressure product and transcardiac oxygen content difference), coronary sinus blood decreased 10% ± 7% (from 135 ± 20 to 118 ± 15 mL/min), coronary vascular resistance increased 22% ± 11% (from 0.87 ± 0.07 to 1.06 ± 0.08 mm Hg/mL · min), and mild diffuse constriction of the left anterior descending and circumflex coronary arteries occurred (Table 1). No subject developed chest pain or electrocardiographic alterations suggestive of ischemia.

In the five patients who received an intracoronary infusion of saline after cocaine administration (group 2A), the hemodynamic and arteriographic responses that occurred after cocaine administration were not altered (Table 3A). In the ten patients who received intracoronary propranolol after cocaine administration (group 2B), systolic arterial pressure declined slightly, whereas mean arterial pressure and rate-pressure product were unchanged (Table 3B). Although there was no change in myocardial oxygen demand (as reflected by rate-pressure product and transcardiac oxygen content difference), coronary sinus blood flow decreased an additional 15% ± 18% (22% ± 20% from baseline) (139 ± 28 mL/min at baseline; 120 ± 20 mL/min after cocaine administration; 100 ± 14 mL/min after propranolol administration), and coronary vascular resistance increased an additional 19% ± 28% (46% ± 44% from baseline) (0.87 ± 0.10 mm Hg/mL · min at baseline; 1.05 ± 0.10 mm Hg/mL · min after cocaine administration; 1.20 ± 0.12 mm Hg/mL · min after propranolol administration). In five of the ten group 2B subjects (four with and one without coronary artery disease), one or more epicardial coronary arterial segments constricted more than 10% in response to propranolol administration and, in one subject, complete coronary artery occlusion occurred (Figure 1) with clinical symptoms of myocardial ischemia and electrocardiographic ST segment elevation. Rapid resolution of symptoms, electrocardiographic changes, and coronary vasoconstriction was achieved with sublingual nitroglycerin, and there was no rise in serum creatine kinase.

## Discussion

Cocaine is a local anesthetic that produces central and peripheral adrenergic stimulation by blocking presynaptic reuptake of norepinephrine and dopamine, thus increasing their postsynaptic concentration (48). It may induce tachycardia and hypertension (49), and its abuse has been associated with several cardiovascular complications, including aortic dissection (50), ventricular tachyarrhythmias (3, 4, 8), pulmonary edema (51, 52), dilated cardiomyopathy (53), myocarditis (54, 55), pneu-

**Table 2.** *Hemodynamic and Arteriographic Responses to Intranasal Saline Administration Followed by Intracoronary Propranolol Administration**

| Variable | Baseline† | After Intranasal Saline | | After Intracoronary Propranolol‡ | |
|---|---|---|---|---|---|
| | | Mean Change from Baseline§ | *P* Value | Mean Change from Baseline§ | *P* Value |
| Heart rate, *beats/min* | 59 ± 5 | 0 (−2 to 1) | 0.37 | −1 (−3 to 1) | 0.21 |
| | | | | −2 (−4 to 0) | 0.10 |
| Systolic arterial pressure, *mm Hg* | 148 ± 15 | −2 (−6 to 3) | 0.38 | −5 (−17 to 6) | 0.27 |
| | | | | −7 (−15 to 1) | 0.07 |
| Heart rate-systolic arterial pressure double product, × $10^3$ | 9.0 ± 1.8 | −0.1 (−0.4 to 0.1) | 0.24 | −0.5 (−1.4 to 0.4) | 0.21 |
| | | | | −0.6 (−1.3 to 0.04) | 0.06 |
| Mean arterial pressure, *mm Hg* | 101 ± 9 | −2 (−6 to 2) | 0.29 | 1 (−7 to 8) | 0.88 |
| | | | | −1 (−7 to 4) | 0.49 |
| Coronary sinus blood flow, *mL/min* | 148 ± 59 | −1 (−5 to 3) | 0.51 | −2 (−6 to 2) | 0.19 |
| | | | | −3 (−12 to 5) | 0.30 |
| Coronary vascular resistance, *mm Hg/mL · min* | 0.92 ± 0.22 | −0.02 (−0.08 to 0.04) | 0.43 | 0.01 (−0.07 to 0.09) | 0.66 |
| | | | | −0.01 (−0.03 to 0.02) | 0.60 |
| Arterial-coronary sinus oxygen content difference, *mL/dL* | 9.9 ± 0.2 | 0 (−1.3 to 1.3) | 1.00 | −0.1 (−0.7 to 0.6) | 0.50 |
| | | | | −0.1 (−0.7 to 0.6) | 0.50 |
| Coronary arterial diameter, *mm* | | | | | |
| Left anterior descending | | | | | |
| Proximal | 2.53 ± 0.28 | −0.04 (−0.22 to 0.15) | 0.62 | −0.10 (−0.30 to 0.11) | 0.27 |
| | | | | −0.13 (−0.44 to 0.17) | 0.30 |
| Mid | 1.85 ± 0.28 | −0.13 (−0.64 to 0.38) | 0.38 | 0.12 (−0.38 to 0.61) | 0.42 |
| | | | | −0.02 (−0.29 to 0.26) | 0.82 |
| Distal | 1.38 ± 0.14 | −0.07 (0.41 to 0.28) | 0.59 | 0.09 (−0.09 to 0.27) | 0.20 |
| | | | | 0.03 (−0.24 to 0.29) | 0.76 |
| Left circumflex | | | | | |
| Proximal | 2.55 ± 0.27 | 0 (−0.29 to 0.28) | 0.99 | −0.05 (−0.35 to 0.24) | 0.64 |
| | | | | −0.06 (−0.30 to 0.19) | 0.56 |
| Mid | 1.65 ± 0.06 | −0.11 (−2.46 to 2.25) | 0.67 | 0.01 (−1.58 to 1.59) | 0.98 |
| | | | | −0.10 (−0.86 to 0.66) | 0.34 |
| Distal | 1.48 ± 0.03 | 0.04 (−0.19 to 0.28) | 0.61 | 0.07 (−0.11 to 0.25) | 0.32 |
| | | | | 0.11 (−0.02 to 0.24) | 0.08 |

* Values were measured at baseline, after intranasal saline administration, and after intracoronary propranolol administration in five patients.
† Baseline data are expressed as mean ± SE.
‡ For propranolol data, the first row represents the change compared with that caused by saline, and the second row represents the change compared with baseline values.
§ For mean-change-from-baseline values, CIs are 95%.

**Table 3A.** *Hemodynamic and Arteriographic Responses to Intranasal Cocaine Administration Followed by Intracoronary Saline Administration**

| Variable | Baseline† | After Intranasal Cocaine | | After Intracoronary Saline‡ | |
|---|---|---|---|---|---|
| | | Mean Change from Baseline§ | *P* Value | Mean Change from Baseline§ | *P* Value |
| Heart rate, *beats/min* | 82 ± 7 | 0 (−2 to 2) | 0.82 | 1 (−11 to 12) | 0.82 |
| | | | | 1 (−9 to 11) | 0.76 |
| Systolic arterial pressure, *mm Hg* | 142 ± 11 | 9 (−3 to 21) | 0.11 | −7 (−19 to 5) | 0.18 |
| | | | | 2 (−6 to 10) | 0.49 |
| Heart rate-systolic arterial pressure double product, × *10³* | 11.5 ± 0.9 | 0.8 (−0.5 to 2.0) | 0.16 | −0.5 (−2.7 to 1.7) | 0.54 |
| | | | | 0.2 (−1.2 to 1.7) | 0.66 |
| Mean arterial pressure, *mm Hg* | 99 ± 6 | 10 (1 to 18) | 0.034 | −6 (−14 to 1) | 0.09 |
| | | | | 3 (−1 to 8) | 0.09 |
| Coronary sinus blood flow, *mL/min* | 126 ± 25 | −13 (−25 to −2) | 0.034 | 0 (−8 to 8) | 0.95 |
| | | | | −13 (−29 to 3) | 0.08 |
| Coronary vascular resistance, *mm Hg/mL · min* | 0.87 ± 0.12 | 0.21 (0.05 to 0.37) | 0.023 | −0.08 (−0.18 to 0.03) | 0.11 |
| | | | | 0.13 (0.03 to 0.23) | 0.021 |
| Arterial-coronary sinus oxygen content difference, *mL/dL* | 10.7 ± 0.2 | 0.5 (0.1 to 0.9) | 0.026 | 0.1 (−0.4 to 0.5) | 0.70 |
| | | | | 0.5 (0.3 to 0.8) | 0.002 |
| Coronary arterial diameter, *mm* | | | | | |
| Left anterior descending | | | | | |
| Proximal | 3.30 ± 0.33 | −0.20 (−0.36 to −0.03) | 0.03 | 0 (−0.02 to 0.02) | 0.80 |
| | | | | −0.2 (−0.36 to −0.03) | 0.029 |
| Mid | 2.03 ± 0.13 | −0.14 (−0.29 to 0.01) | 0.058 | −0.03 (−0.10 to 0.03) | 0.20 |
| | | | | −0.18 (−0.38 to 0.03) | 0.075 |
| Distal | 1.47 ± 0.17 | −0.24 (−0.41 to −0.08) | 0.019 | 0.03 (−0.19 to 0.25) | 0.69 |
| | | | | −0.21 (−0.45 to 0.03) | 0.065 |
| Left circumflex | | | | | |
| Proximal | 2.72 ± 0.33 | −0.41 (−0.82 to 0) | 0.051 | −0.03 (−0.21 to 0.16) | 0.67 |
| | | | | −0.44 (−1.01 to 0.14) | 0.095 |
| Mid | 2.00 ± 0.24 | −0.45 (−0.68 to −0.22) | 0.014 | 0.12 (−0.38 to 0.62) | 0.41 |
| | | | | −0.33 (−1.04 to 0.38) | 0.18 |
| Distal | 1.73 ± 0.11 | −0.27 (−2.43 to 1.89) | 0.36 | −0.03 (−0.85 to 0.80) | 0.77 |
| | | | | −0.30 (−3.28 to 2.69) | 0.43 |

* Values were measured at baseline, after intranasal cocaine administration, and after intracoronary saline administration in five patients.
† Baseline data are expressed as mean ± SE.
‡ For saline data, the first row represents the change compared with that caused by cocaine, and the second row represents the change compared with baseline values.
§ For mean-change-from-baseline values, CIs are 95%.

mopericardium (56), endocarditis (57), sudden death (1, 55), angina pectoris (11), and myocardial infarction (3-26). Although treatment with beta-adrenergic blocking agents has been advocated for acute cocaine-induced cardiovascular complications, including myocardial ischemia (28-37), their influence on the coronary vasculature in humans after cocaine administration has not previously been assessed. Our study was done to provide this information.

Our data, obtained in 30 patients at the time of cardiac catheterization, show that cocaine increases myocardial oxygen demand (by increasing arterial pressure) and reduces myocardial oxygen supply (as reflected by a decrease in coronary sinus blood flow and coronary arterial diameter and an increase in the transcardiac oxygen content difference) (Table 1). These data are in agreement with observations made in previously reported studies in experimental animals (58, 59) and humans (27). Further, this cocaine-induced fall in myocardial oxygen supply is potentiated by the beta-adrenergic blocking agent, propranolol. Administration of propranolol to patients who had been given intranasal cocaine further decreased coronary sinus blood flow and further increased coronary vascular resistance. Thus, beta-adrenergic blockage may increase the magnitude of cocaine-induced myocardial ischemia.

Although the direction of change in coronary sinus blood flow and resistance was similar for all patients who received propranolol after receiving cocaine, there was substantial interpatient variability in the potentiation of vasoconstriction of the large epicardial (conductance) arteries. Administration of propranolol profoundly worsened cocaine-induced epicardial vasoconstriction in one patient (Figure 1), augmented vasoconstriction in four others, and exerted little effect in the remaining five. Although cocaine induces constriction of both the resistance and conductance vessels, propranolol appears primarily to intensify cocaine-induced vasoconstriction of the intramural resistance vessels, and its influence on the large epicardial conductance vessels may vary substantially among individual patients.

Although the effects of beta-blockade in the setting of cocaine-induced coronary vasoconstriction have not previously been reported in humans, propranolol has been shown to increase vascular reactivity in isolated porcine coronary arteries exposed to cocaine (60). In addition, previous studies have shown the deleterious effects of beta-adrenergic blockade in the setting of other causes of alpha-adrenergically mediated coronary vasoconstriction. In patients with coronary artery disease, alpha-adrenergic stimulation from cigarette smoking (61) or exposure to cold (62) decreases coronary

**Table 3B.** *Hemodynamic and Arteriographic Responses to Intranasal Cocaine Administration Followed by Intracoronary Propranolol Administration**

| Variable | Baseline† | After Intranasal Cocaine | | After Intracoronary Propranolol‡ | |
|---|---|---|---|---|---|
| | | Mean Change from Baseline§ | *P* Value | Mean Change from Baseline§ | *P* Value |
| Heart rate, *beats/min* | 74 ± 3 | 1 (−2 to 3) | 0.68 | 2 (−1 to 4) | 0.18 |
| | | | | 2 (−2 to 6) | 0.24 |
| Systolic arterial pressure, *mm Hg* | 140 ± 8 | 12 (4 to 19) | 0.006 | −9 (−16 to −1) | 0.024 |
| | | | | 3 (−5 to 11) | 0.45 |
| Heart rate-systolic arterial pressure double product, × $10^3$ | 10.5 ± 0.9 | 0.9 (0.3 to 1.6) | 0.012 | −0.5 (−1.2 to 2.7) | 0.19 |
| | | | | 0.4 (−0.5 to 1.4) | 0.32 |
| Mean arterial pressure, *mm Hg* | 101 ± 5 | 8 (2 to 14) | 0.015 | −3 (−8 to 2) | 0.23 |
| | | | | 5 (0 to 11) | 0.066 |
| Coronary sinus blood flow, *mL/min* | 139 ± 28 | −19 (−37 to −1) | 0.050 | −20 (−42 to −1) | 0.050 |
| | | | | −40 (−77 to −2) | 0.040 |
| Coronary vascular resistance, *mm Hg/mL · min* | 0.87 ± 0.10 | 0.17 (0.11 to 0.23) | <0.001 | 0.16 (−0.02 to 0.33) | 0.074 |
| | | | | 0.33 (0.12 to 0.53) | 0.005 |
| Arterial-coronary sinus oxygen content difference, *mL/dL* | 10.8 ± 1.1 | 0.7 (−0.7 to 2.1) | 0.21 | 0.3 (−0.7 to 1.3) | 0.44 |
| | | | | 1.0 (−1.2 to 3.2) | 0.25 |
| Coronary arterial diameter, *mm* | | | | | |
| Left anterior descending | | | | | |
| Proximal | 2.51 ± 0.21 | −0.14 (−0.39 to 0.11) | 0.23 | 0 (−0.12 to 0.12) | 1.00 |
| | | | | −0.14 (−0.41 to 0.14) | 0.28 |
| Mid | 1.83 ± 0.16 | −0.17 (−0.28 to −0.06) | 0.007 | 0.12 (−0.11 to 0.35) | 0.25 |
| | | | | −0.05 (−0.27 to 0.17) | 0.59 |
| Distal | 1.47 ± 0.17 | −0.11 (−0.2 to −0.02) | 0.026 | 0.03 (−0.17 to 0.23) | 0.72 |
| | | | | −0.08 (−0.27 to 0.12) | 0.38 |
| Left circumflex | | | | | |
| Proximal | 2.80 ± 0.29 | −0.18 (−0.43 to 0.07) | 0.13 | −0.10 (−0.37 to 0.17) | 0.41 |
| | | | | −0.28 (−0.47 to −0.09) | 0.011 |
| Mid | 1.97 ± 0.20 | −0.03 (−0.23 to 0.16) | 0.70 | −0.31 (−0.82 to 0.19) | 0.19 |
| | | | | −0.34 (−0.91 to 0.23) | 0.21 |
| Distal | 1.49 ± 0.12 | −0.06 (−0.18 to 0.05) | 0.25 | −0.26 (−0.78 to 0.26) | 0.28 |
| | | | | −0.32 (−0.78 to 0.13) | 0.14 |

* Values were measured at baseline, after intranasal cocaine administration, and after intracoronary propranolol administration in ten patients.
† Baseline data are expressed as mean ± SE.
‡ For propranolol data, the first row represents the change compared with that caused by cocaine, and the second row represents the change compared with baseline values.
§ For mean-change-from-baseline values, CIs are 95%.

blood flow and increases coronary vascular resistance, and the changes are potentiated by propranolol.

Our study was designed to examine the direct effects of beta-adrenergic blockade on the coronary vasculature following cocaine administration. We therefore infused a small dose (2 mg) of propranolol via the intracoronary route during coronary sinus pacing. Cocaine caused coronary vasoconstriction, and propranolol further reduced coronary blood flow without altering myocardial oxygen demand (as measured by rate-pressure product). We cannot exclude the possibility that this small dose of propranolol reduced coronary sinus blood flow by diminishing myocardial contractility. However, decreased coronary sinus blood was not seen in those patients receiving propranolol after receiving intranasal saline (group 1B) (Table 2); in addition, decreased myocardial contractility cannot account for the enhanced epicardial vasoconstriction seen after propranolol administration in some patients who had received cocaine (Figure 1).

Our study has several strengths. We assessed the influence of cocaine on the coronary vasculature in vivo by measuring coronary sinus blood flow (by thermodilution), transcardiac oxygen content difference, and coronary arterial diameters (in the proximal, mid, and distal portions of the left anterior descending and circumflex coronary arteries by quantitative arteriography). All three techniques yielded consistent results; cocaine decreased coronary sinus blood flow and coronary arterial dimensions and increased transcardiac oxygen content difference. With these same techniques, we showed that propranolol, a beta-adrenergic blocking agent, potentiated the effects of cocaine: Coronary sinus blood flow decreased and coronary vascular resistance increased in all patients without a change in myocardial oxygen demand, and coronary arterial dimensions decreased in half of the patients. In short, cocaine-induced coronary vasoconstriction and its potentiation by propranolol were shown to occur hemodynamically, metabolically, and arteriographically.

Our study also has some limitations. First, the thermodilution technique does not allow measurement of regional myocardial blood flow; we therefore assessed the effect of cocaine on total coronary flow only. Second, we evaluated the effects of cocaine given intranasally in a dose of 2 mg/kg but did not assess its influence following other routes of administration or other doses. Most of the reported cocaine-associated myocardial infarctions occurred after intranasal administration (22), and its administration by other routes is likely to exert a similar effect on coronary blood flow. The cocaine dose used in our study (one half to two thirds the

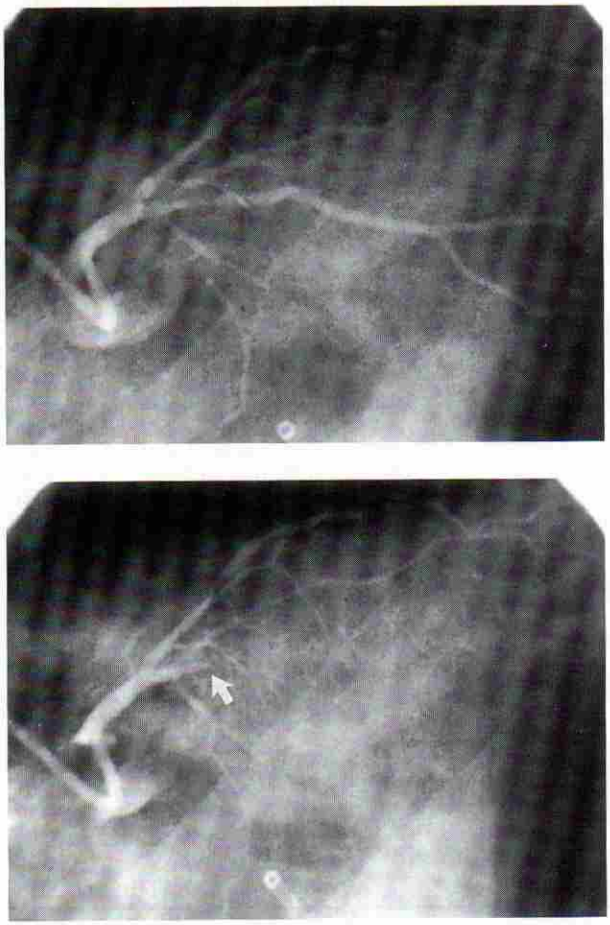

**Figure 1. Top Panel.** An arteriogram of the left coronary artery in the right anterior oblique projection after intranasal cocaine administration. By quantitative analysis, the luminal diameter was reduced diffusely by 12% in comparison with the baseline value (not shown). **Bottom Panel.** An arteriogram of the left coronary artery in the same obliquity after intracoronary propranolol administration. The circumflex coronary artery is occluded (*arrow*). Flow in this artery was quickly restored by administration of sublingual nitroglcerin.

standard dose used for intranasal anesthesia) was selected because of its proven safety (28). Third, we examined the effects of the intracoronary infusion of propranolol but did not assess its influence following other routes of administration. Fourth, the small number of patients in our study confers a low statistical power.

Previous reports of cases of myocardial infarction or sudden death in close temporal proximity to illicit cocaine use have indicated that the amount of cocaine used is often much larger (more than 1000 mg) than the dose used in our study (9, 13, 63, 64). Persons taking such doses probably develop severe, sustained coronary vasoconstriction in response to very high serum cocaine concentrations. Supporting this hypothesis, recurrent angina and myocardial infarctions have been reported after continued cocaine use in persons with angiographically normal coronary arteries (14, 22, 23). Although not proved, the deleterious effects of beta-adrenergic blockade may be more pronounced after ingestion of a substantial amount of cocaine.

In summary, cocaine decreases coronary blood flow and increases resistance via alpha-adrenergic stimulation of the coronary vasculature. This reduction of myocardial oxygen supply may lead to ischemia or infarction in some persons. Beta-adrenergic blockade potentiates this deleterious effect of cocaine, further decreasing coronary blood flow. Therefore, in the patient with cocaine-induced chest pain, beta-adrenergic blockade probably should be avoided. Although not yet proved to be beneficial in this setting, nitrates or calcium antagonists may exert a beneficial influence.

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