Imaging

Cocaine-Induced Vasoconstriction in the Human Coronary Microcirculation
New Evidence From Myocardial Contrast Echocardiography

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Background—Cocaine is a major cause of acute coronary syndrome, especially in young adults; however, the mechanistic underpinning of cocaine-induced acute coronary syndrome remains limited. Previous studies in animals and in patients undergoing cardiac catheterization suggest that cocaine constricts coronary microvessels, yet direct evidence is lacking.

Methods and Results—We used myocardial contrast echocardiography to test the hypothesis that cocaine causes vasoconstriction in the human coronary microcirculation. Measurements were performed at baseline and after a low, nonintoxicating dose of intranasal cocaine (2 mg/kg) in 10 healthy cocaine-naïve young men (median age, 32 years). Postdestruction time-intensity myocardial contrast echocardiography kinetic data were fit to the equation $y = A(1 - e^{-\beta t})$ to quantify functional capillary blood volume ($A$), microvascular flow velocity ($\beta$), and myocardial perfusion ($A \times \beta$). Heart rate, mean arterial pressure, and left ventricular work (2-dimensional echocardiography) were measured before and 45 minutes after cocaine. Cocaine increased mean arterial pressure (by 14±2 mm Hg [mean±SE]), heart rate (by 8±3 bpm), and left ventricular work (by 50±18 mm Hg·mL$^{-1}$·bpm$^{-1}$). Despite the increases in these determinants of myocardial oxygen demand, myocardial perfusion decreased by 30% (103.7±9.8 to 75.9±10.8 arbitrary units [AU]/s; $P<0.01$) mainly as a result of decreased capillary blood volume (133.9±5.1 to 111.7±7.7 AU; $P<0.05$) with no significant change in microvascular flow velocity (0.8±0.1 to 0.7±0.1 AU).

Conclusions—In healthy cocaine-naïve young adults, a low-dose cocaine challenge evokes a sizeable decrease in myocardial perfusion. Moreover, the predominant effect is to decrease myocardial capillary blood volume rather than microvascular flow velocity, suggesting a specific action of cocaine to constrict terminal feed arteries. (Circulation. 2013;128:598-604.)

Key Words: cocaine ■ echocardiography ■ microcirculation ■ myocardial perfusion imaging

Cocaine is the second most widely trafficked drug in the world (second only to marijuana) and constitutes a major cause of cardiovascular disease, especially acute coronary syndrome (ACS).1 The incidence of cocaine-induced ACS has increased steadily over the last 2 decades2 as cocaine use has increased worldwide, especially in Europe, Africa, and Asia.3 Treatment of cocaine-induced ACS, however, remains largely empirical because the underlying pathogenesis is incompletely understood and an efficient method to evaluate putative countermeasures is lacking.2

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Cocaine is a potent sympathomimetic, stimulating adrenergic receptors to simultaneously increase heart rate and blood pressure,4,6 and thus myocardial oxygen demand, and coronary vascular resistance, which could limit oxygen delivery. Indeed, a low, nonintoxicating dose of intranasal cocaine (2 mg/kg) has been shown to decrease both coronary artery diameter and coronary sinus blood flow, an indirect measure of coronary arterial flow, in middle-aged patients undergoing diagnostic cardiac catheterization for the evaluation of chest pain.5-14 In those studies, the reduction in the diameter of the epicardial coronary arteries averaged 8% to 12%, which, by itself, would be far too small to impair myocardial perfusion.15 Thus, the decrease in coronary sinus flow has been viewed as indirect evidence for constriction at the level of the coronary microcirculation. However, the putative effect of cocaine on coronary microvessels has not been tested directly.

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Here, we used echogenic gas-filled microbubbles (ie, myocardial contrast echocardiography [MCE]) to test the hypothesis that cocaine constricts human coronary microvessels. The data show a remarkable decrease in capillary blood volume with unchanged feed artery flow, indicating constriction of the most distal coronary microvessels, when cocaine-naïve healthy young adults are challenged with the nonintoxicating 2-mg/kg dose of intranasal cocaine.

Methods

The research protocol was approved by the Institutional Review Board at Cedars-Sinai Medical Center. Healthy volunteers between 18 and 55 years of age were recruited by advertisement in local media and scheduled for an initial screening visit to determine eligibility. After providing informed written consent, subjects were screened with a physical examination, complete medical history, 12-lead ECG, 2-dimensional transthoracic echocardiogram, and venous blood sampling to assess electrolytes, lipid profile, inflammatory markers (C-reactive protein), glucose levels, and liver function. Exclusion criteria were as follows: history of substance abuse; intracardiac shunt by echocardiogram; evidence of cardiopulmonary disease by history, physical examination, ECG, or echocardiogram; history of kidney or liver disease, diabetes mellitus, systemic illness, or hypertension; blood pressure ≥140/90 mm Hg at screening; hyperlipidemia or elevated blood glucose at screening; and inadequate echocardiography image quality as determined by a senior echocardiography board–certified cardiologist.

All experiments were performed under normothermic conditions (22°C) with subjects in the left lateral decubitus position. Heart rate and blood pressure were measured continuously.

Blood pressure was measured by the oscillometric technique with a highly accurate, validated oscillometric monitor (Datascope Mindray Passport V Monitor, Mindray North America, Mahwah, NJ). Heart rate was monitored by a cardiotachometer triggered by the R wave of an ECG lead. Height was measured by using a standard clinical stadiometer, and body weight was measured with a digital balance scale (Scale-Tronix 5002, Scale-Tronix, White Plains, NY).

Measurement of Left Ventricular Function

Contrast-enhanced 2-dimensional transthoracic echocardiography was performed by a single licensed sonographer using a phased-array probe interfaced with an imaging system (iE33, Philips Medical Systems, Andover, MA) to evaluate left ventricular (LV) systolic function and to estimate cardiac work as a reflection of myocardial oxygen demand. Parasternal short-axis images at the level of the papillary muscles were acquired to measure end-systolic cavity area and end-systolic myocardial area, with the endocardial and epicardial myocardial muscles were acquired to measure end-systolic myocardial cavity area and end-systolic myocardial area, with the endocardial and epicardial cavity areas, respectively, recorded. Apical 4-chamber and 2-chamber images were acquired, with the endocardial surface traced manually at end diastole and end systole for measurement of LV end-diastolic and end-systolic volumes, respectively, with a modified Simpson method. All data are reported as the average of at least 3 cardiac cycles acquired with the breath held at end expiration.

Stroke volume was calculated as end-diastolic volume minus end-systolic volume, and cardiac output was calculated as heart rate multiplied by stroke volume. Indexes of LV systolic function included ejection fraction, calculated as stroke volume divided by end-diastolic volume; LV end-systolic single point elastance, calculated as end-systolic pressure (0.9 times systolic blood pressure) divided by end-systolic volume; LV stroke work, calculated as end-systolic pressure times stroke volume; and LV total work, calculated as LV end-systolic elastance times heart rate. LV end-systolic wall stress was measured by the following equation: \( P/(2h(1+h/2R)) \), where \( P \) is the end-systolic pressure, \( R \) is the internal radius (square root of the end-systolic cavity area divided by \( \pi \)), and \( h \) is wall thickness (end-systolic myocardial area minus end-systolic cavity area). Myocardial oxygen demand was calculated according to a previously validated equation: \( 7.2 \times 10^{-4} \times \beta \times \pi \times (7.2 \times 10^{-4} \times \beta + 1.42) \).

Cocaine Metabolites and Blood Levels

Venous blood was collected 30 minutes after cocaine administration for the detection of the cocaine metabolite benzoylecgonine. Blood samples were immediately centrifuged; the serum was frozen (−80°C) and later analyzed by gas chromatography–mass spectrometry (Pacific Toxicology Laboratories, Chatsworth, CA) for the determination of cocaine blood levels.

Experimental Protocols

Protocol 1: Internal Validation Studies

First, we established within-subject test–retest reproducibility of MCE perfusion indexes in our laboratory. In each subject, baseline measurements were performed twice with at least 15 minutes between measurement, which is the time needed to return the intravascular microbubble concentration to baseline levels.

Then, we assessed the ability of MCE to detect small changes in microvascular perfusion induced by dobutamine, used as an internal coronary vasodilator control. Measurements were performed before and during continuous intravenous infusion of low-dose (5 µg·kg−1·min−1) dobutamine (Harvard Apparatus, Holliston, MA). Previous dog studies have shown that low-dose dobutamine increases microvascular flux rate with little change in capillary blood volume. Whether low-dose dobutamine evokes a similar pattern of microvascular coronary dilation in human subjects has not previously been tested.

Protocol 2: Effects of Low-Dose Intranasal Cocaine on Microvascular Perfusion

After baseline data were obtained, a low, nonintoxicating dose of topical intranasal cocaine hydrochloride (2 mg/kg, 10% solution) was administered, followed by repeat measurements of MCE and LV function. This dose of intranasal cocaine is half the standard clinical dose for rhinolaryngologic procedures and is the same dose used in many previous studies to show that cocaine decreases epicardial
coronary artery diameter by 8% to 12% as measured by quantitative coronary angiography in patients undergoing evaluation for chest pain.9–14

Statistical Methods

All data are expressed as a mean±SEM unless otherwise specified. Statistical analyses were performed with SigmaStat software (Systat, San Jose, CA). In protocol 1, simple linear regressions, calculation of the coefficient of variation, and Bland-Altman analyses were performed to assess test–retest reproducibility. Differences between baseline and dobutamine were assessed by use of a paired-sample t test. In protocol 2, differences between baseline and cocaine were assessed with a paired-sample t test. Significance was set a priori at \( P < 0.05 \).

Results

Twenty-four potential subjects responded to advertisements in the local media and were screened for participation. Thirteen individuals were excluded from the study for the following reasons: suboptimal echocardiographic image quality (n=9), elevated blood pressure at screening (n=2), hyperlipidemia on screening (n=1), and medical history of chronic systemic illness (n=1). The remaining 11 individuals (7 non-Hispanic white men and 4 Hispanic white men) were qualified to participate: age, 33±3 years (mean±SE; range, 22–45 years); height, 179.7±2.5 cm; weight, 83.7±3.6 kg; body mass index, 25.9±1 kg/m²; systolic blood pressure, 113±4 mm Hg; diastolic blood pressure, 62±4 mm Hg; heart rate, 71±5 bpm; LV ejection fraction, 63±0.5%; and Framingham risk scores, <1% to 2%.

Protocol 1: Validation Studies

Test–Retest Reproducibility of Myocardial Perfusion Indexes Under Baseline Conditions

The MCE indexes were highly reproducible with coefficients of variation ranging from 4% to 14% (Table 1). No systematic bias was detected on Bland-Altman plots (Table 1 and Figure I in the online-only Data Supplement).

Effects of Low-Dose Dobutamine

Low-dose intravenous dobutamine increased systolic blood pressure (111±3 to 144±4 mm Hg, mean±SE; \( P < 0.01 \)), diastolic blood pressure (55±2 to 63±2 mm Hg; \( P < 0.01 \)), and mean arterial pressure (74±2 to 90±2 mm Hg; \( P < 0.01 \)), with no change in heart rate (66±3 to 68±4 bpm; \( P = 0.522 \)). Multiple indexes of LV work increased as expected (Table I in the online-only Data Supplement).

An illustrative experiment in 1 subject and group mean data for myocardial perfusion are shown in Figure 1. Microvascular flow velocity (\( \beta \)) increased significantly (from 0.7±0.1 to 120.1±12.0 mL/min) as dobutamine was infused. This effect was maintained for 9 seconds (top). The time-intensity curve in Figure 1B shows increased perfusion (\( \beta \)) with low-dose dobutamine (\( 5 \mu g \cdot kg^{-1} \cdot min^{-1} \)). Figure 1C shows the increase in myocardial perfusion normalized to myocardial oxygen consumption (\( \text{MVO}_2 \)). The increase in myocardial perfusion was significant (\( P < 0.05 \)).
1.1±0.1 seconds−1 from baseline to dobutamine; *P<0.01), whereas capillary blood volume remained unchanged (130±7 versus 124±6 arbitrary units [AU]; baseline versus dobutamine; P=NS). As a result, myocardial perfusion increased by 40% (from 1.3±0.2 to 1.6±0.2 AU·s−1·mm Hg−1; *P<0.05). The ratio of myocardial perfusion to MVO₂ was unaffected by dobutamine (Figure 1C), indicating proportionate increases in oxygen delivery and demand. The ratio of myocardial conductance to MVO₂ was also unaffected by dobutamine (0.2±0.03 versus 0.2±0.02, baseline versus dobutamine).

Protocol 2: Effects of Nonintoxicating, Low-Dose Topical Intranasal Cocaine on Myocardial Perfusion

As expected, none of the subjects developed chest pain, ECG evidence of ischemia or arrhythmias, or other complications from low-dose cocaine. In 1 subject, destruction-refill kinetic data were not of sufficient quality to meet inclusion criteria; thus, data are presented on 10 subjects. Neither cocaine nor the cocaine metabolite benzoylecgonine was detected in the plasma of any subject at baseline. After intranasal cocaine, the mean cocaine blood level was 64.5±13.7 ng/mL; benzoylecgonine was detected in all subjects. Consistent with previous reports,4–8,23,24 low-dose topical intranasal cocaine increased systolic blood pressure (111±3 to 125±4 mm Hg, mean±SE; *P<0.01), diastolic blood pressure (53±2 to 67±2 mm Hg; *P<0.01), mean arterial pressure (72±2 to 86±3 mm Hg; *P<0.01), heart rate (65±2 to 73±3 bpm; *P<0.01), and multiple indexes of LV work (Table 2).

An illustrative experiment in 1 subject is shown in Figure 2, and group mean data are shown in Figure 2 and Table 2. The major new finding of this study is that with short-term low-dose cocaine challenge, myocardial capillary blood volume decreased by 16% (from 134±5 to 112±8 AU; *P<0.01), whereas microvascular flow velocity remained unchanged (Figure 2 and Table 2). As a result, myocardial perfusion decreased by 23% (from 104±10 to 76±11 AU·s−1; *P<0.01) and myocardial conductance decreased by 35% (from 1.5±0.2 to 0.9±0.2 AU·s−1·mm Hg−1; *P<0.01; Figure 2B). Moreover, the ratio of myocardial perfusion to MVO₂ decreased by 35% (from 16±2 to 10±1; *P<0.01; Figure 2C), and the ratio of myocardial conductance to MVO₂ decreased by 44% (from

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Table 2. Myocardial Responses to Intranasal Cocaine

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<tr>
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<th>Baseline</th>
<th>Cocaine</th>
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<tr>
<td>Myocardial contrast echocardiography</td>
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<tr>
<td>Myocardial A, AU</td>
<td>134±5</td>
<td>112±8*</td>
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<tr>
<td>Myocardial β, s⁻¹</td>
<td>0.8±0.1</td>
<td>0.7±0.1</td>
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<tr>
<td>Myocardial perfusion (A·β), AU·s⁻¹</td>
<td>104±10</td>
<td>76±11*</td>
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<tr>
<td>Myocardial conductance, AU·mm·Hg⁻¹</td>
<td>1.5±0.2</td>
<td>0.9±0.2*</td>
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Hemodynamics

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<tr>
<td>Heart rate, bpm</td>
<td>65±2</td>
<td>73±3*</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>111±3</td>
<td>125±4*</td>
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<td>Diastolic blood pressure, mmHg</td>
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<td>LV end-systolic volume, mL</td>
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<tr>
<td>LV stroke volume, mL</td>
<td>96±5</td>
<td>105±7*</td>
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Indexes of LV work, function, and oxygen demand

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<tr>
<td>LV ejection fraction, %</td>
<td>64±1</td>
<td>66±2</td>
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<tr>
<td>LV end-systolic elastance, mmHg·mL⁻¹</td>
<td>1.9±0.2</td>
<td>2.5±0.3*</td>
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<tr>
<td>LV end-systolic wall stress, 10⁶ dynes/cm²</td>
<td>0.7±0.1</td>
<td>0.8±0.1</td>
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<tr>
<td>LV stroke work (×10⁻⁶), mmHg·mL⁻¹</td>
<td>9.6±0.4</td>
<td>11.9±0.8*</td>
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<tr>
<td>LV total work mmHg·mL⁻¹·bpm⁻¹</td>
<td>125.6±14.3</td>
<td>176.9±17.2*</td>
</tr>
<tr>
<td>MVO₂, mL·min⁻¹</td>
<td>6.7±0.3</td>
<td>8.1±0.4*</td>
</tr>
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Data are reported as mean±SEM. AU indicates arbitrary units; LV, left ventricle; and MVO₂, myocardial oxygen consumption. *P<0.05.

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Figure 2. The myocardial contrast echocardiography response at baseline and after nonintoxicating low-dose intranasal cocaine (2 mg/kg). Top, A 2-dimensional myocardial contrast echocardiography images of the left ventricle of a representative cocaine-naïve healthy subject at various time intervals after the destructive pulse sequence (denoted T₀). Note that with cocaine, the rate of bubble replenishment (β) appears only somewhat reduced, whereas the maximum video intensity (capillary blood volume) never becomes as bright as the baseline condition. A, A typical time-intensity plot obtained at baseline and during low-dose intranasal cocaine exposure. B, Summary data showing myocardial perfusion at baseline and in response to cocaine. C, Myocardial perfusion normalized to myocardial oxygen consumption (MVO₂) at baseline and after cocaine. Summary data reported as mean±SE. *P<0.05.
0.2±0.03 to 0.1±0.02; P<0.01), indicating a mismatch between oxygen supply and demand.

**Discussion**

The mechanistic underpinning of cocaine-induced coronary vasoconstriction and the evidence base for treating acute cocaine-induced ACS are limited. Using MCE in cocaine-naïve healthy young adults, we show that a nonintoxicating low-dose intranasal cocaine challenge evokes a sizeable decrease in myocardial perfusion. Moreover, the predominant effect is to decrease myocardial capillary blood volume rather than microvascular flow velocity, suggesting a specific action of cocaine to constrict terminal feed arteries.

The prior clinical research on cocaine-induced coronary vasoconstriction required invasive cardiac catheterization and focused on large epicardial coronary arteries. In contrast, MCE provides a noninvasive approach to study the effects of cocaine on the human coronary microcirculation, which contains 80% of total myocardial blood volume and regulates nutrient exchange in cardiac myocytes. Using echogenic gas-filled microspheres with a size and rheological properties similar to those of red blood cells, the destruction-refill kinetic data permit repeated quantitative measures of microvascular flow velocity and capillary blood volume. Although MCE is technically challenging and has not yet gained widespread use in the clinical diagnosis of coronary artery disease, the technique has been well validated in multiple laboratories and has proven to be a powerful clinical research tool for elucidating the mechanisms of vascular regulation in other conditions (e.g., coronary occlusion, insulin-mediated vasodilation). However, MCE has not been used previously to study the vascular effects of cocaine.

We therefore validated the technique for this specific purpose in our own laboratory by showing a high degree of within-subject test–retest reproducibility and the expected increase in myocardial perfusion with low-dose dobutamine, a positive inotrope used as an internal coronary vasodilator control. That low-dose dobutamine caused a large increase in microvascular flow velocity with unchanged capillary blood volume is a novel finding that replicates in conscious human subjects the same pattern of microvascular response to dobutamine seen previously with MCE in anesthetized dogs. From a mechanistic standpoint, increased cardiac work produced by low-dose dobutamine causes metabolic dilation of intramuscular feed arterioles but does not cause capillary recruitment; the latter occurs only at higher levels of catecholamine stimulation when increases in blood velocity alone are insufficient to meet increased myocardial oxygen demands.

The seminal finding of our study is that cocaine, in marked contrast to dobutamine, decreases myocardial perfusion despite increasing myocardial oxygen demand. Moreover, the decrease in capillary blood volume with unchanged microvascular flow velocity strongly suggests that the major sites of the action of cocaine are the most distal coronary microvessels, that is, terminal arterioles that control inflow to individual capillary networks. This interpretation is supported by previous studies showing that interventions that selectively affect the tone of terminal arterioles (such as insulin or mild exercise) selectively affect capillary blood volume without changing microvascular flow velocity. In marked contrast, acute stenosis or spasm of the large epicardial coronary arteries produces a qualitatively different MCE response characterized by an isolated decrease in microvascular flow velocity with little or no change in capillary blood volume.

Thus, the new MCE data extend previous clinical research on cocaine-induced coronary constriction. Our data substantiate the interpretation of the coronary sinus flow data in the seminal catheterization laboratory studies by Lange et al using the same low, nonintoxicating dose of topical intranasal cocaine (2 mg/kg), but our data differ from those of Majid and coworkers, who found that intravenous infusion of an intoxicating dose of cocaine affected neither myocardial perfusion by MCE performed with intracoronary infusion of microbubbles nor coronary artery diameter by quantitative coronary angiography and actually increased coronary sinus flow by thermodilution. However, the negative findings in the Majid et al study may be attributable to acute cardiovascular tolerance because cocaine challenge was administered to cocaine-addicted patients admitted 24 to 48 hours earlier with documented prolonged cocaine-related ACS or to the MCE technique, which used bolus intracoronary injections, preventing measurement of capillary blood volume, which requires continuous steady-state infusion. Indeed, the major new finding of our study is that in the human coronary microcirculation, cocaine appears to exert its greatest effect at the level of the capillaries.

These new MCE data in humans also extend findings in previous animal studies in several important ways. Our data are consistent with earlier studies in anesthetized dogs and pigs showing decreased coronary blood flow and decreased myocardial perfusion by thallium scintigraphy, as well as conventional (i.e., radiolabeled) microspheres, but our data differ at first glance from more recent studies in conscious dogs and nonhuman primates in which proximal coronary artery flow increased with cocaine (suggesting that the decreased flow in earlier studies was an artifact of anesthesia). In the later study, however, coronary sinus pH fell despite increased large-artery flow, suggesting impaired microvascular perfusion, which we have now shown directly in conscious humans.

Our study has several limitations. We excluded almost half of the subjects screened as a result of suboptimal echocardiographic windows, which limit the application of MCE to a broader population. This initial proof-of-concept study did not have a placebo control; however, the highly reproducible baseline data serve as a time control, and the preferential effect of cocaine on capillary blood volume over microvascular flow velocity shows specificity. We did not perform invasive coronary angiography to exclude cocaine-induced epicardial coronary vasoconstriction. However, 2 pieces of information point to a microvascular site of action. First, multiple prior angiographic studies show only an 8% to 12% reduction in epicardial artery diameter with the same dose of topical intranasal cocaine used in our study. This small reduction in epicardial coronary artery diameter is well below the threshold 85% reduction required to restrict flow, as shown here.
(ie, no change in microvascular flow velocity). Second, reduced resting myocardial blood flow from epicardial artery stenosis is manifest on MCE by a larger reduction in microvascular flow velocity ($\beta$) than capillary blood volume ($A$),$^{27}$ but we have seen the opposite, which further points to a distal arteriolar mechanism. Although we cannot exclude the presence of coronary artery disease in our subjects, by design, all had extremely low Framingham risk scores.

Additional limitations should be considered. Increased LV pressure from diastolic dysfunction could theoretically contribute to the present results by causing extravascular compression of coronary microvessels. Although we did not measure LV end-diastolic pressure, previous invasive hemodynamic studies show that this low dose of intranasal cocaine has no effect on end-diastolic pressure.$^{50}$ For ethical reasons, our studies are limited to low-dose cocaine, which does not expose cocaine-naïve subjects to the potentially addicting effect of cocaine intoxication. Because none of the subjects experienced chest pain or had any ischemic ECG changes with this cocaine dose, the present MCE data do not prove that constriction of coronary microvessels is the major mechanism causing either chest pain or ACS in the clinic setting of cocaine intoxication. Further studies are needed to determine whether the microvascular response differs when an acute cocaine challenge is superimposed on chronic cocaine addiction or common cardiovascular risk factors.

Despite these limitations, the present MCE data document acute cocaine-induced vasconstriction in the human coronary microcirculation and set the stage for future studies to elucidate the underlying mechanism and to evaluate potential countermeasures in a controlled clinical research setting.

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### Disclosures

None.

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**Clinical Perspective**

Cocaine is the second most widely abused drug in the world (second only to marijuana) and constitutes a major cause of cardiovascular disease, especially acute coronary syndrome. The incidence of cocaine-induced acute coronary syndrome has increased steadily over the last 2 decades as cocaine use has increased worldwide. Treatment of cocaine-induced acute coronary syndrome, however, remains largely empirical because the underlying pathogenesis is incompletely understood and an efficient method to evaluate putative countermeasures is lacking. Using myocardial contrast echocardiography in cocaine-naïve healthy young adults, we show that a nonintoxicating low-dose intranasal cocaine challenge evokes a sizeable decrease in myocardial perfusion. Moreover, the predominant effect is to decrease myocardial capillary blood volume rather than microvascular flow velocity, suggesting a specific action of cocaine to constrict terminal feed arteries. These findings establish myocardial contrast echocardiography as an efficient, noninvasive method to elucidate the underlying mechanism of cocaine-induced coronary vasoconstriction and to evaluate potential countermeasures in a controlled clinical research setting.
Cocaine-Induced Vasoconstriction in the Human Coronary Microcirculation: New Evidence From Myocardial Contrast Echocardiography

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Supplemental Table. Myocardial responses to low-dose (5 µg/kg/min) intravenous dobutamine.

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<td>Myocardial β, s⁻¹</td>
<td>0.7 ± 0.1</td>
<td>1.2 ± 0.1*</td>
</tr>
<tr>
<td>Myocardial perfusion (A-β), a.u.-s⁻¹</td>
<td>95 ± 16</td>
<td>145 ± 19*</td>
</tr>
<tr>
<td>Myocardial conductance, a.u.-mmHg⁻¹</td>
<td>1.3 ± 0.2</td>
<td>1.6 ± 0.2*</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats·min⁻¹</td>
<td>66 ± 3</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>111 ± 3</td>
<td>144 ± 4*</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>55 ± 2</td>
<td>63 ± 2*</td>
</tr>
<tr>
<td>Mean Blood Pressure, mmHg</td>
<td>74 ± 2</td>
<td>90 ± 2*</td>
</tr>
<tr>
<td>LV End-diastolic volume, mL</td>
<td>154 ± 8</td>
<td>160 ± 6</td>
</tr>
<tr>
<td>LV End-systolic volume, mL</td>
<td>58 ± 3</td>
<td>35 ± 3*</td>
</tr>
<tr>
<td>LV Stroke volume, mL</td>
<td>97 ± 5</td>
<td>125 ± 5*</td>
</tr>
<tr>
<td><strong>Indices of LV work, function and oxygen demand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Ejection Fraction, %</td>
<td>63 ± 1</td>
<td>78 ± 2*</td>
</tr>
<tr>
<td>LV end-systolic elastance, mmHg·mL⁻¹</td>
<td>1.8 ± 0.1</td>
<td>4.3 ± 0.4*</td>
</tr>
<tr>
<td>LV end-systolic wall stress, 10³ dyn/cm²</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>LV stroke work (x10⁻³), mmHg·mL⁻¹</td>
<td>9.2 ± 0.7</td>
<td>15.1 ± 1.5*</td>
</tr>
<tr>
<td>LV total work, mmHg·mL⁻¹·bpm⁻¹</td>
<td>120.2 ± 11.5</td>
<td>295.7 ± 39.2*</td>
</tr>
<tr>
<td>MVO₂, ml·min⁻¹</td>
<td>6.8 ± 0.3</td>
<td>8.5 ± 0.5*</td>
</tr>
</tbody>
</table>

Data reported as mean ± SEM. *P < 0.05. RBC, red blood cell; LV, left ventricle; MVO₂, myocardial oxygen consumption
Supplemental Figure Legend

**Supplemental Figure.** Bland-Altman analysis of intraobserver/measurement variability of myocardial contrast echocardiography showing (A) capillary blood volume, (B) feed artery flow velocity, and (C) myocardial perfusion [\(=\) capillary blood volume \(\times\) feed artery flow velocity]. Variability of left ventricular volumetric analyses are shown in panel D (end-diastolic volume) and E (end-systolic volume).