Clin. Cardiol. 26, 319–322 (2003)

Increased TIMI Frame Counts in Cocaine Users: A Case for Increased Microvascular Resistance in the Absence of Epicardial Coronary Disease or Spasm

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Summary

Background: Cocaine produces adverse cardiovascular effects, some of which cannot be explained by epicardial coronary artery disease (CAD) or spasm.

Hypothesis: The hypothesis of this study was that cocaine users would have increased coronary microvascular resistance, even in the absence of recent myocardial infarction (MI), CAD, or spasm.

Methods: Microvascular resistance was assessed by the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (cTFC) method in a consecutive series of 59 cocaine users without acute or recent MI or angiographically significant epicardial stenosis (> 50%) or spasm. The cTFCs in these patients were compared with 21 normal controls and with published normal cTFC values.

Results: The cTFC was significantly elevated (by 26–54%) in cocaine users. The cTFCs in the left anterior descending (LAD), circumflex (LCx), and right coronary (RCA) arteries in cocaine users were 30.0 ± 10.9, 34.1 ± 11.5, and 28.6 ± 11.8, respectively, compared with values in normal controls of 21.3 ± 4.3 ($p = 0.001$), 24.4 ± 7.2 ($p = 0.001$), and 22.7 ± 5.1 ($p = 0.04$), respectively, and published normal cTFC values (all $p < 0.01$). An abnormally high cTFC was present in 61% of patients in the LAD, 69% in the LCx, and 47% in the RCA.

Conclusions: Markedly decreased coronary blood flow velocity, indicating increased microvascular resistance, is present in cocaine users, even in the absence of acute or recent MI, or significant epicardial CAD or spasm. Increased microvascular resistance may explain many important cardiovascular manifestations of cocaine use and has therapeutic implications. Slow coronary filling may also suggest the possibility of cocaine use in patients in whom it was not otherwise suspected.

Key words: cocaine, corrected TIMI frame count, microvascular resistance, coronary angiography, chest pain

Introduction

Chest pain is a common reason for emergency room visits and hospitalization in cocaine users.[1, 2] Acute cocaine use is known to be associated with a variety of cardiovascular complications including cardiac ischemia and myocardial infarction (MI), even in the absence of obstructive coronary artery disease (CAD).[3] Proposed explanations for this include coronary artery spasm, diffuse vasoconstriction, sinus tachycardia and other tachyarrhythmias, and augmented myocardial contractility; these effects may produce a deleterious imbalance in myocardial oxygen supply and demand.[3, 4]

Although the systemic, myocardial, and coronary vascular effects of cocaine have been well documented,[5–17] the chronic effects of cocaine use on coronary microvascular function have not been studied extensively. The purpose of the present study was to assess microvascular resistance in cocaine users undergoing coronary angiography using the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (cTFC).

Materials and Methods

The study group was drawn from a consecutive series of 110 cocaine users undergoing coronary angiography at Cook County Hospital. Patients with acute or recent MI or cocaine

This study was supported by departmental funds.

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Received: February 1, 2002
Accepted with revision: July 16, 2002

use within 12 h (n = 30) were excluded. Vessels with angiographically significant epicardial stenosis (> 50%) or spasm were excluded, as were vessels in which cTFC could not be measured; this excluded 21 patients, leaving 59 patients who comprised the study population.

Coronary angiography was performed in standard views by manual injection of 5–10 ml of nonionic contrast with cine frames captured at 30 frames/s. The cTFC was measured as the number of cine frames taken for injected contrast to reach a defined distal landmark in the left anterior descending (LAD), left circumflex (LCx), and right coronary arteries (RCA), according to the method described by Gibson, *et al.*[18] The cTFC was counted in at least two projections whenever possible, with the average taken to be the cTFC for each patient. The cTFC was also measured in 21 patients with normal coronary angiograms to provide a "normal" control group.

Data are presented as mean ± standard deviation. Two-sided *t*-tests were used to compare the cTFC values obtained in cocaine users with those in normal controls and with published values for cTFC in normal coronary arteries. Chi-square or Fisher's exact test were used as appropriate to compare categorical variables between the cocaine and normal groups. A p value < 0.05 was considered to be significant. Informed consent was obtained for the procedure in all patients, and the study was approved by the Scientific Committee of Cook County Hospital.

Results

The characteristics of the cocaine users and normal controls are shown in Table I. Of the cocaine users, 54 patients were black (92%), 2 were white, 2 were Hispanic, and one was Asian Indian. Tachycardia (heart rate > 100) was present in six patients (10%). Systolic blood pressure was > 160 mmHg in three patients (5%), and diastolic blood pressure was > 100 mmHg in five patients (8%). Mean left ventricular ejection fraction was 56 ± 16% in the 46 patients in whom contrast ventriculography was performed. The timing of the last dose of cocaine in these patients ranged from approximately 24 h to several weeks prior to angiography.

TABLE I Baseline characteristics

No. of patients	59
Age (years, mean ± SD)	44.4 ± 7.6
Male (%)	53 (90)
Hypertension (%)	44 (75)
Diabetes mellitus (%)	6 (10)
Smoker (%)	47 (80)
Hyperlipidemia (%)	3 (5)
Family history of early CAD (%)	13 (22)
Heart rate (beats/min)	83 ± 21
Systolic blood pressure (mmHg, mean ± SD)	134 ± 21
Diastolic blood pressure (mmHg, mean ± SD)	86 ± 19

Abbreviation: CAD = coronary artery disease.

Of the 59 patients, cTFC values were excluded for 15 patients in the LAD (3 due to significant CAD in the LAD, 12 because cTFC could not be measured); for 5 patients in the LCx (1 due to significant CAD in the LCx, 4 because cTFC could not be measured); and for 10 patients in the RCA (6 due to significant CAD in the RCA, 4 because cTFC could not be measured). The cTFC was therefore available in the LAD in 44 patients, in the LCx in 54 patients, and in the RCA in 49 patients. No epicardial spasm was evident in any of the study patients. Of the 21 normal controls, cTFC values were excluded for 1 patient each in the LAD, LCx, and RCA (all because cTFC could not be measured); no patient in the control group had angiographically apparent CAD.

Mean cTFCs in the LAD, LCx, and RCA were 30.0 ± 10.9, 34.1 ± 11.5, and 28.6 ± 11.8 frames, respectively, in cocaine users (Fig. 1). These values were significantly higher than values in the LAD (21.3 ± 4.3 frames, p = 0.001), LCx (24.4 ± 7.2 frames, p = 0.001), and RCA (22.7 ± 5.1 frames, p = 0.04) in the normal controls. Values in cocaine users were significantly higher than published normal values for cTFC in the LAD (21.1 ± 1.5 frames), LCx (22.2 ± 4.4 frames), and RCA (20.4 ± 3.0 frames)[18] (all p < 0.01). Compared with normal controls and with published normals, the cTFC in cocaine users was 41–42% higher in the LAD, 40–54% higher in the LCx, and 26–40% higher in the RCA.

The number of cocaine users with normal cTFC (τ15 and δ27 frames[18]) or abnormally high or low cTFC are shown in Table II. A cTFC higher than normal was present in 61% of patients in the LAD, 69% in the LCx, and 47% in the RCA.

Similar results were obtained when the analysis was restricted to the 44 patients in the study with no significant CAD in any epicardial vessel. Mean cTFC in the LAD, LCx, and RCA were 30.2 ± 10.6, 33.9 ± 12.0, and 29.3 ± 12.1 frames, respectively, in these patients. A cTFC higher than normal was present in 62% of patients in the LAD, 68% in the LCx, and 46% in the RCA.

Discussion

In this study, significant slowing of coronary artery blood velocity was observed in the LAD, LCx, and RCA coronary

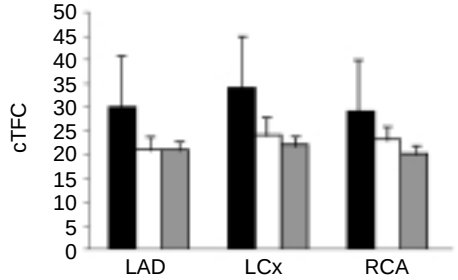

FIG. 1 Corrected TIMI frame count (cTFC) in cocaine users (black bars), normal controls (white bars), and published normal values[18] (hatched bars). LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

TABLE II Number of arteries with normal or abnormal corrected TIMI frame counts

	LAD	LCx	RCA
	n	n	n
High cTFC (> 27 frames) (%)	26 (61)	34 (69)	20 (47)
Normal cTFC (τ15 and δ27 frames) (%)	13 (32)	17 (31)	20 (45)
Low cTFC (< 15 frames) (%)	3 (7)	0 (0)	4 (8)

Abbreviations: TIMI = Thrombolysis in Myocardial Infaction, cTFC = corrected TIMI frame count, LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

arteries of cocaine users without recent MI or epicardial coronary stenosis or spasm, as assessed by the cTFC. A substantial proportion of patients had abnormally high cTFCs (> 60% in the LAD and LCx, and 47% in the RCA). These data indicate that increased microvascular resistance is present in the coronary bed in cocaine users, even after the acute effects of a cocaine dose have resolved.

Acute administration of cocaine is known to produce a number of physiologic effects that may promote the development of myocardial ischemia. Cocaine inhibits central and peripheral neuronal catecholamine reuptake, which can cause coronary vasospasm, peripheral vasoconstriction leading to systemic hypertension, increased myocardial contractility, and sinus tachycardia and other arrhythmias; the local anesthetic effects of cocaine also may precipitate arrhythmias.[5, 6] In addition, platelet activation and thrombosis may produce myocardial ischemia in cocaine users.[7, 8, 12–14]

Laboratory studies in animals[15, 16] and humans[11, 17] have demonstrated that cocaine administration produces an acute increase in coronary microvascular resistance, probably by increased stimulation of alpha-adrenergic receptors, which are plentiful in the myocardium.[6] The risk of MI has been reported to be greatly increased (more than 20-fold) within the first hour after cocaine use,[19] in part because of the relatively short half-life of cocaine (approximately 1 h after inhalation or intravenous injection, 2–3 h after nasal ingestion[5]). Even with repeated doses of cocaine, however, tolerance to the cardiac effects of the drug develops.[20]

Although much of the cardiotoxicity of cocaine occurs acutely, prior studies have shown that evidence of myocardial ischemia or infarction may appear long after the acute effects of the drug have resolved.[1, 21–23] Delayed onset of MI (18–24 h or more) has been reported,[1, 22–26] and ST-segment changes have been recorded 2 weeks after the last cocaine dose.[21] We are not aware of any prior studies that have demonstrated a chronic effect of cocaine use on coronary microvascular tone.

The present study indicates that cocaine use may have long-lasting effects on coronary microvascular resistance. Marked increases in cTFC in the coronary arteries were observed, even though angiography was performed many hours or even weeks after the last dose of cocaine. The cTFC measures coronary artery blood flow velocity.[27] The major determinants of coronary flow velocity are resistance and perfusion pressure. In the absence of a flow-limiting epicardial stenosis and under hemodynamically stable conditions, small-vessel resistance is the major determinant of coronary blood flow velocity. Thus, in this study, increased cTFC is most likely due to elevated microvascular resistance. Other reasons for high cTFC are unlikely, as most patients had normal blood pressures and normal heart rates, and no patient had experienced an acute or recent MI.

An observation by Majid *et al.*[28] may provide a mechanism for the chronically elevated microvascular tone in cocaine users. These authors found severe thickening of small muscular arteries on myocardial biopsy in 7 of 11 cocaine users with no epicardial CAD. Another possible explanation is the persistence of ethyl methyl ecgonine, benzoylecgonine, and other active metabolites of cocaine for up to 3 weeks;[29] perhaps coronary microvascular vasoconstriction is initiated by cocaine and maintained by the metabolites.[30] This may account for the findings in some of our patients, but elevated cTFC was present even in patients whose last dose was > 3 weeks ago. Other potential explanations, not assessed in the present study, include upregulation of adrenergic receptors, chronic catecholamine depletion, effects on mast cells, and stimulation of endothelin release.[21, 22, 31, 32]

Clinical Implications

The heightened microvascular resistance in cocaine users may explain the development of chest pain and myocardial ischemia in many patients who do not have epicardial stenosis due to CAD or spasm. As studies of cocaine users with chest pain have not found a high prevalence of CAD,[19, 24] the small-vessel effects of cocaine may in fact be more important. Because the process is diffuse rather than confined to one vascular territory, electrocardiographic findings may not be localizing. Furthermore, the abnormal microvascular tone seems to be present long after the acute effects of cocaine have dissipated. It has also been suggested that chronically reduced flow velocity in the coronary bed may be an important contributor to the development of left ventricular dysfunction in many cocaine users.[5] Therefore, medical therapy directed against vasoconstriction in cocaine users should be intense and should be continued for extended periods, perhaps indefinitely.

Another clinical implication relates to the recognition of cocaine use. The slowing of coronary flow velocity in these patients is frequently severe enough to be apparent to the angiographer. Attention to the speed of coronary filling may improve the detection of cocaine use in patients in whom it was not otherwise suspected. When coronary angiography reveals markedly slow filling, cocaine use should be considered.

Limitations

The major limitation of this study is the inclusion of some patients with CAD. Although the vessels with CAD were excluded from the main analysis, it is possible that angiographically inapparent CAD may have affected the cTFC values in

nonstenosed vessels in these patients. However, when the analysis was restricted to patients with no evident CAD in any vessel, the results were nearly identical.

Standardized injection rates were not utilized in these patients (cocaine users or controls), but other studies have reported that TIMI frame counts are relatively independent of the variability inherent in hand injections.[18, 33] Nitroglycerin was not systematically administered to these patients; however, because of the recognized utility of nitrates in patients with cocaine-associated chest pain, it is likely that the majority of cocaine patients were receiving nitrates at the time of angiography.

Conclusions

Markedly decreased coronary blood flow velocity, indicating increased resistance to coronary flow at the microvascular level, is present in cocaine users, even in the absence of acute or recent MI, or significant epicardial CAD or spasm. Increased microvascular resistance may explain many important cardiovascular manifestations of cocaine use and has therapeutic implications. Slow coronary filling may also suggest the possibility of cocaine use in patients in whom it was not otherwise suspected.

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