Cocaine and the Heart

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ABSTRACT

The use of cocaine may be associated with either acute or chronic toxicity, and approximately 5% to 10% of emergency department visits in the United States are believed to be secondary to cocaine usage. Chest pain is the most common cocaine-related medical problem, leading to the evaluation of approximately 64 000 patients annually for possible myocardial infarction, of which approximately 57% are admitted to the hospital, resulting in an annual cost greater than $83 million. There is a plethora of cocaine-related cardiovascular complications, including acute myocardial ischemia and infarction, arrhythmias, sudden death, myocarditis, cardiomyopathy, hypertension, aortic ruptures, and endocarditis. There is no evidence to suggest that preexisting vascular disease is a prerequisite for the development of a cocaine-related cardiovascular event, although it may be a potentiating factor, as may be nicotine and alcohol.

Introduction

There has been a persistence of cocaine use in the United States. Associated with this use has been the risk of cocaine-related cardiovascular complications.[1] This article will discuss our understanding of cocaine effects on the cardiovascular system and available therapeutic options.

Epidemiology

In the period between 1994 and 1998, the number of new cocaine users per year increased by 82%. In 2007, there were 2.1 million current cocaine users age 12 or older, comprising 0.8% of the population. These estimates were similar to the number and rate in 2006 (2.4 million or 1.0%). Users are more likely to be young, between 18 to 20 years old. Males are more likely to be users than females by a 2 to 1 ratio.[1]

Cocaine may be associated with either acute or chronic toxicity. Approximately 5% to 10% of emergency department visits in the United States have been attributed to cocaine use. Chest pain is the most common cocaine-related presentation, leading to 64 000 patient evaluations annually for possible myocardial infarction (MI). A total of 57% of these patients are admitted to the hospital with an annual cost of $83 million. Cocaine-related cardiovascular complications include acute myocardial ischemia and infarction, arrhythmias, sudden death, myocarditis, cardiomyopathy, hypertensive crises, aortic dissection or aortic rupture, and endocarditis (Table 1).[2–4]

All authors have read and approved submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. There are no financial or other concerns that could lead to a conflict of interest.

Pharmacology

Cocaine (benzoylmethylecgonine, $C_{17}H_{21}No_4$) is an alkaloid extracted from the leaves of the *Erythroxylon coca*, a plant native to South America. It was first used as a local anesthetic in 1884 and, interestingly, was used as an ingredient in a popular cola beverage in the early 20th century.[5] The alkaloid is dissolved in hydrochloric acid to form the water-soluble salt cocaine hydrochloride that can exist in crystalline, powder, and granular form. Freebase cocaine is the alkaloid in a basic non-salt form, prepared from cocaine hydrochloride by an organic extraction from a basic solution with ether. Freebase melts at 98 °C and can be smoked. When heated, it makes a crackling sound, hence its street name, "crack."[6]

Cocaine is well absorbed through all body mucous membranes and can be administered by nasal, sublingual, intramuscular, intravenous, and respiratory routes. The onset of action varies from 3 seconds to 5 minutes depending on the route of administration. Also dependent on the route of administration are peak effects and duration of action, which vary from 1 to 20 minutes and 5 to 90 minutes, respectively. In humans, cocaine has an elimination half-life of 30 to 60 minutes and is metabolized by plasma and hepatic cholinesterases to the water-soluble compounds, benzoylecgonine and ethyl methylecgonine, which are excreted in the urine.[7] Approximately 5% to 10% of the total cocaine dose is excreted unchanged in urine. Unmetabolized cocaine is usually not present in serum after 6 hours, but the metabolites can be detected for up to 48 hours. Benzoylecgonine has been detected in urine as long as 22 days after the last dose of cocaine in asymptomatic patients who have a history of chronic cocaine abuse.[7,8] This may have important clinical implications, such as establishing a correct diagnosis of myocardial damage in the emergency room secondary to recent cocaine abuse.

Clin. Cardiol. 33, 5, 264–269 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746

Received: November 19, 2009
Accepted with revision: January 12, 2010

Table 1. Putative Pathophysiologic Mechanism of Cocaine-Induced Cardiovascular Complications

Cardiovascular Complication	Pathophysiologic Mechanism
Myocardial ischemia and infarction	Increased sympathomimetic activity with increased myocardial oxygen demand
	Altered calcium flux across myocyte cell membrane
	Altered vascular endothelium integrity: reduced prostacyclin production
	Increased platelet thromboxane production
	Increased plasminogen activator inhibitor production
Cardiomyopathy and myocarditis	Hyperadrenergic state produces contraction band necrosis in myocardium
	Direct toxic effect of cocaine on myofibrils and interstitial fibrosis
	Hypersensitivity reaction of myocardium to cocaine
Cocaine-induced arrhythmias	Increased circulating catecholamines
	Inhibition of repolarization of myocytes by potassium efflux (lengthens QT interval)
	Ischemia and subsequent electrical instability of myocytes
Endocarditis	Possible direct effect on endothelium
Aortic dissection	Increase in systemic blood pressure with resultant increase in shear-stress forces

Pathophysiology

Cocaine is a central nervous system stimulant affecting the release and reuptake of serotonin and dopamine in the brain. It blocks the reuptake of norepinephrine and dopamine at preganglionic synaptic nerve endings, increasing the synaptic concentrations of these monoamines and enhancing the effect of norepinephrine. Cocaine also causes the release of norepinephrine and epinephrine from the adrenal medulla.[9] Thus, cocaine is a powerful sympathomimetic agent that can cause significant central and peripheral vasoconstriction.

Cocaine can cause an increase in heart rate and blood pressure in a dose dependent fashion. Hemodynamic responses include an increase in heart rate up to 34% and an increase in systemic arterial pressure up to 15%. Cocaine has been shown to reduce left ventricular function and increase end-systolic wall stress in dogs. Locally, cocaine has an anesthetic effect inhibiting the initiation or conduction of nerve impulses. This is accomplished by inhibiting sodium permeability during depolarization.[10]

Myocardial Ischemia and Infarction

The cardiac effects of cocaine are complex. While there is increased adrenergic activity increasing myocardial contractility and conduction, there is also a local anesthetic effect that is caused by inhibition of the transient inward flux of sodium across the cell membrane during depolarization. The net result appears to be an increase in sympathomimetic activity, resulting in increased myocardial contractility, heart rate, blood pressure, and increased myocardial oxygen demand while simultaneously decreasing myocardial oxygen supply due to vasoconstriction.[11] Also, instead of exclusively potentiating the effects of endogenous catecholamines with resultant increases in intracellular free calcium levels, cocaine may independently alter calcium flux across the cell membrane. This is possibly due to an increase in receptor-mediated calcium entry that may be secondary to cocaine's interactions with either angiotensin II, histamine H_2, or actual calcium L-channel receptors.[12]

There is a 24-fold increased risk of acute MI during the initial 60 minutes after the use of cocaine in patients who are otherwise at low risk.[13] Acute MI has been reported in 0.7% to 6% of patients with cocaine-associated chest pain.[14] Focal occlusive vasospasm, endothelial dysfunction, diffuse coronary vasoconstriction, or coronary thrombosis may be responsible for cocaine-induced MI in patients with normal coronary arteries.[13,14] Premature coronary atherosclerosis has been seen in young cocaine abusers, with obstructive coronary artery disease (CAD) seen in 35% to 40% of patients who undergo angiography for cocaine-associated chest pain.[15]

Endothelial dysfunction associated with early atherosclerosis has been shown to result in hypersensitivity to the vasoconstrictor effects of cocaine-induced catecholamine release.[16] Thus, cocaine-associated coronary vasospasm is greater in diseased vessels at sites of atherosclerosis. Experimental evidence suggests cocaine alters the integrity of vascular endothelium by reducing prostacyclin production, thereby reducing vasodilation.[17] Cocaine may also directly enhance platelet aggregation through α-adrenergic mediated mechanisms and potentiate platelet thromboxane production. Intranasally administered cocaine is associated with an increase in plasma plasminogen activator inhibitor.[16,17]

While focal coronary vasospasm has been postulated as a primary cause of cocaine-induced MI, it has been angiographically documented in only 2 patients with normal coronary arteries.[18,19] Damaged endothelium at the site of

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746

focal arterial constriction may serve as a nidus for platelet adhesion and resultant coronary thrombosis.[20]

Cocaine causes the release of norepinephrine from adrenergic nerve terminals which has been shown to cause diffuse coronary vasoconstriction of normal human epicardial coronaries both in vitro and in vivo.[21] Two studies have shown that administration of intranasal cocaine results in a significant reduction of coronary diameter as measured by quantitative coronary angiographic analysis.[22,23]

Cardiomyopathy and Myocarditis

Cocaine may depress left ventricular function in the absence of acute coronary ischemia. Cocaine has a direct negative inotropic effect on cardiac muscle. Clinical studies have demonstrated cocaine to be associated with transient left ventricular dilatation and decreased ejection fraction. This is often referred to as transient toxic cardiomyopathy associated with cocaine use, similar to catecholamine cardiomyopathy of pheochromocytoma and possible left apical ballooning syndrome.[24,25] Possible explanations include excess catecholamines leading to myocyte damage due to calcium overload or by transient coronary vasoconstriction with ischemia and subsequent myocyte death. There is still a debate as to whether the appearance of a mononuclear cell infiltrate is a secondary reaction to myocyte death or whether it represents a primary hypersensitivity reaction to cocaine, with a resultant myocarditis.[10]

Cocaine-Induced Arrhythmias

Cocaine exhibits properties of a class I antiarrhythmic agent by sodium-channel blockage. It also prolongs the duration of the QT interval by inhibiting myocyte repolarization that normally occurs by the efflux of potassium. A cocaine-associated long QTc interval may be related to its effect on conduction in the human ether-a-go-go related gene (HERG)-encoded potassium channel. Cocaine also increases intracellular calcium with resultant afterdepolarizations, reduces vagal activity, and increases myocyte irritability by inducing ischemia. When coupled with its ability to produce an enhanced sympathetic state, arrhythmias may occur.[26–28] Cocaine has been reported to produce a transient Brugada-type electrocardiographic pattern, the clinical importance of which is not known.[29] Of importance, studies in animals and humans have shown that cocaine precipitates ventricular arrhythmias and fibrillation mainly in the presence of myocardial ischemia, infarction, or in those with nonischemic myocellular damage.[26–28]

Endocarditis and aortic dissection are also complications due to cocaine abuse, which may be related to the direct effect of cocaine on endothelium and to an increase in systemic arterial pressure, respectively.[27,30,31]

Clinical Presentation and Diagnosis

In patients presenting to the emergency department, the most common cocaine-associated symptoms are cardiopulmonary, including chest pain, dyspnea, palpitations, and syncope. The onset of symptoms usually occurs soon after ingestion with two-thirds of patients presenting within 3 hours. The median time to hospital presentation is 18 hours, with some patients presenting up to 4 days post ingestion. In long-term users, evidence of cocaine has been identified up to 22 days after last reported use.[32] Chest pain description is frequently atypical requiring a high index of suspicion. The evaluation is similar to patients with non–cocaine-associated chest pain using serial electrocardiograms, serial biomarkers, and stress testing.

The literature suggests that up to 84% of patients with cocaine-related chest pain can have abnormal electrocardiograms. Abnormalities include ST-segment elevation, ST-segment depression, voltage criteria for left ventricular hypertrophy, and non-specific ST-segment and T wave abnormalities. As many as 43% of cocaine users without acute MI can have significant ST-segment elevations. Conversely, a relatively normal appearing electrocardiogram may not be sufficient to rule out an MI.[32,33]

The specificity of myoglobin as a marker of acute MI is altered by recent cocaine use. However, the specificity of creatine kinase MB (CK-MB) is affected less and that of cardiac troponin I is not affected by recent cocaine use.[33] Because of the difficulty in being able to accurately assess patients with chest pain and recent cocaine usage, most emergency departments routinely admit such patients for monitoring. Chest pain observation units have been used successfully for the evaluation of cocaine users with potential cardiac symptoms. Once acute MI has been excluded, early exercising testing has been safely used to assess the risk of severe CAD. This is a reasonable approach as patients without MI have only a reported 35% incidence of significant CAD at cardiac catheterization.[32,33]

Treatment

Treatment of patients with cocaine-associated acute coronary syndrome (ACS) closely parallels the treatment of non–cocaine-related ACS with a few important exceptions. According to the American Heart Association (AHA) scientific statement on the management of cocaine-associated chest pain and MI, initial mainstays of treatment in cocaine-induced coronary ischemia include aspirin, nitrates, and benzodiazepines (Figure 1).[34]

Intravenous benzodiazepines should be administered as early as possible for relief of chest pain, control of blood pressure, and management of the neuropsychiatric changes. Benzodiazepines decrease the central stimulating characteristics of cocaine and lessen anxiety. If there is persistent and severe hypertension, nitroglycerine, nitroprusside, or phentolamine can be started. Nitroglycerine reduces

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746

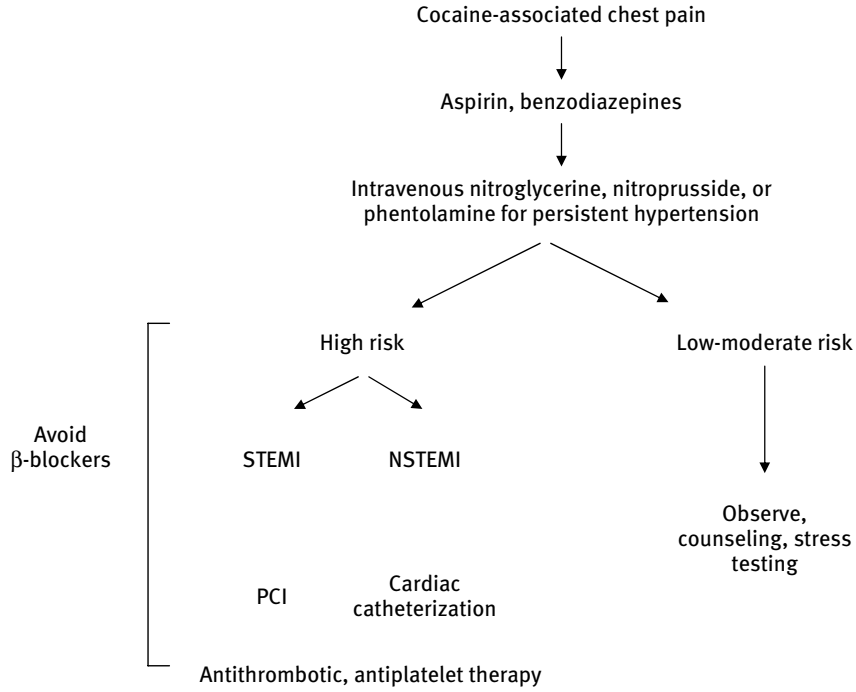

Figure 1. According to the American Heart Association (AHA) scientific statement on the management of cocaine-associated chest pain and MI, initial mainstays of treatment in cocaine-induced coronary ischemia include aspirin, nitrates, and benzodiazepines..

cocaine-associated chest pain. It may achieve this by its ability to reverse cocaine-associated vasoconstriction. Nitroglycerine is also beneficial in controlling cocaine-induced hypertension,[35] with possible mechanisms being a decrease in preload, afterload, and left ventricular end-diastolic pressure.

With persistence of chest pain, the addition of calcium channel blockers and α-blockers may be considered, as cocaine-induced coronary vasoconstriction is largely secondary to α-adrenergic stimulation. Lidocaine may be used as an antiarrhythmic agent during the peri-infarction period. However, it should be used with caution, since it may actually cause an increase in arrhythmias due to the presence of proarrhythmogenic cocaine.[34]

The use of β-blockers in patients with cocaine-induced chest pain remains controversial. Cocaine is associated with coronary artery vasospasm due to both direct smooth muscle stimulation and α-adrenergic stimulation. There is the concern that β-blockers would impede β-adrenergic mediated vasodilation. There have been reports of β-blocker associated decrease in coronary blood flow, increased seizure activity, and possible increased mortality.[36,37] However, β-blockade may be beneficial against the pathophysiologic effects of cocaine in the peri-MI period, including systolic dysfunction heart failure, coronary artery thrombotic occlusion, and ventricular arrhythmias. A recent retrospective cohort study concluded that the administration of β-blockers after the acute event was associated with a reduction in the incidence of MI after cocaine use and that the benefit of β-blockers on myocardial function may offset the risk of coronary artery vasospasm.[38] However, the current AHA scientific statement on the management of cocaine-associated chest pain and MI recommends avoiding β-blockers in the acute setting.[34]

Since cocaine may directly enhance platelet aggregation and potentiate platelet thromboxane production, and since damaged endothelium at a site of focal arterial constriction may serve as a nidus for platelet adhesion,[16,17,20] antithrombotic and antiplatelet agents are also recommended in managing cocaine-associated MIs.[34]

In all causes of aortic dissection, blood pressure control to a target systolic pressure of 110 mm Hg may be achieved using morphine sulfate and intravenous β-blockers. However, with the debate on cocaine and the usage of β-blockers still not resolved, intravenous verapamil or diltiazem may also be used to decrease blood pressure. In addition, vasodilating drugs such as sodium nitroprusside or angiotensin-converting enzyme inhibitors, may also be administered to help achieve target systolic blood pressure.[39]

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746

Conclusion

Cocaine-induced chest pain is a common presentation in emergency departments across the United States. This is largely due to the hyperadrenergic state and prothrombotic properties of cocaine. Cocaine may induce life-threatening arrhythmias and increases the risk of endocarditis. In the acute setting, most patients presenting with cocaine-associated chest pain are admitted for at least 24-hour monitoring. Therapy is largely based on administration of supplemental oxygen, aspirin, nitrates, and benzodiazepines if patients are tachycardic, hypertensive, or anxious. The role of β-blockers in the setting of a cocaine-induced MI remains controversial. The management of cocaine-induced acute MI should follow the AHA scientific statement on the management of cocaine-associated chest pain and MI.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20746