

Cocaine-Associated Chest Pain

The differential diagnosis for cocaine-associated chest pain is broad and can involve symptoms commonly seen with other conditions. In this review, the author describes the complex pathophysiology of these disorders and the specific diagnostic and therapeutic approaches necessary to prevent serious consequences.

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Since the first reported case of cocaine-associated acute myocardial infarction (AMI) in 1982,¹ the incidence of cardiovascular disorders arising from cocaine use has steadily increased.¹ According to the Drug Abuse Warning Network, the number of cocaine-related emergency department (ED) visits reported in 2005 was higher than in 2004, reaching nearly 484,000.^{2,3} Not surprisingly, chest pain is the most common symptom.⁴ Cocaine accounts for 25% of AMIs in patients aged 18 to 45 years.⁵ The incidence of AMI among patients who present with cocaine-associated chest pain is as high as 6%, and AMI is 24 times more likely than not to occur within the first hour after the drug is used.⁶ Thus, the emergency medicine clinician must be vigilant when caring for patients who present with cocaine-associated chest pain.

PHARMACOLOGY

The pharmacology of cocaine plays a significant role in its clinical effects. Cocaine can be ingested, insufflated (snorted), inhaled, and intravenously injected.

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Cocaine possesses local anesthetic properties of the ester type and also has a direct effect on the myocardium, where it blocks fast sodium channels.

The onset of the drug's effects is dependent upon the route of administration. With intravenous injection and inhalation, the effects are almost immediate, whereas with insufflation, they peak within 30 minutes. When smoked, crack cocaine gives an almost instantaneous high, an effect that contributes to the drug's potency and increases the likelihood of addiction. Cocaine possesses local

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anesthetic properties of the ester type and also has a direct effect on the myocardium, where it blocks fast sodium channels. The systemic effects of cocaine are produced from the inhibition of monoamine reuptake pumps (both peripherally and centrally) in the presynaptic membrane for norepinephrine, epinephrine, dopamine, and serotonin. This inhibition, in turn, produces increased extracellular and plasma concentrations of these neurotransmitters, leading to the typical sympathomimetic toxidrome seen with cocaine. The drug's metabolism and elimination occur by several mechanisms. Between 30% and 50% of the drug is quickly hydrolyzed by liver and plasma cholinesterases. Nonenzymatic hydrolysis accounts for another 40% of its breakdown. Several of cocaine's metabolites are thought to be biologically active, including benzoylecgonine, which is typically found in the urine for 48 to 72 hours after the drug is used and is the compound detected by most urine drug screens.⁷ The combination of alcohol and cocaine produces cocaethylene, which has a half-life exceeding 2 hours and prolongs the euphoric experience associated with cocaine. It is also a potent sodium channel blocker and directly depresses the myocardium.^{8,9}

PATHOPHYSIOLOGY

The pathophysiology of cocaine-associated myocardial ischemia may be best explained in terms of the drug's actions on the heart over time. Its immediate effects take two forms. First, the tachycardia and hypertension that accompany this sympathomimetic toxidrome lead to increased myocardial oxygen demand, which is primarily centrally mediated.¹⁰ Second, cocaine causes coronary vasoconstriction of both healthy and diseased epicardial coronary arteries.^{10,11} This effect seems to be greatest at sites involving atherosclerotic lesions, which, when com-

bined with the increased oxygen demand mediated by cocaine, can produce myocardial ischemia.¹²

The intermediate result of cocaine's effect on the myocardium is due to enhanced thrombus formation. The drug's direct effects on platelets lead to aggregation.¹³⁻¹⁵ Although thrombus formation is more common with underlying coronary artery disease, it can occur in healthy coronary arteries.¹¹

The long-term consequences of cocaine use on the heart include accelerated atherogenesis, left ventricular hypertrophy, and dilated cardiomyopathy.^{10,11,16} Prolonged cocaine use increases the risk of premature and more severe coronary atherosclerosis.¹⁷ Angiographic studies show that as many as 40% of long-time users of cocaine have significant coronary artery disease, defined as stenosis involving greater than 70% occlusion, often in the absence of other established risk factors for ischemic heart disease.¹⁸ In addition, this disease is generally more severe than that observed among age-matched control subjects. Left ventricular hypertrophy that occurs with prolonged cocaine use is similar to that seen in other hyperdynamic states such as thyrotoxicosis and aortic stenosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of chest pain associated with cocaine is broad (Table 1). Although the immediate evaluation for myocardial ischemia and infarction is mandatory, it is important for the clinician not to establish a specific diagnosis too quickly. In cases of cocaine use, many other causes of chest pain can be seen, such as pneumothorax and pneumomediastinum. Cocaine has been noted to be a cause for aortic dissection.¹⁹ Pneumonia, pericarditis, endocarditis, myocarditis, and pulmonary embolism have all been associated with cocaine use. If not considered and promptly recognized, all of these disorders can have serious consequences.

EVALUATION

Patients with cocaine-associated chest pain must undergo an evaluation that focuses not only on the toxidrome that may accompany cocaine use but also on specific end-organ disorders. As mentioned previously, chest pain is the most frequent symptom among this population. Unfortunately, such patients may not always be forthcoming about their recent drug use or may present hours after symptoms begin. In one prevalence study, 28% of cocaine users

TABLE 1. Differential Diagnosis of Cocaine-Associated Chest Pain

Acute coronary syndrome	Pericarditis
Pneumothorax	Myocarditis
Pneumomediastinum	Pneumonia
Pneumopericardium	Endocarditis
Aortic dissection	"Crack lung"
Pulmonary embolism	Musculoskeletal pain

initially denied using the drug.²⁰ In addition, the method and amount of cocaine use are not predictive of the development of myocardial ischemia, nor are the location, duration, and severity of the associated symptoms. Almost all cocaine-associated MIs occur within 24 hours after the drug is used.^{6,21}

The ECG is the most important initial test, as the results likely determine the appropriate therapy. Unfortunately, as many as 35% of patients presenting with cocaine-associated chest pain may demonstrate signs consistent with benign early repolarization.²² This, along with ECG evidence of left ventricular hypertrophy in some patients, can make interpretation of ischemia challenging, especially when J-point and ST-segment elevation are considered. Research has shown that the sensitivity of the ECG for AMI is lower in cocaine users than in other patient populations.²¹

Clinicians also rely upon the use of cardiac markers in determining the appropriate treatment for patients with cocaine-associated chest pain. Such assessments can be complicated by false elevations of creatine kinase and creatine kinase MB, which are presumably caused by agitation and rhabdomyolysis.²³ Troponins I and T do not exhibit cross-reactivity with human skeletal muscle troponins and are therefore as sensitive but more specific than the creatine kinase and creatine kinase MB measurements.^{24,25}

Another important diagnostic test is chest radiography, which is useful for determining any noncar-

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TABLE 2. Treatment for Cocaine-Associated Acute Coronary Syndromes

Oxygen	Recommended
Aspirin	Recommended
Benzodiazepines	Recommended
Nitroglycerin	Recommended
Heparin	Recommended
Beta-blockers	Contraindicated
Calcium channel blockers	Consider if benzodiazepines and nitroglycerin are ineffective
Phentolamine	Consider if hypertension persists
Percutaneous coronary intervention	Preferred over fibrinolytic therapy in the treatment of STEMI

STEMI = ST-segment elevation myocardial infarction

diac causes of chest pain. Because significant cocaine intoxication can lead to hyperglycemia and hypokalemia, and severe intoxication can also induce acid-base disorders, routine blood tests can be a valuable complement to the cardiac marker assessment. The urine drug screens can detect the metabolite benzoyl-ecgonine for a period of 48 to 72 hours after a single use (longer in chronic users), but the impact of this finding on the initial treatment is minimal.²⁶

TREATMENT

Traditional emergency medicine protocol emphasizes assessment and stabilization as the paramount first steps of treatment. For patients presenting with cocaine-associated chest pain, the first priority is to stabilize the airway, breathing, and circulation. Afterwards, a more focused assessment and treatment can begin. The recommended treatment strategies for cocaine-associated myocardial ischemia are not strongly evidence supported. As noted in the 2008 American Heart Association (AHA) guidelines, few well-designed randomized trials have addressed the treatment of cocaine-associated chest pain.²⁷ Most studies are based on animal experiments, observa-

tional series, case series and reports, and very small clinical trials. In general, patients who present with cocaine-associated chest pain and suspected myocardial ischemia and injury should undergo the same treatment as those with traditional acute coronary syndrome (ACS); as exceptions, beta-adrenergic blockade must be avoided and calcium channel blockers may be considered as an option (Table 2).

Decades of clinical experience with intravenous benzodiazepines demonstrate that these drugs are effective in attenuating the rise in heart rate and blood pressure associated with cocaine use and lead to a decrease in myocardial oxygen demand.^{10,28}

Aspirin and heparin are important treatments. The pathophysiology of thrombus formation secondary to platelet aggregation suggests that the role of both of these agents makes theoretical sense, although little evidence supports this approach.²⁷ Nevertheless, the benefits of these agents likely outweigh their risks. Nitrates are a mainstay in the treatment of ACS and may also have a role in the treatment of cocaine-associated chest pain, as some studies have demonstrated that these agents can relieve cocaine-induced vasoconstriction.²⁹⁻³¹ Again, their risk-benefit ratio is favorable.

Beta-adrenergic blockade is the standard treatment for patients with AMI. The traditional approach is to avoid beta-blockers in the treatment of cocaine-induced AMI. The concern is that with the blockade of the beta-adrenergic effects of cocaine, unopposed alpha-adrenergic effects with coronary vasoconstriction and increased blood pressure develop. Labetalol can be an alternative, since it possesses both alpha- and beta-blocking properties, but its beta-blockade effects are significant. In a recent retrospective cohort study involving 363 patients admitted for cocaine use, the rates of AMI and death were lower among those who underwent beta-blocker therapy,³² a finding that contrasts directly with the results of previous studies warning against the administration of beta-blockers to patients with cocaine-associated AMI. This study was limited, however, by significant patient selection bias, and it included patients who had and were undergoing treatment for other diseases besides AMI. In addition, the study did not address each patient's actual time of cocaine use. Therefore, in view of this study's shortcomings, these results must be considered preliminary at best and the use of beta-blocker therapy for cocaine-associated myocardial ischemia should continue to be contraindicated. *continued on page 26*

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Two other medications warrant a brief mention. Calcium channel blockers such as verapamil have been shown in laboratory experiments to reverse cocaine-induced coronary artery vasoconstriction.^{33,34} Phentolamine improves coronary artery diameter in cocaine-induced vasoconstriction and has been shown to decrease blood pressure.^{10,28,35} The 2008 AHA guidelines consider these second-line agents.²⁷

Timely percutaneous coronary intervention (PCI) by experienced operators in high-volume centers is preferred over fibrinolysis in ST-segment elevation MI (STEMI) and is even more desirable for treating disorders associated with cocaine use.²⁴ Many young patients demonstrate ECG evidence of benign early repolarization, but only a small percentage of those presenting with cocaine-associated chest pain and J-point elevation are actually experiencing an AMI.^{22,36,37} Case reports document adverse outcomes, including a higher occurrence of intracranial hemorrhage, after fibrinolytic therapy is administered to patients using cocaine.³⁸ Therefore, the AHA recommends fibrinolytic therapy be reserved for patients who are clearly suffering STEMI and cannot undergo immediate PCI.²⁷

Arrhythmia is very common in patients suffering from the acute toxic effects of cocaine use. Most atrial arrhythmias will respond to benzodiazepines and resolve over time. The treatment of ventricular arrhythmias depends on the interval between cocaine use and the onset of arrhythmia. Ventricular arrhythmias occurring immediately after the drug is used

are thought to be secondary to the sodium channel blockade effects of cocaine on the myocardium. The administration of sodium bicarbonate is thus warranted.^{27,39} For those ventricular arrhythmias that occur several hours later,

myocardial ischemia is the more likely culprit. The standard therapeutic approach includes addressing any metabolic derangements and administering antiarrhythmics such as lidocaine.⁴⁰ The efficacy of amiodarone in this setting has not been studied. Torsades de pointes has rarely been observed with cocaine use.⁴¹ If it is present, magnesium is the initial treatment choice.

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DISPOSITION

The disposition for many of these patients will be straightforward. Those with ACS will require admission. As previously mentioned, patients suffering STEMI should undergo immediate PCI. Others should be admitted for ongoing evaluation and treatment. Those experiencing other cardiac complications such as congestive heart failure and significant arrhythmias will also require admission. Noncardiac complications of cocaine, including seizures, stroke, and rhabdomyolysis, will necessitate inpatient management. Most patients with cocaine-associated chest pain, however, will have nondiagnostic test results and an unremarkable ECG, an absence of cardiac markers, and a resolution of symptoms. Research demonstrates that almost all cardiac complications related to cocaine use will be apparent within the first 12 hours of presentation.⁴² A period of observation and serial testing is therefore warranted for such patients at low risk. Several studies support this approach and recommend an observation period of 9 to 12 hours. If serial testing (ECG and cardiac markers) continues to yield negative results, these patients can be discharged and return for outpatient follow-up.⁴³ It should be noted that longitudinal studies have demonstrated that the greatest risk factor for the development of myocardial ischemia in this group of patients is continued cocaine use.⁴⁴ In addition, among patients who have cocaine-associated chest pain and low to moderate cardiac risk and undergo complete evaluation in a chest pain observation unit, the rate of AMI in the ensuing 12 months is less than 1%.⁴⁵ Thus, discharge planning should include drug abuse counseling and aggressive modification of the traditional risk factors.

SUMMARY

The differential diagnosis for cocaine-associated chest pain is broad, and the pathophysiology of cocaine-induced myocardial ischemia is complex. Except for the early administration of benzodiazepines and the avoidance of beta-blocker therapy, the initial treatment of cocaine-associated myocardial ischemia should follow the standard ACS guidelines. Percutaneous coronary intervention is recommended for STEMI. Patients at low risk can be discharged from the ED if the results of observation and serial testing are unremarkable. The long-term prognosis is good for those who abstain from continued cocaine use. □

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