The cardiovascular complications of cocaine first emerged as a clinical concern in the early to mid-1980s, a period of skyrocketing nontherapeutic cocaine use. The epidemic was fueled by the increased supply (and the reduced cost) of pure product from South America and by the ease of administration; cocaine became widely available in forms that could be sniffed, smoked, or injected. Lingering misconceptions of cocaine as a safe recreational drug undoubtedly added to the problem. For instance, although the Controlled Substance Act of 1970 banned cocaine possession except for medical use, the Strategy Council on Drug Abuse in 1973 was still reporting “little morbidity and no confirmed deaths” attributable to cocaine overdose.

However, the first documented cases of cocaine-related myocardial infarction (MI) were reported during this same period, including several cocaine-related celebrity deaths. Like many US hospitals, the University of Texas (UT) Southwestern Medical Center also reported a “spike” in cocaine-related emergency department (ED) visits around this time. For example, in 1987 one of the first patients who presented with a cocaine-related MI at UT Southwestern Medical Center was a 38-year-old man who developed severe retrosternal chest pain within 15 minutes of injecting cocaine. Both the left anterior descending artery and the right coronary artery were completely occluded and, despite thrombolytic therapy, he went into ventricular tachycardia, then cardiogenic shock, and died.

In the 20 years that followed, clinicians and the general public have learned more about the dangers of cocaine. Researchers have explained many of the cardiovascular effects of cocaine—not only those conditions that were reported during this same period, including several cocaine-related celebrity deaths. Like many US hospitals, the University of Texas (UT) Southwestern Medical Center also reported a “spike” in cocaine-related emergency department (ED) visits around this time. For example, in 1987 one of the first patients who presented with a cocaine-related MI at UT Southwestern Medical Center was a 38-year-old man who developed severe retrosternal chest pain within 15 minutes of injecting cocaine. Both the left anterior descending artery and the right coronary artery were completely occluded and, despite thrombolytic therapy, he went into ventricular tachycardia, then cardiogenic shock, and died.

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tions related to myocardial ischemia (ie, angina, infarction, sudden death) but also to aortic dissection, arrhythmias, pulmonary edema, myocarditis, and endocarditis. Staff in the ED are more adept at managing patients with cocaine-related chest pain. However, the number of new users of cocaine in the United States has nearly doubled since 1992.

**Epidemiology**

Government studies and private groups have provided a broader perspective on drug abuse in the United States. The National Household Survey on Drug Abuse in 2001 estimated that the number of new users of cocaine peaked in 1983 at 1.5 million; in 1992, the number of new users was 0.5 million; and in 2000, 0.9 million. In 1998, approximately 1.7 million Americans used cocaine regularly (at least monthly). Data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 2000, showed that 5.3% (532/10 085) of 18- to 45-year olds surveyed reported regular cocaine use. Because of fears of disclosure, it is likely that such surveys underestimate the real prevalence of cocaine abuse.

The National Institute of Drug Abuse found in 2002 that in US public and private schools, 2.3% of 8th graders and 5% of 12th graders had reported cocaine abuse. Such surveys underestimate the real prevalence of cocaine abuse. Between cocaine use and myocardial ischemia is essential for the early recognition and proper management of this common condition.

**Pharmacology and Mechanisms of Action**

Cocaine is derived from the leaf of the Erythroxylon coca bush, which is harvested mainly in the Andes Mountains of Peru and Colombia. When extracted from an acid solution (commonly, hydrochloric acid), the cocaine becomes water soluble; when the solution is heated until all of the water has evaporated, the result is crystalline cocaine hydrochloride. This powder form will decompose if heated but is well absorbed through all mucous membranes; therefore, it can be ingested intranasally, orally, or intravenously. Cocaine can also be extracted from an alkaloid solution (ammonia or sodium bicarbonate), a process that results in a "free base" form of heat-stable cocaine that can be smoked. This "crack" cocaine (named for the popping sound made when heated) has become more available in the past 10 years.

As shown in Table 1, the pharmacokinetics and the resulting "high" will vary with the route of administration. Smoking cocaine produces a notoriously rapid and intense euphoria, but cocaine ingested in this manner has a short duration of action — a profile that is associated with extreme potency and addictiveness. However, smoking cocaine has not been associated with an increased risk of cardiovascular complications.

Intranasal administration, on the other hand, leads to a slower onset of action, the effects of which can linger for as long as 1 or 2 hours.

The serum half-life of cocaine is only 45 to 90 minutes. Although cocaine is rapidly removed from the bloodstream, the major metabolites remain detectable in the blood and urine for 3 to 4 days (provided care is taken to inhibit the serum cholinesterases in the specimen). Cocaine is metabolized by plasma and liver cholinesterases and excreted in the urine. As described in detail later, these
metabolites may remain active in the cardiovascular system and produce late symptoms: MI can occur up to 15 hours after ingestion. Myocardial ischemia has been reported days after ingestion. Individuals with low plasma cholinesterase levels, a genetically inherited condition, are also prone to all cocaine-associated complications, as the serum concentrations of cocaine are elevated in such patients.17

LOCAL ACTION
The local and systemic mechanisms of action of cocaine can be considered separately. The well-known topical anesthetic effect, which is still exploited therapeutically by ear, nose, and throat (ENT) surgeons, is due to the drug's interference with sodium channel permeability. This action blocks the initiation and conduction of electrical signals, essentially stabilizing the axonal membrane and causing anesthesia. Although these sodium channel-blocking properties may contribute to certain cardiovascular problems—dyssrhythmias or perhaps even a direct negative inotropic effect18,19—most of the sought-after effects of cocaine (eg, mental stimulation, decreased fatigue), as well as most of the negative cardiovascular effects, are attributable to the systemic properties of the drug.

SYSTEMIC ACTION
Cocaine binds to the amine reuptake pump in presynaptic neurons and prevents the reuptake of biogenic amines including epinephrine, norepinephrine, and (to a lesser extent) dopamine and serotonin. This produces an excess of neurotransmitters at all postsynaptic neurons. While the excess activity of dopamine and serotonin produces many of the characteristic central nervous system effects of cocaine (eg, euphoria, mood changes, addiction), it is the excess activity of catecholamines at peripheral sites that stimulates the alpha- and beta-adrenergic receptors and produces most of the cardiovascular effects. How this powerful sympathomimetic activity contributes to myocardial ischemia—and how the physician can most effectively manage the episode—will be reviewed later.

Cocaine-Induced Myocardial Infarction
When a patient presents with chest pain following cocaine use, the physician typically attempts to discover whether the patient is having or has had an MI. One researcher tried to establish the likelihood of MI associated with cocaine use by evaluating 246 patients who presented to a municipal hospital ED with chest pain (71% substernal, 47% pressure-like) following cocaine use.20 He found that 14 patients (6%) had had an MI as indicated by elevated creatinine kinase MB (CK-MB) isoenzyme levels. In this prospective study, there was no clinical difference between patients who had experienced an MI and those who did not. This same researcher found that 60 of 359 patients (17%) presenting with chest pain at area EDs had detectable levels of cocaine or cocaine metabolites in their urine.21

Incidence of Cocaine-Related MI
The cocaine-MI question has also been addressed by surveying a population of 18- to 45-year-old patients with a self-reported history of nonfatal MI (n=46), asking how many had used cocaine. In this analysis of the NHANES III data, 1 in every 4 nonfatal MIs (25%) was attributable to frequent cocaine use. Regular users had a significantly higher likelihood of nonfatal MI (but not stroke) than nonusers (odds ratio 6.9; 95% confidence interval of 1.3 to 58).5 Other estimates of the incidence of MI among patients admitted with cocaine-associated chest pain have ranged from 0%22 to 31%23 in retrospective series. The wide variations in the estimates of the incidence of cocaine-related MI can be attributed in part to the fact that even in the absence of MI, cocaine users may have abnormal electrocardiograms and/or serum CK concentrations.15 Still, patients presenting with chest pain after cocaine use are clearly at increased risk of angina and MI. Therefore, heightened awareness of the risk factors and possible complications is warranted.

PATIENT CHARACTERISTICS AND RISK FACTORS
Patient series from the past several decades provide clues about the clinical characteristics of the "typical" patient with cocaine-related MI (Table 2).20,24-26 Overall, about 80% to 90% of these patients are male, most are in their mid-30s, and approximately 20% are under 25 years of age. Other than cigarette smoking, many of these patients have no other risk factors for atherosclerosis. Approximately

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation (smoking)</td>
<td>3-5 sec</td>
<td>1-3 min</td>
<td>5-15 min</td>
</tr>
<tr>
<td>Intravenous</td>
<td>10-60 sec</td>
<td>3-5 min</td>
<td>20-60 min</td>
</tr>
<tr>
<td>Intranasal</td>
<td>1-5 min</td>
<td>15-20 min</td>
<td>60-90 min</td>
</tr>
</tbody>
</table>

75% of patients who present with chest pain after using cocaine have taken the drug by the intranasal route, the most common route of administration among cocaine users. The symptoms of chest pain typically appear within minutes of cocaine use but some individuals report onset as late as 5 to 15 hours after ingestion. Small or large amounts of cocaine can induce the ischemic event; in fact, the serum levels found in these patients vary by 100-fold, from approximately 0.01 mg/L to 1 mg/L. The frequency of cocaine use does not seem to influence risk, as MIs have been reported in chronic, recreational (ie, once or twice per year), and first-time users. Recent studies suggest that using cocaine together with cigarettes or alcohol significantly increases the risk of myocardial ischemia, the former by increasing vasoconstriction and the latter by increasing the number of toxic cocaine metabolites.

Cardiovascular Complications
Approximately one third of patients who are diagnosed with an MI following cocaine use will develop 1 or more cardiovascular complication. A recent retrospective study of 136 episodes of cocaine-induced MI identified at least 1 discrete complication in 49 patients (36%). The main complications seen were bradydysrhythmias (26 cases), nonsustained or sustained ventricular tachycardia (18 and 5 cases, respectively), congestive heart failure (9 cases), and supraventricular tachycardia (6 cases). In an earlier study, the authors state that the relatively low incidence of MI complications may have been due to the young age of the patients (mean age, 38 years). Forty-four of the 49 patients (90%) experienced symptoms of their first complication on arrival or within 12 hours of presentation. The tendency for complications to develop early has practical significance for the primary care physician, who can use this knowledge to keep these patients in a short-stay observation unit for 12 hours to guide the admission decision.

Potential Mechanisms of Cocaine-Induced Myocardial Ischemia
One intriguing finding from studies of patients with cocaine-related MI is that approximately one half have no evidence of atherosclerotic coronary artery disease on angiography. Based partly on this surprising lack of classic underlying atherosclerosis, the pathogenesis of cocaine-related ischemia and MI is now thought to be multifactorial. Studies indicate that the following mechanisms are likely to be involved: (1) increased oxygen demand with or without severe coronary artery disease, (2) decreased oxygen supply due to coronary artery vasospasm, or (3) decreased oxygen supply due to enhanced platelet aggregation and coronary thrombosis (Figure). The factors contributing to the first of these mechanisms—increased oxygen demand—seem clear: adrenergic activation that boosts heart rate, systemic arterial pressure, and left ventricular contractility.

At UT, investigators have studied the supply-side mechanisms that may work together with this cocaine-induced increased oxygen demand to increase the risk of ischemia and the number of ED visits. In the catheterization laboratory, investigators measured coronary sinus blood flow and coronary arterial dimensions before and after cocaine administration in 45 patients who were undergoing routine catheterization to evaluate chest pain. After administering small amounts of intranasal cocaine (2 mg/kg—even less than the usual dose given as topical anesthesia for routine ENT procedures) they observed that heart rate and arterial pressure rose, coronary sinus blood flow dropped by 17%, and the diameter of the left coronary artery decreased by 8% to 12% (P < .01). They subsequently showed that the vasoconstricting effect of the drug on arterial segments with underlying coronary disease was particularly pronounced (a 29% decrease). Although these changes in coronary blood flow and vessel diameter were small, so was the amount of cocaine administered. Individuals presenting at the ED with cocaine-related problems often have serum levels of cocaine 100 times higher than those found in the volunteers in this trial. Finally, they found that cocaine-induced vasoconstriction could be reversed with phentolamine (an alpha-adrenergic blocker), and concluded that the inappropriate coronary vasoconstriction in the face of increased cardiac output was at least partly due to stimulation of alpha-adrenergic receptors.
In contrast, in a follow-up study the same investigators showed that beta-adrenergic blockers actually worsened the cocaine-induced vasoconstriction.\textsuperscript{34} This may seem counterintuitive to clinicians who routinely give intravenous beta-blockers to patients who have experienced an MI. However, since these agents seem to potentiate cocaine-induced vascular reactivity, propranolol and agents with similar mechanisms of action may actually increase the magnitude of the ischemia and should generally be avoided in patients with cocaine intoxication.\textsuperscript{24,35} Even labetolol, which has both beta- and alpha-adrenergic blocking actions, does not reverse cocaine-induced vasodilation.\textsuperscript{36}

Beyond the direct alpha-adrenergic effects of cocaine on the coronary vasculature, recent studies indicate that cocaine may also promote vasoconstriction via its actions on the endothelial cells specifically, by increasing endothelin production and decreasing nitric oxide output. In addition, as recently reported, cocaine may also directly damage the endothelial cell barrier and thereby provide a flashpoint for atherosclerotic formation and progression;\textsuperscript{15} studies linking cocaine use to increased platelet activation and aggregability and increased plasminogen-activator inhibitor indicate that thrombus formation at such plaques may contribute to the ischemic effects of the drug.\textsuperscript{37} A recent study also found that frequent users of cocaine (6 to 20 times per week) had significantly higher levels of an inflammation marker (C-reactive protein) and blood clotting components (von Willebrand factor and fibrinogen) than less frequent users (2 to 6 times per month).\textsuperscript{38}

Two other studies may also be relevant for clinicians. The first was based on the clinical observation that a subset of subjects experienced cocaine-associated ischemia or MI several hours after drug use. To investigate this late reaction, the investigators monitored both the diameter of the coronary artery and the blood concentrations of cocaine and its metabolites at 30, 60, and 90 minutes after intranasal administration of 2 mg/kg cocaine.\textsuperscript{39} As expected, they observed vasoconstriction at blood levels of cocaine increased at 30 minutes, followed by a parallel decrease in these indicators at 60 minutes. At 90 minutes, however, all patients had recurrent coronary vasoconstriction, despite a continuing drop in cocaine blood levels. This rebound vasoconstriction was temporally related to a steadily increasing concentration of the major metabolites of cocaine (benzylecgonine and ethyl methyl ecgonine), suggesting that the vasoactive metabolites are capable of causing chest pain more than an hour after cocaine ingestion.

The second study was prompted by the investigators’ observation that about 9 of every 10 patients with cocaine-induced MI had smoked cigarettes around the time of their cocaine ingestion. Knowing that cigarettes adversely affect myocardial oxygen supply and demand,\textsuperscript{40,41} the investigators designed an experiment enabling them to measure how the cardiovascular effects of cocaine may be exacerbated by concomitant cigarette smoking. They monitored heart rate, blood pressure, and coronary diameter in patients before and after intranasal administration of 2 mg/kg cocaine, with or without an immediate “post-snort” cigarette.\textsuperscript{42} Control groups of patients receiving cocaine or a cigarette alone were also monitored. The mean rate-pressure product (the product of heart rate and systolic arterial pressure that provides a good indication of myocardial oxygen demand) increased by 6%±2% after cocaine use alone, by 12%±4% after smoking 1 cigarette alone, and by 45%±5% after combined cocaine use and smoking. The mean heart rate in volunteers who smoked a cigarette 20 minutes after cocaine use was 91±3 beats/min vs 68±3 beats/min at baseline. As measured by angiography, the diameters of diseased segments of coronary arteries decreased by 9%±2% after cocaine use, by 5%±5% after smoking, and by 19%±4% after combined cocaine use and smoking. Based on these results with relatively small amounts of cocaine, the investigators concluded that smoking immediately after cocaine use greatly increases oxy-
COCAINE

*Gen demand and limits coronary supply, thus increasing the risk of myocardial ischemia or infarction.*

**Management of Cocaine-Induced MI**

These pathophysiologic mechanisms have direct implications for managing the patient who has had a cocaine-induced MI. Identifying patients with cocaine toxicity can be difficult since delayed presentation and denial of drug use are common. The electrocardiograph (ECG) and CK-MB may be useful in defining the injury, but clinicians should be aware that these tests are often abnormal in cocaine-using patients without coronary occlusions. Thus, clinicians should maintain a high index of suspicion for cocaine use in all younger patients with chest pain.

Overall, however, the differential diagnosis of the chest pain should include all the usual mechanical, traumatic, and infectious causes; and the initial evaluation should, as in other cases of possible stimulant intoxication, focus on the fundamentals—airway, breathing, circulation (ABCs). One critical exception in cases involving cocaine is the use of propranolol to reduce heart rate and blood pressure. As described earlier, beta-blockers can actually exacerbate cocaine-induced vasoconstriction in the coronary arteries and are absolutely contraindicated in these patients.

Beyond the routine use of oxygen, aspirin, and cardiac monitoring, an important first-line agent of choice in the patient with cocaine-related MI is nitroglycerine, which can reverse the drug-induced hypertension and vasoconstriction (Table 3). Benzodiazepines such as diazepam or lorazepam are first-line sedatives of choice to treat agitation and to reduce the heart rate and blood pressure.

Verapamil has also been shown to reverse vasoconstriction in some studies and is therefore considered a second-line agent. As described earlier, phentolamine also counteracts cocaine-induced vasoconstriction and is now also listed as a second-line choice for these situations. The exact role of thrombolytic agents in patients who may have cocaine-related MI is less certain. Care is required for several reasons, including: the misleading nature of ECGs (the usual guide for thrombolytic therapy) in these patients; the possibility that the MI is secondary to vasoconstriction instead of thrombus; and the possibility of thrombolytic complications. At present, therefore, the American Heart Association does not recommend thrombolysis or angioplasty unless there is angiographic evidence of occlusion and other agents have failed.

There are several reasons to caution against the routine use of thrombolytic therapy in patients who are suspected to have cocaine-related MI: (1) limited experience with thrombolytic therapy in patients with cocaine-related MI, (2) reports of catastrophic complications associated with thrombolytic therapy in cocaine users, and (3) difficulty involved in using standard electrocardiographic criteria to identify MI. Cardiac catheterization and primary angioplasty are the treatments of choice. Thrombolytic therapy should be considered only after treatment with oxygen, aspirin, nitrates, and benzodiazepines has failed, and when immediate coronary angiography and angioplasty are not available.

**Summary**

Even small doses of cocaine can induce coronary vasoconstriction and MI. This “inappropriate” vasoconstriction is mediated by alpha-adrenergic stimulation, alleviated by alpha-adrenergic blockade, and potentiated by beta-adrenergic blockade with propranolol. Due to an increase in serum metabolites, the vasoconstriction may be recurrent after cocaine use and may be exacerbated by concomitant cigarette smoking. Nitroglycerine and verapamil can be employed to counteract the coronary vasoconstriction, and the related ischemia or infarction, associated with cocaine use. In addition to the potential of cocaine to elicit myocardial ischemia and infarctions, cocaine can also induce dysrhythmias, bacterial endocarditis (with intravenous use), aortic dissection, and myocardial dysfunction. In any young patient presenting with chest pain, cocaine should be considered a potential causative factor. Clinicians should ask these patients about recent cocaine use and be ready to treat them appropriately.

<table>
<thead>
<tr>
<th>Table 3. Recommended Treatment for Cocaine-Related Myocardial Ischemia or Infarction</th>
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<tbody>
<tr>
<td><strong>First-line Agents</strong></td>
</tr>
<tr>
<td>- Oxygen</td>
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<tr>
<td>- Aspirin</td>
</tr>
<tr>
<td>- Nitroglycerine</td>
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<tr>
<td>- Benzodiazepines</td>
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<tr>
<td><strong>Second-line Agents</strong></td>
</tr>
<tr>
<td>- Verapamil</td>
</tr>
<tr>
<td>- Phentolamine</td>
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<tr>
<td>- Thrombolytic agents or primary angioplasty</td>
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<tr>
<td>(after demonstration by arteriography of an occluded coronary artery)</td>
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<tr>
<td><strong>Agent to be avoided</strong></td>
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<tr>
<td>- Propranolol</td>
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Data from American Heart Association, Lange RA, Hills LD.
REFERENCES


