

Cocaine-Induced Chest Pain

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It is estimated that as many as 25 million people in the United States have used cocaine at least once, 3.7 million people have used in the past year, and 1.5 million could be classified as abusers of cocaine [1]. According to the National Institute on Drug Abuse in 2002, the lifetime prevalence rate of cocaine use is 2.7% [2]. Cocaine is implicated as the cause of nontraumatic chest pain in 14% to 25% of patients in urban centers and 7% of those in suburban areas [3]. Chest pain is the most common complaint associated with cocaine use. As many as 25% of acute myocardial infarctions (AMI) in patients 18 to 45 years of age may be attributed to cocaine use [4]. Many of these patients (60%) will continue to use cocaine, and some 75% of these patients will develop recurrent chest pain [5].

History

The use of the erythroxyton coca plant, from which cocaine is derived, dates back to early recorded history. Archaeological evidence suggests that chewing of coca leaves was practiced among South American people 5000 years ago [6]. Incans purportedly used cocaine to relieve thirst and hunger and also used it as a local anesthetic during ritual skull trephination [6].

Cocaine, the alkaloid extract of coca leaves, was first described by Albert Niemann in 1859 [6]. An ophthalmologist, Koller, reported the use of cocaine in surgery in 1884, and cocaine's combined vasoconstrictive and local anesthetic properties made it a welcome adjunct for invasive procedures [6]. Halsted used cocaine as a nerve block agent and became addicted secondary to self-experimentation [6]. Freud advocated cocaine use to treat depression,

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cachexia, and asthma and to overcome morphine addiction [6]. In response to reports of addiction, the Harrison Narcotic Act of 1914 banned cocaine importation except for medicinal use [6]. The Controlled Substance Act of 1970 prohibited manufacture, distribution, and possession of cocaine except for restricted medical purposes [6]. Despite legislative and drug enforcement efforts, cocaine use remains prevalent. Of the more than 600,000 drug-related emergency department (ED) presentations in 2000, cocaine was second only to alcohol in prevalence and was associated with 29% of these patient visits [7].

Pathogenesis

The pathophysiology of cocaine-induced cardiac chest pain is multifactorial and may be best understood in terms of the timeframe of cocaine's effects. One of the most concerning manifestations of cocaine-induced chest pain is AMI. The typical patient who has cocaine-induced chest pain is a young man with minimal or absent coronary artery disease risk factors. AMI is equally likely regardless of the dose, route, or frequency of cocaine use [8]. Often chest pain develops minutes after cocaine use, but AMI has been reported up to 15 hours afterward [8]. A systematic literature review stated that the onset of cocaine-induced ischemia ranged from 1 minute to 4 days after use [5].

Coronary artery tone is mediated by both local metabolic and neural factors. Among the chemical mediators of coronary artery caliber are adenosine, vasopressin, angiotensin II, and endothelial-derived relaxing factor [9]. Neural control is mediated by the balance between the sympathetic nervous system and the parasympathetic nervous system. Even within the sympathetic nervous system, norepinephrine causes vasoconstriction by means of alpha-1 receptors and vasodilatation with its effects on beta-2 receptors. The parasympathetic system causes only vasodilatation, mediated by M3 cholinergic receptors. Myocardial oxygen delivery is largely mediated by the aforementioned mechanisms that alter coronary artery diameter and thus affect coronary blood flow [9].

Vasoconstriction

Animal investigations have demonstrated vasodilatation within the first 1 to 2 minutes of cocaine administration [9]. This vasodilatation was quickly followed by vasoconstriction some 5 minutes later. It has been hypothesized that this early vasodilatory effect may be the result of local sodium channel blockade mediated by cocaine. Several animal models have quantified the magnitude of cocaine-induced vasoconstriction. With a cocaine dose of 2 mg/kg (a commonly used dose for otorhinolaryngologic procedures), a decrease in coronary artery diameter of as much as 19% has been observed in anesthetized healthy dogs [10]. It was also demonstrated

that pretreatment with phentolamine prevented the cocaine-induced vasoconstriction and that propranolol administration increased vasoconstriction, presumably because of the blockade of vasodilatory effects from beta-2 receptors. Higher doses of cocaine, similar to those used recreationally by humans (3 to 9 mg/kg), resulted in decreased coronary diameters of 33% to 46% in a study by Hayes and colleagues [11]. Investigators in two studies with denuded and atherosclerotic coronary endothelial models observed further decreases in the diameters of diseased arteries versus those of healthy arteries [12,13].

In humans, coronary vasoconstriction has been the most commonly observed response. A study by Lange and colleagues [14] demonstrated that phentolamine decreased the amount of vasoconstriction following intranasal (IN) cocaine administration. Using IN cocaine, Flores and colleagues [15] demonstrated that coronary arteries with 50% atherosclerotic stenosis were subject to greater cocaine-induced vasoconstriction than were nondiseased arteries (29% versus 13%). Cigarette smoking may cause a synergistic vasoconstriction with IN cocaine; investigators recorded a 19% decrease in coronary artery diameter among cigarette smokers who used cocaine versus 7% in those who used cocaine alone [16]. Vasoconstriction is not the sole mediator of cocaine-induced myocardial ischemia. A study by Majid and colleagues [17] evaluating typical recreational intravenous cocaine doses (8 mg, 16 mg, and 32 mg) did not result in appreciable coronary artery diameter change nor in ischemia on the basis of echocardiography. Using intracoronary (IC) cocaine, a similar study by Daniel and colleagues [18] showed that diseased coronary arteries did not constrict to a greater extent than native arteries. In a classic study, Lange and colleagues [19] examined the coronary arterial blood flow, coronary artery dimensions, and myocardial oxygen demand in 29 patients referred for cardiac catheterization to evaluate chest pain. Left coronary angiography and hemodynamic monitoring were performed at baseline and 15 minutes after IN cocaine (2 mg/kg) was administered. A significant rise in heart rate and blood pressure with a concomitant decrease in coronary sinus blood flow was noted after cocaine administration. Left coronary arterial diameters shrank 8% to 12%. None of the subjects developed chest pain or ECG changes reflective of ischemia. It is apparent that cocaine is a potent sympathetic agent, given the hemodynamic effects after a small dose as demonstrated in this study.

Multiple case reports of individuals who have sporadic ST-segment elevations and normal coronary arteries on catheterization suggest that vasoconstriction contributes to the development of myocardial infarctions [8]. It is important to note that the pathophysiology of cocaine-induced coronary vasospasm differs from that of Prinzmetal's angina. The ergonovine challenge test, which causes vasoconstriction in 90% of Prinzmetal's angina patients, does not do so in cocaine users [8]. This finding suggests that there are other mediators of cocaine-induced vasoconstriction.

Vasoconstriction may be a result of both alpha-adrenergic stimulation and a direct smooth muscle effect of cocaine. Evidence that cocaine-induced coronary vasoconstriction is alpha-mediated is derived from observations that vasospasm is reversed by phentolamine and exacerbated by non-selective beta-blockers, such as propranolol [14,19]. Other studies demonstrate that vasoconstriction is most severe at sites of atherosclerotic plaques and may be reversed with nitroglycerine [15,20]. Additional studies show that cocaine may directly constrict smooth muscle or act by a calcium-mediated mechanism [8]. Kuhn and colleagues [12] studied an endothelial denuded dog coronary artery model that showed that endothelial injury did not potentiate cocaine-induced vasospasm. Similar results were obtained in a model using human umbilical arteries, which lack sympathetic innervation [21]. It was therefore hypothesized that the sodium-channel blocking properties of cocaine decrease intracellular calcium by reducing the number of sodium ions available for sodium–calcium ion pump exchange [22].

Although most myocardial ischemia occurs within 1 hour of cocaine use, reports of delayed tachycardia and hypertension several hours after use suggest an additional effect of cocaine. A cardiac catheterization study of 10 patients consisted of left coronary angiography at baseline, followed by measurements at 30, 60, and 90 minutes after IN cocaine, 2 mg/kg dose [20]. As in prior experiments, a statistically significant decrease in left anterior descending and left circumflex coronary artery diameters was noted 30 minutes after cocaine administration. This decrease corresponded to the peak blood concentration of cocaine. At 60 minutes after cocaine administration, a return to baseline diameter in the left coronary arteries was observed. Recurrent vasoconstriction was noted in all subjects at 90 minutes, despite further decrease in cocaine blood concentration. This recrudescence of vasoconstriction accompanied a rise in the major active metabolites of cocaine: benzoylecgonine and ethyl methyl ecgonine. Such recurrent or “delayed” coronary vasospasm associated with cocaine use appears to be mediated by these two metabolites [23].

Left ventricular function

A study by Pitts and colleagues [24] suggests that, in addition to the sympathomimetic effects of cocaine, cardiac left ventricular function decreases from cocaine exposure. Twenty patients (aged 39 to 72 years, 14 male) who underwent cardiac catheterization for evaluation of chest pain were given either IC cocaine (n = 10) or saline control (n = 10). Left ventricular pressures and derivative (LV dP/dt), volumes, and ejection fraction were measured at baseline, then every 2 minutes during infusion of cocaine or control. Cocaine levels within the coronary sinus approached those of patients with fatal cocaine intoxications. In this study, cocaine did not significantly change heart rate, LV dP/dt, or LV end-diastolic volume. However, patients who received cocaine did manifest an increase in systolic

and mean arterial pressures (MAP), LV end-diastolic pressures, and LV end-systolic volume and a decrease in LV ejection fraction as measured during cardiac catheterization.

Hemodynamic responses to cocaine were further elucidated in a study by Baumann and colleagues [25]. In this study, ED patients who had a chief complaint of chest pain and a history of cocaine use within 24 hours before presentation were placed on a previously validated noninvasive transthoracic cardiac output monitor. Twenty-seven patients, 74% male with a median age of 37 years, were enrolled. Most patients used crack cocaine (67%), smoked tobacco (82%), and had prior cocaine-associated chest pain (67%), although only 33% had known prior myocardial infarction. Hemodynamic results included a mean MAP of 92 mm Hg, a mean heart rate of 83 per minute, cardiac output of 6.9 L/min, a cardiac index of 3.2 L/min/m², and a stroke volume of 78 mL/beat. The authors concluded that cocaine used in recreational (uncontrolled) doses does not result in myocardial depression, as described in some animal models.

Myocardial demand

Cocaine increases heart rate and systemic arterial pressure in a dose-dependent fashion [23]. The increased chronotropy and afterload thereby elevate the myocardial oxygen demand to meet the increased cardiac workload. Another mechanism by which cocaine increases myocardial oxygen demand is that of decreased contractility [26]. In vitro human myocardium exposure to cocaine resulted in negative inotropy, which was thought to be mediated by a decrease in myofilament response through cyclic AMP [27] or protein kinase C [28]. Methylecgonidine, an active metabolite of cocaine, has been shown to be a negative inotrope in both an animal model and in vitro human myocardium [29].

Thrombogenesis

Cocaine promotes platelet aggregation and affects endothelial cell function, which may potentiate endothelial damage and thrombosis at sites of cocaine-induced vasospasm [8]. In vitro studies have demonstrated that cocaine increases platelet activation (by means of enhanced platelet calcium membrane binding and increased calcium influx), enhances platelet aggregation, and augments thromboxane production [30,31]. Other procoagulant effects of cocaine, besides increased platelet activation and aggregation, include increased production of plasminogen-activator inhibitor [32]. Cocaine activates platelets by means of fibrinogen binding to the platelet's surface mediated by release of alpha-granule content in whole blood studies. In a study referenced by Mouhaffel and colleagues [8], patients who had cocaine-related arterial thromboses demonstrated decreased antithrombin III and combined protein C. This study suggests that cocaine may alter clotting factor function, as described by Mouhaffel and

colleagues [8]. Their assertion is supported by the normalization of these factors following cessation of cocaine use. Cocaine induces platelet activation through degranulation of alpha-granules and P-selectin expression as well as through increased epinephrine and blockade of serotonin uptake by platelets [33].

Chronic use: elevated catecholamines, atherogenesis, cardiomyopathy

Long-term cocaine use is associated with chronically elevated catecholamine levels, accelerated atherosclerosis, and myocardial remodeling. Chronic cocaine use may cause alterations in catecholamine levels and result in an increase in myocardial oxygen demand several weeks after cocaine cessation [34]. In a study by Nademanee and colleagues [35], ambulatory electrocardiographic monitoring among patients who were withdrawing from cocaine demonstrated spontaneous ischemic episodes. These were thought to be due to a relatively dopamine-deficient milieu that predisposes recovering cocaine users to coronary vasospasm.

Long-term users of cocaine exhibit accelerated atherosclerosis independent of other known risk factors. Among young adult users of cocaine, intimal hyperplasia and large atherosclerotic lesions have been noted in epicardial coronary arteries on autopsy after AMI [8]. In another postmortem study, increased aortic and right coronary atherosclerosis was noted among cocaine users [36]. Endothelial-cell barrier changes in response to cocaine enhance permeability to low-density lipoprotein, based on in vitro models [37]. Cocaine further accelerates atherosclerosis by expression of endothelial adhesion molecules and leukocyte migration [38]. Additional evidence supporting cocaine-induced atherogenesis is the electron-beam computed tomography study by Lai and colleagues [39]. This study used electron-beam and high-speed spiral CT technology to quantify calcium deposition as a surrogate marker of atherosclerosis. This methodology is commonly used to detect calcium deposits within subclinical atherosclerotic plaques. The authors examined data from an ongoing study of African American patients aged 25 to 45 years with a history of intravenous drug use. Multiple regression analysis to adjust for age and gender demonstrated that cocaine was independently associated with an increase in coronary calcium deposition.

Chronic cocaine use has been associated with left ventricular hypertrophy and systolic dysfunction. In addition, a dilated cardiomyopathy may ensue after long-term cocaine abuse [23]. One possible mechanism of myocardial damage induced by cocaine may be contraction band myonecrosis [34]. Elevated levels of catecholamines are associated with a hypercontracted sarcomere and myofibrillary disruption [40]. Karch and Billingham [40] hypothesized that contraction band necrosis may represent reperfusion injury. Contraction band necrosis has been found with greater prevalence among fatal cocaine-induced myocardial infarctions in some but not all

studies [34]. Aside from contraction band necrosis, cocaine-induced myocardial infarction may result in dilated cardiomyopathy from binge use or repeated exposure [41–43]. Adulterant agents taken with cocaine have been implicated in myocarditis [23]. Finally, animal studies have revealed that cocaine deranges cytokine production from endothelial cells and leukocytes, which induces transcription of myosin and collagen and thereby alters myocardial structure [44–46]. Myocyte apoptosis by such a mechanism has been linked to cocaine use.

Coexisting coronary artery disease

Although patients with normal coronary arteries may suffer myocardial infarction following cocaine use, cocaine-induced myocardial infarction is more likely to occur among patients with coronary artery disease. Kontos and colleagues [47] described a 50% prevalence of significant coronary artery disease among 90 patients with cocaine-associated chest pain who underwent coronary angiography. Of these patients who sustained myocardial infarctions, 77% had significant coronary artery disease. This finding is similar to data presented by Hollander and Hoffman [48], in which the percentage of cocaine users undergoing angiography with thrombotic occlusion or critical stenosis was 34 of 54 (55%) in one study and 42 of 63 (67%) in another multicenter study. Single-vessel disease was the most prevalent type of coronary atherosclerosis among patients described by Kontos and colleagues [47]. Immediate effects of cocaine that can induce cardiac ischemia include increased myocardial workload, coronary artery vasoconstriction, and potentiation of coronary thrombosis (Table 1). It has been estimated that, among otherwise healthy patients, myocardial infarction risk increases 24 times for cocaine users versus nonusers [49].

Cocaethylene

Consumption of ethanol along with cocaine is common [50] and results in the formation of a toxic compound, cocaethylene, by hepatic transesterification [23]. Cocaethylene, like cocaine, prevents reuptake of dopamine, which further exacerbates the sympathomimetic effects of cocaine [51]. In animal models, cocaethylene is deadlier than cocaine or ethanol alone [52]. A study by Pirwitz and colleagues [53] portrayed the vasoconstrictive effects of cocaethylene on coronary arteries and also demonstrated increased myocardial oxygen demand in human subjects.

Differential diagnosis

As in the case of almost all patients who present with chest pain, immediate evaluation for myocardial ischemia and infarction is mandatory in patients with cocaine-associated chest pain. However, other diagnostic

Table 1
Mechanisms of cocaine-induced myocardial ischemia

Time line of cocaine use	Pathophysiologic effects	Pathogenesis
Immediate	Increased cardiac oxygen demand	Sympathomimetic effects (increased chronotropy, inotropy, and peripheral vascular resistance)
	Compromised coronary blood flow	Coronary vasoconstriction
Immediate	Thrombogenesis	Increased platelet activation and aggregation, enhanced fibrin deposition, altered clotting factor function, endothelial dysfunction
Intermediate	Prolonged (or recurrent) systemic and coronary artery vasoconstriction	Active metabolites of cocaine Cocaethylene
Long-term	Accelerated atherosclerosis	Increased low-density lipoprotein deposition, altered endothelial function, endothelial injury
Long-term	Cardiomyopathy	Deranged myocardial structure and function

possibilities must be kept in mind. Insufflation and inhalation of cocaine may result in pneumothorax, pneumomediastinum, or pneumopericardium. Intravenous use may lead to the development of endocarditis. Aortic dissection has been described in this setting [54,55]. Infectious, traumatic, and other causes of chest pain must still be considered (Box 1). The differential diagnosis must initially be broad, and it is incumbent on the evaluating physician to consider a host of possibilities.

Diagnostic evaluation

Unfortunately for the evaluating physician, patients with cocaine-associated chest pain may not be forthcoming about their recent drug use [3] or may present hours after the initial symptoms began [56]. A prevalence study demonstrated that as many as 25% of patients initially denied the use of cocaine in relation to their presentation of chest pain [3]. In a prospective study of patients presenting to the ED with cocaine-associated chest pain, 19% of patients presented later than 24 hours, with the chest pain beginning at a median time of 60 minutes after cocaine use and persisting for an average of 120 minutes. Reasons for delayed presentation are multifactorial [56].

Traditionally, the clinical characteristics of a patient's chest pain have been used by physicians to help determine a pretest probability that the

Box 1. Differential diagnosis of cocaine-associated chest pain

- Aortic dissection
- Endocarditis
- Musculoskeletal pain
- Myocardial ischemia and infarction
- Myocarditis
- Pericarditis
- Pneumomediastinum
- Pneumonia
- Pneumopericardium
- Pneumothorax
- Pulmonary embolus

patient's chest pain is ischemic in origin. This rule does not hold true for cocaine-associated chest pain. Neither the location, duration, quality, nor associated symptoms of the chest pain have been shown to be predictive of myocardial ischemia in this patient population [56].

The ECG, despite its shortcomings, is a time-honored tool that clinicians rely on heavily for evaluating patients presenting with chest pain. A cross-sectional study compared ECGs in patients with cocaine-associated chest pain against matched controls [57]. Benign early repolarization (BER) was found in 35% of the cocaine group and 30% of the controls. Normal readings or nonspecific were found in 46% of each group. The authors found no difference in the mean frequencies of ECG diagnoses between the two groups and concluded that normal variations (BER) account for many of the ECG changes observed in this patient population. This phenomenon has the potential to mislead the treating physician, who might mistake BER for an acute injury pattern. Hollander and colleagues [56] calculated a sensitivity of 35.7% and a specificity of 89.9% for the ECG in this clinical setting. In other words, the ECG possesses a high false-negative rate under these circumstances. Positive and negative likelihood ratios for the ECG would be 3.5 and 0.72, respectively.

Just as they use the ECG, clinicians use cardiac markers to make management and disposition decisions for patients with cocaine-associated chest pain. One can intuit that the creatine kinase (CK) and CK-MB levels might be elevated following cocaine use, secondary to agitation and subsequent skeletal muscle injury. Cardiac troponin I, by contrast, has no cross-reactivity with human skeletal muscle troponin I. Hollander and colleagues [58] tested the performance of cardiac markers in 97 patients with potential myocardial ischemia (20% with recent cocaine use). Myoglobin, CK-MB, and troponin I were drawn at the time of presentation and then serially every 8 to 12 hours. The specificity of myoglobin for AMI in patients without cocaine use was 82%, compared with only 50% in patients who had

recently used cocaine. For CK-MB, the specificity was 88% (no cocaine) versus 75% (with cocaine), and for troponin I the specificity was 94% for both groups. The authors concluded that the specificity of troponin I was not affected by recent cocaine use. Kontos and colleagues [59] studied the usefulness of troponin I in patients with cocaine-associated chest pain. The study included 526 patients presenting to the ED with cocaine-associated chest pain, of which 246 patients were admitted. CK-MB criteria for AMI were found in 14% of the admitted patients, and for troponin I the figure was 16%. The authors concluded that troponin I has equivalent diagnostic accuracy to CK-MB in this patient population.

Myocardial perfusion imaging may provide the clinician with useful information in the assessment of the patient who has worrisome chest pain. Kontos and colleagues [60] used technetium-99m sestamibi scanning to study 216 low- and moderate-risk patients with cocaine-associated chest pain. All patients were injected with the isotope in the ED and then scanned within 60 to 90 minutes. No negative scan patients were found to have biochemical evidence of AMI. A total of five patients had positive scans, two of whom were found to have AMI. All patients with negative scans were followed for 90 days (8% were lost to follow-up), and no cardiac events occurred during this period. The authors concluded that early perfusion scanning could offer an alternative to inpatient evaluation.

Treatment

As with every sick or potentially sick patient, the clinician's initial focus should be on the patient's airway, breathing, and circulation (ABCs). Once these steps are completed, more goal-directed assessment and treatment may commence.

Only a few well-designed studies have compared the efficacy of the various treatment strategies for cocaine-associated chest pain. Recommendations for treatment are based on animal studies, observational series, case series, case reports, and small clinical trials. The American Heart Association (AHA), in its 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, openly acknowledges that its recommendations related to the treatment options for cocaine-associated chest pain are based on a small number of studies [61].

The central nervous system plays a key role in many of the sympathomimetic manifestations of cocaine toxicity [62]. Clinical experience has confirmed that benzodiazepines blunt this response. Benzodiazepines have anxiolytic properties and hence may curb psychomotor agitation. Benzodiazepines also attenuate the rise in blood pressure and pulse secondary to cocaine. These effects could therefore result in a reduction of myocardial oxygen demand. The 2000 AHA guidelines recommend benzodiazepines as primary therapy [61].

On the premise that aspirin will impede thrombus formation, the 2000 AHA guidelines recommend aspirin as first-line therapy [61]. No clinical studies substantiate this premise, but it makes intuitive sense based on the pathophysiology involved (cocaine is thrombogenic), aspirin's safety profile and minimal cost, and the extensive investigations that have confirmed aspirin's efficacy in patients with coronary artery disease, myocardial ischemia, and myocardial infarction.

Nitrates are a mainstay of the treatment of myocardial ischemia, and they are believed to provide benefit in the setting of cocaine-associated myocardial ischemia as well. Hollander and colleagues [63] studied 246 patients with cocaine-associated chest pain. Of these, 83 patients were treated with nitroglycerin (NTG) at the discretion of the physician. NTG was found to be beneficial in nearly half the patients, and the only adverse outcome (hypotension) occurred in a patient with a right ventricular myocardial infarction. Two studies have compared nitroglycerin with benzodiazepines in this clinical setting. The first study, by Baumann and colleagues [64], enrolled 40 patients who had cocaine-associated chest pain and blindly randomized them to one of three treatment arms: sublingual NTG only, diazepam only, or sublingual NTG and diazepam. The investigators found no difference among the three treatment groups regarding change in vital signs or chest pain. They concluded that there is no clinical difference in response between agents and appears to be no additive effect. A second study by Honderick and colleagues [65] compared the use of lorazepam plus NTG with that of NTG alone in 27 patients with cocaine-associated acute coronary syndromes. The lorazepam-plus-NTG group experienced significantly greater pain relief at both 5 and 10 minutes. The authors concluded that the early use of lorazepam and NTG is both efficacious and safe in relieving cocaine-associated chest pain. The 2000 AHA guidelines view nitrates as first-line therapy [61].

As with aspirin, the efficacy of heparin in this patient population has not been studied [61]. Lewin and Hoffman [62] and Hahn and Hoffman [6] support the use of heparin based on the pathophysiology involved (thrombus formation). The risks of heparin, specifically bleeding, must be weighed against the potential for aortic dissection and intracranial hemorrhage in these patients.

Beta adrenergic blockade is standard treatment for patients with AMI. Traditionally, beta blockers have been avoided in the setting of cocaine-associated chest pain, based on the rationale that beta blockade would lead to the unopposed alpha adrenergic effects of cocaine. Clinically, this process could lead to an increase in blood pressure and a failure to control heart rate, with significant consequences. Labetalol might be an attractive alternative in this setting, but its beta blockade effects far outweigh its alpha blockade effects. No clinical ED studies have investigated this issue. One study evaluated intravenous labetalol in 15 patients undergoing cardiac catheterization who experimentally received IN cocaine [66]. The observed

cocaine-induced coronary artery vasoconstriction was not diminished with labetalol. Other investigators call into question the strict avoidance of beta blockers in this setting [67]. The author of this editorial questions the traditional reasoning, arguing that the pathophysiology involved is probably more complex than the simple sympathomimetic model and that more selective beta blockers are now available. Others, too, have reported on the clinical safety of using beta antagonists in treating the cardiotoxic effects of cocaine [68].

Morphine is often used as a supplement in the setting of acute chest pain to help control the patient's discomfort. Saland and colleagues [69] studied 16 patients undergoing elective cardiac catheterization for evaluation of chest pain. Patients were randomized into two groups: cocaine/saline and cocaine/morphine. The findings showed that cocaine increased myocardial oxygen demand, and the subsequent administration of morphine did not further alter oxygen demand. At the same time, the administration of morphine following cocaine reversed the cocaine-induced arterial vasoconstriction. The investigators concluded that morphine was both safe and beneficial in this clinical setting.

Calcium channel blockade is not routinely advocated in the treatment of AMI. However, in the setting of cocaine-associated chest pain, some evidence indicates that calcium channel blockade may be of benefit. A study of 10 healthy volunteers demonstrated that verapamil relieved cocaine-induced vasospasm [70]. The 2000 AHA guidelines recommend calcium channel blockade as a second-line therapy [61]. Others do not endorse this concept and call for further clinical investigation [6].

Phentolamine, because it is a pure alpha antagonist, is theoretically an option in this clinical setting. A case report documented its efficacy in a patient unresponsive to traditional treatments for cocaine-associated chest pain who improved dramatically with its use [71].

Thrombolysis is an attractive treatment choice for cocaine-associated AMI because of the pathology of enhanced thrombogenesis noted with cocaine. However, several concerns must be kept in mind. First and foremost, the clinical benefit of thrombolysis in this setting is unclear (risk/benefit assessment). Vasospasm is thought to play a role in some patients. At catheterization, some of these patients are found not to have thrombus. Moreover, in this patient population, a high prevalence of BER is seen on ECG, leading to the possibility of false-positive interpretations meeting thrombolytic criteria. Overall, morbidity and mortality in this clinical setting are low. Unfortunately, there have been case reports of intracranial hemorrhage when thrombolysis is used in this patient population [72]. The most complete study that has attempted to address this clinical dilemma is a retrospective, cross-sectional study by Hollander and colleagues [73]. The primary endpoint of the study was the safety of thrombolytics in patients who had cocaine-associated AMI. Thrombolytics were given to 25 patients, who were then compared with 41 well-matched patients who met

thrombolysis in myocardial infarction criteria but did not receive thrombolytics. No deaths occurred in either group, and there were no major complications (eg, intracranial hemorrhage, need for transfusion). Approximately two thirds of the patients were believed to have reperfused when given thrombolytics. No difference was found regarding peak cardiac marker levels or time to peak levels (indirect measures of efficacy). The authors advocate for adoption of a “cautious” policy for the use of thrombolytics in patients with cocaine-associated ST segment elevation. The 2000 AHA guidelines state that thrombolysis should not be considered unless there is evidence of evolving myocardial infarction that persists despite other medical therapy and timely percutaneous coronary intervention (PCI) is not accessible [61].

The 2000 AHA guidelines go on to suggest that PCI, when available, is the treatment of choice for ongoing ischemia. No studies have compared these two interventions in this patient population. Kontos and colleagues [47] reported on 90 patients who underwent coronary angiography within 5 weeks of an ED evaluation for cocaine-associated chest pain. They found that significant disease, defined as coronary artery, major branch, or bypass graft stenosis of greater than or equal to 50%, was present in 50% of patients. Significant disease was present in 77% of patients with AMI or elevated troponin levels, compared with 35% of patients without myonecrosis. These findings demonstrate that a high percentage of this patient population has underlying coronary artery disease, and thus lends credence to the argument that PCI should be the primary treatment for cocaine-associated AMI.

Several mechanisms have been suggested for the development of cocaine-associated dysrhythmias. These include increased ventricular irritability, lower ventricular arrhythmia threshold, prolonged QRS and Q–T intervals, similar to the effects of class I antiarrhythmics, and reduced vagal tone (Box 2). Most of the more lethal arrhythmias have been noted in the context of hemodynamic or metabolic derangements (ie, hypoxia, hypotension, seizure, AMI) and occur early in the course of the patient’s presentation [56,74]. Because of cocaine’s cardiac sodium channel blocking properties, sodium bicarbonate is suggested for the treatment of wide-complex tachycardias. Lidocaine, despite some concerns, has been used for cocaine-induced ventricular arrhythmias [6]. Class Ia (quinidine, procainamide, and disopyramide) should be avoided [75]. No literature reports the efficacy of amiodarone for cocaine-induced ventricular tachycardia or fibrillation.

Morbidity and mortality

Unsurprisingly, patients presenting with cocaine-associated chest pain may experience complications and death. Fortunately, their morbidity and mortality are strikingly low.

Box 2. Potential dysrhythmias secondary to cocaine

- Asystole
- Atrial fibrillation
- Bundle branch block
- Complete heart block
- Sinus bradycardia (early)
- Sinus tachycardia
- Supraventricular tachycardia
- Torsade de Pointes
- Ventricular tachycardia
- Ventricular fibrillation

Brody and colleagues [76] retrospectively summarized hospital visits for cocaine-related medical problems. This study consisted of a series of 233 consecutive visits to an urban ED. Most of the presenting complaints were cardiopulmonary in nature (56%), and the most common complaint was chest pain (40%). Acute mortality was less than 1%, with one of the ED deaths being preceded by a prehospital cardiac arrest and the other being a cardiac arrest in a patient with recent endocarditis. Hollander and colleagues [56] presented data from a prospective, cohort, multicenter study that evaluated 246 patients who had cocaine-associated chest pain. Approximately 90% of these patients reported insufflation or inhalation as the preferred route of use. The prevalence of myocardial infarction was 5.7%; congestive heart failure developed in four patients (1.6%), 10 patients sustained arrhythmias (4.0%), and two patients (0.8%) suffered a cardiac arrest—both in the prehospital setting. Once in the ED, no patients experienced a life-threatening complication. The authors were unable to identify any data from the history that could assist the physician in predicting or excluding myocardial ischemia or infarction. The clinical description of the pain and associated symptoms, along with cardiovascular risk factors, was not helpful.

A retrospective study by Weber and colleagues [74] evaluated 250 admitted patients who had cocaine-associated chest pain. The “rule-in” rate for AMI was 6%, and complications were uncommon. No complications developed more than 12 hours after ED presentation. A fourth study went one step further and reported on 130 patients with 136 episodes of AMI secondary to cocaine [77]. Mortality was 0% (confidence interval 0%–2%), with cardiovascular complications occurring in 36% of patients. Approximately 90% of these complications occurred within the first 12 hours (congestive heart failure in nine patients, arrhythmias in 55 patients), and all episodes of ventricular tachycardia and ventricular fibrillation occurred before hospital arrival. All patients who had complications were identified

by one of the following: a 12-hour period of observation, an initial abnormal ECG, or an elevated CK-MB within the first 12 hours. From these data the authors make calculations and state that, for 1000 patients presenting to the ED with cocaine-associated chest pain, 1.6 patients might be expected to develop cardiovascular complications not identified by the above criteria. Notably, 52 of these patients went on to cardiac catheterization, and 67% were found to have at least single-vessel disease (more than 50% narrowing).

From this information, the clinician may draw several conclusions regarding the ED and hospital course for these patients. Approximately 6% of patients with cocaine-associated chest pain will ultimately be diagnosed with an AMI. Almost all anticipated complications will occur within the first 12 hours of presentation, with life-threatening arrhythmias being most prevalent in the prehospital setting, and the mortality for patients with cocaine-associated chest pain is low (less than 1%).

The previous section on differential diagnosis mentioned the possibility of an aortic dissection being present in the setting of cocaine-associated chest pain. Hsue and colleagues [55] report on a retrospective case series of 38 patients with acute aortic dissection. Fourteen patients (37%) had a dissection related to cocaine use, with a mean interval of 12 hours between cocaine use and the onset of symptoms (range 0–24 hours). The pattern of the dissection was type A in six patients and type B in eight patients. The majority (79%) of these 14 patients also had a history of hypertension. There were four deaths (29%).

Prognosis

Data are available regarding the prognosis of this patient population once discharged from the hospital. Hollander and colleagues [5] reported on 203 patients who were followed for a mean of 408 days after discharge for cocaine-associated chest pain. Mortality data were available for all 203 patients. The study endpoints consisted of 1-year mortality and the incidence of AMI. The survival rate was 97%. Six deaths occurred: three from HIV, one from end-stage renal disease, one from congestive heart failure, and one from sepsis. Two AMIs occurred, and both of these patients continued to use cocaine. Approximately 60% of the patients continued to use cocaine, and 75% of these patients experienced recurrent chest pain. No deaths or AMIs occurred in those patients claiming abstinence.

Disposition

At the crux of every ED patient encounter is the decision whether to admit the patient to the hospital or discharge the patient, usually to home. Several recent studies may help guide the clinician with disposition decisions in the patient with cocaine-associated chest pain. Kushman and colleagues

[78] from the Cincinnati Chest Pain Center retrospectively reported on 197 patients with cocaine-associated chest pain. Their evaluation protocol consisted of an initial ECG, continuous ST segment monitoring, and cardiac marker assays at 0, 3, 6, and 9 hours. Patients without evidence of myocardial necrosis or ischemia then underwent graded exercise testing. The investigators found that this provocative test was not positive in any patient for whom the initial evaluation protocol was negative. Weber and colleagues [79] prospectively evaluated 344 patients with cocaine-associated chest pain. Of this study population, 42 (12%) of the patients were admitted to the hospital, and 302 (88%) were evaluated in an ED chest pain observation unit. The initial ED evaluation protocol included provocative testing in all patients, but, because of the extremely low rate of positive tests (the number was not cited in the article), the protocol was altered, and stress testing before discharge ceased to be mandatory. Patients who had normal troponin I levels (0, 3, 6, and 9 hours), who were without new ischemic ECG changes, and who experienced no cardiovascular complications during the 9- to 12-hour period of observation were discharged home. During the 30-day follow-up period, four of the 256 patients for whom follow-up data were available had a nonfatal AMI. All these events occurred in patients who continued to use cocaine.

These studies lend strong support to the belief that if the initial and ongoing cardiac evaluation is unremarkable, the patient's symptoms resolve, and no other abnormalities are found, these patients may be safely discharged from the ED with appropriate follow-up arrangements. The studies also demonstrate that the patients at greatest risk are those who continue to use cocaine. Therefore, the physician should consider offering drug rehabilitation opportunities to these patients.

Summary

The pathophysiology of cocaine leading to myocardial ischemia is multifactorial. Given the paucity of well-designed clinical studies, treatment is directed toward the potential mechanisms involved in the development of myocardial ischemia. Fortunately, morbidity and mortality in this patient population are low, and the vast majority of patients will not suffer AMI or other cardiac complications. Long-term prognosis is excellent for those who abstain from continued cocaine use.

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