The Effects of Acute and Chronic Cocaine Use on the Heart

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Cocaine use in the United States is widespread, with an estimated 25–30 million Americans having used the substance and an estimated 5–6 million individuals using the drug on a regular basis. The effects of cocaine on the heart have been popularized by the sudden deaths of sports figures who used the drug and a series of case studies showing a temporal relation between the use of cocaine and cardiac illness.1–6 Although there had been widespread belief among users that cocaine is safe and nonaddicting, it is now clear that its cardiototoxic effects in any given individual are unpredictable.

Determining the exact effects of cocaine in humans is difficult because of various purities of cocaine used among the populace, different routes of administration, different doses, underlying risk factors, and concomitant use of other drugs such as alcohol, caffeine, and amphetamines, which may all interact with cocaine’s effects on the heart. A large variety of cardiovascular diseases have been associated with cocaine use, including acute myocardial ischemia and infarction,1,4–12 arrhythmias and sudden death,1–3 myocarditis14–18 hypertension,19 ruptured aorta,20 cerebrovascular aneurysm,21 accelerated atherosclerosis,22 and endocarditis.23

The purpose of the following review is to clarify the effects of an acute cocaine dose on the heart both in experimental animals and in humans and to compare this with the effects the drug may have when used chronically.

Pharmacology

Cocaine has two primary pharmacological properties that affect the heart and vascular system. First, it blocks the reuptake of catecholamines, including norepinephrine and dopamine, at the presynaptic level in the central and peripheral nervous systems.24–26 It increases the release of catecholamines from both central and peripheral stores.26 Chiueh and Kopin27 reported that cocaine released norepinephrine and epinephrine from the rat adrenal medulla. Nahas and Trouve28,29 showed that cocaine increased plasma adrenaline, dopamine, and noradrenaline in squirrel monkeys and rats. Karch et al30 described increased serum catecholamine levels in patients with cocaine cardiotoxicity. The excess catecholamine accumulation at the postsynaptic receptor sites results in sympathomimetic stimulation not only of the central nervous system31 but also of the heart muscle and the vascular smooth muscle.

The increased levels of norepinephrine in the vascular smooth muscle result in stimulation of postsynaptic α-receptors, with a subsequent increase in calcium flux and a vasoconstrictor response. A recent study by Egashira et al32 showed that intracellular calcium, as measured with aequorin, rose in isolated ferret aortas exposed to cocaine; that the increase in calcium was associated with vasoconstriction; and that the α-blocker prazosin could prevent the vascular response. Cocaine-induced vasoconstriction leads to an increase in blood pressure and coronary vascular resistance. Some evidence exists that the vasoconstrictor response may be mediated by mechanisms other than potentiation of norepinephrine alone.9 Cocaine apparently induces a vasoconstrictor response in isolated human umbilical arteries,33 which are devoid of sympathetic innervation; Isner and Chokshi34 have postulated that cocaine may directly stimulate calcium flux into smooth muscle cells, leading to the vasoconstrictor response.

Accumulation of catecholamines in the myocardium stimulates the β-adrenergic receptors. This results in an increase in heart rate in conscious preparations,19 an increase in cardiac automaticity, and possibly other tachyarrhythmias. As recently reviewed by Billman,25 stimulation of β-adrenergic receptors in the heart activates adenyl cyclase, with a subsequent increase in cyclic AMP levels and activation of cyclic AMP–dependent protein kinase with phosphorylation of regulator proteins (calcium channel, phospholamban), which increases free calcium level in the myocardial cells. This results in an increased inotropic effect that has been reported with low doses of cocaine34 in some conscious animal studies and may contribute to the formation of contraction bands.13

α-Adrenergic stimulation of the heart by cocaine also may contribute to higher systolic calcium levels.

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within the myocardium by several different mechanisms, as recently reviewed by Billman.25

The second pharmacological property of cocaine that affects the heart is its local anesthetic effect.25 Cocaine blocks the fast sodium channel in the myocardium, resulting in a depression of depolarization and a slowing of conduction velocity. On the ECG, this is manifested by a prolongation of the PR, QRS, and QT intervals;35 cocaine also prolongs the refractoriness of atrial and ventricular muscle.36 In this sense, the drug’s electrophysiological properties are similar to other type 1 antiarrhythmic agents such as procainamide and quinidine. This direct local anesthetic or membrane-stabilizing property may be responsible for a negative inotropic effect of cocaine.

Most of the reported effects of cocaine cardiotoxicity (both acute and chronic use) can be related to its two major pharmacological effects: increasing sympathetic output (including increased tissue catecholamines) and reduction in sodium transport (local anesthetic effect, membrane-stabilizing property). Other effects, including hypersensitivity reactions, increased platelet aggregation, leukocyte natural killer cell activity (which may be related to increased catecholamines), and interaction with the renin–angiotensin system, may contribute to cardiotoxicity.37

In studies in both animals and humans, cocaine functions as a positive reinforcer.38 Dingeon et al39 studied rats fitted with osmotic pumps that received chronic cocaine or saline for 7–14 days. Administration of acute doses of cocaine resulted in a blunted increase in blood pressure in those animals already receiving the drug compared with saline controls, suggesting some degree of cardiovascular tolerance. When subjects are given a choice of self-administration of saline versus cocaine, they will generally choose cocaine over saline. There is evidence that in humans, an acute tolerance to cocaine may develop.40,41 In a series of volunteers, cocaine levels were maintained constant after an intravenous injection followed by infusion. Patients described a euphoric high that peaked at 1 hour and then declined; there was an increase in heart rate, which peaked at 10 minutes but fell by 31 minutes despite a constant plasma level of cocaine.40 Other studies, however, have debated the presence of acute cocaine tolerance.42

The nature of cocaine cardiotoxicity has been elucidated by experimental studies in which cocaine is acutely administered to the heart. The following two sections review the cardiac effects of acute cocaine administration, first in animals and then in humans.

Effects of Acute Dose of Cocaine in Animals

Cocaine has been administered to both anesthetized and conscious animals. Its hemodynamic effects vary with the animal model; both the conscious and unconscious preparations are clinically relevant, however, because cocaine is still used medically for oral/nasal surgery and for intubation procedures, when patients may be anesthetized.

Effects on Heart Rate and Blood Pressure

In general, an acute dose of cocaine in an awake animal will increase heart rate and/or blood pressure;43–46 in anesthetized animals, the effects on heart rate and blood pressure are variable, and these parameters may actually decline.47,48 In one study, Wilkerson44 observed that pentobarbital abolished the cocaine-induced increase in blood pressure observed in the conscious dog, suggesting that the anesthetic agent masked the cocaine effect. The effects of cocaine on these parameters also vary with the dose administered. Schwartz et al49 studied both conscious and anesthetized dogs and reported that blood pressure increased at the lowest dose range, remained unchanged at intermediate doses, and fell at the highest doses, whereas changes in heart rate were variable at all doses.

Effects on Left Ventricular Function

We studied the effects of acute doses of 10 mg/kg i.v. cocaine on cardiac function in anesthetized dogs.47 At 15 minutes, left ventricular (LV) end-diastolic pressure was elevated and LV dP/dt fell significantly. Cocaine caused an early LV dilatation when assessed by two-dimensional echocardiography. In subsequent studies, Hale et al50 observed significant reductions in angiographically determined LV ejection fraction and stroke volume. One question that arose in connection with these studies was whether the depression in LV function was a primary effect of cocaine’s direct local anesthetic properties or secondary to a reduction in coronary blood flow (presumably a result of α-sympathetic effect or direct calcium flux effect causing vasoconstriction). In one study, dogs were instrumented with coronary flow probes and LV cavity pressure transducers. We observed within the first 30 seconds of cocaine injection that LV dP/dt fell at a time when coronary blood flow was either unchanged or actually increasing.50 This observation strongly supports the concept that cocaine has a direct negative inotropic effect on the heart (perhaps because of its local anesthetic properties) independent of a reduction in coronary blood flow. In anesthetized animals, this direct negative inotropic effect overpowers any positive inotropic effect from secondary sympathetic stimulation of the heart. Studies by Abel et al51 and Fraker et al45 also suggest that cocaine has a direct negative inotropic effect in an anesthetized canine preparation. Doses of 50 mg of cocaine given 10 minutes apart to dogs progressively depressed LV positive dP/dt, negative dP/dt, and time to peak LV pressure.51 Other studies52,53 have supported the notion that cocaine can reduce LV function without inducing coronary spasm; in one study, this was related to an increase in systemic vascular resistance.52 Further support for a direct negative inotropic effect comes from work by Morcos et al,54 who investigated the effect of cocaine in an isolated rabbit ventricular septum preparation. Developed tension, rate of tension development, and
rate of tension relaxation were all depressed after cocaine infusion despite constant flow to the septum. Perreault et al. have also described negative inotropic effects of cocaine in isolated perfused cardiac ventricular trabeculae.

The effects of cocaine on LV hemodynamics are dependent on both the type of animal preparation and the dose. For example, Shannon et al. studied the effects of a lower dose of cocaine (1 mg/kg i.v.) in conscious instrumented dogs. LV dP/dt initially fell by 4% but had increased by 21% at 5 minutes. The later increase was blocked with either ganglionic or β± plus cholinergic blockade. It is likely that the early decrease in dP/dt caused by local anesthetic effect of the drug was overcome by sympathetic stimulation in this conscious preparation. This contrasts with the anesthetized canine preparation, in which cocaine almost always depresses contractility. This study is also in contrast with a study by Fraker et al., who observed a significant reduction in ejection fraction after administration of 4 mg/kg i.v. cocaine to conscious dogs. Herman and Vick showed in an isolated blood-perfused canine heart that low doses of cocaine (<2 mg) had a variable effect on cardiac contractility. Higher doses (2–25 mg) consistently decreased contractility. In summary, most animal studies suggest that an acute dose of cocaine depresses LV function.

**Effects on Coronary Caliber and Blood Flow**

Most studies but not all studies have documented a fall in coronary artery caliber and flow shortly after administration of cocaine. We observed a fall in coronary caliber of about 15% and up to 29% in the anesthetized canine preparation, accompanied by a moderate fall in regional myocardial blood flow (38% in the subepicardial and 27% in the subendocardium). Hayes et al. reported that cocaine caused a dose-dependent vasoconstriction of the epicardial coronaries, with a 46% reduction in cross-sectional area with 9 mg/kg and peak effect at 60 minutes. Fraker et al. reported a fall in coronary flow from 104 ml/min to 85 ml/min in sedated dogs after a 4-mg/kg dose of cocaine. In conscious dogs, however, the same dose did not reduce coronary blood flow but rather increased it, along with a significant increase in rate–pressure product. Reduction in coronary artery diameter has also been reported in anesthetized pigs receiving 1–10 mg/kg of cocaine. A study by Vitullo et al. found that cocaine-induced coronary vasoconstriction in arteries up to 65 μm in diameter, whereas larger-caliber vessels did not demonstrate vasoconstriction.

Thus, in intact animals or whole-heart preparations, most studies describe that an acute dose of cocaine reduces coronary artery caliber and blood flow. A reduction in caliber and flow, however, could be an autoregulatory response to reduced LV function (with reduced oxygen demand). Although some of the reduction in coronary flow might be related to reduced oxygen demand, it is unlikely that this fully explains cocaine’s effects on the coronary tree in experimental animals. First, in a study by Kuhn et al. gave sufentanil-sedated dogs reduced the diameter of the left anterior descending coronary artery by 19% and increased coronary vascular resistance by 55% at the same time that heart rate, blood pressure, and cardiac output were increased. Thus, coronary flow was decreasing at the same time that determinants of myocardial oxygen demand were increasing. Studies by Ron- gione, Isner et al., and Egashira et al. have described that isolated vascular rings exposed to cocaine or its metabolite norcocaine develop constriction, suggesting that cocaine has a direct effect on the vasculature. It is important to remember that there may be an interplay between cocaine’s effect of directly depressing contractility and its ability to vasoconstrict coronary arteries. In our studies, myocardial depression occurred within seconds of administration of cocaine, whereas coronary flow initially appears to increase. Within minutes, however, coronary caliber fell, along with flow. Once coronary flow falls, this may further depress contractility. Vatner has shown that even slight reductions in coronary flow may result in some reduction of LV function. Conversely, a fall in LV contractility, through autoregulation, tends to reduce myocardial blood flow. Despite this interplay, however, in vitro animal studies showing cocaine’s direct negative inotropic effect on ventricular trabeculae and direct vasoconstrictor effect on isolated blood vessels support the concept that cocaine’s cardiotoxic effects involve both mechanisms.

**Effect on ECG and Electrophysiology**

Several experimental animal studies have shown that cocaine alters the ECG and electrophysiology of the heart. Hale et al. observed that 10 mg/kg i.v. cocaine in dogs prolonged the PR interval and QT duration on the ECG; one dog developed transient ventricular tachycardia during cocaine administration. Another study, in anesthetized rats, an acute dose of cocaine resulted in prolongation of PR, QRS, QT, and QT; intervals at 3 hours. Kabas et al. showed that the conscious dog, 3–5 mg/kg of intravenous cocaine prolonged the HV interval and R wave duration. Schwartz et al. observed that an infusion of 2.8 mg/kg of cocaine prolonged atrioventricular nodal conduction time and maximum sinoatrial conduction time. Acute cocaine administration may induce arrhythmias. Cocaine induced atrial fibrillation in dogs. Other studies have described cocaine-induced ventricular tachycardia in animals. Frequent atrial extrasystoles and atrial tachycardia were observed in four of six cocaine-treated rats, associated with further QRS widening or block, and ventricular extrasystoles were observed in one rat.

The fact that cocaine can exacerbate arrhythmias during myocardial ischemia has been documented in several studies. Inoue and Zipes induced myo-
cardiac infarction by coronary ligation in anesthetized dogs. Spontaneous or induced ventricular tachycardia developed in only one dog without concomitant administration of drugs but developed in three dogs that received norepinephrine and in seven dogs given norepinephrine plus cocaine. Cocaine induced ventricular arrhythmias, including ventricular fibrillation, during exercise plus coronary occlusion in conscious dogs; the effect was prevented by verapamil.  

Other Effects

Besides cocaine’s direct effect on the heart and vasculature, there is also evidence that cocaine can alter platelet function. Tognna et al. 70 showed that incubation of rabbit platelet-rich plasma increased platelet aggregation and thromboxane production to arachidonic acid.

Some studies have suggested that there is an interaction between cocaine and the renin–angiotension system. Trouve et al. 71 observed that angiotensin antagonists improved survival in rats given an otherwise lethal dose of cocaine. The angiotensin converting enzyme inhibitor enalaprilat also improved survival to a lesser degree. Vica et al. 72 observed that enalaprilat inhibited cocaine-induced vasoconstriction of the rat microvasculature, as assessed with a video microscopy technique. It has been suggested that cocaine deregulates basic regulating mechanisms of the sympathoadrenal and renin–angiotension systems, which leads to its cardiotoxicity. 71

In summary, the acute effects of cocaine in animals have shown, in general, 1) an increase in blood pressure and heart rate in conscious animals (sympathomimetic effect), 2) variable effects (including a decrease) in blood pressure and heart rate in anesthetized animals, 3) a direct negative inotropic effect (sodium channel effect), 4) an indirect increase in contractility in some conscious studies (sympathomimetic effect), 5) a reduction in coronary caliber and myocardial blood flow (α-mediated vasoconstriction and/or direct effect mediated by calcium, plus some indirect autoregulatory effect when there is concomitant reduction in contractility), and 6) electrophysiological abnormalities, including prolongation of ECG intervals and increased ventricular arrhythmias occurring in the setting of ischemia (both type I antiarrhythmic–sodium channel effects and increased sympathethic stimulatory effects). Of note, many studies have suggested that these toxic effects of cocaine are related to dose and the type of animal preparation. At least in canine preparations, the toxic effects of cocaine are more readily and consistently observed with doses >5 mg/kg and less common at doses <2 mg/kg.

Effect of Acute Dose of Cocaine in Humans in Controlled Clinical Settings

Many studies have shown that acute administration of cocaine to humans increases heart rate and/or blood pressure. 19,42,73,74 Fischman et al. 73 showed that intravenous cocaine caused a dose-related increase in heart rate and blood pressure. Whereas a single dose of 4 mg of cocaine did not have an effect, 8 mg caused a 21% increase in heart rate; 16 and 32 mg increased heart rate by 32% and 34%, respectively. Increase in heart rate began 2–5 minutes after injection and peaked at 10 minutes. By 45 minutes, the effect on heart rate was gone. Cocaine did not affect systolic blood pressure at 4- or 8-mg doses but increased blood pressure by 10% and 15% at 16- and 32-mg doses, respectively. Peak change in blood pressure occurred by 10 minutes. Blood pressure returned toward baseline by 45 minutes. Few studies have examined the acute effects of cocaine on other parameters of cardiac function. In one study, Lange et al. 75 performed cardiac catheterization, including coronary angiography, in awake patients who received a small dose of intranasal cocaine (2 mg/kg), simulating a medicinal dose used for oral–nasal–pharyngeal surgery. They observed an acute but mild diffuse reduction in coronary caliber (8–12% compared with baseline), a significant reduction in coronary sinus blood flow (17%), and a significant increase of 33% in coronary vascular resistance. There was also a modest increase in heart rate and blood pressure. The α-blocker phentolamine prevented the increased coronary vascular resistance and reduction in coronary caliber. This is an important study in that it documented in the conscious human that cocaine increased determinants of oxygen demand (heart rate, blood pressure) at the same time as it reduced supply (coronary vasoconstriction). Although the fall in coronary flow was modest, the dose of cocaine used was probably lower than street use; higher doses might have worsened flow. The same investigators have recently reported that intracoronary β-blockade with propranolol may exacerbate the effects of cocaine on the coronary vasculature, resulting in further reductions in flow 76 (presumably by blocking β-receptors in the coronary artery, leaving increased α-sympathetic stimulation by cocaine relatively unopposed).

Flores et al. 77 observed that the magnitude of vasoconstriction to intranasal cocaine (2 mg/kg) was greater in coronary artery segments narrowed by atherosclerosis (29%) than in nondiseased segments (13%). The observations by Lange, Flores, et al. 75–77 have been studied in an in vitro model by Chokshi et al. 78 They studied isolated human coronary artery rings from patients undergoing cardiac transplantation. Cocaine induced a dose-dependent vasoconstriction in both atherosclerotic and nonatherosclerotic rings; the degree of constriction, however, was greater in nonatherosclerotic vessels (which is contrary to what Flores et al. 77 observed in vivo).

When cocaine is administered as a local anesthetic agent for laryngoscopy, the frequency of premature ventricular beats is increased. 79 Chiu et al. 80 reported a case of acute myocardial infarction following topical cocaine administration for nasal surgery.

The effect of acute cocaine in human fetal myocardium was studied by Richards and coworkers. 81 Portions of human fetal LV were placed in a muscle bath and received oxygen and glucose. Cocaine de-
pressed action potential amplitude, developed force of contraction, and at 90 minutes of exposure, suppressed all electrical and mechanical activity. These findings provide direct evidence that cocaine has a local anesthetic or membrane-depressing property on human myocardial tissue.

In summary, controlled studies in humans have shown that cocaine causes an increase in heart rate and blood pressure while reducing coronary caliber and coronary sinus flow and increasing coronary resistance. Coronary vasodepressor response and reduced contractility have now been documented in isolated human tissue.

**Effect of Chronic Cocaine Administration in Animals**

Few studies have examined the effects of chronic cocaine administration in animals. One study in rats given 10 mg/kg i.p. cocaine every 12 hours for 10 days revealed a wide array of histochemical abnormalities at 60 days. Reductions in glucose 6-phosphate dehydrogenase, lactate dehydrogenase, myosin-ATPase, and other enzymes were observed in myocytes and smooth muscle cells. Maillet et al. fitted rats with osmotic pumps and delivered 40 mg/kg/day of cocaine for 8 days. Although no gross pathological abnormalities of the hearts were observed, four of 12 animals receiving cocaine demonstrated zones of atypical contraction bands and mononuclear infiltrates by light microscopy. Electron microscopy of the hearts receiving cocaine showed disorganization of myofibrillar architecture, edema, vacuolization, mitochondrial swelling, and disruption of intramitochondrial cristae.

Studies in which animals have received cocaine or its metabolite norcocaine chronically have revealed that the animals can show addictive behavior.84

Two preliminary reports suggest that rabbits fed a high-cholesterol diet and given cocaine develop accelerated atherosclerosis.85,86 Langner et al.85 studied rabbits fed a 0.5% cholesterol diet and injected with either saline or cocaine (4.5–5.5 mg/kg/day). At 14 days, the thoracic aorta from each rabbit was removed and inspected for the presence of atherosclerosis. Rabbits that had received cocaine developed atherosclerotic lesions in the thoracic aorta and demonstrated an increase in aortic collagen and noncollagen protein synthesis.

Kolodgie et al.86 fed rabbits a 0.5% cholesterol diet for 60 days and administered either cocaine (0.25 mg/kg b.i.d.) or saline. The extent of atherosclerotic involvement was determined by Sudan staining; light microscopy was used to determine plaque thickness and cellular morphology. Atherosclerotic plaque area of the intimal surface of the aorta was significantly greater in the rabbits that received cocaine. Mean plaque thickness was 0.18 mm in the cocaine group compared with 0.09 mm in the untreated group. Plaques consisted of both foam cells and smooth muscle proliferation. There was no difference in serum total cholesterol levels between groups.

These two studies suggest that chronic cocaine use may damage the endothelium, leading to acceleration of atherosclerosis. As described below, there are now some clinical case reports that would tend to support this troubling observation.

In summary, chronic cocaine administration in animals may deplete various enzymes within the myocardium. In rabbits on a high-cholesterol diet, cocaine can accelerate the development of atherosclerosis.

**Effects of Cocaine in Humans in Noncontrolled Clinical Settings**

The vast majority of our knowledge concerning the effects of cocaine in humans comes from clinical case reports and autopsy material.1,5,6,9,87,88 Whereas some of these reports may reflect the acute use of cocaine (in that patients or family may have claimed that the event occurred after the patient’s very first use of the drug or occasional use of the drug), other reports may reflect chronic use of the substance. Still other reports of cardiac events after cocaine use may reflect an acute toxicity of the drug on a cardiovascular system that has been altered by chronic use of the drug.

**Acute Myocardial Infarction Temporally Related to Cocaine Use**

Many clinical cases of myocardial infarction reported in the literature show a temporal association with cocaine.1,4–11,37 The true incidence of cocaine-induced infarction, however, is not known. Of the reported cases, patients tend to be young (mean age in the 30s) men, and only a few claimed to have been first-time users.1,9 Most used the drug chronically. As pointed out by Isner et al.,1 the route of administration by which patients develop acute infarction is most commonly intranasal, intravenous, or by smoking. The time from use of cocaine to onset of symptoms appears to be highly variable, ranging from minutes to several hours.3 Both Q wave and non-Q wave infarcts have been described.4 The underlying coronary anatomy has been investigated in some patients by either cardiac catheterization or autopsy. About one third of the cases reported have had normal coronary arteries.1,5,10,11,37,89 This suggests that some infarcts may result from either coronary artery spasm or coronary artery thrombus that lyse spontaneously, or perhaps some combination of both events.90 Ergonovine testing in most patients with clean coronary arteries was shown not to induce focal vasospasm.9 Thrombus has been reported in about one third of cases.9,37 While most thrombi have been associated with underlying atherosclerotic narrowing, others have not.9,37 Of note, thrombotic therapy10,89 has been successful in lysing intraluminal coronary thrombi in patients with acute infarction temporally related to cocaine. Coronary narrowing has been reported in both left and right coronary systems in patients developing infarcts related to cocaine. In one series of nine patients, all had involvement of the left anterior descending artery.10 Whereas autopsy studies have revealed coronary atherosclerosis in
several cases, one case reported a pattern suggesting fibromuscular hyperplasia as a cause of the coronary narrowing. Although intimal plaque hemorrhage has been reported in a few cases, Virmani et al recently pointed out that most patients with cocaine-related infarcts do not demonstrate typical plaque fissuring.

Besides myocardial infarction, ischemic chest pain without infarction also has been described. These episodes may be associated with ST-T wave abnormalities on the ECG. One study by Majid found this syndrome in patients with normal epicardial coronary arteries on angiography but marked thickening of the walls of the intramural coronary arteries. Nade-manee et al documented the presence of frequent episodes of transient ST segment elevation, similar to that observed in patients with Prinzmetal’s angina pectoris, on ambulatory ECG monitoring in eight of 21 chronic cocaine users during the first 2 weeks of withdrawal from cocaine. Of these episodes of ST segment elevation, 87% were silent. After 6 weeks off cocaine, none of the patients showed ST segment changes by ambulatory ECG monitoring. The authors concluded that chronic cocaine use is a risk for coronary vasospasm and that this risk continues for several days after patients discontinue the drug. A case report by Zimmerman et al also suggested that cocaine caused coronary artery spasm in a patient without angiographic evidence of atherosclerosis.

Despite such observations, Gitter et al cautioned that cocaine-related chest pain may not all be caused by myocardial infarction or perhaps even ischemia. They reported that of 101 consecutive patients admitted to Hennepin County Medical Center (Minneapolis) complaining of chest pain after cocaine, none had MB–creatine kinase documentation of infarction. The quality of chest pain was described as pressure in 46%, sharp in 33%, and dull in 20%. Pleuritic pain was present in 18%, and dyspnea was common. It was noted that many of these patients had ST-T wave abnormalities resulting from early repolarization or LV hypertrophy. The investigators concluded that before thrombolysis is administered to such patients who might have a presumptive diagnosis of acute myocardial infarction, an echocardiogram should be obtained to help confirm myocardial infarction.

Besides preliminary animal data suggesting that chronic cocaine use may speed the development of atherosclerosis, several case reports have now suggested this deleterious effect of cocaine in humans as well. Dressler and coworkers studied the coronary arteries of cocaine addicts at necropsy. Of these, 36% had one or more coronary arteries narrowed more than 75%. The extent of atherosclerotic narrowing was greater than expected for a group of patients with a mean age of 32. The authors concluded that either coronary atherosclerosis is accelerated by cocaine addiction or cocaine provides a fatal stress in patients who have premature development of coronary artery disease for other reasons. In another autopsy study, Virmani et al also pointed out that atherosclerosis appeared to be accelerated in young patients who had used cocaine. One patient was a 23-year-old woman who had a history of chronic free-base cocaine use. She had atherosclerotic narrowing of the left anterior descending coronary artery with an overlying thrombus composed of platelets. Kolodgie et al reported five patients (mean age, 29) with one or more coronary arteries severely narrowed by atherosclerosis.

In a study by Mittleman et al, severe atherosclerosis was described in 15 of 24 cases of sudden death associated with cocaine abuse. Thrombotic coronary artery occlusion was found in three patients. Two patients had acute myocardial infarction, and healed infarcts were observed in 10. The mean age was 47, older than the other case reports.

What are the mechanisms by which cocaine leads to myocardial ischemia and infarction in humans? One possibility is that cocaine use may prompt diffuse or local coronary spasm in either otherwise normal or atherosclerotic coronary arteries. As described earlier, the degree of vasoconstriction appears to be increased in arteries already manifesting atherosclerosis. This could account for ST elevation observed on Holter monitoring as reported by Nade-manee. Spasm may lead to stasis of blood with thrombus formation, and cocaine’s effect on increasing platelet aggregability may also contribute to thrombus. Cocaine, by increasing heart rate and blood pressure, increases oxygen demand. Thus, cocaine works both to reduce oxygen supply and to increase oxygen demand. Chronic use may cause repetitive episodes of spasm with or without platelet deposition, and this may eventually cause endothelial damage and subsequent acceleration of atherosclerosis. It is unlikely that cocaine acts by increasing serum lipid levels; these were not elevated by cocaine in one experimental study. Finally, Kolodgie et al have suggested that an increase in adventitial mast cells associated with atherosclerosis could potentiate thrombus and vasospasm in young patients with cocaine-associated deaths. In the same study, the authors pointed out the interesting observation that atherosclerotic lesions in cocaine users with coronary thrombosis did not demonstrate plaque rupture or hemorrhage, suggesting a pathophysiology of acute myocardial infarction different from that observed in non–cocaine users (in whom plaque rupture and hemorrhage are common).

Cocaine as a Cause of Myocarditis and Dilated Cardiomyopathy

As described previously under animal studies, cocaine is known to have a direct negative inotropic effect on cardiac muscle. A case report by Chokshi et al described a 35-year-old woman who, after a day of smoking crack cocaine, developed hypotension, seizures, and hypoxemia. A two-dimensional echocardiogram revealed severe global LV hypokinesis (estimated ejection fraction, 10%) and
LV dilatation. Right heart catheterization revealed a pulmonary capillary wedge pressure of 30 mm Hg; endomyocardial biopsy revealed only occasional contraction bands, which the authors cautioned are not uncommon in biopsy specimens. Inotropic support was continued, and by day 8 the patient was normotensive and required no pressor agents. A repeat echocardiogram revealed an ejection fraction of 45%. This case of reversible depression of LV function may have been a result of cocaine’s direct local anesthetic effect or of “toxic” cardiomyopathy induced by excess catecholamines similar to that in patients who develop catecholamine cardiomyopathy with pheochromocytoma.99

Hoffman et al100 described five patients who developed transient pulmonary edema on chest x-ray that was temporally associated with cocaine use. Bertolet et al101 reported that LV dysfunction was discovered in 7% of 84 asymptomatic cocaine users. Radionuclide ventriculography revealed regional wall motion abnormalities in two patients; a more global hypokinesis with ejection fraction less than 50% was described in four of 84 patients.

Weiner et al16 reported two cases of dilated cardiomyopathy associated with chronic cocaine use. One patient was a 28-year-old woman who developed progressive dyspnea, edema, palpitation, and paroxysmal nocturnal dyspnea. Physical examination revealed signs of congestive heart failure. Two-dimensional echocardiography showed a dilated LV cavity and global hypokinesis. A second patient probably did not represent pure cardiomyopathy; he had development of what appeared to be myocardial infarction, although on angiography the coronary arteries appeared normal.

Hogya and Wolfson18 described the case of a 39-year-old male cocaine user who presented with fatigue, dyspnea, and chest pain. Cardiac catheterization revealed mild global hypokinesis of the LV but normal coronary arteries.

These clinical case reports suggest that besides causing confluent areas of necrosis of the heart by inducing myocardial infarction, cocaine may also have a more direct global toxic effect on the myocytes in humans. Further support of this concept comes from autopsy reports by Virmani et al14 Tazelaar, Karch, and Billingham,13,102 and Peng et al.15 Virmani et al14 reported autopsy data on 40 patients who died with detectable cocaine levels. A prominent finding in patients who died with detectable cocaine levels was myocarditis typified by mononuclear infiltrate in 20% of patients, compared with 3.7% in a control group of patients who died of sudden traumatic death. The predominant cell types in these cases of myocarditis were lymphocytes and macrophages; myocyte necrosis in these foci of inflammation was often limited to an individual myocyte. Although contraction band necrosis often was present in these hearts (23% in cases of natural death and 33% in those on cocaine who died of homicide), they were not associated with leukocyte infiltration and did not correlate with blood levels of cocaine. Moreover, contraction bands were more common in patients who died with sudden traumatic death who were not on cocaine. In only one case in this study was there a total thrombotic occlusion within an atherosclerotic coronary artery.

Isner et al1 also described the case of a 25-year-old man who used free-base cocaine and presented with chest pain, dyspnea, syncpe, and complete heart block. ECG also revealed diffuse ST segment elevation. An endomyocardial biopsy revealed foci of myocyte necrosis and diffuse inflammatory cell infiltration, including eosinophils.

The prominent finding from an autopsy study by Tazelaar et al,13 in which 30 cases of cocaine-related sudden death were studied, was the presence of myocardial contraction bands in 93% of cases. The number of patients with this finding was significantly greater than in a group of control patients who died of sedative–hypnotic overdose. The severity of contraction band necrosis in this study, in contrast to that of Virmani, correlated with the serum and urine concentration of cocaine. In addition, there were a few cases with focal neutrophilic infiltration associated with contraction bands. In three patients, mild atherosclerotic of the coronary arteries was described; mild interstitial fibrosis was present in one of them. In four cases without coronary artery disease, focal myocardial fibrosis was observed. The authors suggested that these areas of fibrosis may have represented zones of healed contraction band necrosis. Tazelaar et al13 postulated that catecholamine excess (which may increase calcium flux) caused by cocaine use contributed to contraction band necrosis, which may have supplied the anatomic substrate for ventricular arrhythmias.

The differences between the Tazelaar study13 (showing contraction bands) and the Virmani study14 (showing primarily myocarditis) are not clear. Virmani suggested that “differences in cocaine preparations, contaminants, adjuvants in the drugs of abuse, route of drug delivery, and chronicity of drug abuse” may have explained the different findings in these patients. Despite their differences, both studies support the notion that chronic cocaine use may induce direct toxic effects on the myocyte.

A study by Peng et al15 also supports this concept. These investigators obtained endomyocardial biopsies from seven patients who had a history of chronic cocaine abuse. The mean age of the patients was 32, most had a history of recent-onset congestive heart failure, two had a history of chest pain, and one had ventricular arrhythmias. Coronary angiography revealed normal coronary arteries in this group of patients. Small foci of myocyte necrosis were scattered throughout these hearts, including some with contraction bands. Zones of necrosis were associated with mononuclear cell infiltrates in two patients. Electron microscopy of the lesions revealed extensive loss of myofibrils and vacuolization of the sarcoplasmic reticulum. Most biopsy specimens showed vari-
ous degrees of interstitial fibrosis. The investigators concluded that cocaine has a direct toxic effect on myocytes that can lead to structural abnormalities of myocytes. They postulated that catecholamine effects may have contributed to the damage, possibly by calcium overload.

In summary, clinical case reports have described a transient toxic cardiomyopathy associated with cocaine use. Autopsy studies support the concept that cocaine may induce scattered foci of necrosis and myocarditis independent of coronary artery disease or clinically documented acute myocardial infarction. The most likely explanation is that excess catecholamines lead to the cell damage, possibly by inducing direct calcium overload of the myocytes themselves or by inducing transient vasoconstriction of the coronary vessels, which might also lead to foci of necrosis. A mononuclear cell infiltrate may be a secondary reaction to the foci of myocyte cell death. Alternatively, some have postulated that the mononuclear cellular infiltrate may be primary and be caused by a hypersensitivity reaction to cocaine or to contaminants taken along with cocaine. Cocaine’s stimulation of endogenous catecholamines may also alter lymphocyte function and has been shown to increase natural killer cell activity. Stimulated leukocytes could conceivably be directly responsible for myocyte cell death. Scattered foci of myocardial necrosis could then serve as a nidus for ventricular arrhythmias, lead to ventricular dysfunction, and ultimately lead to the clinical picture of a more permanent dilated cardiomyopathy.

**Arrhythmias and Sudden Death**

There have been several case reports of ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation, and sudden death, temporally associated with cocaine use. Nanji and Filipenko described a 23-year-old woman who presented with asystole and ventricular fibrillation after cocaine use. Benchimol et al. described a patient with accelerated ventricular rhythm and cocaine use. Isner et al. described a case of cocaine-related ventricular tachycardia in the setting of myocardial infarction. He also described a patient with ventricular tachycardia/ventricular fibrillation after use of cocaine who did not have a myocardial infarction and had clean coronary arteries at the time of catheterization. However, the ECG after cardioversion did show ST segment elevation in leads V1 and V2, suggesting the possibility that the arrhythmia was related to transmural regional ischemia, perhaps caused by transient spasm of the left anterior descending artery. Isner et al. also reported two cases of sudden death temporally associated with cocaine use. One case was associated with recent coronary thrombus; the second occurred in a patient without evidence of definite coronary obstruction or acute myocardial infarction.

Wang et al. reported the case of a 22-year-old man who, after “snorting” 1 g of cocaine, developed runs of ventricular tachycardia in the setting of acute myocardial infarction. A case report by Sternberg et al. described a 38-year-old man who presented shortly after using cocaine with an acute myocardial infarct associated with complete heart block as well as ventricular tachycardia and fibrillation. Indirect support for the concept that cocaine may promote arrhythmias comes from epidemiological studies showing a higher occurrence of palpitations in cocaine and marijuana users than in nonusers.

Cocaine prolongs the QT interval, and Rollinger et al. have reported a case of cocaine-associated torsades de pointes, a ventricular arrhythmia associated with prolonged QT interval.

In summary, cocaine abuse has been associated with sudden death and with cardiac arrhythmias. Although some of these cases suggest that the arrhythmias are associated with myocardial ischemia or infarction induced by cocaine, it is feasible that cocaine may induce arrhythmias without causing an acute ischemic event. As pointed out by Tazelaar, Billingham, and associates, sudden death in their autopsy study may have been related to foci of contraction band necrosis forming a substrate for arrhythmias. Cocaine’s direct membrane effect with prolongation of the QT interval as well as its sympathomimetic effect could contribute to ventricular arrhythmias. The effects of catecholamines on increasing automaticity, decreasing atrioventricular node refractoriness, and increasing His–Purkinje system conduction velocity all could lead to arrhythmias.

**Miscellaneous Clinical Disorders**

A case report of rupture of the ascending aorta during cocaine use was reported by Barth et al. A 45-year-old man died while smoking cocaine. At necropsy, there was a circumferential tear through the ascending aorta. Medial dissection extended proximally to the aortic valve cusps. The authors postulated that acute rupture may have been related to an increase in systemic blood pressure associated with high levels of cocaine.

Chambers et al. showed an association between intravenous cocaine use and endocarditis, suggesting that the risk with injecting cocaine was worse than with other substances. Of 115 cases of patients with fever and intravenous drug use, endocarditis was present in 20%. Cocaine use was reported in 80% of the endocarditis cases. The authors suggested that an effect of cocaine on host immunity, clearance of intravascular pathogens, or an alteration in susceptibility of endovascular cells may have contributed to their finding.

**Therapy for Cocaine Cardiotoxicity**

There is no one therapy that is universally agreed upon for the treatment of cocaine cardiotoxicity. Although β-blockers had initially been suggested, a recent study by Lange et al. showed that propranolol further decreased coronary sinus blood flow and increased coronary vascular resistance in patients receiving 2 mg/kg intranasal cocaine. The potential-
tution of cocaine-induced coronary vasoconstriction by propranolol is presumably caused by blocking β-receptors in the coronary vasculature, leaving α-receptors unopposed. Therefore, β-blockers probably should either not be used or be used with extreme caution if there is evidence of cocaine cardiotoxicity. Some patients who present in a hyperexcitable state with severe hypertension might benefit from β-blockade, but coupling this with an α-blocker might be considered. An earlier study by Lange et al²⁵ showed that in the catheterization laboratory, the α-blocker phentolamine reversed the cocaine-induced increase in coronary vascular resistance. An agent such as labetalol that has α- and β-blocking properties might be useful. However, although there is a case report using this agent,¹⁰⁶ there have been no definitive clinical trials. In addition, labetalol is a more potent β- than α-blocker, and when it is used in patients with pheochromocytoma, hypertensive crisis has been reported.¹⁰⁷

Several experimental trials have suggested that calcium blockers might be useful for cocaine cardiotoxicity. Billman and Hoskins⁶⁹ showed that verapamil attenuated hemodynamic effects and prevented ventricular arrhythmias in dogs subjected to coronary occlusion during exercise and receiving cocaine. Trouve and Nahas¹⁰⁸ observed that the calcium blocker nifedipine suppressed cocaine-induced ventricular arrhythmias and prolonged survival time in rats. Nifedipine also reduced cardiac histological abnormalities (vascular congestion, sarcolemmal disruption, disorganization of myofibers) induced by cocaine.¹⁰⁸–¹¹⁰ Recently the same group observed that the calcium blocker nimodipine²⁹ reduced cocaine-induced increases in catecholamine levels and blood pressure in squirrel monkeys. In one clinical study, Rowbotham et al¹¹¹ studied the effects of pretreatment with the calcium blocker diltiazem in men who received an intravenous injection of 0.2 mg/kg cocaine. Cocaine alone increased heart rate and blood pressure and decreased skin temperature. Pretreatment with diltiazem was associated with a smaller decrease in skin temperature but caused no change in heart rate or blood pressure. Hale et al¹⁵⁰ have recently shown that pretreatment of dogs with the calcium blocker nifedipine prevented cocaine-induced fall in coronary blood flow and deterioration in LV function. However, administration of nifedipine after cocaine had a less beneficial effect. Large clinical trials with calcium antagonists and cocaine cardiotoxicity are not available. Thus, although calcium blockers show some promise, additional information is needed before they can be prescribed routinely for cocaine cardiotoxicity. They may need to be given in a prophylactic fashion to high-risk patients.

In a canine model similar to that described above, we were unable to show a beneficial effect of angiotensin converting enzyme inhibitor on cocaine toxicity.¹¹² In contrast, Nahas et al¹⁰⁹ reported a beneficial effect of enalaprilat in a rodent model.

One recent study showed that sodium bicarbonate reversed cocaine-induced prolongation in the QRS interval in anesthetized dogs.¹¹³ A recent clinical report by Brogan et al¹¹⁴ showed that sublingual nitroglycerin abolished cocaine-induced vasoconstriction in both atherosclerotic and nonatherosclerotic segments of coronary arteries. The dose of cocaine used (2 mg/kg intranasal) was similar to that used for surgical procedures and may be lower than that used on the street. Since sublingual nitroglycerin is a fairly benign drug, it might be reasonable to consider it for patients presenting with angina-type chest pain temporally related to cocaine in which there are transient ECG changes suggesting ischemia rather than infarction.

As described above, some case reports of acute myocardial infarction temporally associated with cocaine use have documented thrombus in the coronary arteries assessed by acute angiography¹⁰,⁸⁹,⁹¹ with or without underlying atherosclerotic obstruction. Thrombolysis has been successful in these cases.¹⁰,⁸⁹ If patients present with an acute Q wave myocardial infarction temporally related to cocaine and there are no contraindications to thrombolytic therapy (hypertension, seizures, stroke, etc.), thrombolytic therapy should be considered. However, one group⁹⁶ suggested that obtaining confirmatory evidence of infarction (such as regional wall motion abnormality on two-dimensional echocardiography) might be prudent. In addition, if the patient is a known intravenous drug abuser, the risk of bleeding from mycotic aneurysms must also be considered.¹¹⁵

Summary

It is clear that cocaine has cardiotoxic effects. Acute doses of cocaine suppress myocardial contractility, reduce coronary caliber and coronary blood flow, induce electrical abnormalities in the heart, and in conscious preparations increase heart rate and blood pressure. These effects will decrease myocardial oxygen supply and may increase demand (if heart rate and blood pressure rise). Thus, myocardial ischemia and/or infarction may occur, the latter leading to large areas of confluent necrosis. Increased platelet aggregability may contribute to ischemia and/or infarction.

Young patients who present with acute myocardial infarction, especially without other risk factors, should be questioned regarding use of cocaine. As recently pointed out by Cregler,¹¹⁶ cocaine is a new and sometimes unrecognized risk factor for heart disease.

Acute depression of LV function by cocaine may lead to the presence of a transient cardiomyopathic presentation.

Chronic cocaine use can lead to the above problems as well as to acceleration of atherosclerosis. Direct toxic effects on the myocardium have been suggested, including scattered foci of myocyte necrosis (and in some but not all studies, contraction band necrosis), myocarditis, and foci of myocyte
fibrosis. These abnormalities may lead to cases of dilated cardiomyopathy. Left ventricular hypertrophy associated with chronic cocaine recently has been described.117

Arrhythmias and sudden death may be observed in acute or chronic use of cocaine.

Miscellaneous cardiovascular abnormalities include ruptured aorta and endocarditis.

Most of the cardiac toxicity with cocaine can be traced to two basic mechanisms: one is its ability to block sodium channels, leading to a local anesthetic or membrane-stabilizing effect; the second is its ability to block reuptake of catecholamines in the presynaptic neurons in the central and peripheral nervous system, resulting in increased sympathetic output and increased catecholamines (Figure 1). Other potential

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**FIGURE 1.** Schematic describing potential mechanisms of cocaine's cardiotoxic effects. Two primary mechanisms are suggested. First, cocaine inhibits presynaptic reuptake of catecholamines, resulting in a potentiation of the sympathetic nervous system and an increase in catecholamine levels. Second, cocaine inhibits sodium transport across the sarcolemmal membrane, leading to a membrane-stabilizing or local anesthetic effect that has been likened to a type I antiarrhythmic effect. In conscious preparations, increased sympathetic output and catecholamine levels result in an increase in heart rate and in some studies inotropy, which can increase oxygen demand. α-Stimulation of blood vessels causes a vasoconstrictor response with increase in blood pressure in conscious preparations, also resulting in increased oxygen demand. α-Sympathetic stimulation decreases coronary artery caliber, increases coronary vascular resistance, and may lead to coronary spasm in both conscious and anesthetized preparations, thus reducing oxygen supply. Repetitive bouts of coronary spasm might alter or damage the endothelium, contributing to accelerated atherosclerosis that has been reported with cocaine. Increased platelet aggregability has been reported with cocaine (and may be related to increased catecholamines), which can contribute to thrombus formation. All these factors contribute to an imbalance between oxygen supply and demand and may thus lead to myocardial ischemia with subsequent infarction and associated left ventricular dysfunction and arrhythmias. Increased sympathetic output may also contribute to tachyarrhythmias. Catecholamine excess is known to lead to contraction band formation, and this is thought to be related to calcium overload. Recently Isner and Chokshi postulated that cocaine may have a direct effect on calcium flux into blood vessels (and perhaps myocytes), leading to vasoconstriction that may be independent of the sympathetic nervous system (shown in dashed lines). Cocaine's local anesthetic effect may cause direct depression of inotropy (which in most studies surpasses any indirect positive inotropic response caused by sympathetic stimulation) and can lead to a transient cardiomyopathic presentation. This local anesthetic effect can also lead to prolongation of ECG intervals, including QRS and QT duration, perhaps leading to arrhythmias and sudden death, much like the proarrhythmic aspects of agents such as quinidine. Hypersensitivity to cocaine has been postulated but not absolutely proved as a cause of myocarditis. Also, an increase in natural killer cell activity (which may be related to increased catecholamines) has been reported with cocaine and could lead to myocarditis. Scattered foci of myocarditis could lead to a cardiomyopathic presentation and form the nidus for arrhythmias. Not shown in the figure is a potential interaction of cocaine with the renin–angiotensin system. HR, heart rate; BP, blood pressure; WBCs, white blood cells.
mechanisms of cocaine cardiotoxicity include a possible direct calcium effect leading to contraction of vessels and contraction bands in myocytes, hypersensitivity, and increased platelet aggregation (which may be related to increased catecholamine).

The correct therapy for cocaine cardiotoxicity is not known. Calcium blockers, α-blockers, nitrates, and thrombolytic therapy show some promise for acute toxicity. β-Blockade is controversial and may worsen coronary blood flow. In patients who develop cardiomyopathy, the usual therapy for this entity is appropriate.

Note added in proof. Since submission of this manuscript one study suggested that chronic cocaine use is associated with left ventricular hypertrophy and additional cases of cocaine-associated myocardial infarcts in patients with normal appearing coronary arteries have been published.

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