Cardiovascular Complications of Cocaine*

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Cocaine use and abuse continue to overwhelm urban economic, social, and health-care systems. The recreational cocaine use has increased dramatically over the past 15 years as a result of the increased availability of "crack," the inexpensive freebase form. It is estimated that 30 million Americans (about 10% of the population) have used cocaine at least once, 5 million Americans use it routinely, while an additional 5,000 use it each day.1 Approximately 5 to 10% of emergency department visits in the United States are thought to be related to cocaine use.2 Although neurologic, obstetric, gastrointestinal, renal, and endocrine complications have all been associated with cocaine use, the most common complaints from patients entering emergency departments are related to the cardiovascular system.3 The effects of cocaine use place a substantial economic and social burden on the health care system. The widespread use of cocaine and the potential for serious, even lethal, medical complications has led to increased interest in all facets of this complex drug. The large body of information has added to the present understanding of the actions of cocaine and the relation of cocaine use to serious organ dysfunction. The intent of this communication is to review the pharmacologic actions of cocaine and recent literature describing cocaine-induced cardiotoxicity.

Pharmacology

Cocaine (benzoylmethylecgonine, C17H21NO4) is an alkaloid prepared from the leaves of the erythrolyon coca plant.4 The crystalline (powder) form of cocaine is prepared by dissolving the alkaloid in hydrochloric acid to form the water soluble salt, cocaine hydrochloride. Cocaine freebase or "crack" is the cocaine alkaloid in its basic, nonsalt form and is prepared from cocaine hydrochloride by organic extraction from a basic solution with ether.5 Crack, so-called because of the popping sound made when it is heated, is not water soluble, melts but does not decompose when heated, and vaporizes at higher temperatures, thus allowing it to be smoked. When inhaled, vapors are rapidly absorbed across the large surface area of the alveolar membrane.6 Cocaine is absorbed from all body mucous membranes, including nose, lung, and gastrointestinal tract. It can be administered by sublingual, intravenous, rectal, intramuscular, intravenous, and respiratory routes. Onset of cocaine action ranges from 3 s to 5 min depending on the route of administration. Peak effect varies from 1 to 20 min while duration of action ranges from 5 to 90 min. Peak effect and duration of action are also dependent on route of administration.

The peak cocaine serum level occurs within seconds following intravenous administration, and cocaine has an elimination half-life of 30 to 60 min in man.7 It is metabolized by plasma and hepatic cholinesterases to water-soluble compounds, benzoylresorcinol and ecgonine methyl ester, which are excreted in the urine.8 Cocaine is associated with lethal cardiovascular events, including myocardial infarction and ventricular fibrillation. The mechanisms responsible for these cardiotoxic effects of cocaine remain largely unresolved. Cocaine blocks the reuptake of norepinephrine and dopamine at the preganglionic sympathetic nerve endings.9 Because this is the major mechanism for the termination of action of locally released and circulating catecholamines, cocaine increases the synaptic concentration of these monoamines available for binding to adrenergic receptors, thereby enhancing the effect of exogenously administered norepinephrine.10-13 In fact, cocaine potentially increased the response of the blood pressure to injected norepinephrine in experimental cats.10 Cocaine has also been shown to directly release dopamine in the brain, and there is evidence that cocaine, acting via a central nervous system...
mechanism, causes the release of norepinephrine and epinephrine from the adrenal medulla.\textsuperscript{14,15} The net result of this combination of cocaine-induced changes on neurotransmitter release and reuptake is a significant elevation of catecholamine concentration in adrenergic synapses. Several studies have demonstrated dose-related increases in blood pressure and heart rate, mydriasis, and other physiologic consequences of enhanced sympathetic activity following cocaine administration in man.\textsuperscript{16-18}

**Cellular Effects**

Cocaine has local anesthetic by inhibiting the transient inward flux of sodium across the cell membrane during depolarization.\textsuperscript{9} Neurotransmitters released from cardiac sympathetic nerves bind to both \(\alpha\)- and \(\beta\)-adrenergic receptors eliciting a cascade of intracellular responses. Stimulation of \(\beta\)-adrenergic receptors activates adenylate cyclase, increasing cyclic adenosine monophosphate (AMP) levels leading to increased \(\text{Ca}^{++}\) influx into the myocardial cells. This results in further calcium entry, release from cytosolic stores, and increased intracellular free calcium levels, the end result being an increased force of contraction. Whereas \(\alpha\)-adrenergic receptor stimulation activates phospholipase C, increasing inositol triphosphate, stimulation of \(\alpha\)-1-adrenergic receptors activates phospholipase C, which hydrolyzes phosphatidylinositol into two second messengers: inositol triphosphate and diacylglycerol. Diacylglycerol, in turn, activates protein kinase C, which phosphorylates and regulates the calcium channels. These second messengers, in turn, elicit increases in cytosolic calcium. Elevations in cytosolic calcium can provoke oscillatory depolarizations of the cardiac membrane, triggering sustained action potential generation and extra systoles.\textsuperscript{19}

Few studies have analyzed the effect of cocaine on calcium flux at the molecular level. Wide variations in experimental design, including the choice of an animal model vs an *in vitro* study or the administration of a high vs a low dose of cocaine, may confound this attempt. Studies with skinned ferret myocardial fibers,\textsuperscript{20} denervated tissues, and human umbilical arteries *in vitro*,\textsuperscript{21} which are devoid of sympathetic innervation, all support the concept that cocaine may directly alter calcium flux across the cell membrane and contradict the traditional concept of cocaine as exclusively potentiating the response to endogenous catecholamines.\textsuperscript{21} Cocaine-induced alterations in calcium flux were demonstrated by fluorescence using \(\text{Ca}^{++}\) in experiments using the rat aorta.\textsuperscript{22} In these studies, low doses of cocaine (10\textsuperscript{[−5]} M) caused enhanced norepinephrine- and serotonin-induced \(\text{Ca}^{++}\) influx, while high doses (10\textsuperscript{[03]} M) caused decreased \(\text{Ca}^{++}\) influx. Although cocaine potentiated NE- and 5-HT-induced contractions, it had no effect on high-K\textsuperscript{+}-induced contractions. Consequently, the authors concluded that cocaine most likely causes increased receptor-mediated \(\text{Ca}^{++}\) entry, but not voltage-dependent \(\text{Ca}^{++}\) entry.\textsuperscript{22} Other investigators agree that cocaine probably does not increase \(\text{Ca}^{++}\) entry through voltage-dependent channels, since it is unlikely that it causes depolarization of the myocyte.\textsuperscript{21} By inference, therefore, it appears that cocaine increases calcium influx through receptor-operated membrane channels.\textsuperscript{21}

*In vitro* studies examining cocaine’s effect on the working ferret myocardium indicate that low concentrations of cocaine (<10\textsuperscript{[−5]} M) produce positive inotropic responses associated with an increased amplitude and shortened duration of the tricellular \(\text{Ca}^{++}\)transient recorded with aequorin.\textsuperscript{20} Conversely, high cocaine concentrations (> 10\textsuperscript{[−4]} M) not only decreased the amplitude of the aequorin response, but also prolonged the time course of the \(\text{Ca}^{++}\) transient. The higher concentrations were associated with a negative inotropic effect. The mechanisms by which high concentrations of cocaine decrease intracellular calcium is unclear. It has been proposed that it is related to blockade of the sodium channels in the sarcolemma via cocaine’s local anesthetic properties.\textsuperscript{23} Blockade of these channels decreases the amount of sodium entering the cell during each depolarization, which in turn would decrease the amount of sodium available for sodium-calcium exchange. This exchanger consists of an outward sodium current coupled with calcium influx across the sarcolemma during depolarization in a ratio of three sodium ions to one calcium ion. Therefore, cocaine’s local anesthetic properties may lead to decreased intracellular calcium levels and diminished \(\text{Ca}^{++}\) release during each depolarization.\textsuperscript{23}

Another study suggests that cocaine’s negative inotropic effect at high doses may be related to a decrease in myofilament responsiveness.\textsuperscript{23} In this *in vitro* study using human cardiac ventricular trabeculae and coronary artery segments obtained at heart transplantation, cocaine (10[−6] - 10[−3] M) produced negative inotropic and relaxant effects in both vascular smooth muscle and myocardium. In contrast to other studies, low doses of cocaine did not cause a vasconstrictor response or positive inotropy. In cardiac muscle, the negative inotropic response was associated with a simultaneous decrease in peak intracellular \(\text{Ca}^{++}\). However, this decrease was not reproduced in vascular smooth muscle. It was concluded that the depressant effects of cocaine on cardiac vs vascular smooth muscle occur by different mechanisms and that the negative inotropy in smooth muscle is related to a decrease in myofilament responsiveness. Other investigators have also pro-
posed that negative inotropy is associated with decreased Ca\(^{2+}\) sensitivity of the contractile proteins or myofilaments after cocaine administration.\(^{20,24,25}\) Thus, the vascular response to cocaine at high doses may be related to changes in myofilament calcium responsiveness, and this response may be mediated through intracellular changes in cyclic AMP (cAMP)\(^{25}\) or the protein kinase-C system.\(^{26}\) Cocaine may act directly on a second messenger system, such as inositol triphosphate associated with \(\alpha\)-adrenergic receptors or the G protein associated with \(\beta\)-adrenergic receptors, to effect a change in phosphorylation and activation of the calcium channels, resulting in altered calcium flux. Previous studies with vasodilators have demonstrated that agents associated with increased cytoplasmic cAMP levels can uncouple calcium-force relations.\(^{27}\) Perhaps cocaine works in a similar manner to produce its negative inotropic effect at high concentrations. This concept that cocaine may directly interact with second messenger systems rather than the membrane receptors themselves is quite alluring, and future studies are needed to further investigate this theory.

Cocaine’s exact site of action, in terms of altering calcium ion flux, remains unclear. It has been suggested by Isner and Chokshi\(^{21}\) that cocaine may interact with either angiotensin II or histamine H\(_2\) receptors. Kalsner\(^{28}\) speculated that cocaine may alter channel gating characteristics by fitting into a portion of the actual calcium L-channel receptor or its environment.

The cardiac effects of cocaine are extremely complex, with increased adrenergic activity enhancing myocardial contractility, pacemaker activity, and impulse conduction. The local anesthetic actions of cocaine, however, depress these same measures of myocardial function. It appears that the mechanism by which cocaine exerts its cardiotoxic effect is also complex and incompletely understood. Evidence suggests that cocaine-induced alterations in calcium availability or responsiveness play a key role in its ability to exert a direct toxic effect on the myocardium and vasculature.\(^{29}\)

**Myocardial Infarction**

Acute myocardial infarction (MI) is the most frequently reported cardiac consequence of cocaine abuse.\(^{30,31}\) More than 100 cases of cocaine-induced MIs have been reported in the literature since 1982.\(^{32}\) All patients were relatively young, ranging in age from 19 to 71 years, with a mean age of 34 years. Almost 90% of patients with infarction associated with cocaine use are men.\(^{33}\) In fact, a typical profile of a patient with cocaine-induced MI is usually a young man with minimal or absent risk factors for coronary artery disease (CAD). Habitual, recreational, or first-time users may be equally affected. Most patients develop chest pain within minutes; however, MI has been reported up to 15 h after cocaine use. The occurrence of MI is unrelated to the dose of cocaine ingested, frequency of use, or route of administration. Acute MI in patients with angiographically normal coronary arteries has been reported.\(^{34-41}\) Several mechanisms have been proposed for cocaine-induced myocardial ischemia; namely, (1) coronary thrombosis; (2) increased myocardial oxygen demand in the setting of limited myocardial oxygen supply; (3) coronary artery vasoconstriction; and (4) accelerated atherosclerosis.

**Coronary Thrombosis**

Cocaine-induced thrombosis is an important mechanism in the development of MI in the presence of normal or diseased coronary arteries. Coronary arteriography has occasionally demonstrated occlusive coronary thrombi in patients with cocaine-related MI. In addition, autopsies following cocaine-related deaths have also revealed complete thrombotic occlusions of normal and atherosclerotic coronary arteries.\(^{36,42-44}\) Coronary artery thrombosis and subsequent ischemia could be attributed to alteration in platelet and endothelial cell functions.\(^{45}\) Endothelial damage may occur at the site of vascular spasm resulting in thrombus formation, and it has been suggested that cocaine may cause coronary artery thrombosis by initiating coronary artery spasm.\(^{46-48}\) *In vitro* studies have shown that cocaine activates platelets, increases platelet aggregation, and potentiates platelet thromboxane production.\(^{49-51}\) Kugelmass et al\(^{52}\) used flow cytometric analysis of whole blood to which cocaine was added to detect activated platelets. The results of this study indicate that cocaine induces platelet activation in whole blood by release of platelet \(\alpha\)-granule content and the binding of fibrinogen to the platelet’s surface. Pathologic examination of coronary arteries from patients with cocaine-related MI has also demonstrated platelet deposition and platelet-rich organizing mural thrombus.

The possibility of cocaine-induced procoagulant effects was recently suggested by the finding of combined protein C and antithrombin III depletion in patients with cocaine-related arterial thromboses.\(^{53}\) Following discontinuation of cocaine use, the thromboses resolved and levels of both anticoagulants returned to normal. Similarly, Lisse et al\(^{54}\) have reported a high incidence of upper extremity deep venous thrombosis (Paget-Schroetter syndrome) among cocaine users. While superficial thrombophlebitis has been a recognized consequence of intravenous cocaine abuse,\(^{55}\) deep venous thrombosis has not; the apparent association suggests that the role of cocaine may be thrombogenic in nature. Thus, *in situ*
thrombosis resulting from cocaine-induced procoagulant effects may represent another basis for acute MI in patients with previously normal or minimally diseased coronary arteries.

**Increased Myocardial Oxygen Demand**

The sympathomimetic effects of cocaine induce a dose-dependent increase in heart rate and systemic arterial pressure with resultant increase in myocardial oxygen demand. In the setting of fixed coronary artery stenosis, cocaine may cause a mismatch between myocardial oxygen supply and demand, leading to ischemia or infarction. Several studies correlated cocaine with increased rate-pressure product and coronary sinus acidosis. The deleterious effects of cocaine on myocardial oxygen supply and demand are exacerbated by concomitant cigarette smoking.\(^5^6\)

**Coronary Artery Vasospasm**

Focal coronary artery spasm has been suggested as a mechanism whereby cocaine causes MI in individuals free of coronary artery disease.\(^4^0,5^7\) Several case reports are clinically consistent with coronary spasm as a causative factor in patients presenting with acute MI following cocaine use. Sporadic ST-segment elevation associated with chest pain is often seen in these patients who are subsequently shown to have normal coronary arteries by angiography.\(^3^4,3^5,4^0,5^8-6^0\) Ergonovine provocation testing in patients with cocaine-induced ischemia and infarction has been almost uniformly unsuccessful in eliciting vasospasm. Hence, these patients differ pathophysiologically from those with Prinzmetal’s angina.

Mechanisms of coronary spasm from cocaine use are not completely understood. Lange et al\(^6^1\) have demonstrated that small doses of topical, intranasal cocaine result in a significant reduction in epicardial coronary arterial diameters (6 to 9%) and coronary blood flow despite the fact that myocardial oxygen demand increases. These researchers have also shown that cocaine-induced coronary vasoconstriction is mediated by \(\alpha\)-stimulation because it can be reversed by phenolamine and potentiated by \(\beta\)-adrenergic blockage with propranolol.\(^6^1,6^2\) Coronary vasoconstriction appears to have a predilection for the site of an atherosclerotic plaque\(^6^3\) and can be alleviated with nitroglycerine.\(^6^4\)

Chokshi et al\(^6^5\) in experimental models and in humans, have lent support to the concept that cocaine may act independently to produce constriction of vascular smooth muscle. In these experiments, pretreatment with prazosin or phenolamine produced no consistent effect on cocaine-induced vasoconstriction; however, pretreatment with calcium antagonist markedly inhibited cocaine-induced constriction. Similar effects were noted in human umbilical arterial segments, which are devoid of sympathetic innervation.\(^5^2\)

**Accelerated Atherosclerosis**

Several recent autopsy reports indicate an increased prevalence of coronary atherosclerosis in ischemic heart disease temporally associated with cocaine abuse. Intimal hyperplasia and premature atherosclerosis of large epicardial coronary vessels have been observed in young patients with fatal myocardial infection after cocaine use. Examination of endomyocardial biopsy specimens from patients with cocaine-induced chest pain has demonstrated marked thickening of small coronary vessels suggestive of previous arterial injury. Kolodgie et al\(^6^6\) studied 26 subjects, 16 of whom had positive toxicologic screen for cocaine at autopsy. Postmortem blood was collected for lipoprotein analysis. The aorta and right coronary arteries were stained with Sudan IV and the degree of extent of sudanophilia was quantitated by image analysis. They found that habitual use of cocaine, through unknown mechanisms, increased aortic sudanophilia independent of traditional risks.\(^5^7\) Animal studies with rabbits fed a 0.5% cholesterol diet and injected with either saline solution or cocaine showed that rabbits that received cocaine developed atherosclerotic lesions in the thoracic aorta with increased aortic collagen and noncollagen protein synthesis.\(^6^7\)

In summary, cocaine leads to myocardial ischemia and infarction by multiple factors. One possibility is that cocaine use may prompt diffuse or local coronary spasm in normal or atherosclerotic coronary arteries that may lead to stasis of blood with thrombus formation, and cocaine’s effect in increasing platelet aggregability may also contribute to thrombus. Cocaine also increases oxygen demand by increasing heart rate and blood pressure. Long-term use may cause repetitive episodes of spasm and this may cause endothelial damage and subsequent acceleration of atherosclerosis.

**Cardiomyopathy and Myocarditis**

Cocaine has been shown to cause acute depression of myocardial function.\(^6^8-7^1\) Growing numbers of clinical reports have established that cocaine may depress ventricular function directly in the absence of acute MI. Such ventricular dysfunction may result from direct toxic effect of cocaine on cardiac muscle, myocarditis, or both. In addition to its acute myocardial effects, cocaine has been implicated as a cause of chronic myocardial dysfunction. Wiener et al\(^7^2\) reported two cases of dilated cardiomyopathy with normal coronary arteries following long-term use of
caine. Two other reports linking cocaine use to left ventricular dysfunction have been published since then.73,74

Bertolet et al75 have studied the incidence of myocardial dysfunction associated with long-term cocaine use. Eighty-four asymptomatic cocaine abusers underwent cardiac evaluation, including radionuclide angiography, after a 2-week period of abstinence from the drug. Seven percent of these drug abusers (six patients) were found to have left ventricular dysfunction. Four had globally depressed left ventricular function and two had regional wall motion abnormalities. All these patients were asymptomatic, healthy, had no evidence of myocardial dysfunction by physical examination, or significant risk factors for CAD. The effects of cocaine on myocardial contractility have also been investigated, in vivo, in intact animals. Hale et al70 found that bolus injections of 10 mg/kg of cocaine produced a marked reduction in dp/dt and a significant increase in left ventricular size (by echocardiography) in anesthetized dogs. Wilson et al71 studied the effects of intravenous cocaine in phenobarbital-anesthetized open-chest dogs. Doses in excess of 100 mg produced a decrease in dp/dt that was followed by a reduction in coronary artery and sinus blood flow, as well as myocardial oxygen consumption. These findings suggested that myocardial depression was not ischemic as the rate-pressure product was kept constant.

Fraker et al76 compared the effects of cocaine on left ventricular function in both conscious and sedated dogs. Mean blood pressure, heart rate, coronary blood flow, and rate-pressure products increased after intravenous administration of cocaine at 4 mg/kg in conscious dogs, but with the exception of coronary blood flow, no significant changes were seen in sedated dogs. Coronary vascular resistance, despite an increase in myocardial oxygen demand resulting from the rise in rate-pressure product, actually increased significantly in conscious dogs in response to cocaine. After sedation with phenobarbital, the same dose of intravenous (IV) cocaine did not alter blood pressure or heart rate. Coronary blood flow, however, was decreased at 2 and 5 min after cocaine administration in these sedated dogs. Regional ejection fraction was significantly decreased in both conscious and sedated groups. These findings suggest that the observed myocardial depression resulted from the local effect of cocaine on myocardium rather than O2 consumption demand mismatch.

Reversible depression of myocardial systolic function has been attributed to a direct "toxic" effect of high levels of circulatory catecholamines on cardiac myocytes. Eisenberg et al77 studied the effect of cocaine in 20 subjects after single IV doses (1.2 mg/kg body weight vs 0.6 mg/kg) using 12-lead electrocardiography and quantitative two-dimensional echocardiography. Eisenberg et al concluded that IV cocaine, in doses commonly self-administered in nonmedical settings, does not cause myocardial ischemia or left ventricular dysfunction. They speculate that cardiac complications of cocaine are induced by idiosyncratic coronary artery vasospasm, by exceptionally high dosage, or by cocaine-induced coronary artery thrombosis.72

Profound sympathetic stimulation causes subendocardial ischemia and myocarditis characterized by contraction band necrosis. Several autopsy studies have reported a high incidence of myocardial contraction bands in cocaine-related deaths as compared with controls.44,78,79 Cocaine use is also associated with adrenergic stimulation that may be prolonged and recurrent in habitual users. Recurrent exposure of the myocardium to cocaine-induced catecholamine excess may result in myocarditis, contraction bands, and cardiomyopathy as is known to occur from catecholamine excess associated with pheochromocytoma.80-82 Cocaine-induced hypersensitivity or immunologic reaction could also potentially lead to cardiomyopathy.

Myocarditis has been frequently reported in cocaine abusers dying of drug-related causes. Histologic examination of myocardial tissue from 40 patients who suffered cocaine-related deaths revealed active myocarditis in 20%.42 Inflammatory cellular infiltrates consisting of lymphocytes and eosinophils were noted. The cause of myocarditis is unknown; however, infectious agents are a possible primary or contributing factor. Histologic sections did not show any bacteria, fungi, or viral inclusions, but no serologic tests were available in these patients. The presence of eosinophil infiltrations may represent a hypersensitivity myocarditis secondary to cocaine or associated contaminants. Cardiotoxic heavy metals, eg, manganese have also often been found in street preparations of cocaine. In long-term users, these heavy metals may also contribute to development of a cocaine-related cardiomyopathy.

**Arrhythmias**

There is increasing evidence that the use of cocaine can trigger cardiac arrhythmias presumably from an enhanced sympathetic state and from direct effects of this drug on the heart. To our knowledge, however, electrophysiologic studies assessing its effects in humans have not yet been published. Several mechanisms for cocaine-induced cardiac arrhythmias have been proposed: (1) alteration of myocardial automaticity by direct effect on myocardial tissue; (2) automatic dysregulation by enhanced adrenergic and neurohumoral stimulation; (3) induction of ischemia...
with resultant electrical disturbances; and (4) potential of reentrant arrhythmias.

Cocaine used as a local anesthetic agent during laryngoscopy has been observed to increase the frequency of premature ventricular complexes. Nanji and Filipenko reported asystole and ventricular fibrillation as the presenting sign of cocaine intoxication. Ventricular fibrillation, polymorphic ventricular tachycardia, and supraventricular tachycardia have been documented in ischemia and myocardial infarction after cocaine use. Benchimol et al reported an accelerated ventricular rhythm with left bundle branch block configuration in young men who presented with palpitations (but no chest pain) following cocaine administration. Isner and associates previously described ventricular tachycardia and ventricular fibrillation in young patients following cocaine use who subsequently had no evidence of MI, angiographically normal coronary arteries, a negative ergonovine challenge, and normal results of electrophysiologic study. Recent evidence suggests that calcium channel blockers may protect against cocaine-induced ventricular fibrillation. Elevations in intracellular calcium levels may provoke oscillatory after-depolarization during diastole. If the amplitude of the after-potential is sufficient to reach threshold, a sustained action potential may result. There is evidence to support the theory that a calcium-dependent ionic current may contribute to both the initiation and maintenance of ventricular fibrillation and studies in vitro have shown that calcium loading can induce spontaneous after-depolarization in isolated myocardial cells. Furthermore, intracellular calcium levels are known to increase during myocardial ischemia, and studies have shown cocaine-induced arrhythmogenesis in the presence of myocardial ischemia. The authors of this study concluded that one potential mechanism by which verapamil offered protection against arrhythmias was by antagonizing catecholamine-mediated increases in cellular calcium. Kimura et al studied the effect of cocaine on isolated feline ventricular myocytes by recording action potentials and membrane currents using a patch clamp technique and found that cocaine can prolong action potential duration and induce early after-depolarization (EAD) and triggered activity by blocking the delayed rectifier K current. Although this may be an important mechanism, cocaine arrhythmias may not all be due to primary disturbances in ion flux.

Circulating levels of epinephrine and norepinephrine in actively intoxicated cocaine users are elevated as much as fivefold. It is well known that norepinephrine and increased sympathetic tone reduce cardiac electrical stability and predispose to lethal arrhythmias, particularly under conditions of ischemia. In addition, during postmortem examination of cardiac tissue, contraction bands have been found in 93% who experienced sudden cardiac death related to cocaine use. These bands have been implicated as a possible cause for lethal reentrant arrhythmias. Recent studies in humans have shown that long-term cocaine use is associated with increased left ventricular mass and wall thickness. Because left ventricular hypertrophy is known to be an independent risk factor for ventricular arrhythmias, this may provide the substrate for myocardial ischemia and arrhythmias in cocaine users.

In humans, large doses of cocaine prolong the PR, QRS, and QT intervals by inhibition of sodium channels at the membrane level. In excess, cocaine acts as type I antiarrhythmic agent. Recent electrophysiologic studies have demonstrated that cocaine causes prolongation of the atrial effective refractory period, AV nodal effective refractory period, AH interval, HV interval, and intra-atrial conduction time. Cocaine has also been shown to cause sinoatrial nodal and atrioventricular nodal block. Isner et al reported a case of complete heart block related to cocaine. The patient was treated with a transvenous temporary pacemaker.

**Aortic Rupture**

Death from acute aortic rupture has been described in an otherwise healthy young man who died while smoking freebase cocaine. Autopsy examination of the aorta revealed a circumferential tear through the intima and media of the ascending aorta 2 cm above the sinotubular junction. This complication was thought to result from acute and substantial increase in systemic arterial pressure induced by cocaine. In addition to aortic rupture, cocaine-related rupture of myotic and intracerebral aneurysm have also been reported.

**Endocarditis**

An association has been noted between cocaine use and endocarditis among IV drug-abusing populations. Use of cocaine, in comparison with other drugs, has been reported to be an independent risk factor for the development of endocarditis. Intranasal cocaine use has been suggested as a cause of staphylococcal bacteremia in one patient. Why cocaine use would more likely predispose to endocarditis than would other injected drugs is not immediately obvious, but the association might reflect usage patterns, differences in bacterial flora, or perhaps a more direct effect of cocaine itself. The manner in which cocaine is prepared for injection could explain the increased risk for endocarditis. For
example, heroin is “cooked” to dissolve it before injection; cocaine is not.

Stress predisposes to endocarditis. Cocaine use and addiction constitute intense physiologic stress. Perhaps the elevations in heart rate and systemic arterial pressure that accompany cocaine use induce valvular and vascular injury that predisposes to bacterial invasion. Also, cocaine, through unknown mechanisms, may play a more direct role in the pathogenesis of endocarditis. Perhaps prolonged use causes subtle interstitial or endothelial valvular damage leading to platelet-fibrin deposition, the hypothesized trigger for bacterial endocarditis.

As opposed to endocarditis associated with other illicit drugs, the left-sided cardiac valves may be more commonly infected in cocaine abusers who develop endocarditis.

**Pneumopericardium**

Aedrouny and Magnusson have described a case of pneumopericardium related to cocaine inhalation. This complication of cocaine abuse apparently results from the user’s attempts to enhance the drug effects by applying positive ventilatory pressure.

**Left Ventricular Hypertrophy**

Brickner et al. studied left ventricular mass in 30 cocaine abusers and 30 control subjects using two-dimensional echocardiography. Patients and controls had similar baseline characteristics, including age, resting blood pressure, height, weight, and body surface area. The cocaine-abusing group was found to have increased left ventricular mass index. Also, posterior wall thickness was increased in 13 cocaine abusers (43%) compared with 4 controls (13%). It is speculated that long-term adrenergic stimulation of the myocardium, intermittent cocaine-induced blood pressure elevation, or both may be responsible for this phenomenon.

**Conclusion**

Cocaine is a complex drug with dangerous cardiac side effects. The complexity of the cardiovascular action of cocaine undoubtedly results from the wide diversity of the biologic activities inherent in this one drug. The increase in cocaine abuse has resulted in an increase in the cocaine-related emergency department visits, hospital admissions, and mortality. The possibility of cocaine effect should be seriously considered in young patients with minimal risk factors for cardiac disease presenting with MI, dilated cardiomyopathy, myocarditis, or cardiac arrhythmias.

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