Cardiac Effects of Cocaine: A Review

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Over the past 15 years, there has been a dramatic increase in the abuse of purified cocaine preparations throughout the industrialized world. The potential lethality of the drug is now recognized, and a growing series of case reports indicate that cardiotoxicity may be an important factor in the morbidity and mortality associated with the drug. Acute myocardial infarction is a demonstrated risk both in subjects with and without pre-existent coronary artery disease. The arrhythmogenic potential of cocaine is less clear and appears to have been overemphasized, although several documented cases of ventricular arrhythmia following cocaine use have been reported. Cardiomyopathy and myocarditis associated with cocaine have also been described, but an etiologic relationship is presently inferential. Based upon presumed pathophysiologic mechanisms, beta adrenergic blocking agents are recommended for arrhythmias, and calcium channel blocking agents and/or nitrates for ischemic syndromes related to cocaine. It is emphasized that these recommendations are based upon a paucity of relevant clinical studies, and controlled clinical trials to establish their efficacy have not been performed.

In recent years, it has become clear that cocaine represents a major long-term hazard to the physical as well as the psychological well-being of its users. The rapid sequence of deaths, during the 1970s and 1980s, of musicians and other entertainment figures known to have been heavy cocaine abusers has made that fact painfully apparent. It now seems reasonable that the conclusions drawn by Bozarth and colleagues in their animal experiments applies equally to man as to the laboratory rat—unlimited access to cocaine often results in an unstable pattern of massive self-administration which is attended by a very high short-term mortality [1]. It is noteworthy that, in Bozarth’s experiments, animals given unlimited access to cocaine had more than double the mortality of animals given unlimited access to heroin.

The unexpected death in 1986 of University of Maryland star basketball player, Len Bias, was attributed by the Maryland medical examiner to an acute cardiac arrhythmia resulting from recreational use of cocaine. Although the fatal sequence of events in the Bias case is far from clear, this incident was widely reported in the lay press and drew national attention to the issue of cocaine cardiotoxicity. Because it is estimated that between five and ten million Americans use the drug with some regularity, the issue is one of significant public health importance. As its use has increased in the past ten years, there has been a concomitant increase in emergency room visits and deaths associated temporally with that use [2]. The degree to which cardiovascular toxicity contributes to these events is the subject of this literature review, which focuses on a description of specific clinical events and their laboratory manifestations.

Abbreviations: AV: atrioventricular  ECG: electrocardiogram

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PHARMACOLOGY

Cocaine is an alkaloid of the South American shrub Erythroxylon coca which has been extensively cultivated in the mountainous regions of Peru and Bolivia since at least the seventh century A.D. Revered by the Incas for its psychopharmacologic properties, it is the only known naturally occurring local anesthetic. Its use in ophthalmologic, ear, nose, and throat surgery is well known but declining, primarily because of a perceived higher toxicity in the form of cardiac arrhythmias [3]. In general, cocaine is well tolerated as an anesthetic agent, and clear-cut episodes of cardiac toxicity are not well documented. It is emphasized, however, that use of cocaine in the medical care setting is in no way comparable to "street use" in which dosage, route of administration, level of activity, and other factors are highly variable and uncontrolled.

Cocaine's major pharmacologic effect relative to the cardiovascular system appears to be its inhibition of the re-uptake of norepinephrine released into the synaptic cleft by sympathetic neurons [4]. Because re-uptake is a major route for clearance of neurotransmitter from its active receptor sites, the result is a potentiation of the response of sympathetically innervated organs to infused catecholamines as well as to direct sympathetic stimulation. In vascular smooth muscle derived from the rat tail artery, for example, addition of cocaine to the muscle bath results in an increase in the percentage of maximal contractile response seen after exposure to given concentrations of norepinephrine (Fig. 1) or to specific rates of electrical nerve stimulation [4]. In addition, there is experimental evidence that cocaine may, in peripheral tissues, produce direct alpha adrenergic stimulation through release of norepinephrine stored in sympathetic nerve terminals [5].

The importance of the sympathetic nervous system in the regulation of cardiovascular hemodynamics, energetics, and electrophysiology is well established. Activation of post-junctional alpha receptors is the major determinant of coronary and peripheral vascular resistance. Norepinephrine-medicated cardiac beta receptors regulate heart rate and myocardial contractility—both of which are major determinants of myocardial oxygen consumption. Cardiac sympathetic innervation affects the rate of spontaneous depolarization (automaticity) of myocardial Purkinje fibers, the speed of atrioventricular (AV) nodal impulse transmission, and regional myocardial repolarization (refractory periods). Sympathetic stimulation is believed to play a critical role in the arrhythmogenic long QT interval syndromes, ventricular arrhythmias occurring during the course of acute myocardial infarction, and sudden death related to psychologic stress. For these reasons, the theoretical potential for a potent sympathomimetic agent such as cocaine to produce untoward cardiac events is great.

In man, the acute effects of cocaine on basic cardiovascular parameters have been studied under controlled conditions. The pattern of response to intravenous, intranasal, or inhaled "freebase" cocaine is similar. After single-dose administration, the drug induces a dose-dependent increase in blood pressure and heart rate, which reaches a peak within 30 minutes and dissipates within approximately one hour. The magnitude of these effects is modest. Intranasal administration of 100 mg of cocaine (a usual recreational dose) produces a mean heart rate increase of about 20 beats/minute and a mean increase of systolic and diastolic blood pressure of approximately 20 mm Hg [6]. The effects are somewhat greater with intravenous administration, where 25–32 mg results in an increase in heart rate of approximately 30 beats/minute and a 25 mm Hg increase in blood pressure. The response to "freebase" inhalation is similar to that after intravenous administration [7] (Fig. 2).
Although these effects are significant and clearly serve to increase myocardial oxygen demand, they are well within the range of physiologic changes observed in normal man. During treadmill exercise, for example, plasma catecholamines increase dramatically, heart rate increases of more than 50 beats/minute are expected, and systolic blood pressures in excess of 200 mm Hg are commonly observed. These changes regularly produce myocardial ischemia in patients with fixed obstructive coronary lesions. Myocardial infarction and life-threatening arrhythmias are rare, however, even in patients with far-advanced coronary artery disease.

Sympathetic activation consequent to cocaine may differ from that accompanying exercise, however. Whereas peripheral vascular and coronary vasodilation are expected during muscular exercise, cocaine may increase coronary vascular resistance and reduce coronary blood flow, as was seen in one cocaine study [8]. It should be emphasized that the effects of cocaine on coronary blood flow and other important physiologic parameters, including peripheral vascular resistance, myocardial contractility, and electrophysiologic parameters, have not been studied in man.

**CLINICAL SYNDROMES**

*Fatal Cocaine Poisoning*

The importance of direct cardiotoxicity in the acute syndrome most often associated with cocaine-induced fatality is uncertain, but it appears to be minimal. This
syndrome, which has been labeled "cocaine poisoning," is characterized by generalized central nervous system stimulation and includes agitation, hallucinosis, hyperthermia, and diaphoresis [9]. Generalized seizures are prominent and usually play an important role in producing a fatal outcome. Sinus tachycardia and hypertension are observed, and the terminal event is often related to cardiovascular collapse. The cause of death appears to be multifactorial and related to cardiorespiratory collapse secondary to a combination of hyperthermia, hypoxia, acidosis, and central nervous system stimulation. There is no evidence that direct cardiotoxicity is a major factor leading to terminal hypotension which, in animal studies, does not occur if hyperthermia and seizures are prevented.

Ventricular arrhythmias and/or asystole also occur but do so in the context of profound metabolic acidosis secondary to prolonged seizure activity [9]. Because these metabolic derangements may produce or exacerbate ventricular arrhythmias in any

FIG. 2. Comparison of the global rating of subjective high and of the cardiovascular effects of smoke inhalation of freebase cocaine and of intravenous injection of cocaine HCl. Reproduced from [7]. Courtesy of The C.V. Mosby Company.
setting, their occurrence cannot be ascribed directly to cocaine. A contributory effect cannot be excluded, however, on the basis of available data.

Recent animal experiments also suggest that hyperthermia and seizures, not cardiac arrhythmias, are the major cause of death after cocaine overdose. In the conscious dog, Catravas et al. reported that continuous infusion of cocaine HCl (0.5 mg/kg/minute) resulted in incessant tonic-clonic seizures and a progressive decline in arterial pH [5]. Heart rate and blood pressure increased progressively, and there was little change in peripheral vascular resistance. Approximately one to two minutes prior to death, an abrupt decline in blood pressure to zero was noted, followed by respiratory arrest. Pre-treatment with agents which prevent the development of hyperthermia and/or seizures was effective in preventing a fatal outcome [10]. Cardiac arrhythmias were not observed, and pre-treatment with propranolol had no effect on survival. Although occasional subendocardial hemorrhages were noted at autopsy, these studies do not suggest that direct effects of cocaine on the cardiovascular system are critical in producing the fatal syndrome.

**Cardiac Arrhythmias**

The arrhythmogenic potential of cocaine in man remains uncertain. Although it is frequently stated in the medical literature that cocaine may induce a variety of supraventricular and ventricular arrhythmias, only a handful of well-documented cases have been reported. In many instances, cardiac arrhythmias ascribed to cocaine have occurred, as noted above, in the setting of profound metabolic derangements resulting from generalized seizures [9]. (In the Len Bias case, a seizure accompanied by apnea and cardiac arrest appears to have been the terminal event [11]. Despite the medical examiner's subsequent statements, no evidence has been presented to suggest that a cardiac arrhythmia was primary). Other documented arrhythmic episodes have accompanied acute ischemic syndromes such as myocardial infarction [12]—a setting in which fatal ventricular arrhythmias are regularly noted in the absence of drug use.

Nevertheless, because of its pharmacologic properties and ability to produce a hypersympathetic state, it is probable that cocaine may produce or exacerbate cardiac arrhythmias under certain circumstances. Benchimol has observed accelerated idioventricular rhythm following repeated intravenous injections of cocaine [13] (Fig. 3), and there are several case reports in which cocaine may have been the primary factor in malignant ventricular arrhythmia production [14]. Considering its widespread use and the fact that no arrhythmias have been noted in studies in which cocaine was administered to healthy volunteers, its arrhythmogenic potential appears to be modest. This conclusion must be considered preliminary, however, as systematic study of the effects of cocaine on cardiac electrophysiology and arrhythmia occurrence in man has not been performed. Of particular interest, the effects of large repeated doses of cocaine taken over periods of days or weeks have not been examined.

**Ischemic Syndromes**

Coronary ischemic syndromes have been definitely related to cocaine use and constitute the bulk of untoward cardiovascular events directly attributable to the drug. Over the past five years, approximately 20 cases of cocaine-associated myocardial infarction have been reported [12,14–24]. In some cases, the relationship of the ischemic event to cocaine remains uncertain. In the case reported by Schachne et al. in a letter to the *New England Journal of Medicine* [16], for example, the onset of chest
pain occurred fully five hours after drug ingestion. It is difficult to relate an event occurring in this time frame to cocaine on the basis of known pharmacologic actions of the drug. Nevertheless, there are well-documented cases in which chest pain has followed immediately upon administration of cocaine. It is important to emphasize that the occurrence of myocardial infarction after cocaine use does not appear to be related either to dose or to route of administration. Instances of myocardial infarction are documented in which small doses administered via the intranasal route have been implicated.

The most dramatic instances of cocaine-associated myocardial infarction have occurred in young individuals without fixed obstructive coronary disease. In a case reported by Rollingham et al., a 24-year-old man presented to an emergency room following his first exposure to intravenous cocaine [12]. Shortly after drug injection, the patient experienced nausea, diaphoresis, and agitation. One hour later, substernal chest pain developed, and the patient sought medical attention. Blood pressure was 160/100 mm Hg, and sinus tachycardia (168 beats per minute) was noted. Recurrent ventricular tachycardia and ventricular fibrillation requiring resuscitation occurred. An electrocardiogram showed ST elevation in the anterior precordial leads (Fig. 4), and an acute anterior myocardial infarction with a peak creatine phosphokinase elevation greater than 5,000 U/L evolved. Coronary angiography performed 12 days following admission revealed normal coronary arteries.

At least five similar cases, all involving individuals in their twenties, have been reported in which no significant coronary artery disease was demonstrable by coronary angiography [14,15]. The pathogenesis of this syndrome has given rise to intense speculation. The leading hypothesis is that it results from acute coronary spasm induced by cocaine. Coronary spasm is a known precipitant of transmural ischemia, and in some instances myocardial infarction, in patients with vasospastic (Prinzmetal's) angina. In most such patients, however, focal coronary spasm is usually observed when intravenous ergonovine is administered in the cardiac catheterization laboratory. Although ergonovine challenge has been given to several patients with cocaine-induced myocardial infarction and normal coronary arteries, induced coronary spasm has not occurred [14]. The scientifically critical but ethically questionable human experiment—rechallenge with cocaine—has not been reported, and the hypothesis that coronary spasm is the responsible mechanism remains unproven. The possibility that in situ thrombosis alone or in conjunction with focal coronary spasm is a factor in the pathogenesis of this syndrome must also be considered.

In the majority of instances, cocaine-associated myocardial ischemic syndromes
have occurred in patients with demonstrable coronary artery disease. Such individuals are usually somewhat older (in their thirties or forties) than the group discussed above, and many have additional coronary risk factors such as cigarette smoking. At the time of coronary angiography, critical narrowings are noted in one or more coronary arteries, with the majority exhibiting single-vessel disease. Thus, in these patients, cocaine appears to play a role in precipitating an acute event but cannot be considered exclusively responsible.

Several pathogenetic mechanisms may be invoked to explain the occurrence of angina and infarction in patients with pre-existent coronary obstruction. As noted previously, cocaine increases heart rate and blood pressure and so leads to a significant augmentation in myocardial oxygen requirements. In patients with regional myocardial blood flow limited by fixed coronary obstruction, this process may result in a critical oxygen supply/demand imbalance. In addition, coronary vasospasm may play an important ancillary role. It is now apparent that dynamic reduction in coronary artery diameter—often at the site of an atherosclerotic plaque—is an important precipitating or contributing factor in the development of unstable angina and acute myocardial infarction in many patients with underlying coronary artery disease. If cocaine proves capable of inducing localized spasm in patients with normal coronary arteries, this effect could also be a factor in those individuals with underlying fixed obstructive lesions.

Generalized reduction in coronary flow is another potential factor. In a study reported by Pierre et al. in abstract form, intravenous administration of cocaine in the anesthetized dog produced a significant fall in coronary blood flow and an increase in coronary vascular resistance [8]. In patients with fixed obstructive coronary disease, an increase in myocardial oxygen demand coupled with a reduction in coronary blood flow can precipitate ischemia and result in myocardial infarction.
flow would constitute a potent stimulus for provoking an acute ischemic syndrome even in the absence of localized spasm. Again, it must be emphasized that the effects of cocaine on coronary blood flow in man are unknown, and this mechanism is at present hypothetical.

Cardiomyopathy and Myocarditis

Several reports have recently appeared in which cardiomyopathy has been attributed to cocaine [25]. Clearly, patients who have sustained one or more episodes of myocardial infarction frequently develop regional wall motion abnormalities, a reduction in left ventricular ejection fraction, and congestive heart failure. In such patients, the cardiomyopathy produced is secondary to infarction and is termed "ischemic cardiomyopathy." Most reported instances of cocaine-associated cardiomyopathy fall into this category and are not related to direct cardiotoxicity of the drug. Other case reports suggest the possibility that diffuse cardiomyopathy may result from cocaine abuse in the absence of infarction. None are definitive. Nevertheless, it is known that profound sympathetic stimulation may produce subendocardial necrosis in experimental animals and, as mentioned above, such lesions are noted in dogs given lethal intravenous infusions of cocaine. In patients with pheochromocytoma exposed to chronically elevated catecholamine levels, diffuse cardiomyopathy is known to occur [26]. For these reasons, cocaine, despite the lack of clear-cut documentation, must be considered theoretically capable of producing the syndrome of diffuse cardiomyopathy. Controlled observation of cocaine users over time will be required to establish this syndrome with certainty.

Recently, Isner et al. reported a case of acute myocarditis in a 25-year-old man who presented with chest pain, dyspnea, syncope, and complete heart block following long-term use of "freebase" cocaine [14]. An endomyocardial biopsy demonstrated a diffuse inflammatory cell infiltrate and foci of myocardial necrosis. The patient was treated with prednisone and azathioprine with resolution of the biopsy findings. Although it is possible that this case represents cocaine-induced myocarditis, the association must be considered inferential.

OTHER CARDIOVASCULAR SYNDROMES

Several other cardiovascular syndromes have been associated with cocaine use in isolated case reports. In a dramatic case reported by Barth et al., rupture of the ascending aorta occurred during cocaine intoxication [27]. At necropsy, a circumferential tear was present in the ascending aorta. The patient had a history of chronic hypertension, and it is probable that aortic dissection occurred secondary to increases in systemic blood pressure following cocaine use. Adrouny and Magnusson [28] described an unusual practice adopted by some "freebase" cocaine users in which exhaled vapors containing the drug are passed to a partner via direct mouth-to-mouth contact. In the case reported, pneumopericardium and pneumomediastinum developed in the 20-year-old, previously healthy man subsequent to this practice. Other similar cases have been reported [29,30]. An episode of fatal pulmonary edema following the use of "freebase" cocaine was described by Alred and Ewer [31].

TREATMENT

Recommendations concerning the treatment of cardiac events resulting from cocaine are based upon fragmentary clinical data and animal studies. In the 1970s
Rappolt et al. reported on the successful use of intravenous propranolol in patients who became agitated following cocaine use [32]. They reported that this drug appeared to be a specific antidote to the restless and mental symptoms resulting from cocaine intoxication. As noted earlier, however, propranolol is not effective in preventing a fatal outcome in experimental studies of lethal cocaine poisoning [5] and is probably of little value in case of serious overdose [33]. It should also be noted that, in one case report, intravenous propranolol administration resulted in paradoxical hypertension in a patient treated for presumed cocaine intoxication. Nevertheless, beta blockers are frequently recommended for use in treating supraventricular or ventricular arrhythmias in the setting of the hypersympathetic state induced by cocaine. In instances, such as acute myocardial infarction where concern exists regarding the myocardial depressant effects of beta adrenergic blocking agents, use of the short-acting agent, esmolol, may be advantageous.

Because coronary spasm is suspected to play a role in cocaine-induced myocardial ischemia and infarction, nitrates and/or calcium channel blockers are logical therapeutic choices in patients presenting with acute myocardial ischemic syndromes in the setting of cocaine use. Sublingual or intravenous nitroglycerin may be used, and this agent will have the additional property of lowering elevated blood pressure, if given parenterally. Relief of coronary spasm as well as blood pressure reduction might also follow administration of sublingual nifedipine or intravenous verapamil. Care should be taken when using the latter agent in settings in which its negative inotropic effects might be deleterious. It is interesting that, in contrast to propranolol, concomitant administration of the calcium channel blocking agent nitrendipine produced a fourfold increase in the required lethal dose of cocaine in the laboratory rat [34]. Prophylactic administration of calcium channel blockers to patients with a history of cocaine-induced coronary ischemic syndromes may prove useful in patients who cannot be persuaded to discontinue drug use. Controlled clinical trials will be required to substantiate the efficacy of these interventions.

CONCLUSION

Cocaine is widely abused throughout the industrialized world. Although well known to produce a hypersympathetic state similar to that produced by amphetamines, its potential for serious cardiotoxicity has only recently been appreciated. It would appear, from the paucity of well-documented case reports, that serious cardiotoxicity is a statistically uncommon phenomenon. Nevertheless, acute myocardial infarction is a demonstrated risk even in subjects without pre-existent coronary disease. The extent to which cocaine produces cardiac arrhythmias and direct myocardial damage is presently uncertain. Further animal experiments, observational studies, and clinical trials are necessary to determine the incidence, pathogenesis, and optimal management of cardiovascular reactions to cocaine. Of particular interest might be case-control studies designed to ascertain the prevalence of ischemic heart syndromes in young individuals who do and do not use cocaine recreationally. Additional human and animal studies of interest would include pharmacologic studies in which cocaine is administered in combination with other recreational drugs, including alcohol.

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