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Cardiovascular Complications of Cocaine Use

Carla Gambarana

Department of Neuroscience, Pharmacology Unit, University of Siena, Italy, EU

Summary

As cocaine use has become prevalent, an increasing number of reports of cocaine-associated morbidity and mortality, largely because of central nervous system and cardiovascular toxicity, appeared. Cardiovascular toxicity is broad, and it may also lead to neurological, psychiatric and other organ-specific symptoms. Cocaine may induce myocardial ischemia by increasing myocardial oxygen demand while simultaneously decreasing myocardial oxygen supply. Most of the cardiovascular toxic effects elicited by cocaine are likely related to its ability to selectively bind to the L-type calcium channels and the potassium channels that modulate the *I_{Kr}* current. In addition, cocaine may promote intracoronary thrombosis in the absence of coronary atherosclerosis. This article briefly reviews the current knowledge regarding the cardiovascular effects of cocaine, providing insight into some of the underpinning mechanisms.

Key Words: adrenergic receptors, monoamine uptake, L-type calcium channels, acute coronary events

In the United States cocaine is, after marijuana, the most often used substance of abuse [4]. It is also the drug of abuse most widely involved in requests for emergency intervention [15]. Approximately 40% of the subjects who visit an emergency department because of a substance-related condition have been using cocaine; of these, 37% are aged between 35 and 44. The number of requests for emergency intervention associated with cocaine use increased by 47% in the period ranging between 1999 and 2002, and is assumed to be on a steady upward path. Cocaine use is the most frequent cause of death correlated with substances of abuse [14]. Forty percent of those who apply to an emergency unit for cocaine-related issues present with chest pain, and 25% of all cases of non-fatal heart attacks in young subjects are associated with cocaine use [8]. The acute and long-term uses of cocaine have both been correlated with a variety of cardiovascular complications: angina pectoris, myocardial infarction, cardiac arrhythmias, acute reversible myocarditis, dilatative cardiomyopathy and sudden death [3, 7, 9]. Moreover, a wide range of cardiovascular complications may develop, involving both large arteries and small vessels and leading to a variety of neurological, psychiatric or other specific organ related symptoms (Table 1) [7, 2]. Despite all these issues, there is a widespread

belief that recreational use of cocaine is safe.

Both cocaine chlorhydrate and free-base cocaine are well absorbed via all transmucosal routes. Peak plasma concentrations and onset of the effects have been recorded in an interval ranging between 30 seconds and 2 minutes after intravenous administration or inhalation; the effects peak about 30 minutes after intranasal administration; when absorption occurs gastrointestinally the peak may come as late as 90 minutes after administration. The duration of effects is proportional to the speed of onset; it is around 15-30 minutes after intravenous administration or inhalation, 1 hour after intranasal administration and up to 3 hours after gastrointestinal absorption.

The risk of acute myocardial infarction is greatest in the 60 minutes that follow cocaine use in subjects with a relatively low risk factor [7]. Myocardial infarction subsequent to use of cocaine is not correlated with the dose taken, its route of administration, or the frequency of use: it has been described at doses ranging between 200 and 2,000 mg, after each of the different routes of administration just indicated, both in habitual and first-time users. Moreover, there is no evidence to suggest that the onset of cardiovascular complications occurs solely in the presence of pre-existing vascular disorders or other conditions [3, 7, 9]. In about 50% of patients

Correspondence: Carla Gambarana, MD, Dept. Neuroscience, University of Siena, Via Aldo Moro, 4 - 53100 Siena, Italy
E-mail: gambarana@unisi.it

| Table 1. Vascular complications of cocaine use | |
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| System | Complications |
| Central nervous system | Intracerebral hemorrhage, cerebral infarction (stroke), seizures, migraine, vasculitis, blindness |
| Cardiac system | Coronary vasospasm, heart attack, myocardial infarction, arrhythmias, myocarditis, cardiomyopathy |
| Aorta and vascular system | Dissection and / or aortic rupture, hypertension |
| Gastrointestinal system | Mesenteric ischemia and infarction, gastrointestinal perforation, liver failure, splenic infarction |
| Respiratory system | Pulmonary edema, lung infarction |
| Musculoskeletal system | Rhabdomyolysis |
| Cutaneous system | Ischemia |
| Female reproductive system | Abruptio placentae, miscarriage, prematurity, developmental delays, growth retardation, congenital malformations |
| Genitourinary system | Renal or testicular infarction myoglobinuria with renal failure |

Modificato da: Goldfrank and Hoffman, 1991

affected by cocaine-related myocardial infarction, angiographic examination revealed no signs of atherosclerosis of the coronary arteries. Several autoptic studies have, however, demonstrated the presence of atherosclerotic lesions associated with the formation of thrombi in young cocaine users: thus, cocaine use seems to be correlated with early-onset atherosclerosis and thrombosis. Many of the patients affected by cocaine-related ischaemia or myocardial infarction present with chest pain within one hour of substance use when plasma concentrations of cocaine have risen. Conversely, other patients only report their awareness of chest pain several hours after use, when plasma levels have already fallen or have, at times, become undetectable [3, 7, 8].

Hypotheses put forward to explain the physiopathology of cocaine-related ischaemia or myocardial infarction tend towards a multifactorial pathogenesis in the presence of a condition of stimulation of the central nervous system, cardiovascular system and the respiratory tract. The following factors are involved :

- 1) a higher demand for oxygen (due to an increased heart rate and contractility, and a rise in arterial blood pressure);
- 2) a concomitantly lower or limited myocardial oxygen supply due to vasoconstriction of the coronary arteries;
- 3) a pro-thrombotic condition induced by an increased platelet aggregation and an imbalance between pro- and anti-coagulant factors;

4) an acceleration of atherosclerotic phenomena.

In addition, the positive chronotropic effect produced by cocaine is strengthened by the concomitant use of alcohol. Association with cigarette smoking likewise potentiates the effect of cocaine on heart rate and vasoconstriction, eliciting a greater effect than that induced by cigarette smoke or cocaine alone [3]. This potentiating effect is highly significant, considering the high number of young smokers among cocaine users.

1. Mechanisms underlying the cardiovascular effects of cocaine

Cocaine stimulates the central nervous system, eliciting a state of alert which is itself sufficient to lead to activation of the sympathetic nervous system. Up till the 1970s cocaine-associated cardiovascular complications were explained on the basis of the experimental use of cocaine in distinguishing between direct-acting and indirect-acting sympathomimetic amines. Indirect-acting sympathomimetic amines act at a presynaptic level, as they are transported inside the adrenergic terminals, where they release stored noradrenaline. Cocaine, a membrane transporter inhibitor, when administered immediately prior to tyramine injection, prevents the onset of the cardiovascular effects produced by this classic, indirect-acting monoamine. Noradrenaline, the naturally occurring peripheral sympathomimetic monoamine, prototype of direct-acting amines, is rapidly taken up

by synaptic terminals; this leads to the inhibition of its effects. Cocaine inhibits the re-uptake, or active transport, of monoamines; as a result, its administration potentiates and prolongs the cardiovascular effects of an intravenous injection of noradrenaline. The excessive consequences entailed by central sympathetic activation could be accounted for in this way: inhibition of the re-uptake of the noradrenaline released from sympathetic postganglionic nerve terminals intensify the strengthening of synaptic transmission, leading to severe vascular damage.

The mechanisms underlying cocaine-induced cardiovascular toxicity are actually still more complex than this. Following the advent of tricyclic antidepressants, which display an efficacy comparable with that of cocaine in distinguishing between direct- and indirect-acting monoamines by means of the model outlined above, it soon became clear that these drugs are incapable of potentiating or prolonging the effects of noradrenaline released spontaneously from sympathetic postganglionic nerve terminals. The strengthening effect produced by noradrenaline or other direct-acting amines (noradrenaline transporter substrates) is only expressed at pharmacological doses; the amounts released under physiological conditions undergo rapid dilution, and inhibition of their re-uptake is therefore devoid of any biological relevance. It has since been discovered that preparations made from cardiac tissue or arterial blood vessels respond with greater intensity to specific contractile stimuli in the presence of cocaine when compared with identical untreated preparations. It is generally acknowledged that this sensitization to contractile stimuli is not correlated with sympathetic stimulation mechanisms. Moreover, the clinical use of dihydropyridine calcium antagonists has documented their efficacy in treating many cocaine-related cardiovascular complications. It is likewise a well-established fact that cocaine not only acts as a central stimulant, but also possesses potent local anaesthetic properties.

Local anaesthetics are capable of inhibiting the transport of a stimulus along a nerve or membrane of any type of cell with electrical activity, such as muscle cells. Inhibition is induced by a functional blockade of the voltage-gated sodium channels that are crucial to the distribution and transport of the electric stimulus. Cell membranes expressing various types of ion channels selective for sodium, calcium, potassium, and chloride play an essential role in cell physiology. The effects of a local anaesthetic on these different types of channel may occur in a gradual, selective (dose-dependent) manner. For example, several antiarrhythmic drugs also act as potent local anaesthetics that, when given at low doses (antiarrhythmic doses) bind to the sodium channel during some of its functional phases: they display higher affinity when the channel is activated (open) or inactivated (closed and not activatable), whereas they are rapidly unbound during the resting phase (closed but activatable). Voltage-gated sodium, calcium, and some potassium channels belong to a large family of protein macromolecules with

marked structural similarities; so it is hardly surprising that a local anaesthetic may also display affinity for a calcium or potassium channel. In particular, cocaine is capable of inhibiting sodium, calcium and potassium channels. This capability, however, only applies to local anaesthetic doses that would never be achieved through general use, even during lengthy binges, and would rapidly lead to a fatal outcome. Under specific conditions, it is likely that similar concentrations may be achieved in localized areas, eliciting the onset of arrhythmias or epileptic convulsions (symptoms that may, alternatively, be induced by a vascular spasm accompanied by localized hypoxia). At doses markedly lower than those underlying the blockade of all channels, cocaine is also capable of interfering with L-type calcium channel function (sensitive to calcium antagonists, including dihydropyridines, used in clinical contexts) and a specific potassium channel active in phase 3 (repolarization) of the action potential of cardiomyocytes. This channel determines the I_{kr} current and is targeted both by antiarrhythmic drugs that prolong the action potential, and by drug toxicity that prolongs the QT interval. When low concentrations of cocaine were applied to coronary artery preparations, they produced sensitization to contractile stimuli that were completely antagonized by the presence of nifedipine in the medium [5]. Moreover, cocaine fails to strengthen the action of contractile stimuli that act by releasing calcium from the sarcoplasmic reticular system (from the intracellular reserves) and also fails to activate L-type calcium channels. Coronary arteries express a majority of β -adrenergic receptors and a low number of α -adrenergic receptors on the membrane surface; as a result, synaptic stimulation mainly modulates vasodilation; thus, vasoconstrictor activity exerted by cocaine on coronary arteries is not correlated with stimulation of the synapses. In arterial districts in which the action of α -adrenergic receptors is of an excitatory nature, the sensitizing effects of cocaine to synaptic stimulation, with its many severe implications, is easy to foresee. When applied to an aorta preparation, cocaine potentiated the contractile activity of methoxamine, a direct-acting sympathomimetic amine not susceptible to reuptake by adrenergic terminals [6]; this experiment provided confirmation that the sensitization effect of cocaine is independent of its mechanism of monoaminergic reuptake inhibition.

The myocardium is another key target for these cocaine-elicited effects. L-type calcium channels present on the surface membrane of cardiomyocytes open during the rapid depolarization phase of the action potential (phase 0), so facilitating the slow influx of calcium that characterizes phase 2 (plateau) and are gradually inactivated, preceding to the relaxation phase 3. The probability that these channels will open during the depolarization phase depends on their degree of phosphorylation, with phosphorylated channels being activated at a higher rate. Phosphorylation is mediated by the stimulation of cardiac β_1 -adrenergic receptors. Calcium influx inside

the cardiomyocyte is fundamental in maintaining calcium concentration in the sarcoplasmic reticular system at the levels required by cardiac functions: sympathetic stimulation increases heart rate (as well as the rate of cycles of voltage-gated channel activation), phosphorylates the L-type channels and increases the intracellular calcium reserve. As a result, a greater quantity of calcium is released from the sarcoplasmic reticular system by the contractile apparatus, producing an increase in the contractile strength of the heart. Maintaining a balance between calcium influx, calcium output and the storage capacity of the sarcoplasmic reticular system is of the utmost importance: an excess of intracellular calcium may produce potentially fatal arrhythmias and elicit processes of cell deterioration resulting in apoptosis.

A study performed on isolated ventricular cardiomyocytes demonstrated that cocaine, at concentrations similar to those detected in plasma from recreational users (approx. 1 μM), produces a marked selective increase in currents recorded in voltage-gated L-type calcium channels [13]. The latter effects are rapidly reversible, independent of the degree of phosphorylation of channels and are antagonized by the addition of nifedipine to the medium. Another study conducted on ventricular cardiomyocytes demonstrated how, at a concentration of 4 μM , cocaine prolonged the duration of the action potential as modulated by means of selective inhibition of the I_{Kr} current [1]. In other words, cocaine is capable of prolonging the QT interval with all the negative consequences this may determine.

To conclude, cocaine has shown a proven ability to bind selectively at low concentrations to a specific domain in the L-type calcium channels or potassium channels activated during the repolarization phase in cardiomyocytes that modulate I_{Kr} current. These two actions may explain most of the toxic cardiovascular effects elicited by cocaine. The cardiovascular complications manifested after a single dose of cocaine may be readily explained by a drug-induced state of alert caused by the 'preparatory' action of the sympathetic system and the hypothalamic-pituitary-adrenal axis. A rise in the release of noradrenaline from sympathetic postganglionic nerve terminals determines an increased heart rate, strength of contraction and peripheral vasoconstriction; the increase in peripheral resistance and strength of cardiac contractility is likewise supported by the sensitization of L-type calcium channels and a higher calcium influx into cells at each depolarization. In predisposed tissues or tissue districts, particularly intense vasoconstriction phenomena may be expressed; myocardial hypoxia is associated with repolarization deficits and increase in extracellular potassium that may lead to foci of ectopic depolarization. The increase in the influx of calcium into cardiomyocytes implies a high energy consumption both in terms of increased contractile strength and the activation of the mechanisms involved in its rapid removal from cytoplasm. Hypoxia induces a decrease in ATP

production, promoting the accumulation of intracellular calcium which, if acutely manifested, may elicit the onset of devastating arrhythmias. Autoptic findings obtained from habitual cocaine users have provided indications that chronic calcium accumulation may be implicated in ventricular hypertrophic processes and in the genesis of several morphological alterations, particularly at the level of the contractile apparatus.

It should, in any case, be stressed that the activating action exerted by cocaine on L-type calcium channels is not limited to the cardiovascular system, but has also been implicated in brain neuronal systems to explain complex mechanisms underlying gene activation and synaptic plasticity [10-12]. This mechanism also appears to be involved in the central effects elicited by cocaine. Indeed, the administration of calcium antagonists is not only capable of preventing the onset of severe cardiovascular events, including ventricular fibrillation, but also of interfering with the behavioural and reinforcing effects of cocaine. Moreover, the action on L-type calcium channels may help to explain, at least in part, the increased secretion of adrenaline from the adrenal medulla and various peptide hormones observed following the acute administration of cocaine.

2. Cardiac complications

Cardiac complications including ischaemia and myocardial infarction have been reported both during cocaine intoxication and abstinence. Myocardial infarction was diagnosed in 0.7 to 6% of subjects presenting to an emergency unit for cocaine-associated chest pain; myocardial infarction associated with cocaine use undoubtedly accounts for a significant percentage of the cases that occur at an early age [3, 8]. Heart attacks have been observed in subjects aged between 19 and 40 irrespective of the cocaine dose consumed, and often not associated with convulsions or anxiety. Patients with cocaine-associated myocardial infarction frequently present with: atypical chest pain (usually referred as an 'oppressive' pain), delayed onset of pain that may come hours or days after the last administration of cocaine, or even absence of pain (a study revealed how only 41% of patients reported a sensation of pain prior to hospitalization) [8]. Dyspnoea and diaphoresis are particularly frequent. ECG abnormalities recorded at the time of hospitalization take the form of ST segment elevations and T wave inversions, even if ECG alterations are not found in all patients with acute myocardial infarction [3, 7, 8]. Several studies have demonstrated that the ECG alterations typically observed in the presence of myocardial infarction only affect a small minority of patients. Moreover, the frequency of Q wave and non-Q wave heart attacks is quite similar. High plasma concentrations of troponin and cardiac enzymes are usually detected in both. As emphasized previously, angiographic or autoptic findings obtained from subjects affected by cocaine-associated myocardial infarction

frequently reveal no signs of atherosclerotic lesions or other cardiac disorders. Many patients resume their use of cocaine after discharge from hospital, so determining an extremely high cumulative risk of myocardial infarction and associated complications.

A further potential complication linked to the use of cocaine is the onset of arrhythmias of varying nature: sinus tachycardia, atrial fibrillation, ventricular extrasystoles, onset of idioventricular rhythm, tachycardia or ventricular fibrillation. Besides this, a cocaine-induced ischaemia or myocardial infarction may underlie the onset of arrhythmias that are indistinguishable from atherosclerosis-associated arrhythmias. Experimental animal studies have demonstrated a marked cocaine-induced prolongation of the QRS and QT intervals. These arrhythmias may involve a low level of brain perfusion, with transient loss of consciousness — a frequent occurrence in subjects displaying signs of cocaine intoxication. From a clinical point of view, in a context of cocaine intoxication it is important that a distinction be made between symptoms of cardiac origin and the direct effects produced by cocaine on the central nervous system, particularly in terms of epileptic convulsions or vascular brain spasms.

As the therapeutic strategies applied in the treatment of acute coronary episodes or arrhythmias associated with the use of cocaine differ considerably from those usually employed, when a patient visits an emergency department for chest pain and is examined to confirm the presence of a potential acute coronary syndrome (or arrhythmia), it should first be established whether he or she has recently used cocaine. A pertinent question on this topic should always be asked, especially to young subjects. Urine testing for detection of metabolites should only be performed under specific conditions: for example, when the patient is not capable of communicating and there is no other way of obtaining a reliable patient history.

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