

COCAINE IN ACUTE MYOCARDIAL INFARCTION

**Giuseppe Lippi,^{*,1} Mario Plebani,[†] and
Gianfranco Cervellin[‡]**

***U.O. Diagnostica Ematochimica, Dipartimento di Patologiae
Medicina di Laboratorio, Azienda Ospedaliero-Universitaria
di Parma, Italy**

**[†]Dipartimento di Medicina di Laboraotorio, Azienda
Ospedaliero-Universitaria di Padova and Leonardo Foundation,
Abano Terme (PD), Italy**

**[‡]U.O. Pronto Soccorso e Medicina d'Urgenza, Dipartimento
di Emergenza-Urgenza, Azienda Ospedaliero-Universitaria
di Parma, Italy**

1. Abstract	53
2. Structure and Metabolism of Cocaine	54
3. Epidemiology of Cocaine Abuse	55
4. Cocaine Testing	56
5. Toxicity of Cocaine Abuse	59
6. Cocaine and Chest Pain	60
7. Should Cocaine Use Be Screened in Patients with Acute Myocardial Infarctions?	63
8. Conclusions	67
References	67

1. Abstract

Cocaine, a crystalline tropane alkaloid which is obtained from the leaves of the coca plant, acts a powerfully addictive stimulant that directly targets the central nervous system. The effects of the drug appear almost immediately after a single dose (intravenous, intranasal, or inhaled), and disappear within a few minutes or hours. Although the free commercialization of the drug is illicit

¹Corresponding author: Giuseppe Lippi, e-mail: glippi@ao.pr.it

and severely penalized in virtually all countries, its use remains widespread in many social, cultural, and personal settings. There is a variety of well-recognized side effects of cocaine abuse, which involve virtually every organ system. There is also emerging evidence, however, that cocaine abuse might trigger a variety of cardiac disorders, ranging from arrhythmias to acute myocardial infarction (AMI), heart failure and even sudden cardiac death, especially in relatively young male patients (e.g., those in the mid-1930s), in those who concomitantly use tobacco and alcohol, in those having experienced a trauma or a car accident and lack traditional risk factors for atherosclerosis. Since the use of cocaine may influence the treatment strategies of patients being evaluated for possible acute coronary syndrome (ACS) as well as the prognosis of an AMI, it might be advisable to introduce cocaine screening in patients admitted with chest pain at the emergency department, especially in high-risk patients (i.e., young males with concurrent use of tobacco or alcohol, suffering from a recent accident and with no traditional atherosclerotic risk factors), or in those who are unresponsive and unreliable. This strategy might be helpful to adopt the best therapeutic approach for reducing the risks associated with cardiovascular disease in these patients, and also to deter relapse.

2. Structure and Metabolism of Cocaine

Cocaine (benzoylecgonine) is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant (*Erythroxylum coca*). It is specifically a serotonin–norepinephrine–dopamine reuptake inhibitor, which acts as a powerful stimulant of the central nervous system [1]. The biological function of cocaine is complex and multifaceted, but mostly involves the blockade of the dopamine transporter protein (i.e., cocaine binds tightly to the dopamine transporter forming a complex that neutralizes its function), so that dopamine accumulates in the synaptic cleft. Most specifically, cocaine binds directly to the DAT1 transporter, inhibiting reuptake more efficiently than amphetamines which phosphorylate it causing internalization. This inhibition persists for up to a month following cessation of cocaine administration. The main targets of cocaine have been recognized within the mesocorticolimbic circuitry and the pathway originates with dopaminergic cell bodies in the ventral tegmental area (VTA), and projects to numerous limbic loci, including the prefrontal cortex (PFC), hippocampus, amygdala, and nucleus accumbens. In synthesis, it is now acknowledged that the reinforcing effects of cocaine are primarily mediated by enhanced dopamine transmission. Alterations related to dopamine and serotonin are mainly responsible for the physical and behavioral manifestations, whereas the cardiovascular toxicity is related to its sympathomimetic effects due the fact that cocaine inhibits the presynaptic

reuptake of noradrenalin. The transition from casual drug use to addiction, and the intense drug craving that accompanies it, result from neuroadaptations within the limbic system caused by repeated drug exposure [2]. Cocaine, on the other hand, has been shown to also inhibit 5-hydroxytryptamine (5-HT) 3 receptor function in a dose-dependent manner [3].

Cocaine is extensively metabolized primarily in the liver, while approximately 1–5% of the drug is excreted unaltered through the kidneys within 6 h after intake. The metabolism is dominated by hydrolytic ester cleavage by hepatic esterases and plasma pseudocholinesterase, resulting in the formation of ecgonine methyl ester (EME). Spontaneous nonenzymatic hydrolysis of another 30–40% results in benzoylecgonine (BZE). Both products are water-soluble, metabolically active. BZE, which has a half-life of 7.5 h, is therefore the main metabolite excreted in the urine, while EME and ecgonine are excreted in lesser amounts. Further minor metabolites include norcocaine (NCOC), *p*-hydroxycocaine (*p*-HO-COC), *m*-hydroxycocaine (*m*-HO-COC), *p*-hydroxybenzoylecgonine (pOHBE), and *m*-hydroxybenzoylecgonine (*m*-HO-BZE) [4]. A recent report has detailed the urinary excretion and terminal elimination kinetics for cocaine and eight metabolites (BZE, EME, NCOC, benzoynorecgonine (BNE), *m*-HO-BZE, *p*-HO-BZE, *m*-HO-COC, and *p*-HO-COC) in healthy males administered approximately equipotent doses of cocaine by the intravenous (IV), smoking (SM), and inhalation (IN) routes. Urine specimens were collected for a minimum of 3 days after drug administration, screened with two immunoassays and further analyzed by gas chromatography–mass spectrometry (GC–MS). The elimination half-lives for cocaine and metabolites were generally shorter following SM, intermediate after IV, and longest following IN administration. Among the various metabolites, *m*-HO-BZE has been reported to display the longest half-life (mean range 7.0–8.9 h) [5].

3. Epidemiology of Cocaine Abuse

The practice of chewing the coca leaves dates back at least 5000 years, based on archaeological findings in Equador [6]. This practice was continued by Incans, who recognized coca's ability to boost energy, relieve fatigue, and lessen hunger [7]. The German chemist Friedrich Gädcke was the first to isolate the alkaloidal cocaine from the coca leaf in 1855, while Albert Niemann is credited for chemically characterizing the substance, in 1859 [6]. Cocaine use has become popular in the United States in the 1880s and 1890s. During this time, cocaine was also included in many patented medicines, including Cocaine Toothache Drops, Vin Mariani (a coca-based wine), and Coca Cola [8]. Sigmund Freud proposed using cocaine as a treatment for patients' depression, cachexia, asthma, and morphine addiction [9].

Three-quarters of the world's annual yield of cocaine is being produced in Colombia, from cocaine base imported from Peru (primarily the Huallaga Valley) and Bolivia. Although the free commercialization of cocaine is illicit and severely penalized virtually worldwide, its use remains widespread in many social, cultural, and personal settings. Presently, cocaine is the second most popular illegal recreational drug behind marijuana, due to the ease of administration (intravenous, intranasal, or inhalation), widespread availability, relatively modest cost, and the misperception that its use might be safe [10]. According to the 2008 National Survey on Drug Use & Health issued by the U.S. Department Of Health And Human Services (which provides the latest data on prevalence and correlates of substance use, serious psychological distress, depression, related problems, and treatment in the civilian population aged 12 or older in the United States) [11], marijuana was the illicit drug with the highest rate of past year dependence or abuse (4.2 million persons), followed by pain relievers (1.7 million persons), and cocaine (1.4 million persons). It was also estimated that the persons who had used cocaine for the first time within the past 12 months were 722,000, and most of them (67%) were 18 or older when they first used. The average age at first use was 19.8 years among recent initiates aged 12–49. Cocaine use in western Europe has also increased between 1998 and 2007, according to the annual report of the United Nations Commission on Narcotic Drugs (CND). Globally, the number of cocaine users has increased, with “a serious epidemic” registered in the Russia and central Asia. Remarkably, cocaine use has become part of adolescent development in many Western countries. In Switzerland, Australia, and the United States, about half of all the people born since 1980 will have tried the drug before the age of 21. Supported by the evidence that the prevalence of drug abuse is largely underestimated, the use of cocaine—especially in the young—must be now regarded as a serious public healthcare problem. Nearly 450,000 cocaine-related visits were registered in U.S. Emergency Departments (EDs) in the United States in 2005, and chest pain has been reported in nearly half of these patients. The most frequent age group for the visits was 35–44 years of age (37% of all cocaine-related ED encounters). Interestingly, cocaine-related visits in the ED have increased by 47% from 1999 to 2002 [12].

4. Cocaine Testing

In clinical toxicology, purely quantitative results are only available using specific methods including GC–MS, high-pressure liquid chromatography (HPLC), and GC. Basically, HPLC and GC are chromatographic techniques, whereas MS is a detection system which can be coupled to a gas chromatography (GC–MS) or to a liquid chromatography (LC–MS).

The latter technique is now being increasingly used not only in toxicological laboratories (for the analysis of drugs of abuse) but also in clinical laboratories (for therapeutic drug monitoring).

Quantitative GC/MS analysis (usually performed by isotope dilution) is considered the reference method, with a sensitivity <10 ng/mL. The HPLC has similar sensitivity to GC/MS applications, does not require preparation of volatile derivatives, but detection is less specific. GC is robust and sensitive, but lacks detector specificity. Nitrogen/phosphorus detectors for GC systems are very sensitive but expensive, even though cheaper than MS detectors. Since GC/MS, HPLC, and GC are only performed using sophisticated and costly instruments, time-consuming, involves multiple steps (e.g., GC/MS requires extensive specimen preparation encompassing extraction, derivatization, isotopically labeled internal standards), and must be operated by highly qualified personnel, they are mostly unsuitable for emergency settings like that of an ED, where a rapid diagnosis might be necessary for the triage of the patients [13]. Alternative techniques, which allow faster results, include enzyme-linked immunosorbent assays (ELISAs), enzyme-multiplied immunoassay (EMIT), fluorescence polarization immunoassay (FPIA), cloned enzyme donor immunoassay (CEDIA), and point of care (POC) devices. Thin-layer chromatography (TLC) is also used, but requires sample preparation steps. All cocaine screening immunoassays currently marketed use antibodies against benzoylecgonine as the antigenic target, so that they can be termed more precisely “cocaine metabolite screening assays” or “benzoylecgonine screening assays” [14]. Most of them are calibrated to a threshold of 300 ng/mL (urine), which corresponds to the Substance Abuse and Mental Health Services Administration (SAMHSA) specifications, and may be adapted to other specimens [14]. Nevertheless, BZE is not the principal metabolite in all specimens, so that the commercial immunoassays can detect cocaine (parent drug) weakly, with cross-reactivities (equal to 300 ng/mL BZE) only occurring for cocaine concentrations ranging from 10,000 ng/mL (Abbott AxSYM) to 80,000 ng/mL (Syva EMIT). The recent use of cocaine, even in large amounts, may thereby produce a negative result when little time has elapsed for the generation of BZE. These marketed assays also vary widely in detecting other metabolites such as ecgonine, EME, and BNE [14]. Regardless of these limitations, EMIT, FPIA, and CEDIA methods are enough sensitive to assess whether a sample is positive for cocaine compounds without differentiating between the parent compound, the major and minor metabolites. The sensitivity of these tests is close to 100% when compared with the reference standards sensitivity for detecting drug use in individuals (false negatives rarely occur) [13, 15–19], but depends directly on timing of drug use and the urinary excretion of drug metabolites. In general, the various immunoassay systems also exhibit a satisfactory imprecision, with coefficient of variations (CVs) $<20\%$ at analyte concentrations below the

SAMHSA cutoffs [20]. Least but not last, cross-reactivity between cocaine screen and substances other than cocaine are nearly nonexistent [16].

The use of POC and on-site or near-patient testing devices (i.e., any method that can be used to analyze specimens outside on the laboratory setting) is a well-recognized approach for allowing rapid generation of biomedical results, including drugs-of-abuse screening [21]. The POC testing devices for drug-of-abuse screening have been designed for either single- or multiple-drug detection, and typically use immunochromatographic methods that allow visually read results. The packaging formats range widely, from dipsticks to cup devices, cards, or to plastic cassettes. Urine is the specimen of choice, although assays for other biological samples are now available. Some devices allow very rapid results, since the tests involve only one step after depositing the sample in the container [22].

Although the effectiveness and diagnostic performances of the first marketed POC devices for cocaine screening have been strongly questioned (e.g., the KDI Quik Test was able to correctly identified only 50% of the samples when compared with the reference GC–MS assay), the results of a study investigating the application of the EZ-Screen enzyme immunoassay card test for cocaine revealed satisfactory performances (sensitivity, specificity, and efficiency were 95%, 67%, and 87%, respectively) [23]. In 1993, Wu et al. assessed the diagnostic performances of Triage 7 NPT device, which is designed to detect amphetamines, barbiturates, benzodiazepines, cocaine, opiates, PCP, and tetrahydrocannabinol. As compared with the Syva EMIT, the Triage system produced identical results, with a sensitivity of 93–100% and a specificity of 95–100% [24]. In a further study involving three laboratories participating in the NHTSA-funded project, 40 urine specimens were tested with three on-site test kits (EZ-SCREEN, ONTRAK, and TRIAGE) for cocaine and other drugs (e.g., amphetamines, benzodiazepines, cannabinoids, opiates) and further qualitatively and quantitatively confirmed by GC–MS. On-site false-positive results were rare, and only one cross-reactive error was recorded for cocaine with EZ-SCREEN and ONTRAK. It was also concluded that although more donor samples would have resulted positive for cocaine by the on-site devices than by EMIT immunoassay according to the current federal guidelines for workplace urinalysis testing, fewer would have been reported as positive because most contained GC–MS-determined drug concentrations lower than the federal confirmation and reporting limits [25]. Cone et al. reported that sensitivity, specificity, and predictive values for urine specimens screened with two commercial immunoassays (for EMIT and TDx) were comparable at the 300-ng/mL cutoff concentration as compared with GC–MS. At lower cutoff concentrations, predictive values of positive results for TDx were, however, diminished, indicating a higher risk of false-positive results, that is, positive results that failed to meet administrative cutoff criteria [26]. Some on-site devices have been

recently developed for the analysis of saliva specimens to be applied in the road safety setting. Their effectiveness has been checked (by comparing the results with those obtained by LC/MS–MS) for laboratories from all over the world, including the European Union, United States, and Australia. Currently, they are being used in many countries to control driving “under the influence of drugs,” and they might also be used in the ED [21, 22].

In the triage of patients in the ED, the need to confirm positive results obtained by preliminary screening methods by another analytical technique (HPLC, GC, or GC–MS) might be unnecessary because this determination has no legal implications [27]. As such, the modern immunoassays offer satisfactory diagnostic performances and real advantages over confirmatory methods, with an acceptable rate of false-positive results. These methods can in fact provide rapid and relatively accurate presumptive results, which may be sufficient for the immediate triage of drug-abusing individuals, and are especially suited for large-scale screening through automation. NPT might be a reliable alternative, but it is essential that they are used appropriately, with a full understanding of the specific test device limitations with respect to sensitivity and specificity, and that the results are interpreted accurately. Additional essential aspects include (i) the training of the staff in the use of specific devices, (ii) the recordkeeping [28], (iii) the establishment of a chain-of-custody procedures as well as (iv) the implementation of a reliable policy of data management which is aimed to prevent ramifications of false-positive results, limitations of confidentiality protection, and the practice of testing without the patient’s knowledge [29].

5. Toxicity of Cocaine Abuse

Conventionally, the effects of the drugs can last from 15–30 min to 1 h, depending upon the method of administration, and virtually involve every organ system. The most frequent include increased alertness, feelings of well-being and euphoria, energy and motor activity, feelings of competence and sexuality. Athletic performance may be enhanced as well. Additional effects include anxiety, paranoia and restlessness, while tremors, convulsions and increased body temperature might occur with excessive dosage. There is a variety of well-recognized side effects, which are mostly classified in acute and chronic, and that might be life-threatening in persons with coexisting cardiac problems (Table 1) [30]. Physical side effects from chronic smoking of cocaine also include hemoptysis, bronchospasm, pruritus, fever, diffuse alveolar infiltrates without effusions, pulmonary and systemic eosinophilia, chest pain, lung trauma, sore throat, asthma, hoarse voice, dyspnea (shortness of breath), and an aching, flu-like syndrome [30]. Last but not least, cocaine dependence (or addiction) might develop as a psychological dependency

TABLE 1
LEADING CLINICS AND SIDE EFFECTS OF COCAINE USE

<i>Acute</i>
1. Itching
2. Chest pain
3. Tachycardia
4. Hallucinations
5. Paranoid delusions
6. Tachyarrhythmias
7. Hypertension
<i>Chronic</i>
1. Hunger
2. Aches
3. Insomnia/oversleeping
4. Lethargy
5. Persistent runny nose
6. Depression with suicidal ideation
7. Long-term damage of dopamine neurons

which results in physiological damage, lethargy, psychosis, depression, and fatal overdose. Consideration should be given to the potential cocaine abuse when making treatment decisions in patients with severe hypertension. In a study including 107 consecutive patients presented to an ED with a diastolic pressure equal or greater than 120 mmHg, 99 were tested for cocaine use. Thirteen of these tested positive for the drug, and five had cardiovascular and/or pulmonary complaints [31].

6. Cocaine and Chest Pain

The ED visits for cocaine-related problems include, but are not limited to psychiatric, neurologic, cardiopulmonary, trauma, and addiction-related symptoms and complaints. Cardiopulmonary complaints related to cocaine use are common, with chest pain being the most frequent symptom (20–40%) [32]. Cocaine intoxication is the most prevalent cause of drug-related death reported by medical examiners, and these events are most often related to the cardiovascular manifestations of the drug [33]. In the 1986, Isner et al first reported that high-grade ventricular arrhythmias, AMI, and even sudden death might be temporarily related to the abuse of cocaine. Interestingly, the authors observed that these pathologies were not confined to the parenteral use of the drug (nearly all the patients took the drug intranasally), that underlying heart disease was not a prerequisite for cocaine-related cardiac disorders, and—especially—that the cardiac consequences were not limited

to massive doses of the drug [34]. The most reliable evidence of an association between cocaine use and heart attack came, however, in 2001 from a nationally representative study of 10,085 American adults aged 18–45 years. It was observed that regular use of cocaine was associated with an increased likelihood of AMI (odds ratio (OD): 6.9; 95% confidence interval (CI): 1.3–58) after adjusting for demographical variables and major risk factors (i.e., age, sex, race/ethnicity, education, hypertension, diabetes mellitus, cholesterol level, body mass index, and cigarette smoking). Most importantly, nearly one of every four nonfatal AMIs in persons aged 18–45 years was attributed to frequent use of the drug (defined as >10 uses in a lifetime) [35] (Table 2).

The most striking evidence comes, however, from a recent MEDLINE search carried out to identify all English language articles from January 2000 to June 2008 with the subject headings and key words “cocaine,” “heart,” “toxicity,” and “cardiotoxicity.” This research demonstrated a significant association between cocaine use and AMI, arrhythmia, heart failure, and sudden cardiac death. The postulated mechanisms that may lead to AMI included coronary artery vasoconstriction, accelerated atherosclerosis, prothrombotic abnormalities. Among the potential conditions predisposing to arrhythmia, blockage of K⁺ channels, increase L-type Ca²⁺ channel current, and inhibit Na⁺ influx during depolarization were cited. Cocaine use was

TABLE 2
PATHOPHYSIOLOGICAL MECHANISMS LINKING COCAINE ABUSE AND HEART DISEASE

-
1. Premature coronary atherosclerosis
 - Increased levels of C-reactive protein
 2. Generation of a prothrombotic state
 - Increased levels of tissue plasminogen activator (tPA)
 - Decreased production of antithrombin and coagulation protein C
 - Increased levels of von Willebrand factor and fibrinogen
 - Platelet hyperreactivity (alpha-adrenergic-mediated increase of platelet aggregation)
 3. Vasoconstrictive effects
 - Increases synthesis of endothelin
 - Decreases production of nitrous oxide (NO)
 - Coronary artery spasm by Increasing influx of calcium across endothelial cell
 - Inhibition of dopamine-mediated coronary vasodilatation secondary to dopamine depletion
 4. Direct myocardial damage
 - Myocarditis due to microvascular injury
 - Dilated cardiomyopathy
 - Left ventricular hypertrophy
 - Transient toxic cardiomyopathy
 - Increased myocardial oxygen demand
 5. Hypertension and tachycardia
-

also associated with left ventricular hypertrophy, myocarditis, and dilated cardiomyopathy, which can lead to heart failure if drug use is continued. The clinicians must always remember that rates of tobacco use in cocaine-users range from 80% to 90% [36].

A multicenter ED-based study evaluated chest pain patients with a history of cocaine abuse with 64-slice coronary computed tomography. Forty-four cocaine-related chest pain patients, matched with 132 controls, showed a sixfold higher risk for ACS, but no association with a higher prevalence of any plaque, calcified or noncalcified plaque, or significant stenosis [37].

A further large study designed to examine the association between self-reported cocaine use and physician-diagnosed AMI in the Third National Health and Nutrition Examination Survey (NHANES III) concluded that there was no statistically significant association between any exposure to cocaine and AMI (age-adjusted OR: 1.56, 95% CI: 0.44–5.50; $p = 0.48$) in the group aged 18–59 years. The participants aged 18–45 years who reported >10 occasions of cocaine use had, however, a significantly elevated prevalence of AMI in age-adjusted models (OR: 4.60; 95% CI: 1.12–18.88; $p = 0.035$), thereby supporting a substantial association between cocaine use and AMI [38]. Recently, Burrillo-Putze and coworkers obtained urine sample from 119 consecutive ED patients with probable ischemic chest pain, and reported a 21% prevalence of undeclared use of cocaine [39]. A prospective consecutive cohort study included patients (18–60 years) admitted to an urban ED with cocaine-associated chest pain risk. Patients were initially stratified according to low and intermediate cardiac risk, and reevaluated at 3, 6, and 12 months. Sixty-six percent of the patients who returned to the ED for chest pain had a positive cocaine urine screening result, whereas none had an AMI within the 1-year follow-up period. Patients with continued cocaine use were more likely to have a recurrent ED visit ($p < 0.001$), but these repeated visits were most often related to musculoskeletal pain (21%) and injury (30%), rather than potential cardiac complaints [40].

A very recent prospective clinical study on the leading causes of sudden death in southwest Spain has revealed that 3% of these deaths are cocaine-related and that the majority of these are cardiovascular (62%) and cerebrovascular (14%). AMI, in particular, has been identified as the most common cardiac condition responsible for sudden death following cocaine use, supported or possibly triggered by a kaleidoscope of structural cardiac abnormalities that include cardiac hypertrophy, obstructive small vessel disease, premature coronary artery atherosclerosis, with or without lumen thrombosis. Most interestingly, adverse complications were observed in a wide range of serum cocaine concentrations, from 0.1 to 24 mg/L, so that it was concluded any amount of the drug can be considered to have the potential for toxicity

(i.e., some patients have poor outcomes with relatively low blood concentrations, whereas others tolerate large quantities without consequences) [41].

A variety of effects has been advocated to justify the detrimental effects of cocaine on heart biology, including premature coronary atherosclerosis, the generation of a prothrombotic state, vasoconstrictive effects on coronary arteries, direct myocardial damage, hypertension, and tachycardia [42, 43]. There is also evidence of myocardial ischemia after cessation of cocaine use in patients withdrawing from cocaine addiction [44].

The ECG is nondiagnostic in 60% of patients who later prove to have cocaine-induced AMI, and is abnormal in 56–84% of patients with cocaine-associated chest pain [45]. Among the various ECG abnormalities observed in cocaine-associated chest pain, Langstrom et al. reported on a case of pseudo-Wellens syndrome in a 46-year-old man who later admitted to have smoked cocaine for the previous 2 days. The patient experienced several minutes of severe chest pain associated with palpitations, diaphoresis, and stomach cramps. Initial ECG showed biphasic T waves in leads V2 to V5 (meeting the criteria of Wellens), and reverted to normal after 48 h. The coronary angiography showed completely normal coronary arteries, and an ejection fraction of 65% [46].

Patients presenting to the ED with chest pain after cocaine use must be evaluated also for others triggering pathologies, not in a limited way addressed to myocardial ischemia and infarction. Barotraumas resulting in pneumothorax, pneumomediastinum, and pneumopericardium have been reported in patients smoking crack cocaine. This seems to be related to the increase in the intra-alveolar pressure caused by deep inhalation followed by Valsalva maneuver, or from severe cough triggered by the cocaine [47]. Aortic dissection, although rare, has been reported after cocaine use, and it is believed result from a rapid increase in blood pressure and heart rate [48]. Endocarditis should also be considered in patients using IV cocaine presenting with chest pain and fever [49].

7. Should Cocaine Use Be Screened in Patients with Acute Myocardial Infarctions?

The attempt to answer to the provocative question that entitles this chapter must obviously be supported by reliable clinical and epidemiological evidences. First, cocaine abuse and especially overdose may closely resemble several other pathologies including serotonin syndrome, lithium toxicity, toxicity due to tricyclic antidepressants (TCAs), neuroleptic malignant syndrome (NMS), thyroid storm, and other hyperadrenergic states, so that a laboratory screening might be necessary for establishing a differential

diagnosis. According to 1999 Drug Abuse Warning Network (DAWN) data, patients visiting the ED for a drug-related cause provided the following reasons for using cocaine: dependence (49%), recreational use (37.6%), other psychic effects (19.7%), and suicide (8.7%). The current epidemiological data also support the hypothesis that clinicians should always be suspicious of cocaine use in their differential diagnosis of chest pain, especially in the younger male population. Clinicians should proceed more cautiously when cocaine use is suspected, considering the different course of disease and the different therapy. Hollander et al. assessed the clinical features and outcomes of cocaine users with those of randomly selected control patients and age-matched controls with resuscitated cardiac arrest without cocaine use. Fifty-five percent of the patients who used cocaine had complete neurologic recovery, in contrast to only 15% unmatched controls and 17% age-matched controls. Moreover, only 46% cocaine users died compared with 75% unmatched controls and 78% age-matched controls. As such, the authors concluded that although cocaine use is associated with cardiac arrest, cocaine users are younger than nonusers and more likely to survive with neurologic recovery, even compared with age-matched controls [50]. It has also been recently demonstrated that the TIMI risk score has not clinically useful predictive value in patients with cocaine-associated chest pain [51].

Although the therapeutic approach of AMI in cocaine users does not differ substantially from that of a “traditional” heart attack, the use of beta-receptor antagonists and class Ia and III antiarrhythmics is strongly discouraged, due to the documented adverse effects [33, 52]. In a large study on patients admitted to a large inner city ED with chest pain and positive urine drug screen for cocaine, it was observed that preexisting use of beta-blockers was associated with a significant risk of AMI in patients presenting with cocaine-related chest pain and that the routine initiation or continuation of beta-blockers after admission more than doubled the likelihood of developing cardiac myonecrosis during hospitalization (23% vs. 11%; $p < 0.01$). In the lack of prospective controlled data, these observational findings would suggest that the use of beta-blockers in these patients should be discouraged [53]. On the contrary, another group of authors observed that beta-blocker administration in patients presenting to an ED with cocaine-related chest pain was associated with reduction in incidence of AMI (1.7% vs. 4.5%, OR: 0.6), and the authors argued that the benefit of beta-blockers on myocardial function may offset the risk of coronary artery spasm [54]. Although vasospasm may play a role *in vivo*, the pathophysiology of cocaine cardiac toxicity is complex, and involves increased blood pressure, pulse rate, oxygen demand. Several lines of evidence also indicate that coronary artery thrombosis may be the major pathway in cocaine-triggered AMI [55]. Nevertheless, the preponderance of evidence continues to argue against the

use of beta-adrenergic antagonists in this setting and, according to the 2008 American Heart Association Scientific Statement for managing patients with cocaine-induced chest pain [43], patients with cocaine-associated AMI should be treated similarly to those with traditional AMI except for notable exceptions, which include (i) benzodiazepines for reversing anxiety, relieving chest pain and producing beneficial cardiac hemodynamic effects, (ii) nitrate (0.4 mg every 5 min for three times) for reversing cocaine-associated vasoconstriction and controlling hypertension when a patient does not respond to benzodiazepines, (iii) calcium channel blockers for patients who do not respond to benzodiazepines or nitroglycerin, and (iv) phentolamine for returning coronary arterial diameter to baseline. The suggestion against administering beta blocker is reiterated, and calcium channel blocker are the drug of choice in these patients. The ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) suggest that UA/NSTEMI patients should be questioned about the use of cocaine and methamphetamine. The same guideline also states that the use of beta-blockers for cocaine-induced ischemia is controversial, and that labetalol, an alpha and beta blocker, has been advocated because it has been shown not to induce coronary artery vasoconstriction [56]. Since cocaine use has been associated with ventricular dysrhythmias (idioventricular rhythm, ventricular tachycardia, ventricular fibrillation) and atrial dysrhythmias (supraventricular tachycardia, atrial fibrillation), the blocking of sodium channels in these patients can precipitate supraventricular rhythms that are aberrantly conducted during severe intoxication. These complex dysrhythmias are similar to those described in TCAs or quinidine poisoning, and also benefit from bicarbonate administration [34].

While reliable therapeutic and clinical evidences would be in support of screening for cocaine use in patients admitted with an AMI, we might face, however, an important economical issue, that is the significant healthcare expenditure due to cocaine testing. As such, it would be reasonable to limit the screening to those subjects who have a greater likelihood to be cocaine users and might achieve the greatest benefits from a specific therapy. Young or relative young patients (e.g., those in the mid-1930s) have the greatest overall prevalence of cocaine use and, especially, are those displaying the most significantly elevated prevalence of AMI in age-adjusted models [38]. A higher prevalence is also observed in male, employed users with concomitant use of tobacco and alcohol, and in those having experienced a recent trauma or a car accident [41]. The lack of traditional risk factors for atherosclerosis is frequent in patients with cocaine-induced AMI, who are exposed to nearly 24-fold greater risk of heart attack in the 60 min after administration [10]. Finally, nearly 50% of cocaine-related sudden deaths occur during the weekends. These epidemiological evidences would allow us to develop a preliminary,

probabilistic algorithm which is supposed to limit cocaine testing to high-risk subjects (i.e., young males with concurrent use of tobacco or alcohol, admitted for a recent accident and with no traditional atherosclerotic risk factors) (Fig. 1), to those unable to communicate, and in whom no other reliable source of the history is available. However, while the use of illicit drugs is usually perceived as behavior of the young, their diffusion among people aged 50 and over is substantially increasing in Europe and the United States, as reflected by the aging of general populations, and the fact that people who use drugs continuing to do so as they age [57]. Therefore, this algorithm is only speculative, and should not prevent clinicians to request cocaine screening when facing uncommon settings, conditions or circumstances.

As regards cocaine testing, the first issue to be considered is the choice of the most adequate sample for analysis, which depends on both the clinical setting and the type of information needed. The best specimens for assessing whether cocaine can be directly associated with AMI are blood or saliva, because they allow the shortest window time of detection. Since AMI can be a consequence of a chronic consumption of the drug during a prolonged period of time, the most reliable approach would be hair testing, which is, however, unavailable as a stat (urgent) analysis. On the other hand, urine analysis can be performed with a very short turnaround time and provides information about the drug which is being currently eliminated after having

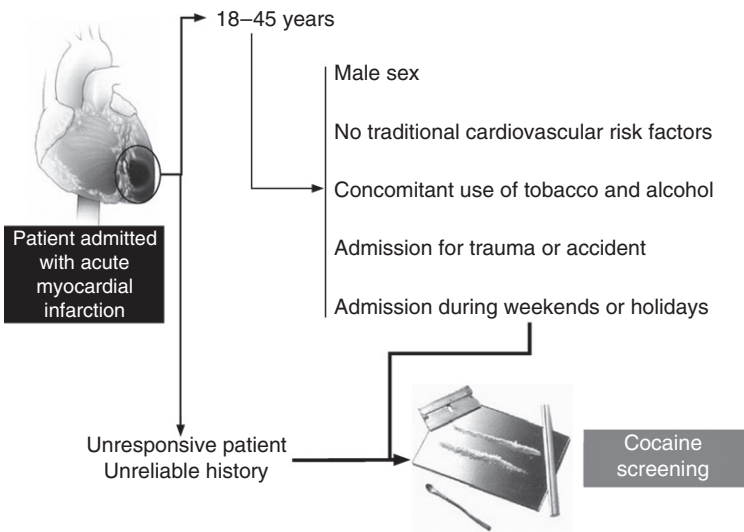


FIG. 1. Flow chart of cocaine testing in patients with acute myocardial infarction.

being metabolized, so that it seems the best approach in the setting of patients urgently admitted to the ED with chest pain.

In further support to our hypothesis that cocaine screening might accompany troponin testing in specific patients with chest pain, is the evidence that chest pain appears to have little value for discriminating an ischemic from nonischemic cause in cocaine users (it is present in less than 50% of the patients), whereas dyspnea and diaphoresis are particularly frequent, occurring in more than half of patients [58]. As such, cocaine screening might provide additional information to the traditional diagnostic approach to patients acutely admitted for suspected AMI, mainly based on serial troponin testing and electrocardiography.

8. Conclusions

Based on ED data, close to 100,000 cocaine-using patients will be seen each year with complaints referable to the cardiovascular system, more than half will be admitted to the hospital at a cost of approximately 83 million dollars, and nearly 6% of them will have suffered an AMI [59]. Since the use of cocaine may influence the treatment strategies of patients being evaluated for a possible ACS as well as the prognosis of an AMI, detecting cocaine use in a patient presenting with chest pain might be advisable, and it cannot rely on clinics, history and self-reporting, especially in younger or unresponsive patients. As such, we are persuaded that the clinical suspicion might be accompanied with urine cocaine screening, especially in high-risk patients, to adopt the best therapeutic approach for reducing the risks associated with cardiovascular disease in these patients, but also to deter relapse.

REFERENCES

- [1] L. Fattore, G. Piras, M.G. Corda, O. Giorgi, The Roman high- and low-avoidance rat lines differ in the acquisition, maintenance, extinction, and reinstatement of intravenous cocaine self-administration, *Neuropsychopharmacology* 34 (2009) 1091–1101.
- [2] S.M. Anderson, R.C. Pierce, Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement, *Pharmacol. Ther.* 106 (2005) 389–403.
- [3] M. Carta, A.M. Allan, L.D. Partridge, C.F. Valenzuela, Cocaine inhibits 5-HT₃ receptor function in neurons from transgenic mice overexpressing the receptor, *Eur. J. Pharmacol.* 459 (2003) 167–169.
- [4] E.A. Kolbrich, A.J. Barnes, D.A. Gorelick, S.J. Boyd, E.J. Cone, M.A. Huestis, Major and minor metabolites of cocaine in human plasma following controlled subcutaneous cocaine administration, *J. Anal. Toxicol.* 30 (2006) 501–510.

- [5] E.J. Cone, A.H. Sampson-Cone, W.D. Darwin, M.A. Huestis, J.M. Oyler, Urine testing for cocaine abuse: metabolic and excretion patterns following different routes of administration and methods for detection of false-negative results, *J. Anal. Toxicol.* 27 (2003) 386–401.
- [6] C. Van Dyke, R. Byck, Cocaine, *Sci. Am.* 246 (1982) 128–141.
- [7] J. Kennedy, *Coca exotica: the illustrated story of cocaine*, Farleigh Dickinson University Press 1985.
- [8] E.A. Warner, Cocaine abuse, *Ann. Intern. Med.* 119 (1993) 226–235.
- [9] D. Streatfield, *Cocaine: an unauthorized biography*, St. Martin's Press, New York, 1998.
- [10] R.A. Lange, L.D. Hillis, Sudden death in cocaine abusers, *Eur. Heart J.* 31 (2010) 271–273.
- [11] U.S. Department Of Health And Human Services, Results from the 2008 National Survey on Drug Use and Health: National Findings. Available at: <http://www.oas.samhsa.gov/2k8/2k8Results.cfm>, 2008, Last accessed: 26 February 2010.
- [12] J. McCord, H. Jneid, J.E. Hollander, J.A. de Lemos, B. Cercek, P. Hsue, et al., American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, *Circulation* 117 (2008) 1897–1907.
- [13] Guide to clinical preventive services. second edn. Williams & Wilkins, Baltimore, MD: Williams & Wilkins, 1996. Chapter 53, Screening for drug abuse. International Medical Publishing, Alexandria, VA, 1996, pp. 583–595.
- [14] M.D. Krasowski, A.F. Pizon, M.G. Siam, S. Giannoutsos, M. Iyer, S. Ekins, Using molecular similarity to highlight the challenges of routine immunoassay-based drug of abuse/toxicology screening in emergency medicine, *BMC Emerg. Med.* 9 (2009) 5.
- [15] D.A. Armbruster, R.H. Hubster EC. Enzyme immunoassay, kinetic microparticle immunoassay, radioimmunoassay, and fluorescence polarization immunoassay compared for drugs-of-abuse screening, *Clin. Chem.* 39 (1993) 2137–2142.
- [16] K.E. Moeller, K.C. Lee, J.C. Kissack, Urine drug screening: practical guide for clinicians, *Mayo Clin. Proc.* 83 (2008) 66–76.
- [17] C.S. Frings, D.J. Battaglia, R.M. White, Status of drugs-of-abuse testing in urine under blind conditions: an AACC study, *Clin. Chem.* 35 (1989) 891–894.
- [18] D. Burnett, S. Lader, A. Richens, B.L. Smith, P.A. Toseland, G. Walker, et al., A survey of drugs of abuse testing by clinical laboratories in the United Kingdom, *Ann. Clin. Biochem.* 27 (1990) 213–222.
- [19] N.T. Lu, B.G. Taylor, Drug screening and confirmation by GC-MS: comparison of EMIT II and Online KIMS against 10 drugs between US and England laboratories, *Forensic Sci. Int.* 157 (2006) 106–116.
- [20] V.I. Luzzi, A.N. Saunders, J.W. Koenig, J. Turk, S.F. Lo, U.C. Garg, et al., Analytic performance of immunoassays for drugs of abuse below established cutoff values, *Clin. Chem.* 50 (2004) 717–722.
- [21] S.E. Melanson, Drug-of-abuse testing at the point of care, *Clin. Lab. Med.* 29 (2009) 503–509.
- [22] R.A. Mirghani, Current status of Point-of-Care Testing in clinical toxicology: focus on drugs of abuse, *Point Care* 7 (2008) 266–270.
- [23] R.H. Schwartz, S. Bogema, M.M. Thorne, Evaluation of the EZ-Screen enzyme immunoassay test for detection of cocaine and marijuana metabolites in urine specimens, *Pediatr. Emerg. Care* 2 (1990) 147–149.
- [24] A.H.B. Wu, S.S. Wong, K.G. Johnson, J. Callies, D.X. Shu, W.E. Dunn, et al., Evaluation of the Triage system for emergency drugs-of-abuse testing in urine, *J. Anal. Toxicol.* 17 (1993) 241–245.

- [25] D.J. Crouch, J.F. Frank, L.J. Farrell, H.M. Karsch, J.E. Klaunig, A multiple-site laboratory evaluation of three on-site urinalysis drug-testing devices, *J. Anal. Toxicol.* 22 (1998) 493–502.
- [26] E.J. Cone, A.H. Sampson-Cone, W.D. Darwin, M.A. Huestis, J.M. Oyler, Urine testing for cocaine abuse: metabolic and excretion patterns following different routes of administration and methods for detection of false-negative results, *J. Anal. Toxicol.* 27 (2003) 386–401.
- [27] R.A. Braithwaite, D.R. Jarvie, P.S. Minty, D. Simpson, B. Widdop, Screening for drugs of abuse. I: opiates, amphetamines and cocaine, *Ann. Clin. Biochem.* 32 (1995) 123–153.
- [28] S. George, R.A. Braithwaite, Use of on-site testing for drugs of abuse, *Clin. Chem.* 48 (2002) 1639–1646.
- [29] E.A. Warner, R.M. Walker, P.D. Friedmann, Should informed consent be required for laboratory testing for drugs of abuse in medical settings? *Am. J. Med.* 115 (2003) 54–58.
- [30] B. Michael, Physical complications of substance abuse: what the psychiatrist needs to know, *Curr. Opin. Psychiatry* 16 (2003) 291–296.
- [31] M.L. Givens, R. Wald, J. Schafer, F. Wians Jr, K. Delaney, Prevalence of cocaine use in ED patients with severe hypertension, *Am. J. Emerg. Med.* 25 (2007) 612–615.
- [32] S.L. Brody, C.M. Slovis, K.D. Wrenn, Cocaine-related medical problems: consecutive series of 233 patients, *Am. J. Med.* 88 (1990) 325–331.
- [33] K. Phillips, A. Luk, G.S. Soor, J.R. Abraham, S. Leong, J. Butany, Cocaine cardiotoxicity: a review of the pathophysiology, pathology, and treatment options, *Am. J. Cardiovasc. Drugs* 9 (2009) 177–196.
- [34] J.M. Isner, N.A. Estes 3rd, P.D. Thompson, M.R. Costanzo-Nordin, R. Subramanian, G. Miller, et al., Acute cardiac events temporally related to cocaine abuse, *N. Engl. J. Med.* 315 (1986) 1438–1443.
- [35] A.I. Qureshi, M.F. Suri, L.R. Guterman, L.N. Hopkins, Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey, *Circulation* 103 (2001) 502–506.
- [36] J.E. Hollander, Cocaine-associated myocardial infarction: mortality and complications, *Arch. Intern. Med.* 155 (1995) 1081–1086.
- [37] F. Bamberg, C.L. Schlett, Q.A. Truong, I.S. Rogers, W. Koenig, J.T. Nagurney, et al., Presence and extent of coronary artery disease by cardiac computed tomography and risk for acute coronary syndrome in cocaine users among patients with chest pain, *Am. J. Cardiol.* 103 (2009) 620–625.
- [38] S. Aslibekyan, E.B. Levitan, M.A. Mittleman, Prevalent cocaine use and myocardial infarction, *Am. J. Cardiol.* 102 (2008) 966–969.
- [39] G. Burrillo-Putze, J.M. Borreguero León, E. Vallbona Afonso, A.M. De Vera González, J.F. Fernández Rodríguez, J.A. García Dopico, et al., Consumo de cocaína y su relación con patología cardíaca y traumática atendida en un servicio de urgencias, *Emergencias* 20 (2008) 380–386.
- [40] R. Cunningham, M.A. Walton, J.E. Weber, S. O’Broin, S.P. Tripathi, R.F. Maio, et al., One-year medical outcomes and emergency department recidivism after emergency department observation for cocaine-associated chest pain, *Ann. Emerg. Med.* 53 (2009) 310–320.
- [41] J. Lucena, M. Blanco, C. Jurado, A. Rico, M. Salguero, R. Vazquez, et al., Cocaine-related sudden death: a prospective investigation in south-west Spain, *Eur. Heart J.* 31 (2010) 318–329.
- [42] S.H. Rezkalla, R.A. Kloner, Cocaine-induced acute myocardial infarction, *Clin. Med. Res.* 5 (2007) 172–176.

- [43] J. McCord, H. Jneid, J.E. Hollander, Cercek B. de Lemos JA, P. Hsue, et al., American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, *Circulation* 117 (2008) 1897–1907.
- [44] K. Nademanee, D.A. Gorelick, M.A. Josephson, M.A. Ryan, J.N. Wilkins, H.A. Robertson, et al., Myocardial ischemia during cocaine withdrawal, *Ann. Intern. Med.* 111 (1989) 876–880.
- [45] J.T. Levis, G.M. Garmel, Cocaine-associated chest pain, *Emerg. Med. Clin. N. Am.* 23 (2005) 1083–1103.
- [46] W. Langstom, M. Pollack, Pseudo-Wellens syndrome in a cocaine user, *Am. J. Emerg. Med.* 24 (2006) 122–129.
- [47] K.C. Wilson, J.J. Saukkonen, Acute respiratory failure from abused substances, *J. Intensive Care Med.* 19 (2004) 183–193.
- [48] P.Y. Hsue, C.L. Salinas, A.F. Bolger, N.L. Benowitz, D.D. Waters, Acute aortic dissection related to crack cocaine, *Circulation* 105 (2002) 1592–1595.
- [49] H.F. Chambers, D.L. Morris, M.G. Täuber, G. Modin, Cocaine use and the risk for endocarditis in intravenous drug users, *Ann. Intern. Med.* 106 (1987) 833–836.
- [50] P.Y. Hsue, D. McManus, V. Selby, X. Ren, P. Pillutla, N. Younes, et al., Cardiac arrest in patients who smoke crack cocaine, *Am. J. Cardiol.* 99 (2007) 822–824.
- [51] M. Chase, A.M. Brown, J.L. Robey, K.E. Zogby, F.S. Shofer, L. Chmielewski, et al., Application of the TIMI risk score in ED patients with cocaine-associated chest pain, *Am. J. Emerg. Med.* 25 (2007) 1015–1018.
- [52] B. Leikin, Cocaine and beta-adrenergic blockers: a remarriage after a decade-long divorce? *Crit. Care Med.* 27 (1997) 688–689.
- [53] T. Mohamad, A. Kondur, P. Vaitkevicius, K. Bachour, D. Thatai, L. Afonso, Cocaine-induced chest pain and beta-blockade: an inner city experience, *Am. J. Ther.* 15 (2008) 531–535.
- [54] P.B. Dattilo, S.M. Hailpern, K. Fearon, D. Sohal, C. Nordin, β -Blockers are associated with reduced risk of myocardial infarction after cocaine use, *Ann. Emerg. Med.* 51 (2008) 117–125.
- [55] R.L. Minor, Cocaine-induced myocardial infarction in patients with normal coronary arteries, *Ann. Intern. Med.* 115 (1991) 797–806.
- [56] ACC/AHA task force on Practice Guidelines, ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction., *JACC* 50 (2007) 652–726.
- [57] C.M. Beynon, Drug use and ageing: older people do take drugs!, *Age Ageing* 38 (2009) 8–10.
- [58] J.E. Hollander, R.S. Hoffman, P. Gennis, P. Fairweather, M.J. DiSano, D.A. Schumb, et al., Prospective multicenter evaluation of cocaine associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group, *Acad. Emerg. Med.* 1 (1994) 330–339.
- [59] R.S. Hoffman, Guidelines for Chest Pain and Myocardial Infarction: One Size Does Not Fit All, Available at: http://www.ahalibrary.com/pt/re/aha/editorial3_20_2008.htm?sessionid=LKnWYB5KpzMcYLWWhpDVPwqHC6DJ2L1h76ppLqctHh4hY1htQRy2!-1639216214!181195628!8091!-1, 2008 2, Last accessed: February 2010.