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THE CARDIOVASCULAR EFFECTS OF COCAINE

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□ **Abstract—Cocaine use continues to be prevalent among all races and socioeconomic groups in the United States. Patients presenting to emergency departments after cocaine ingestion frequently present with a chief complaint of chest pain. Although acute myocardial infarction is perhaps the most concerning diagnosis in this setting, there are many other potential causes of chest pain after cocaine ingestion. This article reviews the pharmacology of cocaine, as well as the etiologies and treatment of cocaine-associated chest pain, with an emphasis on this drug's range of cardiovascular effects.** © 2005 Elsevier Inc.

□ **Keywords— cocaine; myocardial infarction; chest pain; drug; intoxication**

INTRODUCTION

The use of cocaine dates back more than 1200 years, when natives in the South American Andes would chew the leaves of the *Erythroxylon coca*, an indigenous plant, for its stimulant properties (1). Since that time, cocaine has become one of the most commonly used illicit drugs in the United States. During the 1980s, the number of individuals using cocaine reached epidemic proportions, and cocaine has become the most frequently used illicit drug among patients presenting to Emergency Departments (ED) (2–4). In a 1999 survey, 3.7 million Americans reported using cocaine within the previous year, and 1.5 million Americans reported using cocaine regularly (5). Cocaine use is not a problem limited to the inner city, but rather, transcends all racial and socioeconomic groups (6).

Cocaine (benzoylmethyglecgonine, $C_{17}H_{21}NO_4$) is available in two distinct forms; a purified alkaloid free base form and a hydrochloride salt form. The "freebase" variety is produced by alkalinizing the salt with ammonia (or sodium bicarbonate), and then extracting it with nonpolar solvents. This form, which first appeared in the United States in the early 1980s, is also known as "crack," owing to the sound made when heated and smoked through a pipe. The second variety is the hydrochloride form, which is formed by dissolving the alkaloid in hydrochloric acid (HCl), forming a water-soluble powder, which decomposes when heated. This form can be consumed by intranasal, oral, or intravenous routes (7,8).

Chemically, cocaine is a weak base with a pKa of 8.6 (9). Its pharmacodynamics are not altered by the route of administration. However, inhalation produces a more rapid rise in the concentration of cocaine in both the blood and the brain. Thus, inhalation of cocaine produces similar cardiovascular effects to intravenous administration (10). Cocaine is metabolized into several distinct compounds, including benzoylecgonine, ecgonine, and the active metabolite norcocaine. Norcocaine is subsequently metabolized to N-hydroxynorcocaine, which is a potential hepatotoxin (11).

The intravenous injection of a mixture of cocaine and heroin, commonly referred to as "speedballing," ac-

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counts for 12% to 15% of ED visits for cocaine-related complaints (12). Coingestion of cocaine and ethanol results in the formation of the metabolite cocaethylene (13–15). Cocaethylene is more toxic to both the brain and heart than is cocaine alone (15).

CHRONIC COCAINE USE

The use of cocaine has been associated with both acute and chronic toxicities in nearly all organ systems (16). Cocaine use is also associated with both acute and chronic cardiovascular toxicities. Some of the chronic toxicities include an acceleration of underlying hypertension, coronary atherosclerosis, and left ventricular hypertrophy (LVH) (17–19). In addition, chronic cocaine use may result in the development of myocarditis or cardiomyopathy (20). Injection of cocaine also has been implicated in the development of endocarditis.

Chronic use of cocaine has been reported to accelerate atherosclerosis formation (21,22). Cocaine directly induces structural defects in the vascular endothelial cell barrier, which subsequently increases the permeability to peroxidase and low density lipoproteins (23). Furthermore, chronic use of cocaine can result in scattered foci of myocyte necrosis (22). Some studies report that cocaine users have a higher incidence of contraction band necrosis than non-cocaine users, although these findings are not consistently found (22,24–26). Additional non-ischemic cardiovascular effects associated with cocaine use include dysrhythmias and complications of hypertension (7,8,18). Both of these complications can occur in patients with or without coexistent myocardial ischemia or infarction. In addition, papillary muscle rupture, aortic dissection, and rupture of aortic aneurysms can occur (27,28). It is thought that aortic dissection occurs as a result of the high systemic arterial pressures that can occur after cocaine use (7). Although the mechanism is not completely understood, cocaine-induced aortic rupture has been reported in healthy individuals (13). Rupture of extra-thoracic vessels, including mycotic and intracerebral aneurysms, have been attributed to cocaine use (29).

Myocarditis has resulted from both prolonged exposure to cocaine as well as the introduction of infectious agents during intravenous drug use (7). It is hypothesized that cocaine-induced non-ischemic cardiomyopathy occurs via several mechanisms. One proposed mechanism relates to the prolonged exposure to catecholamines (13,30). In addition, heavy metal contaminants, particularly manganese, may contribute to the development of cardiomyopathy (20). Endocarditis has been associated with intravenous injection of many illicit drugs, including cocaine. The intravenous injection of cocaine, however, is felt to bestow an additional, independent risk for the development of endocarditis, for reasons that are not entirely clear (31,32). One plausible explanation relates to cocaine's systemic suppression of interleukin eight (IL-8), resulting in immunosuppression (33).

CHEST PAIN

Chest pain is a frequent presenting complaint of ED patients who have used cocaine, and accounts for approximately 16% of all cocaine-related admissions (13,34,35). Although most cases of cocaine-associated chest pain are non-ischemic, myocardial infarction (MI) remains the most frequent single-reported cardiac complication of cocaine use (13). It is hypothesized that many cases of chest pain in cocaine users result from a musculoskeletal etiology, perhaps from rhabdomyolysis of chest wall muscles (13). Another non-ischemic, but potentially lethal cause of cocaine-associated chest pain results from barotrauma in patients who smoke cocaine. These barotrauma-related injuries include pneumomediastinum, pneumothorax, and pneumopericardium. Pneumoperitoneum has also been a reported complication of recreational cocaine inhalation (36–39).

Cocaine is associated with numerous dysrhythmias, partly owing to its action on both sodium and potassium channels. Cocaine, a slow on-off sodium channel blocker, can lead to the generation of slow monomorphic ventricular tachycardia or idioventricualr rhythms. Its properties as a fast on-off potassium channel blocker can result in the development of torsade de pointes, although this seems to be limited to individuals who are at a predisposed risk for this dysrhythmia (40). Cocaine also has been found to lower the threshold for ventricular fibrillation (41).

MYOCARDIAL INFARCTION

Approximately 6% of patients presenting with cocaine-associated chest pain will be diagnosed with an MI (36,42,43). In a case-crossover study by Mittleman, designed to assess the change in risk of acute myocardial infarction immediately after exposure to cocaine and other potential triggers of MI onset, it was found that infarction risk is 23.7 times greater in the first hour after cocaine use, with a rapid decline therafter (44). They hypothesized that the reasons for these findings are multifactorial, including plaque disruption secondary to hemodynamic stresses, changes in neurotransmitter concentrations, platelet aggregation, and coronary vasoconstriction. Another common etiologic hypothesis is the mismatch of oxygen supply and demand due to