NIDA Conference Report on Cardiopulmonary Complications of “Crack” Cocaine Use*

Clinical Manifestations and Pathophysiology

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Abbreviations: AM=alveolar macrophage; Dco=diffusion of carbon monoxide; DM=pulmonary membrane component of diffusion; IL=interleukin; PChE=plasma cholinesterase; VC=alveolar capillary volume component

Experimental nasal insufflation or IV injection of cocaine hydrochloride (HCl) (water-soluble, powder cocaine) is known to cause both lethal and nonlethal cardiovascular complications in young, otherwise asymptomatic, individuals.1 Currently, smoking of alkaloidal cocaine (freebase or “crack” cocaine) alone or in combination with other smokable substance(s) is on the rise. In 1993, lifetime prevalence of crack cocaine use reached 7 to 8% among young adults.2 Unlike cocaine HCl, crack cocaine is both lipid soluble and resistant to thermal degradation and, therefore, can be smoked. This new mode of drug use has replaced nasal insufflation in some demographic regions as it produces an instantaneous euphoric effect (similar to that achieved by IV injection) due to its rapid absorption through the extensive network of pulmonary capillaries. Along with this increased use, there appears to be a parallel rise in the reported incidence of cardiopulmonary complications in crack cocaine users, particularly crack-related chest pain, the most frequent presenting symptom in cocaine-associated hospital emergency department visits. With the restructuring of the health-care provision system, the treatment of this manifestation alone could be a major concern contributing to the rising cost of medical care in this country. This concern and the paucity of information on the true frequency, clinical significance, and underlying pathophysiology of crack cocaine-induced pulmonary complications prompted the National Institute on Drug Abuse to hold a workshop at which basic and clinical researchers discussed their current findings and identified the gaps and future research opportunities in this area. The workshop was held in Bethesda, Md, on August 3 and 4, 1995. This conference report summarizes the major findings and the issues discussed by the participants and attendees at the meeting.

PULMONARY COMPLICATIONS

Although the true frequency and extent of lung injury caused by crack cocaine and/or its pyrolysis byproducts is uncertain at present, its use has resulted in a broad spectrum of pulmonary complications.3 These range from acute respiratory symptoms to clinical reports of acute exacerbations of asthma, barotrauma (pneumomediastinum and pneumothorax), noncardiogenic pulmonary edema, diffuse alveolar hemorrhage, recurrent pulmonary infiltrates with eosinophilia, and bronchiolitis obliterans with organizing pneumonia, as well as autopsy evidence of pulmonary vascular abnormalities. Acute respiratory symptoms, such as cough productive of carbonaceous sputum, chest pain, and hemoptysis, generally develop within 1 or more hours of smoking crack cocaine4 and are suggestive of a local irritant effect of cocaine on the airways since similar complaints are not reported after nasal insufflation or IV injection of cocaine HCl.

While the number of dramatic examples of acute lung injury that have been reported is relatively small,3 it is possible that regular cocaine smoking might cause more frequent, clinically silent chronic lung damage that could progress with continued use and ultimately be manifested clinically. To assess this possibility, researchers have measured pulmonary function in habitual crack smokers both with and without chronic pulmonary symptoms. Findings to date show no significant long-term adverse effects of habitual crack smoking.

For related material see page 904

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cocaína smoking on lung mechanics, as reflected by normal results of spirometry, even in heavier habitual users. However, its effects on the single-breath diffusing capacity of the lung for carbon monoxide (D\textsubscript{CO}), a physiologic marker of the integrity of the alveolar-capillary membrane, are still unclear. While some investigators, in small-scale studies, have failed to find an effect on D\textsubscript{CO}, Tashkin and his coworkers more recently reported a small but significant decrease in D\textsubscript{CO} in a large cohort of habitual crack smokers after controlling for use of other substances confirming earlier findings. Factors such as sample size, inappropriate controls, concomitant use of other smoked substances, and/or intensity of cocaine use are thought to contribute to the observed differences.

Although the precise mechanism(s) underlying the cocaine-associated impairment in gas transfer in the lung are not yet known, the presence of abnormalities in the diffusing capacity suggest structural lung damage. The lung damage could be reflected by changes in either the pulmonary membrane component of diffusion (D\textsubscript{m}) or the alveolar capillary volume component (V\textsubscript{c}). Findings presented indicated that cocaine-induced reduction in D\textsubscript{m}, rather than V\textsubscript{c}, is probably responsible for the impaired diffusion seen in habitual crack smokers (DP Tashkin, MD, FCCP; unpublished data). Since alterations in pulmonary clearance of \textsuperscript{99m}Tc-DTPA, a sensitive marker of alveolar epithelial integrity, were observed in only 4 of 7 young, otherwise healthy, habitual crack smokers, it was suggested that subtle alveolar epithelial damage may occur even inconsistently in these individuals. These preliminary findings were somewhat different from an earlier study in which more consistent increases in pulmonary clearance of \textsuperscript{99m}Tc-DTPA were observed. Thus, these findings need to be interpreted cautiously until confirmed in a larger cocaine-smoking population. It was also emphasized that the health, duration, intensity of cocaine smoking, and concomitant exposures to other noxious inhaled substances, as well as the size of population, may influence the study outcome.

To delineate the long-term vs short-term functional effects of cocaine smoking on the lung, Tashkin and his associates (DP Tashkin, MD, FCCP; unpublished data) measured airway dynamics, pulmonary gas exchange, and pulmonary vascular pressures (estimated from Doppler echocardiography) in habitual cocaine users both before and after acute administration of smoked alkaloidal cocaine or IV cocaine HCl. Data presented from this pilot study showed that cocaine smoking caused significant decreases in specific airway conductance within minutes following cocaine inhalation. No significant changes in specific airway conductance were noted after IV cocaine HCl, suggesting that the bronchoconstriction was due to a local irritant effect of the inhaled smoke, rather than a pharmacologic effect of cocaine itself. The observed acute bronchoconstriction could also be caused by anhydroecgonine methylester, a major pyrolysate product of cocaine, as has been reported in experimental animals. However, the method of generating cocaine vapor in the studies presented would be expected to maximize the delivery of alkaloidal cocaine while minimizing the generation of the pyrolysate, anhydroecgonine methylester. These physiologic findings are consistent with earlier reports of crack cocaine-induced exacerbations of clinical asthma. Nonetheless, no acute changes were observed in either D\textsubscript{CO} or its components (D\textsubscript{m} or V\textsubscript{c}) after either smoked or IV cocaine. This suggested that the impairment in D\textsubscript{CO} and D\textsubscript{m} observed in habitual crack cocaine users may result from the accumulated effects of long-term cocaine-induced damage to the alveolar-capillary membrane that is not apparent following acute exposure to cocaine. Furthermore, the lack of any demonstrable changes in estimates of mean pulmonary artery pressure as measured by continuous Doppler echocardiography by either route of acute cocaine administration fails to support the concept that crack cocaine-induced lung injury may result from intense pulmonary vasoconstriction, leading to anoxic damage.

Smoking of cocaine is thought to increase susceptibility to infections and inflammatory pulmonary complications implying an impairment in pulmonary host defense. Pulmonary alveolar macrophages (AMs) are known to provide the first line of host defense and are also exposed to the highest concentrations of inhaled cocaine. Data presented showed that AMs recovered from the BAL fluid of cocaine smokers produced less inflammatory cytokines (interleukin [IL]6, IL-8, tumor necrosis factor-\alpha) and more immunosuppressive factor, transforming growth factor-\beta, than AMs from nonsmoking individuals. Enhanced elaboration of activated transforming growth factor-\beta is one of the mechanisms by which cocaine enhances HIV replication \textit{in vitro}. On a functional level, AMs from crack cocaine abusers were less active than AMs from nonsmokers in their capacity to destroy \textit{Staphylococcus aureus} and to prevent growth of cancer cells. Preliminary findings also showed that AMs from cocaine smokers were more susceptible to HIV infection and promoted a several-fold increase in HIV replication when infected \textit{in vitro}. These observations suggest that long-term use of crack cocaine can result in a profound impairment in pulmonary host defense. Cocaine also suppressed the production of interferon-gamma and IL-8 by lymphocytes \textit{in vitro} and acted at the transcriptional level by preventing upregulation of cytokine messenger RNA that normally occurs when lymphocytes are stimulated. In contrast, acute administratio-
tion of cocaine to long-term cocaine users was associated with neutrophil activation. This acute activation of neutrophils may therefore play a role in the syndrome of “crack lung,” while chronic immunosuppression may impact on the risk for HIV and other infections. The mechanisms by which cocaine mediated these immunologic effects are undefined at present.

Mechanisms for pathologic changes seen in lungs of cocaine users at autopsy are also unclear at present. Pathologic evaluations have revealed that pulmonary hemorrhage occurs more often than is described clinically and that chronic interstitial pulmonary fibrosis may develop in long-term cocaine users.\textsuperscript{15} The observed pulmonary vascular alterations could be due to direct toxic effects of cocaine, to cardiac compromise, or to cocaine-induced pulmonary vasoconstriction.\textsuperscript{18} Hypersensitivity response to the drug was speculated to be another possible mechanism for pulmonary interstitial changes. It was suggested that animal models be developed to elucidate the underlying mechanisms for these cocaine-associated pulmonary manifestations.

**Cardiovascular Complications**

Use of cocaine “freebase” or cocaine HCl in humans may cause a number of cardiovascular events, such as myocardial infarction, myocarditis, dilated cardiomyopathy and heart failure, coronary and peripheral vascular spasm, dysrhythmia, and sudden cardiac death. However, the most frequent presenting symptom in cocaine-related cardiac emergencies in chest pain.\textsuperscript{19, 20} Clinical evidence appears to suggest a relationship between cocaine use and myocardial ischemic symptoms even though the latter appear unrelated to cocaine dose, route, or time of administration. This suggests wide interindividual variation in susceptibility to cocaine’s adverse effects. To determine clinical criteria predictive of myocardial infarction associated with cocaine use, a prospective multicenter study was undertaken. Data presented from this study revealed that at present and to our knowledge, there are no clinical parameters available to the emergency physician that can adequately identify patients at very low risk for myocardial infarction.\textsuperscript{21–25} Patients who present to the emergency department with chest pain following cocaine use have a very low likelihood of serious cardiac complications if they do not sustain a myocardial infarction. One retrospective study estimated that only 1.6 per 1,000 patients with cocaine-associated chest pain would experience cardiovascular complications not identified during a 12-h monitored observation period utilizing cardiac marker determinations and electrocardiography. It was stressed that 9- to 12-h observation periods should not be used routinely until prospective validation confirms the safety of this strategy.

It is speculated that predisposition to cardiotoxic effects of cocaine could be due to a genetic determinant such as its metabolic disposition. Observational studies show that levels of plasma cholinesterase (PChE), one of the cocaine metabolizing enzymes, are decreased in patients with life-threatening cardiac events following cocaine compared to those with non-lethal cardiac complications, confirming previous results.\textsuperscript{24} Experimental findings also showed that pretreatment of mice with human PChE lowered cocaine-induced lethality and seizure with concomitant increases in PChE activity.\textsuperscript{25} However, decreases in PChE activity induced by protein calorie malnutrition in animals was associated with increased sensitivity to cocaine (RS Hoffman, MD; 1995; unpublished data). These findings, although preliminary, raise questions: whether a change in PChE profile occurs with long-term cocaine use in humans and, if it does, what impact does this change have on the susceptibility of an individual to cocaine’s toxic effects. Other experimental findings presented also showed that a subpopulation of animals may be more sensitive to the cardiotoxic effects of cocaine since exposure to the same cocaine regimen produced different hemodynamic responses in different subgroups of animal.\textsuperscript{26} Central monoaminergic sites appeared to be involved in these varied responses. For example, norepinephrine overflow was significantly higher in the striatum of rats whose cardiac output increased after cocaine, whereas in rats whose cardiac output was decreased, dopamine overflow was augmented.\textsuperscript{27} Additional studies showed ultrastructural changes in the myocardium of stressed rats similar to those in cocaine-exposed rats, suggesting that cocaine-evoked cardiovascular responses may in part be induced by behavioral stress.\textsuperscript{28} Other pathologic evaluations have shown that the presence of focal myocardial necrosis observed in cocaine abusers may have increased their susceptibility to ventricular arrhythmia.\textsuperscript{29}

Although acute myocardial infarction has been reported in young, otherwise healthy, individuals following cocaine use, its mechanism(s) remains speculative. One of the proposed physiologic mechanisms is that cocaine causes a diffuse increase in coronary vascular resistance, which may lead to a decrease in coronary blood flow. Studies performed in miniature swine showed that cocaine produced decreases in coronary blood flow and increases in vascular resistance that were partially reversed by adenosine.\textsuperscript{30} Similar changes in vasoconstriction have been reported in isolated vessels and whole heart preparations. These findings suggest that cocaine can produce profound microvascular spasm that may contribute to the ischemia/infarction reported in patients who abuse cocaine and are subsequently found to have normal epicardial
coronary arteries. Other recent findings suggest that there may be a cholinergic component to cocaine-induced coronary vasoconstriction since pretreatment with atropine blocked cocaine-induced contraction of bovine coronary artery rings in vitro.\textsuperscript{31} Cholinergic modulation of cocaine-induced coronary vasoconstriction has also been reported in conscious dogs.\textsuperscript{32}

Changes in vascular endothelial function due to cocaine may also play a role in cocaine-associated myocardial infarction since such changes may predispose to the development of thrombosis resulting in myocardial ischemia/infarction. In vitro results presented showed that cocaine enhanced the permeability of vascular endothelium which could augment the diffusion of atherogenic lipoproteins into the intima and thereby increase the predisposition to atherosclerosis development.\textsuperscript{33} Pathologic findings presented also showed moderate to severe aorta and coronary artery atherosclerosis in a population of young cocaine abusers who were otherwise at low risk for coronary atherosclerosis.\textsuperscript{34,35} Interestingly, atherosclerotic lesions in cocaine abusers with acute coronary thrombosis did not demonstrate plaque rupture or hemorrhage suggesting that the pathophysiology of acute myocardial infarction is different from that in noncocaine users. Augmented release of vasoactive mediators through enhanced activation of platelet and recruitment of mast cells may also be involved in cocaine-related vasospasm and thrombosis.\textsuperscript{34,36} Thus, cocaine-induced myocardial infarction appears to result by direct and indirect actions of cocaine at various cellular levels.

Cardiovascular sequelae such as increases in heart rate, mean arterial BP, cardiac index, and transcardiac oxygen uptake seen in humans following cocaine use are thought to be due to activation of the sympathetic nervous system.\textsuperscript{37,38} Similar changes in cardiovascular responses have also been reported in experimental animals exposed to an acute or long-term cocaine regimen. These observations are not unexpected because one of the known fundamental pharmacologic actions of cocaine is to increase peripheral sympathetic tone by inhibition of neuronal reuptake of monoamines. At present, however, it is unclear whether the sites of sympathomimetic actions of cocaine are primarily peripheral or a combination of both peripheral and central sympathetic sites. Experimental findings presented showed that at least acute effects of cocaine on the cardiovascular system are mediated via its peripheral sympathomimetic actions which appear to involve inhibition of catecholamine uptake into postganglionic sympathetic nerve terminals and increased release of epinephrine from the adrenal medulla.\textsuperscript{39,40} Data also indicate that cocaine alters parasympathetic nervous system activity at the level of the heart.\textsuperscript{41} At present, it is unclear whether the modulation is due to inhibition or enhancement of its activity and this issue needs further clarification. In vitro experiments reported that both catecholamine-dependent and -independent mechanisms may be involved in cocaine-induced inotropic and lusitropic responses in ferret myocardium.\textsuperscript{42} The positive inotropic and lusitropic responses seen in myocardium at low and moderate doses of cocaine were mediated probably via catecholamine release from adrenergic nerve terminals, while at higher doses the decreases seen in myofilament calcium sensitivity and maximal calcium-activated force were mediated most likely by mechanisms independent of catecholamines.

Cocaine has been thought to cause cardiac dysrhythmias, which may precipitate into sudden death in humans. The potential mechanisms could be its proarrhythmic action due to inhibition of the sodium channel, its direct action on the heart, or alteration in the activity of the autonomic nervous system. Experiments in isolated hearts showed that cocaine attenuated lethal arrhythmias and, in conscious dogs, it blocked the induction of ventricular arrhythmia induced by programmed electrical stimulation (G Friedrichs, PhD and B Lucchesi, MD; 1995; unpublished findings). These findings suggest that cocaine has antiarrhythmic actions which appear to be mediated via its local anesthetic effect.

**Future Research Directions**

Discussion at this workshop centered on future research requirements. Appropriate animal models, cellular and subcellular investigations, and multicenter studies of large numbers of well-characterized users of crack with or without other abused substances are needed for a better understanding of the cardiopulmonary complications of crack cocaine, their clinical significance, and their underlying physiologic, cellular, and molecular mechanisms. Ultimately, the results of these studies will yield information that should enable us to provide better treatment protocols for these medical complications in the substance-abusing population.

**References**


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