Reviews

Can Cocaine Abuse Exacerbate the Cardiac Toxicity of Human Immunodeficiency Virus?

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Summary

Both cocaine use and human immunodeficiency virus (HIV) infection alone have been associated with an increased incidence of cardiac dysfunction. Concomitant exposure to cocaine and HIV infection may exacerbate the cardiac toxicity of either agent alone, a hypothesis that is examined in this review article. A possible unifying hypothesis based on enhancement of adrenergic stimulation is proposed.

Key words: myocarditis, catecholamines, heart failure, human immunodeficiency virus, cocaine, virus, drug abuse

Introduction

Unsafe sex and drug abuse are behaviors not commonly associated with the development of cardiovascular disease. However, we are currently in the midst of two sexual and drug-abuse related epidemics: (1) infection with human immunodeficiency virus (HIV) and (2) cocaine abuse, both of which may have serious cardiovascular complications. These two epidemics are in fact “entangled,” as the title of one review article suggests.^{1–6} In its clinical expression as the autoimmune deficiency syndrome (AIDS), HIV infection has become a leading cause of death among young adults worldwide; 2.5 to 7.5% of patients demonstrate clinically significant cardiac dis-

ease; and autopsy series suggest that cardiovascular pathology occurs in over 30% of infected patients.⁷ The absolute number of patients with HIV infection who manifest cardiac involvement is likely to increase as measures to combat AIDS once acquired continue to improve.⁸

Cocaine became the drug of abuse of choice for a large segment of the population in the 1980s; in 1997 the National Household Survey on Drug Abuse estimated that 1.5 million Americans were current users of cocaine, representing 0.7% of the population age > 12. Even casual use of cocaine has been associated with a significantly increased incidence of ischemic and nonischemic cardiac and vascular complications, observations that become even more striking by their occurrence among the younger age groups of patients⁹ who typically abuse the drug, a group that normally exhibits a low incidence of cardiovascular abnormalities. Several studies have documented an increase in the incidence of infection with HIV among the drug-abusing population, which is in part attributable to activities that increase exposure to the virus through sharing of drug paraphernalia or needles and unsafe sexual practices.^{10, 11}

Since both HIV and cocaine can independently produce cardiac complications, it is reasonable to hypothesize that the combination of these two toxic agents in a single patient might exacerbate some of the adverse effects of each and increase the incidence of heart and vessel pathology. Unfortunately, conclusive data are not as yet available for definitive support of this hypothesis, in part because of the difficulties inherent to tracking the drug-abusing population.¹² In recognition of these problems and their potential importance in terms of public health, the National Institutes of Health recently launched an initiative to encourage clinical trials and animal studies on the clinical manifestations and the potential mechanisms of interaction of HIV with cocaine.¹³ It will probably be years before definitive data are available, but in the meantime it seems reasonable to assume that combined exposure to HIV and cocaine is likely to be particularly toxic to the cardiovascular system. The purpose of this review is to summarize our existing knowledge about the cardiac toxicity of these two agents and thereby to emphasize their potential for exacerbating each other's individual toxicities, particularly with regard to myocarditis and its sequelae of acute and chronic cardiac dysfunction and heart failure.

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Human Immunodeficiency Virus and Myocarditis

A variety of viruses have been reported as causative agents of myocarditis in humans, including coxsackie, echo, and influenza viruses, cytomegalovirus, poliomyelitis virus, Epstein Barr virus, herpes simplex virus, adenovirus, and several others.¹⁴⁻¹⁸ In recent years, a growing body of evidence has accumulated indicating that cardiac dysfunction can occur in patients infected with HIV. Among the complications associated with HIV disease are pericarditis, myocarditis, ventricular tachycardia, endocarditis, and metastatic involvement from Kaposi's sarcoma and dilated cardiomyopathy.¹⁹⁻²⁷ Levy *et al.*²⁶ have prospectively evaluated HIV-infected patients with clinical evidence of cardiac dysfunction and documented that the prevalence of abnormalities was higher with more advanced disease, but was no more frequently observed in patients with active infection than in those whose infection appeared quiescent at the time of study. Depressed absolute CD4 lymphocyte counts correlated strongly with the presence of echocardiographic abnormalities in this study; therefore, the authors suggested the possibility that HIV may be a cardiac pathogen acting through direct or indirect mechanisms. Potential direct mechanisms include cytolytic infection of cardiocytes, or exacerbation of cardiac dysfunction by viral product interaction with myocardial tissue. Indirect mechanisms may include triggering of an immune process or cardiac disease mediated by release of lymphokines or cytokines from mononuclear cells.

Studies conducted by Herskowitz *et al.*²⁷ have shown a higher prevalence of myocarditis in HIV-seropositive patients undergoing endomyocardial biopsy for suspected myocarditis than in patients without HIV risk factors. The prevalence of myocardial dysfunction in HIV-positive patients was found to be 14.5% with a 5.8% prevalence of symptomatic cardiac dysfunction.²⁸ Immunoperoxidase studies demonstrated induction of major histocompatibility complex (MHC) class-I antigen expression on myocytes in the majority of HIV myocarditis cases, in contrast to HIV-seronegative patients who expressed MHC class-I and class-II antigen on myocytes. Foci of inflammation appeared to be enriched for CD8+ cells and mature T cells (CD2+ or CD3+). Several studies have demonstrated the presence of HIV gene transcripts in cardiac myocytes, but transcripts have also been demonstrated in cardiac tissues from patients with and without known cardiac dysfunction.^{29, 30} Studies by the same investigators have shown that nonpermissive or latent infection of myocytes with cytomegalovirus immediate-early (CMV IE-2) genes can be identified in a subgroup of HIV-infected patients presenting with left ventricular dysfunction. These authors also suggested that cytokines may play a role in the pathogenesis of HIV-associated myocarditis because all the patients with biopsy-proven myocarditis and HIV had significantly elevated levels of IL-6. Consistent with this hypothesis, Matsumori *et al.*³¹ have demonstrated that 38% of patients with idiopathic dilated cardiomyopathy and 50% with active myocarditis had elevated serum levels of tumor necrosis factor (TNF). Evidence for cardiac-specific autoimmunity in HIV seropos-

itive patients with symptomatic cardiac dysfunction has been described.³² In autopsy series, lymphocytic myocarditis was seen in 35-52% of cases, and lymphocytic myocarditis has been associated with left ventricular dysfunction and ventricular tachycardia.^{14, 19} The cause of lymphocytic myocarditis is not known, but it could be related to opportunistic infection with viral, protozoan, bacterial, fungal, or microbacterial pathogens. It has not yet been convincingly demonstrated that HIV can infect and directly damage or kill cardiac myocytes. However, despite the uncertainty over the exact mechanisms, a strongly positive correlation between HIV infection and myocarditis has been established.

Cocaine, Human Immunodeficiency Virus, and Myocarditis

Cocaine abuse is associated with an increased incidence of HIV risk-taking behavior, even among those without a history of drug use by injection.¹⁻⁶ Cocaine abuse alone has been associated with a variety of cardiac complications, including myocardial ischemia, infarction, and heart failure. It has also been reported to cause myocardial cell damage through direct and catecholamine-mediated effects, as well as by producing myocardial ischemia and infarction.³³⁻³⁸ A variety of reports have demonstrated an increased prevalence of myocarditis among cocaine abusers, and both lymphocytic and eosinophilic myocarditis has been reported.³⁹⁻⁴³ For example, Isner *et al.*⁴² reported the clinical and pathologic findings in seven cocaine abusers. Two of these patients had some evidence of myocarditis; one patient at autopsy had scattered foci of myocardial fibrosis and the other had myocyte necrosis and diffuse inflammatory cell infiltrates, including eosinophils. Virmani *et al.*⁴³ found the evidence of myocarditis among an autopsy series of cocaine abusers to be 20%, with cellular infiltrates consisting of lymphocytes, macrophages, and occasional eosinophils. Tazelaar *et al.*⁴⁴ reported the presence of myocardial contraction bands in 93% of patients and postulated that catecholamine excess caused by cocaine use contributed to contraction band necrosis, which may have supplied the anatomic substrate for ventricular arrhythmias. Other reports are consistent with the hypothesis that catecholamines may play a central role in producing the cardiac toxicity of cocaine.^{26, 45-49}

It has not as yet been convincingly demonstrated that cocaine use by an HIV-infected patient places that individual at increased risk of cardiac complications, although there is a compelling rationale as to why this should be so. Both cocaine and HIV infection alone have been associated with an increased incidence of myocarditis and cardiac dysfunction, as described above, and it is reasonable to propose that an additive or synergistic relationship may exist between these two agents. Possible mechanisms of such an interaction include enhanced infectivity of the virus through a diminished immune response and cocaine-induced damage to the endothelial/endocardial cells or to the myocytes themselves, thereby reducing structural and immunologic barriers to cellular penetration of the virus and increasing the vascular permeability

and diffusability of viral particles. Evidence supporting this possibility includes reports suggesting that cocaine can damage the endothelial lining of cells after even a single exposure, thereby accelerating atherosclerosis in animal models.⁵⁰⁻⁵² Cocaine has also been reported to increase natural killer cell activity.⁵³ Both lymphocytic and eosinophilic myocarditis have been reported in cocaine abusers,³⁹⁻⁴¹ and heart failure is a common finding.^{26, 45, 47-49} Alternatively, cocaine may exacerbate viral myocarditis by enhancing the toxicity of the viral agent once it has penetrated the cell membrane. Such an effect may occur through a direct or catecholamine-mediated alteration in the cellular milieu that, in turn, could alter viral transcription and replication. Such effects could include a change in cellular pH, shift in osmolarity, or depletion of high-energy stores necessary for protective proteolytic enzyme activity. Of course, it is likely that the effects of cocaine on the animal or a patient with myocarditis are complex and involve several mechanisms or conditioning factors, including drug diluents with pharmacologic activity or sensitizing effects.^{54, 55} However, the observation that exacerbation of myocarditis seems to occur with cocaine but not with other commonly abused drugs without prominent cardiac effects, including heroin and phencyclidine, suggests that cocaine may have a unique combination of properties that make its use in patients exposed to or infected with viral pathogens likely to enhance development of myocarditis and its sequelae. It is tempting to propose that the unique ability of cocaine to increase local release and circulating levels of catecholamines is the primary effect responsible for exacerbation of myocarditis.^{36, 38, 56}

Catecholamines, Cocaine, and Myocarditis

Evidence from several different sources indicates that catecholamines may exacerbate viral myocarditis in animals and patients. The most direct evidence arises from carefully controlled studies of murine myocarditis, indicating that hypercatecholaminergic states, such as pheochromocytoma and during infusion with sympathomimetic drugs, can cause or significantly exacerbate myocarditis.⁵⁷⁻⁷⁰ Reports of a prospective study by Karch⁷¹ show significantly elevated levels of epinephrine and norepinephrine in a group of patients who presented with cardiac symptoms immediately after using cocaine. Moreover, sympatholytic agents and states may ameliorate the manifestations of myocarditis and decrease mortality, although this effect is controversial.⁷²⁻⁸⁰ It is provocative that many of the interventions shown to ameliorate viral myocarditic pathogenicity, including calcium-channel blockers, act predominantly to modulate the cellular effects of catecholamines, perhaps by enhancing nitric oxide levels, which has been shown to attenuate sympathomimetic effects on the heart.⁷⁶⁻⁸⁰ Additional evidence includes the observation that, among commonly abused substances in the HIV and general populations (alcohol, nicotine, caffeine, marijuana, and cocaine most notably;³⁴⁻³⁶), cocaine has been most strongly associated with an increased incidence of myocarditis, suggesting that its unique sympathomimetic properties, not shared

with these other agents, may be the causative factor. Moreover, in the clinical arena, it has been accepted clinical practice for many years to restrict the activities of patients with myocarditis, primarily based on circumstantial evidence that exercise exacerbates the disease.¹⁴⁻¹⁹ In addition to increasing the work of the heart directly, normal exercise is associated with a marked increase in circulating catecholamine levels.⁸¹⁻⁹⁵ The effects of sympathomimetic drugs and interventions require additional testing in animal models of myocarditis and in humans, but production of a hyperadrenergic state provides a promising unifying hypothesis to explain the apparent exacerbation of myocarditis by cocaine abuse and may be relevant to other infectious etiologies with cardiac sequelae.

Conclusions

We are currently in the midst of two sexual and drug-abuse related epidemics, that is, infection with human immunodeficiency virus (HIV) and cocaine abuse, both of which may have serious cardiovascular complications. Since both HIV and cocaine can independently produce cardiac complications, it is reasonable to hypothesize that the combination of these two toxic agents in a single patient might exacerbate some of the adverse effects of each and increase the incidence of heart and vessel pathology. Although anecdotal supporting evidence exists, it has not as yet been convincingly demonstrated that cocaine use by an HIV-infected patient places that individual at any increased risk of cardiac complications; however, there is compelling rationale as to why this should be so. Both cocaine and HIV infection alone have been associated with an increased incidence of myocarditis and cardiac dysfunction, and it is reasonable to propose that an additive or synergistic relationship may exist between these two agents. We propose that production of a hyperadrenergic state by cocaine provides a promising unifying hypothesis which may explain the apparent exacerbation of myocarditis and its complications in the cocaine abuser.

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