

THE CONTROVERSY OVER COCAINE USE AND BETA-BLOCKADE CONTINUES TO BREW

Ankitkumar K. Patel, MD, MPH

Cocaine Abuse Epidemiology

Cocaine is the second most commonly used illicit drug and the most frequent cause of drug-related deaths in the United States.¹ Approximately 24 million people in the United States have used cocaine at least once, and five million abuse cocaine on a regular basis.² Its use is associated with acute and chronic complications affecting many organ systems, the most common being the cardiovascular system.³

Cocaine Pharmacology

Cocaine acts as a powerful sympathomimetic agent. Cocaine has two main mechanisms of action. Its first mechanism involves the inhibition of cellular sodium ion transport through blockade of fast sodium ion channels, resulting in membrane stabilization and a local anesthetic effect. In the myocardium, this effect is similar to that produced by class I antiarrhythmic agents.⁴ The second mechanism is a marked increase in catecholamine levels at the synapse by blockage of presynaptic reuptake of epinephrine, norepinephrine, and dopamine. The result is elevated levels of these neurotransmitters at the postsynaptic receptors.⁵

Stimulation of α -adrenergic receptors leads to coronary vasoconstriction.⁶ Cocaine not only causes spasm of the large coronary arteries but is toxic to cardiac muscle. Excessive β -adrenergic stimulation from cocaine causes calcium overload, which directly leads to cardiac myocyte toxicity.⁷ Stimulation of β -adrenergic receptors has positive chronotropic and inotropic effects on the myocardium and thus increases myocardial oxygen demand. Due to increased norepinephrine activity on α - and β -adrenergic receptors, cocaine produces a dose-dependent increase in heart rate and blood pressure, which usually remains within physiological levels in recreational use.⁸ In human volunteers, intranasal cocaine produces a significant increase in blood pressure, heart rate, coronary vascular resistance, and myocardial oxygen consumption compared to intranasal saline administration.⁹

Lastly, cocaine can precipitate coronary thrombosis.¹⁰ It increases platelet aggregation through elevated levels of thromboxane A_2 and epinephrine.¹¹

Cocaine and Chest Pain

Chest pain is the most common symptom reported by cocaine users.¹² Data suggests that most patients with chest pain are not questioned about cocaine use and if they are, the answer is often not documented.¹³ Fifty-seven percent of cocaine users complaining of chest pain are admitted to the hospital.¹⁴

Acute coronary events and myocardial infarction can occur within minutes to days after cocaine administration.¹⁵ Cocaine-induced myocardial infarction is difficult to diagnose since the most common ECG finding is early repolarization and left

ventricular hypertrophy.¹⁶ The anterior wall is involved in 77% of cases of cocaine-induced myocardial infarction.¹⁷ A small case study found users of cocaine have a transient 24-fold increase in risk of myocardial infarction in the first hour after use which decreases rapidly thereafter.¹⁸

Management of Cocaine-induced Chest Pain

Patients who have myocardial ischemia secondary to cocaine use are medically treated differently from patients who have myocardial ischemia unrelated to cocaine. Current recommendations for the treatment of cocaine-induced myocardial ischemia include use of benzodiazepines, cautious use of thrombolytics, and avoidance of beta-blockers.¹⁹

Controversy over β -blocker usage

During myocardial infarctions, β -blockers prevent the excessive catecholamine stimulation that leads to myocardial necrosis or stunning.²⁰ The benefit of β -blockers in myocardial infarction is the prevention of reinfarction and ventricular fibrillation.²¹

In 1976, Rappolt *et al* recommended the use of intravenous propranolol in the management of cocaine intoxication based on their observations of over 50 cases of successful treatment.²² As a result of these findings, propranolol became the preferred treatment for cocaine-induced hypertension until 1985 when Ramoska and Sacchetti suggested that propranolol should be used with caution due to its potential for causing paradoxical hypertension via “unopposed alpha stimulation.”²³ By blocking the β -adrenergic receptors, available neurotransmitters predominantly bind α -adrenergic receptors on smooth muscle and cause vasoconstriction of blood vessels, thereby elevating blood pressure.

However, a recent retrospective study of 363 consecutive telemetry and ICU patients who were admitted to a municipal hospital for chest pain and had positive urine toxicology results for cocaine demonstrated a decrease, rather than an increase, in the risk of death and myocardial infarction with β -blocker administration. The incidence of myocardial infarction in the group of patients treated with β -blockers was significantly lower than the group without therapy (6.1% vs. 26%; 95% CI: 10.3-30%).²⁴ In a corresponding editorial, Freeman and Feldman question the premise that cocaine chest pain is due to coronary artery spasm.²⁵ Firstly, cardiac catheterization in initial studies of patients with cocaine-induced chest pain was conducted in a delayed fashion, so that spontaneous thrombolysis could not be excluded.²⁶ Secondly, reversible coronary perfusion defects, consistent with coronary vasospasm, are rarely demonstrated in acute myocardial perfusion imaging.²⁷

In a small clinical study, labetalol was shown to reverse the cocaine-induced rise in mean arterial pressure, but does not alleviate cocaine-induced coronary vasoconstriction.²⁸ However,

to date no clinical trials have been conducted on the initial management of cocaine-associated ischemia or infarction.²⁹ Specifically, a study to assess the risk-to-benefit ratio of β -blocker usage in patients who complain of chest pain and test positive for cocaine would provide much needed clarification.

References

1. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. *National household survey on drug abuse: main findings*. Rockville, MD: Department of Health and Human Services, 2000.
2. Cregler LL, Mark H. Relation of acute myocardial infarction to cocaine abuse. *Amer Journ Cardiol*. 1985;56:794.
3. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *NEJM* 2001; 345:351-8
4. Stouffer GA, Sheahan RG, Lenihan DJ et al. Cocaine-associated chest pain. *Amer Journ Med Scien* 2002;324:37-44.
5. Cregler LL. Cocaine: the newest risk factor for cardiovascular disease. *Clin Cardiol* 1991;14:449-56.
6. Beckman KJ, Parker RB, Hariman RJ et al. Hemodynamic and electrophysiological actions of cocaine. *Circulation* 1991; 83:1799-807.
7. Kloner RA, Hale S, Alder K et al. The effects of acute and chronic cocaine use on the heart. *Circulation* 1992;85:407-419.
8. Orr D, Jones I. Anesthesia for laryngoscopy: a comparison of the cardiovascular effects cocaine and lignocaine. *Anesthesia* 1968;23:194-202.
9. Lange RA, Cigarroa RG, Yancy CW et al. Cocaine-induced coronary-artery vasoconstriction. *NEJM* 1989;321:1557-62.
10. Stenberg RG, Winniford MD, Hillis LD et al. Simultaneous acute thrombosis of two major coronary arteries following intravenous cocaine use. *Arch Pathol Lab Med* 1989; 113:521-4.
11. Kugelmass AD, Oda A, Monahan K et al. Activation of human platelets by cocaine. *Circulation* 1993;88:876-83.
12. Brody SL, Slovis CM, Wrenn KD. Cocaine-related medical problems: consecutive series of 233 patients. *Am Jour Med* 1990;88:325-31.
13. Hollander JE, Brooks DE, Valentine SM. Assessment of cocaine use in patients with chest pain syndromes. *Arch Intern Med* 1998; 158:62-6.
14. Hollander JE, Hoffman RS, Gennis P, et al. Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. *Acad Emerg Med* 1994;1:330-9.
15. Mittleman MA, Mintzer D, Maclure M, et al. Triggering of myocardial infarction by cocaine. *Circulation* 1999;99:2737-41.
16. Egred M, Davis GK. Cocaine and the heart. *Postgrad Med Jour* 2005;81:568-71.
17. Minor RL, Scott BD, Brown DD, et al. Cocaine-induced myocardial infarction in patients with normal coronary arteries. *Ann Intern Med* 1992; 115:797-806.
18. Mittleman MA, Mintzer D, Maclure M, et al. Triggering of myocardial infarction by cocaine. *Circulation* 1999;99:2737-41.
19. Hollander JE. Cocaine-associated myocardial ischemia. *NEJM* 1996;334:536-7.
20. Tazelaar HD, Karch SB, Stephens BG et al. Cocaine and the heart. *Human Pathol*. 1987;18:195-199.
21. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005;366:1622-32.
22. Rappolt RT, Gray GR, Inaba DS. Propranolol in the treatment of cardiopressor effect of cocaine [letter]. *NEJM*. 1976;295:448.
23. Ramoska E, Sacchetti AD. Propranolol-induced hypertension in treatment of cocaine intoxication. *Ann Emerg Med*. 1985;14:1112-1113.
24. Dattilo PB, Hailpern SM, Fearon K et al. β -blockers are associated with reduced risk of myocardial infarction after cocaine use. *Annals Emerg Med* 2008 (In press).
25. Freeman K, Feldman JA. Cocaine, myocardial infarction and β -blockers: time to rethink the equation? *Ann Emerg Med* 2008 (In press).
26. Schachne JS Roberts BH Thompson PD Coronary artery spasm and myocardial infarction associated with cocaine use *NEJM*
27. Feldman JA, Bui LD, Mitchell PM et al. The evaluation of cocaine-induced chest pain with acute myocardial perfusion imaging. *Acad Emerg Med*. 1999;6:103-109.
28. Boehrer JD, Moliterno DJ, Willard JE, et al. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Amer Journ Med* 1992; 94(6):608-10.
29. Hollander JE. The management of cocaine-associated myocardial ischemia. *NEJM*. 1995;333:1267-72.