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EDITORIAL COMMENT

Cocaine, Heart Failure, and Carvedilol

Triangulating the Safety of β-Blocker Therapy*

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"There is nothing more deceptive than an obvious fact."
—Arthur Conan Doyle (1)

Purported to be a gift from the gods by the Incas, used by intellectual luminaries such as Sigmund Freud and Charles Darwin, advertised for its therapeutic uses and abused as a popular club drug in the 1980s, cocaine has had an illicit yet illustrious history spanning the ages (Online Ref. 1). Although recreational use of cocaine has substantially declined since the mid-1980s, a major resurgence, particularly among young adults, is occurring. The most recent National Survey on Drug Use and Health found that the number of young Americans between 18 and 25 years of age who admitted to trying cocaine for the first time increased by 61% from 2013 to 2015 (Online Ref. 2). Additionally, the National Center for Health Statistics also reported that the age-adjusted mortality rate for cocaine overdoses rose from 1.6 per 100,000 population in 2011 to 3.6 in 2016, reflecting an average annual increase of 18% (Online Ref. 2) Many factors have contributed to this increase in cocaine-related deaths, including greater cultivation and production of cocaine in South America, increased state and national restrictions on prescribing and acquiring narcotics due to the opiate epidemic, and the practice of mixing cocaine with alcohol, heroin, ecstasy, and ketamine to enhance the feeling of euphoria. An illicit drug recently thought to be a cliché is now back in the limelight (Online Ref. 3).

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Not surprisingly, cocaine-use disorder (CUD) often overlaps with heart failure (HF). According to an analysis of the 2014 National Inpatient Sample of 989,080 HF hospitalizations, 6.2% (n = 61,510) HF cases had a documented substance abuse disorder, and cocaine was the most frequent substance-specific drug (n = 11,700) (2). For this subset of patients, clinicians face a clinical conundrum in the choice of guideline-directed medical therapy. Even at low doses, cocaine acts not only as a potent sympathomimetic by directly stimulating central sympathetic outflow but also as a presynaptic reuptake inhibitor of norepinephrine and dopamine (**Figure 1**) (3). Thus, using an evidence-based β-1 selective β-blocker such as bisoprolol or metoprolol succinate in a patient with HF and reduced left ventricular ejection fraction (HFrEF) could lead to coronary artery vasoconstriction and hypertension exacerbation as catecholamines are shunted to the α-adrenergic receptor (**Figure 1**). Therefore, β-blockers with α activity are theoretically more appealing for use in patients with HFrEF who are also intoxicated with cocaine. However, the actual safety of such an approach is, surprisingly, poorly understood. The 2012 American College of Cardiology (ACC)/American Heart Association (AHA) unstable angina/non-ST-segment elevation myocardial infarction management guidelines suggest that a combined α- and β-blocking agent (e.g., labetalol) may be reasonable therapy for patients after cocaine use with hypertension (systolic blood pressure: >150 mm Hg) or those with sinus tachycardia (pulse: >100 beats/min), provided a vasodilator is added (Class IIb, Level of Evidence: C) (4).

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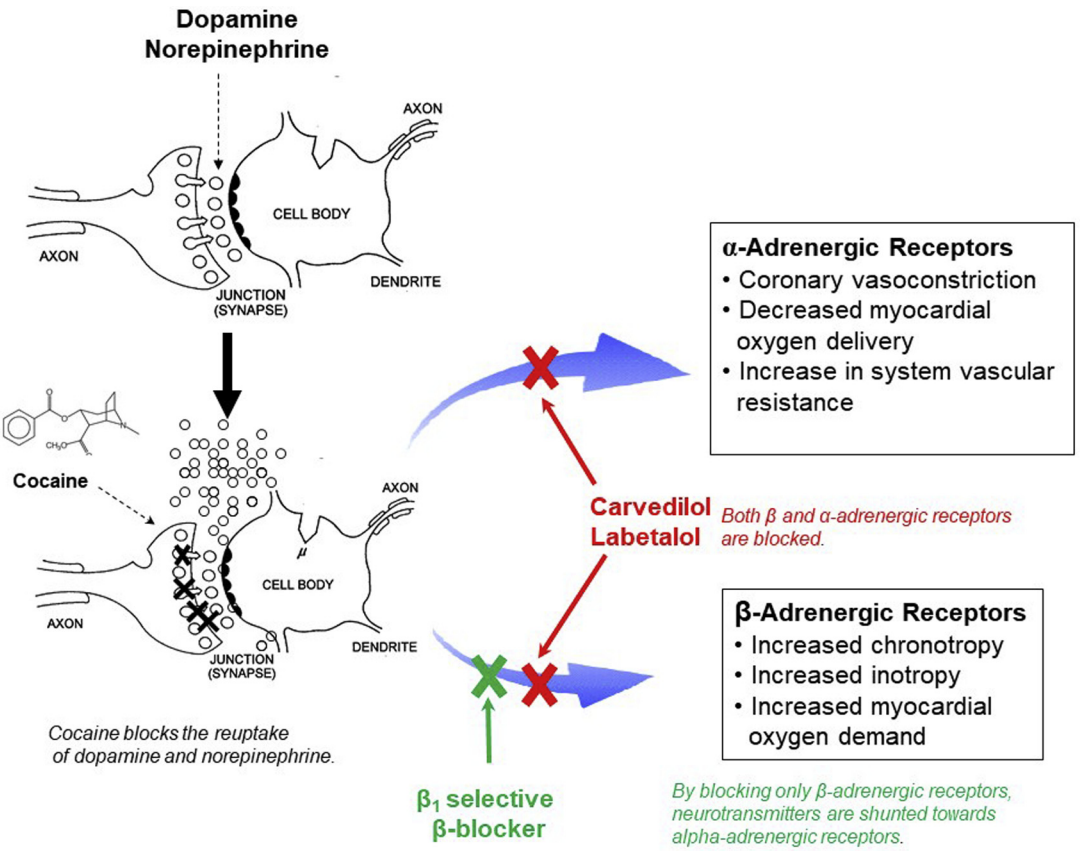
FIGURE 1 Mechanism of the Cardiovascular Effects When Cocaine Is Used



Potential mechanism of the cardiovascular effects when cocaine is used in combination with a third-generation combined α- and β-blocker compared to a second-generation β-1 selective β-blocker. Modified from Page et al. (5).

In contrast, the 2013 ACC/AHA/Heart Failure Society of America guidelines for the management of heart failure remain silent on recommending a specific β-blocker for chronic use due to lack of safety and efficacy data (Online Ref. 4).

In this Issue of *JACC: Heart Failure*, Banerji et al. (5) present the largest and most detailed experience to date evaluating the safety of carvedilol among HF patients with CUD. In this single-center evaluation, from a registry of 2,578 patients admitted to the Bronx-Lebanon Hospital in 2011 with a diagnosis of HF, 503 patients (20%) also had CUD based on positive urine toxicology. These patients were then stratified based on β-blocker use, carvedilol (n = 404), or no β-blocker (n = 99), and by the type of HF, reflective of left ventricular ejection fraction (LVEF) ≤40% (n = 230), 41% to 49% (n = 18%), or ≥50% (n = 179). The primary endpoint consisted of the rate of major adverse cardiac events (MACE), defined as the composite of cardiovascular mortality and 30-day HF readmission. With a median follow-up of 19 months, no differences existed in the rates of MACE among treatment groups for the entire HF cohort (p = 0.26), and between those with HF with preserved ejection fraction (p = 0.67) and those with mid-range ejection fraction (p = 0.70) but was significantly lower in those with HFrEF (p = 0.04%). In the adjusted analysis, carvedilol was associated with a 33% lower rate of MACE in patients with a LVEF ≤40% (hazard ratio = 0.67; 95% confidence interval: 0.481 to 0.863; p = 0.01). In addition, concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) on admission and at discharge were obtained as a reflection of myocardial wall stress. The authors found lower levels of NT-proBNP on both admission and at discharge among those receiving carvedilol, also suggestive of a cardioprotective effect of carvedilol in this population.

A major strength of this study was the collection of self-reported cocaine use paired with detailed clinical information from the health record. Cocaine frequency, type of cocaine, and mode of administration did not seem to be associated with significant differences in outcomes.

These findings are only reflective of carvedilol and not of other β-blockers, as the patients in this registry from Bronx-Lebanon Hospital appeared to receive carvedilol or no β-blockers. Although carvedilol therapy may make sense for HFrEF and CUD, some physicians may reach for labetalol in HF with preserved LVEF or in patients with coronary disease (as suggested by guidelines) (4). However, when choosing between the 2 third-generation nonselective β-blockers, the present authors believe the positive carvedilol findings from Banerji et al. (5) further support our preference for carvedilol over labetalol due to clinical, pharmacological, and economic considerations. From a clinical standpoint, labetalol has not been sufficiently evaluated in large clinical trials in patients with HFrEF, nor has the appropriate dose been determined. As seen from the bucindolol BEST (Beta-Blocker Evaluation of Survival Trial) and the COMET (Carvedilol Or Metoprolol European trial), not all β-blockers are "created equal" (Online Refs. 5-7). From a pharmacological standpoint, carvedilol's α-adrenergic receptor blockade appears to be dose-dependent, and carvedilol, 25 mg, may be 4-fold more effective than labetalol, 200 mg, at the α-receptor (6) (Online Refs. 8-10). Additionally, unlike labetalol, the more lipophilic carvedilol at recommended doses has good penetration into the central nervous system and, in turn, would be expected to block both peripheral and central adrenergic receptors, which may attenuate the physiological and behavioral response to cocaine (6) (Online Ref. 10). Finally, from a cost perspective, carvedilol is more affordable. Based on data from the Website GoodRx, carvedilol, 25 mg twice daily, compared to labetalol, 200 mg twice daily, averages approximately 4-fold less in terms of out-of-pocket dollar prices without insurance (Online Ref. 11).

In addition to the lack of comparative effectiveness data for other β-blockers and the single-center nature of the study, additional limitations should be recognized. Observational treatment-outcome associations are notoriously fraught with selection bias, and decisions about whether or not to give carvedilol to patients with HF and CUD are likely to include unmeasured confounding. We know from other HFrEF registries that patients not receiving β-blockers are typically sicker with more advanced disease and that appears to be the case in this cohort. Furthermore, the number of patients with HFrEF and CUD not taking a β-blocker is very small, limiting the ability to perform complex multivariate modeling and widening the confidence of estimated treatment affects.

Cocaine use disorder is a public health concern that has arisen from the ashes of the opioid epidemic and will continue to rise. While additional larger prospective studies are needed to define optimal treatment in the hospitalized setting, the study by Banerji et al. (5) provides reassurance that carvedilol can be safely used in patients with HF and CUD. Ironically, it has taken more than 2 decades for the publication of a study that confirms what we already knew.

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REFERENCES

1. Doyle AC. The Adventures of Sherlock Holmes. London. England: George Newnes Ltd; 2014:204.

2. Snow SC, Fonarow GC, Ladapo JA, Washington DL, Hoggatt KJ, Boback Zieian B. National rate of tobacco and substance use disorders among hospitalized heart failure patients. Am J Med 2019;132:478–88.

3. Havakuk O, Rezkalla SH, Kloner RA. The cardiovascular effects of cocaine. J Am Coll Cardiol 2019;70:101–13.

4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr., et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e179–348.

5. Banerji D, Alvi RM, Afshar M, et al. Carvedilol among patients with heart failure with a cocaine-use disorder. J Am Coll Cardiol HF 2019;7:771–8.

6. Page RL, Utz KJ, Wolfel EE. Should beta-blockers be used in the treatment of cocaine-associated acute coronary syndrome? Ann Pharmacother 2007;41:2008–13.

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APPENDIX For supplemental references, please see the online version of this paper.