

# $\beta$ -Blockers Are Associated With Reduced Risk of Myocardial Infarction After Cocaine Use

**Philip B. Dattilo, MD**  
**Susan M. Hailpern, DrPH, MS**  
**Kerrie Fearon, MD**  
**Davendra Sohal, MD, MPH**  
**Charles Nordin, MD**

From the Department of Medicine, Jacobi Medical Center, Bronx, NY (Dattilo, Fearon, Sohal, Nordin); and the Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (Hailpern).

**Study objective:**  $\beta$ -Blocker use is associated with coronary artery spasm after cocaine administration but also decreases mortality in patients with myocardial infarction or systolic dysfunction. We conduct a retrospective cohort study to analyze the safety of  $\beta$ -blockers in patients with positive urine toxicology results for cocaine.

**Methods:** The cohort consisted of 363 consecutive telemetry and ICU patients who were admitted to a municipal hospital and had positive urine toxicology results for cocaine during a 5-year period (307 patients). Fifteen patients with uncertain history of  $\beta$ -blocker use before admission were excluded. The primary outcome measure was myocardial infarction; secondary outcome measure was in-hospital mortality. Logistic regression analysis using generalized estimating equations models and propensity scores compared outcomes.

**Results:**  $\beta$ -Blockers were given in 60 of 348 admissions. The incidence of myocardial infarction after administration of  $\beta$ -blocker was significantly lower than without treatment (6.1% versus 26.0%; difference in proportion 19.9%; 95% confidence interval [CI] 10.3% to 30.0%). One of 14 deaths occurred in patients who received  $\beta$ -blockade (incidence 1.7% versus 4.5% without  $\beta$ -blockade; difference in proportion 2.8%; 95% CI -1.2% to 6.7%). Multivariate analysis showed that use of  $\beta$ -blockers significantly reduced the risk of myocardial infarction (odds ratio 0.06; 95% CI 0.01 to 0.61).

**Conclusion:** In our cohort, administration of  $\beta$ -blockers was associated with reduction in incidence of myocardial infarction after cocaine use. The benefit of  $\beta$ -blockers on myocardial function may offset the risk of coronary artery spasm. [Ann Emerg Med. 2007;xx:xxx.]

0196-0644/\$-see front matter

Copyright © 2007 by the American College of Emergency Physicians.

doi:10.1016/j.annemergmed.2007.04.015

## SEE EDITORIALS, P. ■■ and ■■.

## INTRODUCTION

### Background

Cocaine has many deleterious effects on the heart.<sup>1-3</sup> The pharmacologic effects of cocaine include both  $\alpha$  and  $\beta$  receptor stimulation, as well as acute myocardial depression, which is not related to reduced coronary blood flow.<sup>1</sup> Cocaine has also been associated with coronary artery spasm.<sup>4-6</sup> This effect appears to be mediated by both  $\alpha$  stimulation and a direct effect of cocaine on vascular smooth muscle.<sup>1</sup> Because  $\beta$ -adrenergic stimulation leads to vasodilatation of the coronary arteries, the safety of using  $\beta$ -adrenergic blockers in patients with history of cocaine use has been questioned repeatedly.<sup>1-3</sup> Lange et al<sup>7</sup> presented evidence

that  $\beta$ -adrenergic blockade increases vasoconstriction when given after cocaine exposure, as measured physiologically by reduced coronary blood flow and increased coronary vascular resistance. Labetalol, which is a combined  $\alpha$ - $\beta$  receptor-blocker, does not reduce cocaine-induced coronary vasoconstriction,<sup>8</sup> whereas both nitroglycerin<sup>9</sup> and verapamil<sup>10</sup> are effective agents for this purpose. Case reports have also documented evidence for spasm of large coronary arteries in the genesis of myocardial infarction associated with cocaine use.<sup>4-6</sup> These considerations have led to the recommendation that  $\beta$ -adrenergic blocking agents not be used in patients with acute exposure to cocaine.<sup>1-3</sup>

However, cocaine produces other pathophysiologic effects that are likely to be ameliorated by use of  $\beta$ -blockers, including myocardial infarction, systolic dysfunction heart failure, and

**Editor's Capsule Summary***What is already known on this topic*

Most physicians believe that sole  $\beta$ -blockade should be avoided in patients with clinical evidence of cocaine toxicity because of the risk of unopposed  $\alpha$  receptor stimulation. Some believe that  $\beta$ -blockers should be avoided in any patient with chest pain and a history of cocaine use.

*What question this study addressed*

The outcome of patients who received  $\beta$ -blockers in the presence of a positive urinary drug screen result for cocaine.

*What this study adds to our knowledge*

In this 348-patient retrospective review, there were proportionately fewer myocardial infarctions and deaths in the 60 patients who received  $\beta$ -blockers.

*How this might change clinical practice*

Although case reports suggest that some patients may experience adverse cardiovascular events during  $\beta$ -blocker administration, it is possible that others actually benefit. To guide clinical practice, research focusing on the population effect of  $\beta$ -blocker avoidance in patients with cocaine toxicity is needed.

ventricular arrhythmias.<sup>1-3</sup> The mortality of patients with myocardial infarction<sup>11</sup> and systolic dysfunction heart failure<sup>12,13</sup> is improved by  $\beta$ -blockers. In both conditions, studies suggest that nitrates alone have no effect on mortality, whereas calcium channel blockers may exacerbate symptoms or increase mortality.<sup>14-17</sup> Furthermore, adrenergic stress, which is an effect of cocaine exposure, may lead to acute ventricular fibrillation, contraction band necrosis, and, in the longer term, myocardial disarray and dilated cardiomyopathy.<sup>18,19</sup> More recently, studies have shown acute hazardous effects of high-level catecholamine stimulation on ventricular function. Such stimulation can lead to the development of apparent myocardial infarction and acute congestive heart failure.<sup>20</sup> The effect of other inducers of dilated cardiomyopathy may also be exaggerated after cocaine exposure.<sup>21</sup> Thus, there are compelling reasons to use  $\beta$ -blockers or combined  $\alpha$ - $\beta$ -blockers in patients who expose themselves to cocaine.

**Importance**

To our knowledge, there are no clinical studies that have evaluated the effect of  $\beta$ -blockers on the outcomes of myocardial infarction and death in patients with exposure to cocaine.

**Goals of This Investigation**

We therefore undertook a retrospective cohort study of the effects of  $\beta$ -blocker administration on the development of

myocardial infarction or death after hospital admission with documented cocaine use by urine toxicology.

**MATERIALS AND METHODS****Study Design and Setting**

This was a retrospective cohort study of patients admitted to monitored units of the Jacobi Medical Center, Bronx, NY. All visits originated in the emergency department (ED).

**Selection of Participants**

We included all patients admitted to the telemetry, medical, and coronary ICUs of the Medicine Service who tested positive for cocaine on urine toxicology test between July 1, 2000, and June 30, 2005. Patients who had been prescribed  $\beta$ -blockers as an outpatient but did not receive them during the course of their admission were excluded. Admissions during which cardiac markers were not checked were excluded from the myocardial infarction outcome analysis.

**Data Collection and Processing**

We used an electronic medical record (MYSIS), which includes clinical histories, laboratory values, and prescribed medications for all inpatients and outpatients. The database was searched electronically for all urine toxicology tests during the study period. We confirmed each test that was positive for cocaine. Manual review of each patient's paper medical record was also conducted to review the ED course, ECGs, telemetry strips, and handwritten notes. Records were analyzed for information about clinical presentations, previously prescribed medications, laboratory tests, medications prescribed during the hospitalization, whether  $\beta$ -blockers were prescribed in the ED or later in the course of admission, and finally the outcomes of myocardial infarction and death during the hospitalization (ie, inhospital mortality). Because the orders and laboratory tests are entered by time and date, we were also able to ascertain whether  $\beta$ -blockers were prescribed before or after troponin test results were obtained.

**Outcome Measures**

The primary outcome was myocardial infarction. The secondary outcome was inhospital mortality. Myocardial infarction was defined by a troponin I level greater than 0.10 or significant ST elevations in 2 contiguous leads by ECG, associated with chest pain or anginal equivalents (eg, shortness of breath). This definition is consistent with the joint European Society of Cardiology/American College of Cardiology Committee guidelines for the definition of myocardial infarction.<sup>22</sup> Myocardial infarction associated with  $\beta$ -blocker use was defined as a myocardial infarction after  $\beta$ -blocker administration before a documented increase in troponin I or ECG changes. Mortality associated with  $\beta$ -blocker use was defined as death from any cause and at any time in the course of the hospitalization after  $\beta$ -blocker administration.

## Methods of Measurement

We tested for cocaine metabolites in the urine with the EMIT II PLUS d.a.u. Cocaine Metabolite assay test (GMI, Inc., Ramsey, MN). The test uses an enzyme-multiplied immunoassay technique, with reagents from Dade-Behring (Glasgow Business Community, Newark, DE), run on a Bayer Advia 1650 machine (Bayer Advia, Tarrytown, NY). The assay measures benzoylecgonine, the major metabolite of cocaine, which can be detected within 4 hours of cocaine use and can remain detectable in concentrations greater than 100 ng/mL for as long as 48 hours. Cutoff value for positive urine toxicology was 300 ng/mL, as recommended by the Substance Abuse and Mental Health Services Administration.<sup>23</sup>

Serum troponin I levels were measured in the hospital central laboratory. We used a 2-site sandwich chemiluminescence immunoassay from Bayer Diagnostics, measured with the ADVIA Centaur System. According to manufacturer data, the assay has a 99th percentile cutoff of less than 0.07 and a correlation coefficient of 0.99 with the Bayer ACS: 180 cTnI assay, which was used in the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) study.<sup>24</sup>

## Primary Data Analysis

Continuous variables were expressed as mean (SD). Categorical variables were expressed as No. (%). Because patients had multiple admissions, independent variables (ie, demographic and clinical characteristics) may represent the same individual and lack independence. To account for the correlated nature of these data, generalized estimating equations were used to assess associations between demographic and clinical characteristics by  $\beta$ -blocker use and by outcome measures.

To evaluate the independent effect of  $\beta$ -blocker administration before myocardial infarction, parsimonious, or best fit, multivariate generalized estimating equations regression models were constructed, with a  $P < .05$  as a criterion for inclusion. In addition, any variable found to act as a confounder in the association between  $\beta$ -blocker administration before myocardial infarction, as noted by a change in the  $\beta$  coefficient greater than or equal to 10%, was included in the model. Covariates considered for inclusion in the regression model were those with a  $P < .25$  on bivariate analyses. Potential candidate covariates included age, sex, systolic blood pressure, history of heart disease, history of heart failure, history of diabetes, current smoking status, and admission laboratory values, including serum albumin, potassium, blood urea nitrogen (BUN), creatinine, and glucose. Because this was an observational study and there was nonrandomized assignment to  $\beta$ -blocker treatment, propensity scores were used. The propensity score is an established method used to address selection bias caused by observed factors.<sup>25,26</sup> It is the estimated probability of being treated with  $\beta$ -blocker rather than no  $\beta$ -blocker. The propensity score, which was derived from a separate generalized estimating

equations regression model that predicts  $\beta$ -blocker administration by using covariates in the best-fit model according to the covariates presented above, is the single summarized confounding covariate used in the generalized estimating equations model.

## Sensitivity Analyses

Sensitivity analysis was performed by using the first admission for each patient for myocardial infarction and in-hospital death outcomes. For these 2 models, logistic regression analysis was used because there was 1 admission per patient. In addition, a separate sensitivity analysis for myocardial infarction outcomes was performed with only patients admitted with a primary diagnosis of chest pain. A parsimonious multivariate generalized estimating equations regression model was constructed (as described above) for the full cohort admitted with a primary diagnosis of chest pain, and a logistic regression analysis was used for sensitivity analysis by using the first admission for each patient admitted with a primary diagnosis of chest pain. A separate propensity score was calculated for each regression model.

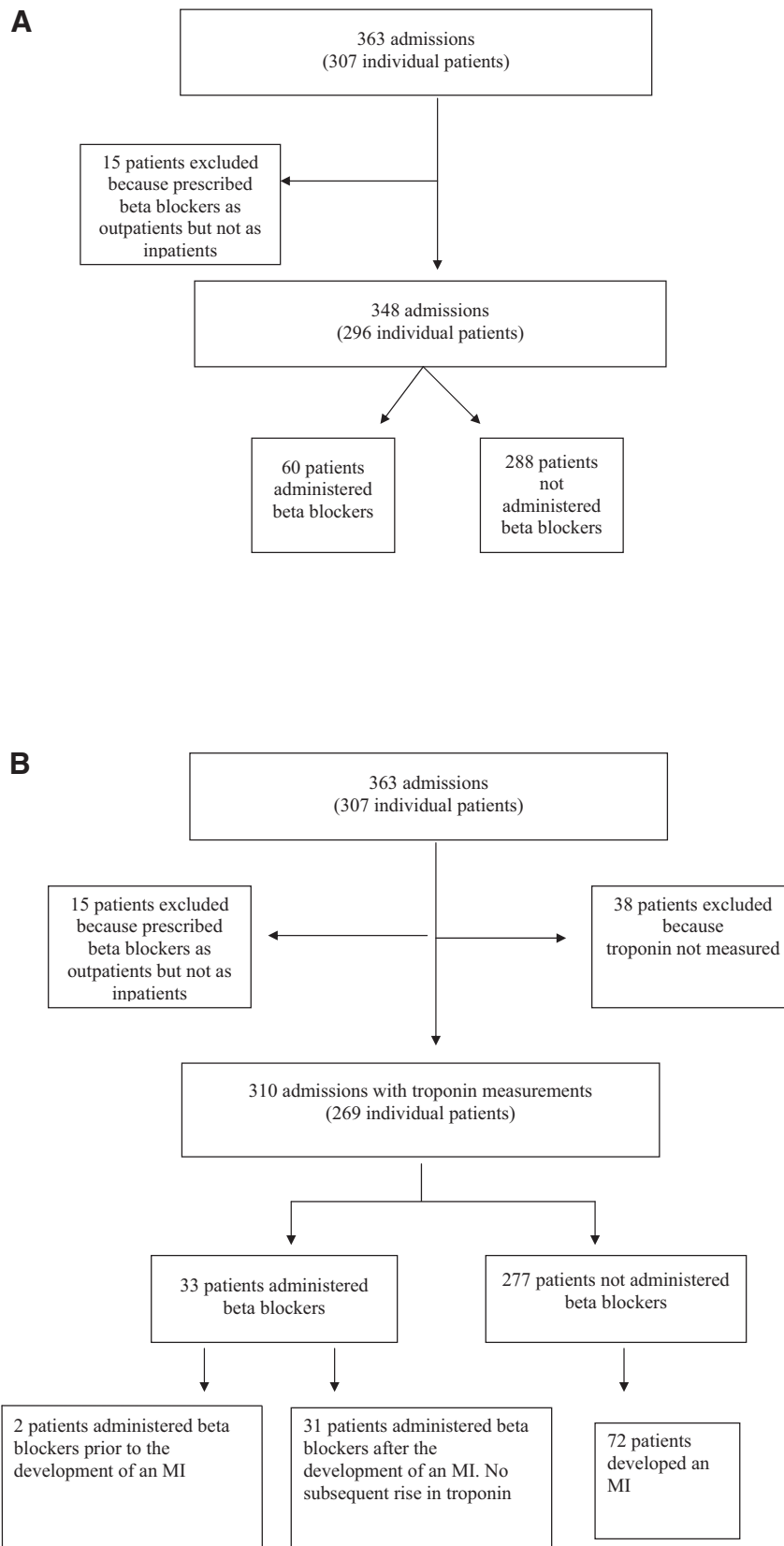
All regression models were assessed to ascertain that logistic regression model assumptions were met. The scale of continuous covariates in the models was checked using 2 methods: fractional polynomials and visually using a univariable lowess smoothed logit plot. The Hosmer and Lemeshow goodness-of-fit test<sup>27,28</sup> was performed on each model, with an adaptation of the goodness-of-fit test performed on generalized estimating equations models. All statistical tests used a 2-tailed alpha of 0.05. Statistical analyses were performed using STATA/SE 9.2 (StataCorp, College Station, TX).

The Committee on Clinical Research (institutional review board) of the Albert Einstein College of Medicine approved this study.

## RESULTS

There were 363 admissions involving 307 patients during the 5-year period (Figure 1A). Thirty-six patients had more than 1 admission. For the analysis, we excluded 15 patients who were prescribed  $\beta$ -blockers as outpatients within the past year but who were not prescribed  $\beta$ -blockers during the hospitalization because we could not determine whether  $\beta$ -blockers were present on admission. The total cohort available for analysis was 348 admissions, for 296 patients. The most common admission diagnosis was chest pain ( $n=165$ ). Patients were also admitted for congestive heart failure ( $n=8$ ), stroke ( $n=11$ ), seizure ( $n=12$ ), and overdose ( $n=15$ ), as well as several other diagnoses.

The Figure (Figure 1B) represents the myocardial infarction subgroup of the cohort. We included all admissions in the original cohort that had troponin I measurements during hospitalization. This group consisted of 310 admissions involving 269 patients. Baseline characteristics of the myocardial infarction subgroup were similar to those of the complete group



**Figure.** Study design *A*, Schema showing the entire cohort. *B*, Schema showing the myocardial infarction cohort. *MI*, Myocardial infarction.

**Table 1.** Characteristics of the full cohort.\*

Characteristics	Received $\beta$ -Blocker (n=60) <sup>†</sup>	Received No $\beta$ -Blocker (n=288)	Total (n=348)	Odds Ratio (95% CI) <sup>‡</sup>
Mean age, y	49 (10)	43 (9)	44 (10)	1.06 (1.03–1.10) <sup>§</sup>
Male patients	40 (67)	173 (60)	213 (61)	0.80 (0.43–1.47)
History of coronary artery disease	13 (22)	43 (15)	56 (16)	1.89 (0.90–4.00)
History of congestive heart failure	9 (15)	17 (6)	26 (8)	2.55 (1.05–6.15) <sup>§</sup>
History of hypertension	41 (68)	104 (36)	145 (42)	4.28 (2.17–8.44) <sup>§</sup>
History of asthma	10 (17)	92 (32)	102 (30)	0.43 (0.20–0.92) <sup>§</sup>
Albumin on admission (g/dL)	3.8 (0.8)	4.1 (0.6)	4.0 (0.7)	0.57 (0.37–0.87) <sup>§</sup>
Creatinine on admission (mg/dL)	2.3 (3.3)	1.2 (1.9)	1.4 (2.3)	1.16 (0.98–1.36)
Systolic blood pressure on admission (mm Hg)	150 (42)	137 (30.0)	139 (33)	1.01 (1.00–1.02) <sup>§</sup>
Glucose on admission (mg/dL)	173 (163)	140 (109)	145 (120)	1.02 <sup>  </sup> (1.00–1.04) <sup>§</sup>
Ejection fraction (%)	55 (15)	61 (10)	59 (12)	0.96 (0.94–0.99) <sup>§</sup>

\*Continuous variables presented as mean (SD). Categorical variables presented as No. (%).

<sup>†</sup>n refers to number of submissions.

<sup>‡</sup>Unadjusted odds ratios and 95% CI for difference between groups calculated by generalized estimating equations.

<sup>§</sup> $P < .05$ .

<sup>||</sup>Odds ratio represents a 10 mg/dL increase in glucose.

of patients who received  $\beta$ -blockers. To determine whether  $\beta$ -blocker use was associated with the development of a myocardial infarction, we excluded from the  $\beta$ -blocker group all those who received the medication after the development of positive troponin because such patients would not have  $\beta$ -blocker use as a cause of the myocardial infarction. Two of 33 patients receiving a  $\beta$ -blocker developed a myocardial infarction. In contrast, 72 of 277 patients who did not receive  $\beta$ -blockers developed a myocardial infarction.

### Characteristics of Study Subjects

Table 1 presents baseline characteristics of the cohort with respect to  $\beta$ -blocker use.  $\beta$ -Blockers were given during 60 admissions (17%). They were first given in the ED in 18 cases. These included 40 (66%) patients who received  $\beta$ -selective agents (metoprolol, atenolol, or propranolol), 13 (21%)  $\alpha$ - $\beta$ -blockade (labetalol, carvedilol), and 8 (13%) both types. Reasons recorded for giving  $\beta$ -blockers included one or more of the following: rule out myocardial infarction or postmyocardial infarction (n=56), receiving  $\beta$ -blocker as an outpatient (n=21), cirrhosis or variceal prophylaxis with propranolol (n=5), and arrhythmia (n=3).

Patients who received  $\beta$ -blockers were older and had more frequent history of hypertension and heart failure and less frequent history of asthma. In addition, patients given  $\beta$ -blockers had higher systolic blood pressure on admission, as well as higher glucose and lower serum albumin levels. Among the patients who had echocardiograms, the ejection fraction was lower for patients who received  $\beta$ -blockers. Thus, those patients in the cohort who received  $\beta$ -blockers were at greater risk for coronary artery disease and systolic dysfunction congestive heart failure.

### Main Results

Table 2 presents characteristics of the subgroup who had troponin I measurements with regard to the administration of

$\beta$ -blockers. Two patients received  $\beta$ -blockers before the development of a myocardial infarction. One of these patients was ordered to receive  $\beta$ -blockers 3.5 hours before the troponin test result became positive; the effect of  $\beta$ -blockade in this case is therefore questionable. Including both patients, the incidence of myocardial infarction was significantly lower than that for patients who did not receive  $\beta$ -blockers before the development of myocardial infarction (6.1% versus 26.0%; difference in proportion 19%; 95% confidence interval [CI] 10.3% to 30%; odds ratio [OR] 0.17, 95% CI 0.04, 0.08 calculated by generalized estimating question). No patient given  $\beta$ -blockers before positive troponin tests had a value greater than 1.0, whereas 33 patients who did not receive  $\beta$ -blockers or received them after the myocardial infarction had a troponin level greater than 1.0 (difference in proportion 57.9%; 95% CI 45.1% to 70.1%). No patient given  $\beta$ -blockers had an ST-elevation myocardial infarction, whereas 9 patients not given  $\beta$ -blockers before the event had ST-elevation myocardial infarctions.

Among the cohort, 25 patients had positive troponin I values but did not meet the European Society of Cardiology/American College of Cardiology criteria for myocardial infarction. To test whether  $\beta$ -blockers might have induced silent (asymptomatic) myocardial infarctions, we analyzed the effect of  $\beta$ -blockers, given before serum enzyme measurements, for the entire group of patients by using only a troponin value of 0.1 as a cutoff for all patients in the cohort. Only 1 of the patients without a myocardial infarction but with a positive troponin test result received a single dose of metoprolol 24 hours before the measurement. Including this case in the  $\beta$ -blocker group, there was still a trend toward a beneficial effect of  $\beta$ -blockers on preventing troponin level greater than 0.10 (difference in proportion 15.1%; 95% CI 0.8% to 31%).

Because some patients received  $\beta$ -blockers after myocardial infarctions, we analyzed the possibility that those patients might have had second myocardial infarctions after  $\beta$ -blockade,

**Table 2.** Characteristics of the myocardial infarction cohort.\*

Characteristics	$\beta$ -Blockade (n=33) <sup>†</sup>	No $\beta$ -Blockade (n=277)	Total (n=310)	Odds Ratio (95% CI) <sup>‡</sup>
Mean age, y	50 (9)	44 (9)	45 (10)	1.08 (1.03–1.12) <sup>§</sup>
Male patients	24 (73)	175 (63)	199 (64)	0.67 (0.30–1.52)
History of congestive heart failure	6 (18)	18 (7)	24 (8)	1.70 (1.23–9.07) <sup>§</sup>
History of hypertension	24 (73)	109 (39)	133 (43)	5.70 (2.34–13.88) <sup>§</sup>
History of asthma	4 (12)	83 (30)	87 (28)	0.31 (0.11–0.90) <sup>§</sup>
History of coronary artery disease	9 (27)	47 (17)	56 (18)	2.14 (0.93–4.93)
BUN on admission (mg/dL)	24 (22)	19.5 (20)	20 (21)	1.00 (0.99–1.02)
Albumin on admission (g/dL)	3.7 (0.8)	4.1 (0.6)	4.0 (0.6)	0.44 (0.25–0.80) <sup>§</sup>
Myocardial infarction	2 (6)	72 (26)	74 (24)	0.17 (0.04–0.80) <sup>§</sup>

BUN, Blood urea nitrogen.

\*Continuous variables presented as mean (SD). Categorical variables presented as No. (%).

<sup>†</sup>n refers to number of submissions.

<sup>‡</sup>Unadjusted odds ratios and 95% CI for difference between groups calculated by generalized estimating equations.

<sup>§</sup>P<.05.

**Table 3.** Selected observations in patients with in-hospital mortality.

Admitting Diagnosis	Acute Cause of Death	Received $\beta$ -Blockers	Peak Troponin Measurement (ng/mL)	Days from Positive Urine Toxicity Result to Death
STEMI	Cardiac arrest	Yes (after MI)	3.42	3
Malaise, anemia, epistaxis	Cardiac arrest	No	N/C*	25
SOB/cardiac arrest	Cardiac arrest	No	0.04	4
Cardiac arrest	Cardiac arrest	No	0.2	0
Altered mental status	Cardiac arrest	No	4.56	22
Cardiac arrest as a result of smoke inhalation	Cardiac arrest	No	69.8	4
Endocarditis	Sepsis	No	N/C	4
SOB/pneumonia	Sepsis	No	N/C	5
SOB/diarrhea	Sepsis	No	0	7
SOB/ARF	Sepsis	No	0	27
Altered mental status	Sepsis	No	0.69	4
Abdominal pain	Sepsis	No	0.78	0
SOB/sepsis	Sepsis	No	7.7	1
Upper GI bleed	GI bleed	No	0.01	0

STEMI, ST-elevation myocardial infarction; SOB, shortness of breath; N/C, not checked; ARF, acute renal failure; GI, gastrointestinal.

\*No troponin tests were conducted throughout the course of the admission.

defined by a second increase in serum troponin level. No patient who received  $\beta$ -blockers had a second myocardial infarction during the hospitalization. In contrast, 4 patients who were not given  $\beta$ -blockers had second myocardial infarctions.

Fourteen patients died during hospitalization. Patients who died were significantly more likely to be women and to have a history of HIV disease, history of heart failure, lower systolic blood pressure, lower serum albumin, and higher BUN, potassium, and creatinine level on admission.

Only 1 of the patients who received  $\beta$ -blockers died during the hospitalization compared to 13 patients who did not receive  $\beta$ -blockers (Table 3). The cause of death in the patient receiving  $\beta$ -blocker was pericardial tamponade as a result of thrombolysis for ST-elevation myocardial infarction. The patient received the  $\beta$ -blocker after the development of ST elevations.

Of the deaths, 6 were associated with a cardiac arrest, 1 with an upper gastrointestinal bleed, and 7 with probable sepsis. Troponin measurements were made for 11 of the 14 patients

and were positive for 7 (range 0.2 to 69.8 ng/mL), including 3 of 5 patients with sepsis and troponin values.

The time from positive urine toxicology testing to death was variable, though most deaths occurred within 4 days. In 3 cases, death occurred more than 20 days after the positive urine toxicology measurement.

The unadjusted incidence of death in patients receiving  $\beta$ -blockers was 1.7% versus 4.5% for patients who did not receive  $\beta$ -blockers (difference in proportion 2.8%; 95% CI –1.2% to 6.7%).

Results from the multivariate analyses are shown in Table 4. Parsimonious multivariate myocardial infarction models included  $\beta$ -blocker administration, history of heart failure, systolic blood pressure, and sex.  $\beta$ -Blocker use was associated with significant reduction in the risk of myocardial infarction (OR 0.06; 95% CI 0.00 to 0.61). The goodness-of-fit test showed no significant deviation for lack of fit ( $P=.66$ ). Multivariate analyses using generalized estimating equations

**Table 4.** Adjusted odds ratios of  $\beta$ -blocker administration.

Model	Events, No. (Number of Patients)	Odds Ratio (95% CI)*
<b>MI: all patients</b>		
Full cohort <sup>†</sup>	74 (310)	0.06 (0.01–0.61) <sup>‡</sup>
First admission <sup>§</sup>	62 (269)	0.08 (0.01–0.65) <sup>‡</sup>
<b>MI: primary diagnosis of chest pain</b>		
Full cohort <sup>†</sup>	51 (165)	0.05 (0.00–2.08)
First admission <sup>§</sup>	44 (140)	0.09 (0.01–0.70) <sup>‡</sup>
<b>Inhospital mortality</b>		
Full cohort <sup>  </sup>	14 (348)	0.22 (0.02–2.41)
First admission <sup>¶</sup>	12 (296)	0.01 (0.00–0.33) <sup>‡</sup>

\*Odds ratio estimated by generalized estimating equations analysis with propensity scores.

<sup>†</sup>Model includes  $\beta$ -blocker administration, systolic blood pressure, sex, and a history of heart failure.

<sup>‡</sup> $P < .05$ .

<sup>§</sup>Model includes  $\beta$ -blocker administration, systolic blood pressure, and BUN.

<sup>||</sup>Model includes  $\beta$ -blocker administration, systolic blood pressure, sex, history of diabetes, albumin, and age.

<sup>¶</sup>Model includes  $\beta$ -blocker administration, serum albumin, and BUN.

analysis and propensity scores for inhospital mortality included  $\beta$ -blocker administration, albumin, history of diabetes, age, sex, and systolic blood pressure.  $\beta$ -Blocker use was associated with a nonsignificant reduction in risk of death (OR 0.22; 95% CI 0.02 to 2.41). The goodness-of-fit test showed no significant deviation for lack of fit ( $P = .47$ ).

### Sensitivity Analyses

Sensitivity analyses for myocardial infarction outcomes in which only the first admission for each patient was included in multivariate analysis yielded similar results to those presented above (Table 4).  $\beta$ -Blocker use significantly reduced the risk of myocardial infarction (62 events/269 patients; odds ratio [OR] 0.08; 95% CI 0.01 to 0.65). The goodness-of-fit test showed no significant deviation for lack of fit ( $P = .75$ ). The parsimonious multivariate inhospital mortality model in which only the first admission for each patient was included in multivariate analysis included  $\beta$ -blocker administration, serum albumin, and BUN.  $\beta$ -Blocker use during hospitalization also significantly reduced the risk of inhospital mortality (12 events/296 patients; OR 0.01; 95% CI 0.00 to 0.33). The goodness-of-fit test showed no significant deviation for lack of fit ( $P = .15$ ).

Because of heterogeneity of admission diagnoses in the cohort of patients with positive urine toxicology results for cocaine, we performed another subgroup analysis of myocardial infarctions ( $n = 51$ ) for patients who presented with a primary diagnosis of chest pain ( $n = 165$ ). Parsimonious multivariate myocardial infarction models for the admission diagnosis of chest pain included  $\beta$ -blocker administration, systolic blood pressure, and BUN.  $\beta$ -Blocker use was of borderline significance in reducing the risk of a myocardial infarction (OR 0.05; 95% CI 0.00 to 2.08). The goodness-of-fit test showed no significant deviation for lack of fit ( $P = .83$ ). Sensitivity analysis using only the

first admission in this subgroup ( $n = 140$ ; myocardial infarction events  $n = 44$ ) yielded similar results (OR 0.09; 95% CI 0.01 to 0.70). The goodness-of-fit test showed no significant deviation for lack of fit ( $P = .92$ ). No other subgroup analysis based on primary admission diagnosis was possible, because of insufficient numbers.

### LIMITATIONS

Because of its retrospective design, our study is subject to a number of limitations, including the possibility of selection or other bias and the presence of relevant but undetected or unmeasured clinical variables that may have influenced our results.

We believe selection bias is unlikely. Our only exclusion criterion with respect to the cohort as a whole involved patients who had been prescribed  $\beta$ -blockers as outpatients before admission and were not given  $\beta$ -blockers during the admission. With this exception, our study included all patients without any other preselection criteria who were admitted to a high-risk area and had positive urine toxicology test results for cocaine during a predefined period.

A subtler question of bias relates to the issue of why some physicians decided to give  $\beta$ -blockers to patients who were found to have taken cocaine. There were no guidelines in place about use of  $\beta$ -blockers at the time of the study. However, it seems apparent that patients who received  $\beta$ -blockers had a greater risk for coronary artery disease and poor left ventricular function, as well as higher glucose levels and blood pressure, than those who did not (Table 1). Thus, the group who received  $\beta$ -blockers may have had a higher likelihood of having a myocardial infarction than the group that did not receive  $\beta$ -blockers. These data suggest that the effect of  $\beta$ -blockers may actually be underrepresented in the univariate analysis, and is confirmed by the significance of the multivariate analysis using propensity scores,<sup>25,26</sup> a widely accepted and used method to address selection bias.

Another major consideration is the possibility that other diseases contributed to or interacted with the outcomes we observed. Patients who use cocaine are likely to have other serious diseases, including HIV and hepatitis C. Interactions between these conditions, the drugs used to treat them, and the effects of cocaine are difficult to predict. We used the simplest approach of including all patients with positive urine toxicology result, regardless of other conditions. The use of propensity scores is again the most rigorous way of accounting for possible bias.

Furthermore, the subgroup analysis of patients admitted with a primary diagnosis of chest pain reveals a trend toward the same protective effect of  $\beta$ -blockers on preventing subsequent myocardial infarction as the cohort as a whole (Table 3). The odds ratio of having a myocardial infarction while receiving  $\beta$ -blockers in this subgroup (0.05) is actually lower than for the group as a whole, suggesting that  $\beta$ -blockers had a similar effect on the subgroup as it did in the whole cohort. The borderline significance of the test is most likely due to loss of power from fewer cases. Furthermore, when first admissions only for chest pain are considered, the result remains statistically significant. Thus, we do not believe that interactions caused by other

diseases account for the results. Although propensity score analyses were used to address any potential selection bias, such statistical techniques could adjust for only known and observed confounders. Any unknown and unobserved confounders may have biased these results.

Another limitation of the study relates to the fact that we have no data on the actual time of cocaine ingestion, nor do we have serum levels of cocaine. We cannot rule out, therefore, that the acute effects of cocaine might be different from those associated with positive urine test results.

On the other hand, our study addressed the common clinical problem faced by physicians who are treating patients suspected of cocaine use. For this purpose, urine toxicology is the test of choice and is both widely used and highly reliable. Although such testing may stay positive for at least 48 hours, and possibly up to 72 hours,<sup>29,30</sup> cocaine use has been associated with myocardial infarction for up to 4 days after ingestion.<sup>31</sup> It is therefore not unreasonable to assume that the positive troponin values of this study reflect myocardial damage induced by cocaine. Our study suggests that, for patients who have positive urine toxicology test results, it is safe to give  $\beta$ -blockers.

Finally, our study was too small and lacked sufficient statistical power to fully explore the effect of  $\beta$ -blockers on in-hospital mortality. It is also possible that some conditions that led to mortality, such as sepsis, led physicians to avoid using  $\beta$ -blockers.

## DISCUSSION

Our analysis of consecutive patients who had positive urine toxicology test results for cocaine and were admitted to telemetry units, ICUs, or coronary care units of a municipal hospital indicates that administration of  $\beta$ -blockers was associated with a reduction, rather than an increase, in the risk of death and myocardial infarction. Because the study is retrospective, the results must be considered preliminary. However, for our analysis, we used the method of propensity scores, which is the most rigorous method to assess data when treatments are assigned nonrandomly. The reduction of myocardial infarctions in the group receiving  $\beta$ -blockers (6% odds ratio versus no  $\beta$ -blockers) is striking.

Despite the lower incidence of in-hospital mortality in the group of patients given  $\beta$ -blockers, the number of deaths in the cohort is too small to allow conclusions about the effect of  $\beta$ -blockers on this outcome. Several of the deaths occurred later in the hospitalization from causes such as sepsis. At the same time, no death in the 5-year period could be directly attributed to coronary spasm induced by  $\beta$ -blockers. The single death after administration of a  $\beta$ -blocker appeared unrelated to  $\beta$ -blocker use because the patient died from pericardial tamponade after an ST-elevation myocardial infarction treated with thrombolysis. In this case,  $\beta$ -blockers were given after the ST elevations appeared.

Because we used urine tests as the criterion for cocaine use, it is possible that the effect of  $\beta$ -blockers on patients with positive urine cocaine metabolite results is different from the effect during acute cocaine toxicity. However, the determination of

cocaine use in EDs is most frequently based on urine toxicology. Our results suggest that, at least in patients with the characteristics of our cohort, the use of  $\beta$ -blockers for patients with positive toxicology screen results is not associated with increased myocardial infarctions or death.

Cocaine has multiple deleterious effects on the heart, including not only spasm of the large coronary arteries<sup>4-8</sup> but also toxic effects on cardiac muscle that arise primarily from  $\text{Ca}^{2+}$  overload during excessive  $\beta$ -adrenergic stimulation.<sup>1-3,18,19,21</sup> The effect of  $\beta$ -blockers on each of these effects is contradictory. Our results suggest that the protective effect on muscle may be more important in determining clinical outcomes than the effect on coronary arteries.

Although the mechanisms by which  $\beta$ -blockers reduced myocardial infarctions in our cohort are not clearly defined, the results are consistent with previous studies of the benefit of  $\beta$ -blockers in acute ischemic syndromes. For example, there is evidence that  $\beta$ -blockers prevent the development of reinfarction in other large cohorts of patients admitted for myocardial infarct without cocaine intoxication,<sup>32</sup> which is reflected in our cohort as well. Furthermore,  $\beta$ -blockers should protect against necrosis or stunning, which is caused by direct myocyte toxicity from  $\text{Ca}^{2+}$  overload after excessive catecholamine stimulation.<sup>18-20</sup> In this regard, a recent case report<sup>33</sup> demonstrated that cocaine can acutely depress left ventricular systolic function in the absence of coronary artery disease and spasm: in this patient, dramatic improvement in left ventricular function occurred after treatment with carvedilol.

Our study, although preliminary, suggests that the use of  $\beta$ -blockers is not deleterious and may be beneficial to patients who present to the ED with positive urine toxicology results for cocaine. We believe that the data justify a more definitive, randomized, prospective study in larger groups of patients.

---

*Supervising editor:* Richard C. Dart, MD, PhD

*Author contributions:* PBD and DS conceived the study. PBD and KF collected the data. CN and SMH developed the strategy for data analysis. CN, PBD, DS, and SMH analyzed the data. SMH, PBD, and CN interpreted the data. CN and SMH drafted the article; CN, SMH, and PBD contributed to its revision. CN takes responsibility for the paper as a whole.

*Funding and support:* By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

*Publication dates:* Received for publication December 19, 2006. Revisions received March 8, 2007, and April 4, 2007. Accepted for publication April 13, 2007.

Presented as a poster at the Society for General Internal Medicine annual meeting, April 2006, Los Angeles, CA; and

the American Heart Association Scientific Sessions, November 2006, Chicago, IL.

Address for reprints: Charles Nordin, MD, Department of Medicine, Room 3N1, Jacobi Medical Center, 1400 Pelham Parkway South, Bronx, NY 10461; 718-918-5643, fax 718-918-7460; E-mail: nordin@aecom.yu.edu.

## REFERENCES

1. Kloner RA, Hale S, Alder K, et al. The effects of acute and chronic cocaine use on the heart. *Circulation*. 1992;85:407-419.
2. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med*. 1995;333:1267-1272.
3. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med*. 2001;345:351-358.
4. Schachne JS, Roberts BH, Thompson PD. Coronary-artery spasm and myocardial infarction associated with cocaine use. *N Engl J Med*. 1984;310:1665-1666.
5. Zimmerman FG, Gustafson GM, Kemp HG. Recurrent myocardial infarction associated with cocaine abuse in a young man with normal coronary arteries: evidence for coronary artery spasm culminating in thrombosis. *J Am Coll Cardiol*. 1987;9:964-968.
6. Myers GH, Hansen TH, Jain A. Left main coronary artery and femoral artery vasospasm associated with cocaine use. *Chest*. 1991;100:257-258.
7. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic-blockade. *Ann Intern Med*. 1990;112:897-903.
8. Boehrere JD, Moliterno DJ, Willard JE, et al. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med*. 1993;94:608-610.
9. Brogan WC, Lange RA, Kim AS, et al. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol*. 1991;18:581-586.
10. Negus BH, Willard JE, Hillis LD, et al. Alleviation of cocaine-induced coronary vasoconstriction with intravenous verapamil. *Am J Cardiol*. 1994;73:510-513.
11. Freemantle N, Cleland J, Young P, et al. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730-1777.
12. Packer M, Coats AJ, Fowler MB, et al, for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
13. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
14. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1988;319:385-392.
15. Isikawa K, Nakai S, Takenaka T, et al. Short-acting nifedipine and diltiazem do not reduce the incidence of cardiac events in patients with healed myocardial infarction. Secondary Prevention Group. *Circulation*. 1997;95:2368-2373.
16. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation*. 1990;82:1954-1961.
17. Cohn JN, Ziesche SM, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation*. 1997;96:856-863.
18. Tazelaar HD, Karch SB, Stephens BG, et al. Cocaine and the heart. *Hum Pathol*. 1987;18:195-199.
19. Gardin JM, Wong N, Alker K, et al. Acute cocaine administration induces ventricular regional wall motion and ultrastructural abnormalities in an anesthetized rabbit model. *Am Heart J*. 1994;128:1117-1129.
20. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumeral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352:539-548.
21. Parikh P, Nikolaidis LA, Stolarski C, et al. Chronic exposure to cocaine bingeing predisposes to an accelerated course of dilated cardiomyopathy in conscious dogs following rapid ventricular pacing. *J Pharmacol Exp Ther*. 2005;315:1013-1019.
22. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959-969.
23. Department of Health and Human Services. Mandatory guidelines for federal workplace drug testing programs. *Fed Registr*. 1988; 53:11970-11989.
24. Morrow DA, Cannon CP, Rifai N, et al, TACTICS-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA*. 2001;286:2405-2412.
25. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127(8 pt 2):757-763.
26. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265-2681.
27. Horton NJ, Bebchuk JD, Jones CL, et al. Goodness-of-fit for GEE: an example with mental health service utilization. *Stat Med*. 1999;18:213-222.
28. Hardin JW, Hilbe JM. *Generalized Estimating Equations*. Boca Raton, FL: CRC Press; 2003.
29. Das G. Cardiovascular effects of cocaine abuse. *Int J Clin Pharmacol Ther Toxicol*. 1993;31:521-528.
30. Om A, Ellahham S, DiSciascio G. Management of cocaine-induced cardiovascular complications. *Am Heart J*. 1993;125(2 pt 1):469-475.
31. Hollander JE, Hoffman RS. Cocaine-induced myocardial infarction: an analysis and review of the literature. *J Emerg Med*. 1992;10: 169-177.
32. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *N Engl J Med*. 1989;320:618-627.
33. Arora S, Alfayoumi F, Srinivasan V. Transient left ventricular apical ballooning after cocaine use: is catecholamine cardiotoxicity the pathologic link? *Mayo Clin Proc*. 2006;91:829-832.

## Editor's Capsule Summary *What is already known on this topic:*

Most physicians believe that sole  $\beta$ -blockade should be avoided in patients with clinical evidence of cocaine toxicity because of the risk of unopposed  $\alpha$  receptor stimulation. Some believe that

$\beta$ -blockers should be avoided in any patient with chest pain and a history of cocaine use. *What question this study addressed:* The outcome of patients who received  $\beta$ -blockers in the presence of a positive urinary drug screen result for cocaine. *What this study adds to our knowledge:* In this 348-patient retrospective review, there were proportionately fewer myocardial infarctions and deaths in the 60 patients who received  $\beta$ -blocker. *How this might change clinical practice:* Although case reports suggest that some patients may experience adverse cardiovascular events during  $\beta$ -blocker administration, it is possible that others actually benefit. To guide clinical practice, research focusing on the population effect of  $\beta$ -blocker avoidance in patients with cocaine toxicity is needed.